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Edited by Marcel Van de Voorde and Gunjan Jeswani

Marcel Van de Voorde, Gunjan Jeswani (Eds.)

Ethics in Nanotechnology

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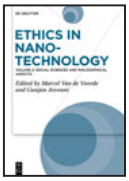

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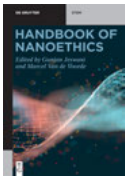

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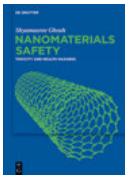

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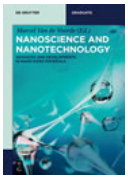

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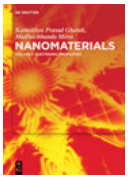

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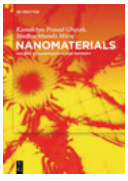

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Ethics in Nanotechnology

Emerging Technologies Aspects

Volume I

Edited by
Marcel Van de Voorde and Gunjan Jeswani

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Nano-Covid-19 Vaccine is a great innovation but also a nano-ethical problem.
Vaccine is a matter of privilege to the rich countries, who take the right to serve themselves first and regrettably treat the rest of the world as second-class people.
Vaccine nationalism takes precedence over world health, human rights, and solidarity.
The rich will regret it once!

Prof. Marcel Van de Voorde, doctor honoris causa

Preface: Converging technologies from the nanoscale require enhanced ethics

Reaching the atomic and molecular levels with investigative and transformative tools has been a historic turning point not only for human knowledge but also for philosophy, manufacturing, and human well-being. The rapid progress of nanotechnology has been mirrored by increased concerns about unknown material behavior, powerful transformative tools, human-technology coevolution, and other societal implications.

Developments at the nanoscale have awakened other foundational science and technology fields such as modern biology, information technology, wireless technologies, artificial intelligence (AI) systems, and cognitive technologies. Together, these are transforming ways of life and societal trends. A new, converging science and technology global platform – nano-bio-info-cogno-AI – has been created worldwide. This platform built from the nanoscale is accelerating economic and human development. Risks of secondary effects on "environmental, health, and safety (nano-EHS)" and "ethical, legal, and societal implications (nano-ELSI)" must be identified and mitigated from the beginning of any large project, in concurrence with the science and technology progress of the respective projects.

Significant nanoscale science and technology research programs continue around the world; once President Bill Clinton announced the U.S. National Nanotechnology Initiative (NNI) in January 2000, national programs sprang up in 80 other economies within just a few years. These programs are pushed by successive nanoscale breakthroughs and convergence with other emerging science and technology fields. Programs are also pulled by their extensive and multifaceted societal benefits, which were recognized early; nanotechnology stakeholders convened on the topic within the first month of NNI, leading to the book *Societal Implications of Nanoscience and Nanotechnology* (Kluwer, now Springer 2001). The NNI's cumulative research and development (R&D) funding has reached about $28 billion in 2019. Between 2000 and 2019, the average annual growth rate of nanotechnology publications was about 14% (faster in the first decade, decelerating slightly after 2010) and of nanotechnology applications was about 25% (accelerating after 2010). Societal implications grew with several kinds of applications, such as those related to human and environmental safety and ethical and legal aspects. The global revenue of products having nanotechnology as the key competitive factor was estimated to reach about $3 trillion in 2020, of which about one quarter was from the United States. New areas of research and engineering such as metamaterials and plasmonics have emerged, and new uses appear in emerging technologies such as molecular manufacturing, regenerative medicine from the nanoscale, and smartphone platforms. Recent R&D programs are directed to future nanosystem architectures and converging technology platforms for production, health, infrastructure, and services. Today, responsible governance focuses attention on the confluence of nanotechnology with other domains, its role on social sustainability, and synergistic

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effect from integration with other emerging technologies ("Convergence of Knowledge, Technology, and Society: Beyond Nano-Bio-Info-Cognitive Technologies," Springer 2013, available at www.wtec.org/NBIC2/).

As part of a worldwide effort, an international community has been established for nano-EHS and nano-ELSI. This has been facilitated by the creation of large networks in the United States, Europe, and Asia, beginning with the networks on "Nanotechnology in Society" (centered at the UC-Santa Barbara and Arizona State University) and "Centers for Environmental Implications of Nanotechnology" (at UCLA and Duke University). After an initial focus on the toxicity of nanomaterials themselves, scientific interest in nanodevices and exposure of industrial and incidental nanoproducts to consumer have risen and led to essential improvements in evaluating and governing the risk. Significant research and regulatory activities have addressed the environmental, health, and safety implications of nanotechnology applications, especially for passive as well as chemically and biologically active nanoparticles. Responsible development of nanotechnology increasingly addresses ethical, legal, and other societal issues, including ecological and human development aspects. Ethical questions have been raised about who will receive the benefits of nanotechnology and who will be affected by its secondary effects. Ethics need to be included in the vision of an R&D program in an emerging area. Based on my experience in planning research initiatives, on average about a third of the overall program's success depends on the initial topic selection, research directions, and consideration of societal implications, including ethical aspects.

The next decade will bring several main advancements to nanotechnology-inspired science and technology fields. Larger and multifunctional nanostructures and devices are already being built with more atoms, complex networking, and information content, increasing the EHS and ELSI risks. They are increasingly used in advanced manufacturing, quantum information systems, AI systems, the bioeconomy, neurotechnology, sustainable society, and advanced wireless. Such technologies will converge to better serve people and contribute to human development, but new safety concerns may arise. Nanoscale science and technology evolve closer together, with more partnerships between academia and the private sector. Translational nanotechnology takes a center stage. The necessary infrastructure becomes more complex and integrated with the needs of the global emerging technology system. Education and training of a flexible nanotechnology workforce are essential requirements for safe and sustainable progress and a long-term challenge strongly connected to changes in the human-technology ecosystem and other societal trends.

With the prospect of these and other emerging convergent areas of nanotechnology before us, the need to incorporate ethics – for both program success and positive societal impacts – is clear and crucial. The complementary volumes Emerging Technologies Aspect and Social Science and Philosophical Aspects assembled by Gunjan Jeswani and Marcel Van de Voorde bring together a rich range of topics and various perspectives from five continents. The first volume defines the characteristics

of nano-ethics of emerging nanotechnology and describes how these characteristics affect human health, and EHS safety, Governance of nanotechnology provides a systematic way to properly address societal dimensions, including setting the main challenges, engagement with the participants in nanotechnology development, and balancing the benefits versus the need for regulatory measures. The co-editors provide guiding remarks and recommendations to nanotechnology providers and users. The collection of opinions presented in this volume is a remarkable selection of research contributions concerning the ethics of nanotechnology research.

The second volume includes 16 perspectives on various aspects of ethics in nanotechnology development, from philosophical concepts to applications. The topics are grouped under international reflection, nanotechnology expansions raising ethical concerns, nanotechnology philosophy: Dilemmas and ethical issues and ethical recommendations for promising technology.

Both of these volumes have to be read together, which cover everything from the basic concepts and definitions to a diverse collection of international perspectives. These bring together some of the most vigorous minds active in nanotechnology ethics in the world. Converging and emerging technologies from the nanoscale bring new health, environmental, ethical, and legal concerns that are highlighted in these volumes. We encourage all research, education, and industry experts to closely read these state-of-the-art contributions on ethics in nanoscale science and technology fields.

Mihail C. Roco
National Science Foundation and National Nanotechnology Initiative
Alexandria, Virginia, July 20, 2020

Forewords

I

When I was invited to write the foreword of this book, I thought it would be important to start by giving justice to the visionary work of Nobel laureate R. Feyman[1] on the groundbreaking capabilities of nanotechnology.

In 1959, Prof. Feyman first mentioned the broad possibilities afforded by substances of an extremely small size. Addressing an audience at the annual American Physical Society, he stated: "[. . .] when we have some control of the arrangement of things on a small scale we will get an enormously greater range of possible properties that substances can have, and different things that we can do [. . .]."[2]

Since this speech, the miniaturization described by Prof. R. Feyman has led to the development of, what is called today, nanotechnology. Nanotechnology enables the manufacturing of materials with size ranging from 1 to 100 nm. Due to the extremely small size of the particles, these materials exhibit novel physical and chemical properties. Considered an area of incredible promise, this disruptive technology has delivered over the years many innovative applications in very different domains.

Several everyday products (e.g., kitchenware, batteries, coatings for solar cells, cosmetics, and sunscreens) show improved features, thanks to the nanomaterials they contain. For example, silver nanoparticles, with their antimicrobial attributes, reduce odor-producing bacteria in sport textiles.[3]

Also, in medical devices, coatings in the nanoscale increase biocompatibility and thus improve integration of a variety of medical implants (e.g., stent coating in cardiology)[4] with the surrounding tissues. The application of nanotechnology to medicine includes the use of precisely engineered materials to develop novel therapies that may reduce toxicity as well as enhance the efficacy of treatments. The first nanotechnology-based cancer drugs are already on the market.[5]

However, as is the case for many other technological breakthroughs, the development of nanotechnology is also hindered by several ethical controversies. Today there is a clear split between those who see the unmet potential of the innovation and those who fear a negative impact on the environment and on health, and question how to ensure a responsible use of nanotechnology.

The different views between scientists and the general public on how to address the balance between the risks and the benefits of nanotechnology create mistrust in

1 https://www.nobelprize.org/prizes/physics/1965/feynman/biographical/.

2 Feyman RP. There's plenty of room at the bottom. *Caltech Engineering and Science* 1959; 23(5): 149–160.

3 https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_039.pdf.

4 https://www.rivm.nl/publicaties/nanotechnologies-in-medical-devices.

5 https://www.cancer.gov/nano/cancer-nanotechnology/current-treatments.

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the deployment of this innovation. This leads to significant barriers to its broad diffusion.

One area in which nanotechnology is facing controversy is the packaged food and beverage sector, a field in which, as chairman emeritus of Nestlé S.A., I am particularly interested. Nanotechnology can have implications, for example, in the reduction of food waste: by using it in packaging we can protect the food from gases and light, which cause degradation of food.

From a consumer's perspective, product safety is what drives the acceptance of any technology, including nanotechnology, in food. This is where and when regulators step in. Indeed, food applications of nanotechnology fall under stringent general food regulations. They are authorized only when safety requirements, based on detailed risk analysis, are fully met. However, despite this high level of institutional reassurance, concerns on the novel technology in food may persist. Consequently, manufacturers may decide not to make any use of it even if allowed by regulators.

Science and novel technologies are drivers of societal change. They can accelerate progress, leading to greater well-being for all. The ethical questions that are raised on the safety and on the responsible use of nanotechnology are legitimate, and the answers available at this stage may not be reassuring enough for some of us. However, the lack of adequate responses should not limit our endeavor to explore new scientific avenues. We are still at the early stages of the nanotechnology journey: research should be encouraged and should continue.

Scientists, policymakers, and other stakeholders can join forces to help understand the major advantages of this new technology to the general public. With this, and as we progress and learn, we can overcome the existing distrust and uncertainty, and bring more reassurance on the unmet benefits that nanotechnology can provide to humanity.

Peter Brabeck-Letmathe
Chairman Emeritus, Nestlé S.A.
Vevey, 29 April 2020

II

It is a pleasure to write the foreword of this book, because we are witnessing the emergence of the next version of the industrial revolution; hence, there is a need for understanding and practice of ethical standards.

In the era of Industry 4.0, dynamic technology is the main growth platform and is playing a crucial role in raising the standards of the society. Nanotechnology has brought several benefits to humanity. Nevertheless, as technological advancement is profound importance, society is facing newer challenges as well. There is still a significant difference for those who perceive the unfulfilled promise of science and those who fear adverse effects on the climate, safety, and the safe usage of the technology. Consequently, ethical discussions among the thought leaders and technical experts are required in order to address the gray areas.

The nuclear power, weapons, biotechnology, and artificial intelligence are the main areas driven by nanotechnology, which raises several legal and moral concerns. The ethical dilemmas, environmental problems, and work displacement are among the key ethical or moral concerns in nanotechnology and are discussed in different chapters of this book.

The fields like nanomedicines, nano-cosmetics, and nanodevices are discussed at length which are interesting and demonstrates significant enhancement in pharmacokinetics, increased tissue selectivity, and effectiveness due to their size, structure, composition, and design. The use of nanomedicines besides benefits raises ethical challenges regarding probable side effects of nanoparticles on humans and disposal in the environment. The overall risk analysis, research involving human embryonic stem cells, germline gene therapy, and gene editing are of great concern. Currently, in more than 40 countries the use of germline editing for reproduction is prohibited. Nanoparticles of zinc oxide and titanium dioxide used in sunscreen products also run the risk of dangerous entry into the systemic circulation, genotoxicity, and cytotoxicity. These points are specifically discussed in the chapter dealing with nano-cosmetics and briefly in others too.

This book on nanotechnology ethics would foster discussion and probable solutions for complexities. The chapters are written by experts representing prestigious organizations around the globe.

I genuinely believe this book will help intellectuals across the various profession and consumers to develop an understanding of ethical challenges in these areas.

Shailendra Saraf
Vice President, Pharmacy Council of India, New Delhi, India

III

Unprecedented situations need unprecedented solutions.
Amin Maalouf

"There is no any challenge beyond the human distinctive capacity to create," said President J. F. Kennedy in June 1963. This is a very important statement: the impossible today can be possible tomorrow and there is no place in the scientific mind for fanaticism, dogmatism, and fatalism. The past cannot be rewritten. The future is to be invented.

Taking into account the potentially irreversible processes, it is our common responsibility to bear in mind "the ethics of time," acting in a way that will prevent us from taking a path that allows no return. We have to specifically take into account next generations: our legacy cannot condemn them to have a worst standard of living and prevents them from fully exercising the distinctive capacities of human beings.

In this context, nanotechnology such as the study, design, creation, synthesis, manipulation, and application of materials, devices, and functional systems through the control of matter at nanoscale and the exploitation of phenomena and properties of matter at nanoscale offer a number of possibilities in different fields to help alleviate situations of great need.

Linked to the scientific research developed by the main public institutions of higher education, nanotechnology fosters a model of interdisciplinary collaboration in fields such as the so-called nanomedicine – application of techniques that allow the design of drugs at the molecular level – nanobiology, and the development of microconductors.

When matter is manipulated on such a tiny scale of atoms and molecules, it demonstrates completely new phenomena and properties. Therefore, scientists use nanotechnology to create new and inexpensive materials, devices, and systems with unique properties. Nanotechnology must be used as a tool to help alleviate the great challenges we face.

The past has already been written. It must now be accurately described. We must learn from the lessons of the past to be able to invent the future, be able to provide all required conditions to each and every human being, so they can all have a dignified life.

The time has come to raise our voices with both serenity and resolution. The time has come for the emancipation of citizenship, for "We, the peoples . . ." as stated in the first phrase of the UN Charter. We need peace within each human being, at home, in the villages, in the cities, and across the world.

Our conscience allows us to progressively discover what we are like, what we are composed of, and how that is reflected in "health" and in mental instability (physiopathology). We research incessantly to uncover the realities of all living beings, of the planet we inhabit, and of the whole universe. We contemplate and reflect on the

cosmos, on the galaxies, and on their colossal dimensions; we do so as well with the smallest particles, the elements that comprise the minimum parts of matter. From the most distant stars to quarks, our curiosity and desire for greater knowledge knows no bounds. And all of this enables us to discover *what we are like* and *where we are*, but it adds little to *who we are*.

I firmly insist that sustainable development and avoid the further deterioration of the environment cannot be postponed, because no return points can be reached. Therefore, the time has come for a great mobilization at the global scale so that people at last take control of their own common destiny. Words are our only "mass construction weapons."

Enough! The time has now come to "rescue" the citizens and, to that end, we must make a quick and courageous shift from an economy of war to an economy of global and sustainable development.

Dare to know! (*sapere aude*) is written in the Oxford County Wall Crest. Yes, but afterward "no how to dare," how to share, and how to care. This is the *crucial role of the scientific community* today: to be closed – never more dependent – to the governments, parliaments, councils, and civil society associations in order to provide them with science and technology assessment, to advise and anticipate, to be watchtowers, to foresee, and to prevent.

Now, more than in the past, is urgent interweaving the real world with the affordable solutions. On this way, particularly in the moments of deep crisis that we are living – financial, environmental, democratic, ethical – that are opportunities as well, the scientists must become actively involved in a new farsighted vision of otherness and brotherhood *taking into account the earth as a whole*. There are no frontiers anymore, and should not be privileged citizens (a minority of 20%) when most of them live in very difficult, even inhuman, conditions.

Time has come for action!

Federico Mayor
Former President, UNESCO, Paris, France
March 4, 2020

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Contents

Introduction: Overall vision of ethics in nanotechnology developments

Book's objective

The new and emerging nanotechnology is remaking the world at an alarmingly rapid pace with many applications in a wide variety of fields ranging from health care over industrial products to crime prevention and defense. Despite the many impactful benefits of nanotechnology, such as the cultivation of new organs for patients, there are potential hazards and risks involved, such as the toxicity of certain nanoparticles that could cross the blood–brain barrier. Nanotechnology, it should be clear, has the potential to profoundly change society for better or for worse.

The societal implications of nanotechnology encompass many ethical issues such as the violation of privacy, the violation of a person's autonomy, environmental pollution, economic abuse, security, and global justice (between developed and developing countries).

The biggest question we are facing is how we should deal with uncertainty and risk in this emerging technology? Uncertainty is one of the major obstacles to the commercialization of nanotechnology – uncertainty about the risks to health and environment and uncertainty about how the governments might regulate nanotechnology in the future. There is an urgent need for answers both in the realm of science and in the realm of law and regulation. In the absence of scientific clarity about the potential health and environmental effects of exposure to nanoparticles, the policymakers must be provided with guidance on how to deal with hazards, risks, and controls.

Nanotechnology will affect everyone; thus, all members of society should have a voice in its development and commercialization. The book focuses on the main societal and ethical issues that arise from the development of nanotechnology. The result is a clear set of questions and solutions proposed by leading researchers working in a variety of fields such as applied ethics, bioethics, ethics of science, ethics of technology, and business ethics.

There is an urgent need for constructive interaction between the natural sciences (physics, chemistry, mathematics, biology, and engineering) and the human sciences (philosophy, law, sociology, and ethics), with the aim of formulating ethical standards for the development of nanotechnology. This book hopes to be an important step in that direction.

This book presents an overview of new and emerging nanotechnologies and their societal and ethical implications. To support sustainable, ethical, and economic nanotechnological development, it is imperative to educate all nanotechnology scientists, engineers, and stakeholders about the long-term benefits, limitations, and risks of nanotechnology. In the introduction, we provide the reader with an insight into the multiple societal and ethical questions raised by nanotechnology.

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Convergence of natural and human sciences in nanotechnology

Nanotechnology is a popular term these days, associated with multiple uses and potential applications in the future. It is a dynamic multidisciplinary field. The applications are constantly extending to various areas, and their implementations are impressive. In fact, the main engineer/alchemist offering nanoscale materials appears to be life's unstoppable force, our mother nature. In ancient times, certain practices created nanoparticles through the customary procedures. One of the most acclaimed ancient applications is the Lycurgus cup, which was created from nanoparticles of gold and silver that were inserted in the glass. However, these were not recognized as nanosystems or nanoparticles until the twentieth century.

One nanometer is basically one billionth of a meter or 10^{-9} of a meter. A newspaper sheet is around 100,000 nm wide, in contrast. Nanotechnology – as we know it – was introduced in 1959 in a talk delivered by Richard Feynman, "There's plenty of room at the bottom." Nevertheless, until 1974, when a Japanese physicist Norio Taniguchi invented and described the word "nanotechnology," the real phrase "nanotechnology" was not coined. Thereafter, the development of scientific instruments such as the scanning tunneling microscope (1981) and the atomic force microscope (1986) generated the impetus for the further development of contemporary nanotechnology. Scientists discovered that atoms and molecules behave differently at the nanoscale. As a result, experts believe that nanotechnology has potential applications in a broad variety of fields with significant consequences for human well-being, the atmosphere, biodiversity, and national security. Although plenty of us do not realize the incredible effect it might have and – to a certain extent – is already having on our everyday lives. A promising indication is the growing amount of capital that policymakers are investing into improving such innovations worldwide.

With the advent of the fourth industrial revolution encompassing robotics, artificial intelligence, machine learning, Internet of things, 3D printing, and so on, the world of nanotechnology will change our lives and our society dramatically. There will be a great number of applications that at present, we cannot even conceive.

Some of the important examples of applications include the following:

In medicine:

- Nanoparticle-based vaccines may one day provide permanent immunity to the common cold and influenza.
- Artificial replacements for body tissue such as the skin, muscle, tendon, and even organs can be produced by nanoscale fabrication, mimicking natural processes.
- Nanoparticles in pharmaceutical products will smartly deliver chemotherapy drugs to specific cells, such as cancer cells.

In consumer product:

- Filters for producing clean drinking water will remove all viruses and bacteria.
- Nanoparticles used in food packaging will reduce UV exposure to prolong shelf life.
- Faster, smaller, and more powerful computers will consume far less power, with biodegradable longer lasting batteries.

In industrial applications:

- Nano-strengthened materials will produce lightweight alloys for cars, reducing fuels.
- Tires will be fabricated with a better grip in wet conditions.
- Electrode materials for rechargeable batteries will be greatly enhanced through nanotechnology, reducing weight and improving performance in the next generation of hybrid and electric vehicles.

History shows that new science and technology is often met by society with unrest. Prominent examples include the development of synthetic chemicals and nuclear power in the mid-twentieth century, and biotech and genomics in the twentieth century. The same goes for nanotechnology and the potential threats it raises. Therefore, there is an urgent need for a better understanding of the safety aspects of nanotechnology applications. For the nanomaterials, numerous toxicological tests have shown that nanoparticles can damage both humans and the ecosystem. Many argue that we should apply the precautionary principle to engineered nanoproducts and particles. An expert study published by the Federal Ethics Committee on Non-Human Biotechnology (ECNH) concluded that the presumption of proof of the harmlessness of synthetic nanoparticles will be the duty of the producers because there are good reasons to believe that such particles may seriously endanger humans and the atmosphere under some circumstances. Moreover, given the unpredictability of the future developments in nanotechnology, governmental authorities and consumers are faced with unknown risks.

Nanotechnology, it should be clear, has the power to revolutionize human lives and transform human societies. We must ask ourselves, what kind of world are we creating? The development of nanoscience and nanotechnology should not be left to engineers and nanoscientists alone. It is of utmost importance that experts in the social sciences and humanities and the public at large are involved. Developments in nanotechnology should be transparently communicated and closely monitored. For this purpose, scientists, engineers, and industrial players should work closely together with ethicists and social scientists and, the public should be informed and consulted.

At present, such a multidisciplinary and ongoing dialogue on the ethical concerns surrounding nanotechnology is, for the most part, lacking. This book hopes to contribute to this urgent task. It addresses the ethical concerns raised by nanotechnology from various perspectives: from a scientific, social, and philosophical point of view. Chapters have been written by experts from various countries across the world,

including the United States, Japan, China, Israel, India, Australia, Canada, and European countries, proposing different strategies but reaching the same conclusion: that there is an urgent need for ethical guidelines as well as regulations to ensure safe and healthy production and use of nanoproducts. It is also clear that these regulations and guidelines should have a worldwide dimension.

The book is divided into two volumes. The purpose of this book is to discuss the theoretical and philosophical/ethical aspects of nanotechnology.

The first volume, entitled *Emerging Technologies Aspects*, deals with the important ethical questions of the implications of nanotechnology on human well-being and health as well as the environment. It comprises 17 chapters divided into 3 sections. The chapters are written by the leading scientists and philosophers in their respective fields. The first section focuses on nanotechnology and its implications for philosophy, ethics, and society. It comprises two chapters: the first chapter covers the orientation of nanoethics, whereas the second chapter discusses the need for nanotechnology to mitigate technological difficulties. This is followed by six chapters in the second section that address ethical concerns in nanoscience. Chapters 3–9 discuss applications of nanotechnology and their future, along with the development of guidelines. Chapters 10–14 in Section 3 deal with ethical reflections in health care and the environment. This includes nanosafety of biomedical nanomaterials, nanomedicine, and nanodrugs. The chapters are authored by experts in these fields, and they have discussed their own researches as well as the developments in their fields of interest. It is our sincere hope that this multiauthored book covering the various aspects of nanotechnology and ethics will be welcomed by the scientific community and philosophers alike. We sincerely hope that the book will assist and enrich readers to understand the ethical challenges of nanomaterials and the discussed solutions to the safe use of nanomaterials.

The second volume, entitled *Social Sciences and Philosophical Aspects*, addresses the ethical and social implications of nanotechnology. It comprises 16 chapters. The book is divided into four sections. The first section has one chapter dedicated to revitalized vision on ethics and safety for technological implications. The second section has five chapters explaining on ethical concerns in nanotechnology developments. The first chapter in this section, Chapter 2, deals with the ethics, and regulatory and governance of nanotechnology in agriculture and food. The subsequent chapters cover the ethical issues for balanced and inclusive nanotechnology in various areas, including nanocosmetics and pharma developments, risk screening tools for engineered nanomaterials, and human health effects impacts on environment and society, respectively. The last chapter of this section presents views about nanoethics from a developing country point of view. The third section is about the philosophy of nanotechnology and nanoethics. It discusses the theological approach toward nanotechnology. Part IV is a special section that deals with ethical recommendations for promising technology.

The book also highlights perception of nanotechnology and ethical concerns from different angles and proposes a holistic approach toward the perceived dangers of nanotechnology.

We believe this book will be equally relevant to scientists and engineers employed in the area of nanotechnology and philosophers involved in nano or any technology-related ethics. The text is structured in such a manner that each chapter stands on its own and can be read independently.

We express our sincere thanks to Ms. Ute Skambraks for her kind help in publication process. Sincere thanks to Dr. Karin Sora for continually supporting us through the publication house. We express our sincere gratitude to all the writers who made diligent efforts to write chapters during the time of the COVID-19 pandemic. We are grateful to all the eminent persons: *Mihail C. Roco* – National Science Foundation and National Nanotechnology Initiative; *Peter Brabeck-Lemathe* – Former President NESTLE; *Shailendra Saraf* – Vice President, Pharmacy Council of India; and *Federico Mayor Zaragosa* – Former President of UNESCO from respectable authorities for the excellent foreword to this book. We appreciate our respective families, for without their continuous support this work could not have been completed.

Marcel Van de Voorde and Gunjan Jeswani, book editors

Embedding ethics in nanomedicine: Europe acted promptly

Preamble

The *Oxford Dictionary* defines nanotechnology as "the branch of technology that deals with dimensions and tolerances of less than 100 nanometres, especially the manipulation of individual atoms and molecules."[1] Nanotechnology has application in multiple scientific fields, such as surface science, organic chemistry, molecular biology, semiconductor physics, energy storage, microfabrication, and molecular engineering. It is a technology capable of creating new materials and devices with a potential vast range of applications, such as in medicine (hence, the term "nanomedicine"), electronics (hence, "nanoelectronics"), biomaterial energy production, and consumer products. As innovative technologies often do, however, nanotechnology applications have raised an intense debate in the circles of scientists, lawyers, and policymakers, including on ethical issues.

In the early 2000s, controversies emerged regarding the definitions and potential implications of nanotechnology, including the safety (for health and/or the environment) of the very first products originating from nanotechnology such as silver nanoparticles, carbon fiber strengthening using silica nanoparticles, and carbon nanotubes. In particular, nanomedicine has acquired a progressive importance on the societal debate on the ethical dimension of this technology and the expectations and concerns on its use.

Nanomedicine: What is possible to do?

A European technology platform on nanomedicine has been created and in 2005 issued its first vision paper.[2] Its activities included diagnosis, drug delivery, and triggering of biomaterials. This activity in nanomedicine is continuing.[3] With no

1 https://www.lexico.com/definition/nanotechnology.

2 http://ec.europa.eu/research/industrial_technologies/pdf/nanomedicine-visionpaper_en.pdf.

3 https://etp-nanomedicine.eu/.

Disclaimer: The information and views set out in this paper are those of the authors and do not necessarily reflect the official opinion of the European Commission.

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pretention of completeness, some applications of nanotechnology in the medical fields include:[4]

Application area	Expected benefits
Drug delivery	Nanotechnology provided the possibility of delivering drugs to specific cells using nanoparticles.
Cancer	Nanoparticles can be used against tumor cells and accumulate at tumor sites.
Imaging	Nanoparticles may be used for in vivo imaging (cardiovascular imaging or oncology imaging)
Sensing	Research on nanoelectronics could lead to tests for the diagnosis and treatment of cancer.
Blood purification	Magnetic microparticles are research instruments for the treatment of systemic infections, and they may also provide alternatives to traditional dialysis methods.
Tissue engineering	Nanotechnology may be used to reproduce, repair, or reshape damaged tissue using suitable nanomaterial-based scaffolds.[5]
Medical devices	Nanoscale enzymatic biofuel cells for nanodevices have been developed that uses glucose from biofluids including human blood and watermelons.

In addition to this set of current applications of nanomedicine, the community of scientists has also advocated the possibility of engineering molecular assemblers (hence, the term "nano-robots"), which could reorder matter at a molecular or atomic scale and then be implanted into the systems or organisms, including the human body, to repair or detect damages and infections.

The safety issues

Because nanomedicine may affect citizens, both directly (trials) and indirectly (possible exposure to free nanoparticles into the environment), it is important to underline the safety of this technology in order to protect their rights and their aspirations. A central consideration in assessing the legitimacy of medical technologies therefore refers to their safety.[6]

4 See also https://www.britannica.com/science/nanomedicine.

5 Nanoparticles such as graphene, carbon nanotubes, molybdenum disulfide, and tungsten disulfide are being used as reinforcing agents to fabricate mechanically strong biodegradable polymeric nanocomposites for bone tissue engineering applications.

6 However, even if it is hard to define a precise borderline between the two dimensions, a distinction needs to be done between risks for the patients undergoing an application of nanomedicine and risks associated with the toxicological and ecotoxicological effects of nanocomponents.

Safety issues of nanotechnology and nanomedicine have been addressed in several reports across the world. The Scientific Committee on Emerging and Newly Identified Health Risks[7] (SCENIHR) report and the White Paper *Nanotechnology Risk Governance*[8] published in June 2006 by the International Risk Governance Council are two examples of reports on risk governance issues of nanotechnology. While using different approaches and methods, the above reports stress the lack of data (in particular, long-term data) on possible risks associated with nanotechnology with regard to both the human health and the ecological consequences of nanoparticles accumulating in the environment. In addition (to quote the UNESCO report on the ethics and politics of nanotechnology[9]), the issue of the safe and responsible use of nanomedicine and nanotechnology raises "two concerns: the hazardousness of nanoparticles and the exposure risk. The first concerns the biological and chemical effects of nanoparticles on human bodies or natural ecosystems; the second concerns the issue of leakage, spillage, circulation, and concentration of nanoparticles that would cause a hazard to bodies or ecosystems." Concerns are also raised by the difficulties of identifying, estimating, and managing risks in an area where there are considerable uncertainties and knowledge gaps, and when the short-term and long-term risks may be different.

The existing framework on ethics and human rights

While the above considerations show the difficulty to assess the safety of biomedical products, it is important to refer to the existing framework on ethics and human rights that constitutes a reference point for the analysis of the ethical dimension of nanotechnology. Let us then consider some international references having a legal or moral authority in this analysis (soft and hard law).

(a) The *Council of Europe* has issued the Oviedo Convention – Convention on Human Rights and Biomedicine.[10] Its main purpose is to "preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances." The Convention also concerns equitable access to health care, professional standards, protection of genetic heritage, and scientific research. It contains several detailed provisions on informed consent. A number of additional protocols supplement the Convention.[11]

7 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).

8 See the White Paper *Nanotechnology Risk Governance* published in June 2006 by the International Risk Governance Council and the references in that report.

9 http://unesdoc.unesco.org/images/0014/001459/145951e.pdf.

10 https://www.coe.int/en/web/bioethics/oviedo-convention.

11 http://www.coe.int/t/e/legal_affairs/legal_cooperation/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.

(b) The *Universal Declaration on the Human Genome and Human Rights*,[12] adopted by UNESCO's General Conference in 1997 and subsequently endorsed by the United Nations General Assembly in 1998, deals with the human genome and human rights. Since the Declaration was drafted in 1997, it does not refer *explicitly* to nanomedicine, but modifications that are targeted to DNA may fall within its scope.[13] The Declaration also contains provisions on the informed consent principle. The *Universal Declaration on Bioethics and Human Rights* (adopted by UNESCO on 19 October 2005) also contains specific provisions on ethical issues related to medicine, life sciences, and associated technologies, and advocates several ethical principles, including human dignity, consent, autonomy and responsibility, privacy, equity and justice, solidarity, and benefit sharing.[14]

(c) The *European Charter of Fundamental Rights*[15] emphasizes that the Union is founded on the indivisible and universal values of human dignity, freedom, equality, and solidarity and on the principles of democracy and the rule of law. It contributes to the preservation of these common values while respecting the diversity of the cultures and traditions of the peoples of Europe, as well as the national identities of the Member States and the organization of their public authorities. The Charter formulates a common set of basic shared values at the EU level.[16] Respect for human dignity, a ban on human reproductive cloning, respect for people's autonomy, non-commercialization of biological components derived from the human body, prohibition of eugenic practices, protection of people's privacy, and freedom of science are examples of values enshrined in the Charter, which was adopted at the Summit of Nice in 2001.

(d) *The precautionary principle*, according to the Commission Communication of February 2000, is the basic constituent of the precautionary principle and the prerequisites for its application are the existence of a risk, the possibility of harm, and scientific uncertainty concerning the actual occurrence of this harm.[17] Although

12 https://en.unesco.org/themes/ethics-science-and-technology/human-genome-and-human-rights.

13 The Declaration asserts, "Dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity."

14 http://portal.unesco.org/shs/en/file_download.php/46133e1f4691e4c6e57566763d474a4dBioethicsDeclaration_EN.pdf.

15 Approved on 28 September 2000 and proclaimed by the European Parliament, the Council, and the Commission on 7 December 2000.

16 For example, Article 1 (respect for human dignity), Article 3 (ban on human reproductive cloning, respect for people's autonomy, non-commercialization of biological components derived from the human body, prohibition of eugenic practices), Article 8 (data protection issues), and Article 13 (freedom of science).

17 The precautionary principle does not necessitate impassable boundaries or downright bans. It is a general risk management tool, which was originally restricted to environmental matters. In the Commission's Communication of February 2000, it is stated, "The precautionary principle is not

the precautionary principle is not explicitly mentioned in the treaty except in the environmental field, its scope is far wider and covers those specific circumstances where scientific evidence is insufficient, inconclusive, or uncertain, and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal, or plant health may be inconsistent with the chosen level of protection.[18]

(e) *The innovation principle* as understood and applied by the Commission[19] promotes smart and future-oriented regulation, which is able to encourage new discoveries and solutions to address the most pressing social and environmental issues.

Bioethical questions

In its opinion on ethics of nanomedicine, the European Group of Ethics[20] has indicated a list of concerns that need to be faced to assess the ethics of this technological sector, such as "How is it possible to give information about future research possibilities in a rapidly developing research area and to make a realistic risk assessment in view of the many unknowns and the complexities? What are the implications of nanomedicine for problems raised in cases where the information obtained by refined nanomedical diagnostic methods is used by third parties, in particular insurance companies and employers? How can the development of nanomedicine and nanotechnology be tailored to the benefit of the public? How can societies remain at least partly autonomous in their decisions, when the development of nanomedicine is closely connected to the economic prosperity of a given society and plays a part in international competition on the global market?"

defined in the Treaty, which prescribes it only once – to protect the environment. But in practice, its scope is much wider, and specifically where preliminary objective scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal, or plant health may be inconsistent with the high level of protection chosen for the Community" (Communication Summary paragraph 3). Accordingly, the Commission believes that "the precautionary principle is a general one" (i.e., a general principle) (Section 3 of the Communication), whose scope goes beyond the EU – as shown by several international instruments starting with the Declaration on Environment and Development adopted in Rio de Janeiro in 1992.

18 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52000DC0001&from=EN.

19 https://ec.europa.eu/info/news/innovation-principle-makes-eu-laws-smarter-and-future-oriented-experts-say-2019-nov-25_en.

20 Group of Ethics examined the ethical aspects of medical applications related to nanotechnology. Some of the basic ethical values include the principle of respect for dignity; the principle of individual autonomy; the principle of justice and of beneficence; the principle of freedom of research; and the principle of proportionality. https://op.europa.eu/en/publication-detail/-/publication/4d7d9c99-2129-42e1-993e-c815b91f256b/language-en/format-PDF/source-77404425, pp. 39-41.

The above questions relate to the ethical dimension of nanomedicine. As other technological mediums they do not induce univocal response, but they refer to a number of values/principles that need to be assessed with regard to each different use of nanomedicine is concerned. Case-by-case analyses are therefore inherent to the ethics of nanomedicine, also reflecting the ethical pluralism of modern society. In whatever views we therefore want to focus the ethical analysis of nanomedicine, whether following utilitarianism, Kantianism, virtue theory, the principles of autonomy, beneficence, non-maleficence, and justice, it is important that specific elements that are embodied in the international ethics frame described above are taken into account.

The protection offered by international declarations and guidelines applies to both health care and medical research; it includes the obligation to obtain free and informed consent from patients and participants in research and specifies the measures to be taken when patients and participants in research are for various reasons (minors, mentally incapacitated, etc.) unable to give consent. The principles stated in the above declarations and guidelines specify the obligations to protect individuals and societies against unpredictable risks based on the precautionary principle and a risk–benefit analysis, which includes also long-term risks and benefits. The principles mentioned earlier are also applied to health-related risks of nanotechnology, not only in the medical contexts, which are in focus here, but also in other contexts where nanotechnology is used. To summarize, the bioethics issue of nanomedicine that deserve specific attention include:

- ***Informed consent***
  Informed consent requires the information to be understood. In view of the knowledge gaps, and the complexity of the matter, concerning the long-term effects of nanomedical diagnostic and therapeutic tools, it may be difficult to provide adequate information concerning a proposed diagnosis, prevention, and therapy needed for informed consent.
- ***Diagnostic complexity and increased personal responsibility***
  Nanomedicine offers new diagnostic possibilities, where the results will be available with high speed, magnitude, and precision at the molecular level. The results may be complex and difficult to interpret. The increased complexity of diagnostic potentials affects the level of responsibility by the medical community to properly interpret diagnostic results and propose therapeutic actions based on the above provisions.
- ***Medical and non-medical uses***
  The fine line between medical and non-medical uses of nanomedical methods for diagnostic, therapeutic, and preventive purposes is often hard to define, but it is possible to give examples of both. Non-medical applications include *intentional* changes in, or to, the body due to what a person wants, when these wants are not related to medical needs, even if such medical needs are difficult to define clearly.

– ***Access from an individual perspective***
  Access to health care and new medical technologies is often seen as a challenge for health-care systems and then opening issues related to fairness. Individuals may struggle to gain access to nanomedical innovations, even taking on considerable financial costs. If they cannot afford new diagnostics, drugs, or therapies offered to them, they might feel left behind or even as second-class citizen.

As stated before, what is described here is a non-exhaustive frame of reference points that need to be confronted with the specific applications of nanomedicine. This method applies to case-by-case analyses and aims to reflect the ethical pluralism of modern society.

In the next part of this chapter, we describe how the approach chosen in the EU intrinsically links ethical considerations (both individual and social ethics) into the policy frame of nanomedicine and nanotechnology.

Embedding ethics in nanomedicine: The policy frame adopted in the EU

When this technology was developed, the European Commission had to face its controversy, not only in terms of public acceptance but also in terms of safety and in terms of adequacy of regulatory frame for nanotechnology-based products. Differently than other technology, items the Commission decided to *anticipate* the debate on both the safety and social acceptability of this medium and the risk management approach were built in terms of an unprecedented transparency, inclusiveness, and anticipatory nature.[21] In its strategic document on nanosciences and nanotechnology, the Commission indicated that nanotechnology products must comply with the high levels of consumer, worker, and environmental protection set in community regulations.[22] In June 2008, the Commission adopted the Communication "Regulatory Aspects of Nanomaterials,"[23] fulfilling a commitment made in the Action Plan.[24] The Communication was accompanied by a Staff Working Document providing a summary of legislation in relation to health, safety, and environmental aspects of nanomaterials, and outlining regulatory research needs and related measures.[25] This regulatory review concluded that existing Community regulatory frameworks cover *in principle* the potential health, safety, and

21 https://ec.europa.eu/research/industrial_technologies/pdf/policy/action_plan_brochure_en.pdf.

22 https://www.europarl.europa.eu/registre/docs_autres_institutions/commission_europeenne/com/2009/0607/COM_COM(2009)0607_EN.pdf

23 *Regulatory Aspects of Nanomaterials*, COM(2008)366.

24 https://ec.europa.eu/research/industrial_technologies/pdf/policy/action_plan_brochure_en.pdf.

25 SEC(2008)2036.

environmental risks related to nanomaterials. Without excluding regulatory change in the light of new information, the Commission stressed that the protection of health, safety, and the environment needed to be enhanced mainly by improving the implementation of existing legislation. In addition to supporting research on risk assessment, the Commission has worked in several regulatory areas to improve implementation, assess the adequacy of existing legislation, and consider whether regulatory changes on specific aspects were necessary.[26]

The above Communication was examined by both the European Parliament[27] and the European Economic and Social Committee.[28] The European Parliament in particular questioned whether, in the absence of explicit provisions for nanotechnology in Community law, legislation can be deemed adequate to cover the risks related to nanomaterials. Given the lack of appropriate data and assessment methods, the Parliament asked that existing regulations be carefully reviewed (not only nanomedicine but also the use of nanotechnology in cosmetics, novel food, and food additives). As planned, the Commission presented an updated regulatory review in 2011, paying particular attention to the points raised by the European Parliament and the European Economic and Social Committee.

The Commission has therefore supported innovation in nanotechnology through different policies and actions. The main initiatives related to nanotechnology included increased emphasis on applications in the research funded under the research and innovation framework programs; a continued commitment to regulatory and standardization activities; and the creation of a nanotechnology observatory, ObservatoryNANO,[29] to study opportunities and risks in various technology sectors. In this context, special attention was also paid to SMEs and start-ups.

Several actions were equally undertaken in pursuit of the general objective of taking people's expectations and concerns into account. In February 2008, the Commission adopted the recommendation for a "Code of Conduct for responsible nanosciences and nanotechnologies research,"[30] which provides guidelines favoring a responsible and open approach. As called for by the Council in September 2008,[31] the Commission regularly monitor the Code, and revise it every two years in order to take into account developments in nanotechnology and their integration in European society.

All research project proposals that were considered for funding (by the European Commission) and raise ethical issues underwent a thorough ethical review. This

26 For example, the working group for nanomaterials under REACH has made progress and published initial results: http://ec.europa.eu/environment/chemicals/reach/pdf/nanomaterials.pdf.

27 Resolution of 24 April 2009 on regulatory aspects of nanomaterials (2008/2208(INI).

28 Opinion of 25 February 2009 on the Communication on Regulatory Aspects of Nanomaterials, INT/456; http://eesc.europa.eu/documents/opinions/avis_en.asp?type=en.

29 www.observatorynano.eu.

30 *Code of Conduct for Responsible Nanosciences and Nanotechnologies Research*, C(2008)424.

31 12959/1/08 REV 1 (2891st Council Meeting Competitiveness).

included many nanotechnology proposals. Such proposals had discussed the ethical dimension of the research to be undertaken and meet community ethical requirements, such as the EU Charter of Fundamental Rights, in addition to national requirements.

Several outreach projects have been funded under the European Commission research programs. These suggest that there is a need for a more permanent public deliberation on nanotechnology in its broad societal context. The Commission has pursued an active policy of engagement and consultation with stakeholders, in particular through their continuous involvement in Commission working groups in charge of coordinating the implementation of regulation; and in the annual nanotechnology "Safety for Success Dialogue" workshops. The call for dialogue and engagement in the action plan has also been reflected in various other initiatives organized by industry, in European Technology Platforms, and in special interest forums such as consumers' groups. The existence of diverse fora indicates a need to monitor the debates at national, European, and international levels, for instance, with support from future European Commission activities, in order to consistently convey messages from public debates to policymakers. The Commission has also published a wide range of informative materials in many languages and for various age groups. In addition, a specific entry for nanotechnology on the Commission's Europa website has helped the public to follow all its nanotechnology activities.

As far as the science for policy aspects of this example are concerned, what it was relevant from the Commission was not only to address the scientific assessment of the nanotechnology products in specific application domains (e.g., medicine and food – SCENIHR), but to ask the European Group on Ethics to assess the governance aspects of this technology. This request was done at European Commission's top level (President of the Commission) and aimed to analyze this technological sector under the remit of this independent advisory body: issuing a set of policy recommendations based on the scientific, legal, social, and ethical implications that may rise from the use of nanotechnology. This work was also done in consultation of key experts in the field, decision-makers, and relevant stakeholders.[32] In addition, a coordination group (ISG/Inter Services Group) clustering 20 commission services was established to check the consistency of actions taken by different Commission Directorates in this specific field. The strategic choice by the Commission was to have scientific advice not only on technical aspects of nanotechnology but also on a strategy to endorse for a transparent, inclusive, responsible, and socially acceptable use of this technology and the products based on its use. In fact, this strategy has showed being successful, and nanotech-based products are part of many innovative industrial productions across the EU.

32 https://ec.europa.eu/archives/bepa/european-group-ethics/archive-activities/activities-2005-2010/index_en.htm and https://ec.europa.eu/archives/european_group_ethics/archive/2005_2010/activities/docs/roundt_nano_21march2006_final_en.pdf.

Conclusions

Pluralism is a characteristic of the EU,[33] mirroring the richness of its traditions and adding the need for mutual respect and tolerance. Respect for different philosophical, ethical/moral, or legal approaches and for diverse cultures is implicit in the ethical dimension of building a democratic Europe. Social and ethical pluralism requires that a culture of debate and communication needs to be established wherever and whenever wide-ranging changes to the lives of individuals, or in social practices, take place or are liable to take place in the future.

The above is relevant also for the controversies prompted by nanomedicine. Such issues have been addressed upfront in Europe, both in the European Commission Communication "Towards a European Strategy for Nanotechnology"[34] and stimulating international cooperation such as with the workshop "Nanotechnology: Revolutionary Opportunities & Societal Implications" co-organized with the US National Science Foundation[35] and launching an open "International Dialogue on Responsible Research and Development of Nanotechnology."[36]

The mentioned European strategy spelled clearly out how ethical principles must be respected and, where appropriate, enforced through regulation. These principles are embodied in the European Charter of Fundamental Rights[37]and other European and international documents.[38] The EU has furthermore taken several steps in the development of policy design of nanomedicine *within* the constraints of the principle of respect for the rights of individuals, respect for multiculturalism, dialogue, and tolerance. The proposed approach did not try to fix ethics rules for nanomedicine, but rather stimulate a flexible approach to the governance of nanomedicine where ethical evaluation, safety, legal clarification (including data protections and patenting), and social debate were all equally requested for the design and use of nanomedical application and research in nanomedicine.

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33 Respect for pluralism is in line with Article 22 of the European Charter of Fundamental Rights, on "Cultural, religious and linguistic diversity" and with Article 6 of the Amsterdam Treaty, which ensures the protection of fundamental rights at EU level, based in particular on international instruments as well as common constitutional traditions, while also stressing respect for the national identity of all Member States.

34 https://ec.europa.eu/research/industrial_technologies/pdf/policy/nano_com_en_new.pdf.

35 https://www.nsf.gov/mps/dmr/lecce_workshop.pdf.

36 https://ec.europa.eu/research/industrial_technologies/pdf/policy/report-third-international-dialogue-2008_en.pdf.

37 See http://www.europarl.eu.int/charter/default_en.htm.

38 See http://europa.eu.int/comm/research/science-society/ethics/legislation_en.html.

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Part I: **Nanotechnology challenges – implications for philosophy, ethics, and society**

Frans W.A. Brom, Rinie van Est and Bart Walhout

1 Nanoethics: Giving orientation to societal reflection

Abstract: We are now looking back at over 20 years of social reflection on nanotechnology. Gaining legitimate trust is vital for the nanotechnology community. That is why nanotechnologists engage in public discussions, social engagement, and interdisciplinary nanoethical research. Ensuring safety is an important element in ensuring trust. The transformative potential of nanotechnology, however, becomes apparent in its convergence with other emerging technologies.

The notion of converging technologies helps to explore this potential. It opens a new perspective for nanoethics and helps to identify societal challenges that need to be on the agenda of societies. The ethical issues raised by nanobiology, nanomedicine, and nanoelectronics illustrate these challenges: from nanobiology to the discussion on synthetic biology, from nanomedicine to the discussion on human enhancement, and from nanoelectronics to the discussion on artificial intelligence (AI). In all three fields, we will show a similar structure: (1) development in these fields is impossible without nanotechnology, (2) these fields raise fundamental and relevant normative issues, and (3) a nanoethics cannot confine itself to the direct and strict impact of nanotechnology itself, but needs to open up to the broader questions raised by the interaction between nanotechnology and other emerging technological fields. This shows us the challenge for nanoethics: it needs to orient societal reflection on the impact of nanotechnology, and in doing so it cannot confine itself to the direct consequences of specific nanotechnologies. Nanoethics needs to orient the societal reflections and discussions on where to go (direction), what to protect, and whom to empower in order to protect themselves (protection), and on practical ways to govern these developments (organization).

Key Words: Public deliberation, Technology Assessment, NBIC-converging, Human Enhancement, Synthetic Biology, Artificial Intelligence, Trust, Intimate technology

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1.1 Introduction

Nanoethics emerged in the debate on nanotechnology. Nanotechnology is new, and nanoethics therefore has two goals: to give orientation to the development of nanotechnology and to structure and orient the social reflection on the future of nanotechnology. Nanoethics can thus be seen as a form of "reflexivity": it is part of social reflection and it looks at ways to stimulate and structure this social reflection. It is important to take this reflexivity into account, because it emphasizes the double task of nanoethics: to support the ethical development of nanotechnology and to support societal reflection on the ethical development of nanotechnology [1]. In this brief introduction, we will combine both tasks. We will use the content of the first task – giving orientation to the development of nanotechnology – as an agenda for the second task – fostering societal reflection. In this way, we develop three fields where nanoethics orients societal reflection: (1) direction, (2) protection, and (3) organization. These three fields revolve around three normative questions: (1) where to go and thus what to stimulate; (2) what to protect and whom to empower to actively protect; and (3) how to organize stimulation and protection in practical terms. These three normative questions require normative answers. Our main message is that, in order to fulfill its goals and to orient societal reflection on the impact of nanotechnology, nanoethics cannot confine itself to the direct impact of specific nanotechnologies. Nanoethics – just like nanotechnology – needs a broad perspective.

In this introductory chapter, we will neither try to give an overview of the ethical issues that nanotechnology raises, nor present all the various methods and approaches that are being developed in the field of nanotechnology. Instead, an in-depth analysis of specific issues in nanoethics will be given in the following chapters. We will give a thematic introduction to the field of nanoethics, showing the challenges for nanoethics in orientating societal reflection in the future of nanotechnology. We start by looking backward. The social reflection on nanotechnology has a history of over 20 years. A core issue in the engagement of scientists and engineers working in nanotechnology in these debates was (and is) the need to gain justified societal trust in the development of nanotechnology (Section 1.2). Ensuring safety is an important element in ensuring trust. That is why we continue this thematic introduction with an inquiry into an issue that is specifically raised by nanotechnology: the safety of nanomaterials (Section 1.3). Next, we will look at the societal and ethical issues that are raised when we consider nanotechnology as an element in the broader development of technology. For this purpose, we explore the notion of converging technologies. The convergence of nanotechnology, biotechnology, information technology, and cognitive science (NBIC convergence) involves increasing interaction between the life sciences and the natural or engineering sciences. This convergence opens a new perspective for nanoethics (Section 1.4). We illustrate this development with an inventory of ethical discussions in nanobiology,

nanomedicine, and nanoelectronics. These sections illustrate how for society the transformative potential of nanotechnology becomes apparent in its convergence with other emerging technologies. Developing a nanoethics from this "converging technologies" perspective helps to identify societal challenges that need to be on the agenda of societies. In each section, we use an actual societal field to illustrate this claim: from nanobiology to the discussion on synthetic biology (Section 1.5), from nanomedicine to the discussion on human enhancement (Section 1.6), and from nanoelectronics to the discussion on AI (Section 1.7). In all three fields, we show a similar structure: (1) development in these fields is impossible without nanotechnology, (2) these fields raise fundamental and relevant normative issues, and (3) a nanoethics cannot confine itself to the direct and strict impact of nanotechnology itself, but needs to open up to the broader questions raised by the interaction between nanotechnology and other emerging technological fields. This brings us to the conclusion of this introduction and the challenge for this book: nanoethics needs to orient societal reflection on the impact of nanotechnology, and in doing so it cannot confine itself to the direct consequences of specific nanotechnologies. Nanoethics needs to orient the societal reflections and discussions on where to go, what to protect, and whom to empower in order to protect themselves, and on practical ways to govern these developments.

1.2 From gaining societal trust to engaged interaction

The social reflection on nanotechnology has a history going back over 20 years. The potential societal impact of nanotechnology was already being discussed in the comprehensive foresight study coordinated between 1996 and 1998 by the Netherlands Study Centre for Technology Trends [2]. And from the start of the twenty-first century, the discussion on the social and ethical implications of nanotechnology [3] got underway, not only in academia but also in public discourse. In 2003, the report "The Big Down" by the ETC group (a Canadian NGO) played an important role in the public debate, because it posed the legitimate question as to what the benefits and risks of this new technology would be for society, and pointed to the many uncertainties with regard to the health impact of nanoparticles [4].

For many scientists, the ETC group's criticism had a familiar flavor, reminding them of the debate on genetically modified organisms (GMOs). They saw GMO technology as one of many promising and useful technologies that had been unable to connect successfully to the broader society, due to negative campaigning by environmental groups such as Greenpeace. As a commentator wrote in *Nature*, "Nanotechnology is set to be the next campaign focus of environmental groups. Will scientists avoid the mistakes made over genetically modified food, and secure trust for their

research?" [5]. One could say that the debate on nanotechnology followed a recurring type of argumentation in which the various societal actors play a pre-scripted role in the debate [6]. As Swierstra and Rip indicate, a debate of this kind takes on a predictable pattern in which different arguments "hang together" in the sense that they provoke each other into existence. The tropes and the "storylines" in the argumentative patterns have become a repertoire that is available in late-modern societies, both as a framing of how actors view issues and expect others to view them, and as a kind of toolkit that can be drawn upon in concrete debates" [7]. Ethical reflection aims to open up these ossified patterns.

For the good development of nanotechnology, a more responsive relationship with society was seen as necessary. This relationship is important because those working in the field of nanotechnology mostly have the honest belief that it can be an important aid to meeting societal challenges. Nanotechnological developments bring hope with regard to fighting famine, helping the transition to non-fossil energy, or developing new treatments for diseases such as cancer. That is why securing adequate societal trust in nanotechnology through a more responsive relationship with society is important. At least two elements are important in this responsive relationship: systematic consideration of the societal and ethical implications of nanotechnology, and more and better communication between the nanotech community and society.

The wish to develop a better understanding of the implications of nanotechnology and better processes of social reflection led to various research programs and organized societal deliberations on nanotechnology in the years 2003–2010. In the Netherlands, for instance, the national research consortium NanoNed decided in 2002 to include research into the societal and ethical implications in their research program and to link these implications with nanoresearch and innovation [8]. In the UK, several "upstream" activities [9] were organized in 2005–2006 to include citizens in the discourse on nanotechnology and its development [10, 11]. And in Germany, the Office of Technology Assessment at the German Bundestag "was already commissioned by the research committee of the German Bundestag to carry out a TA study on nanotechnology as early as 2000. The results were presented to the committee and published in 2003" [12].

As the German example makes clear, a third element is needed to secure societal trust: adequate and democratically legitimized oversight and governance. From our perspective, the search for a more responsive relationship between nanoscience and society can be seen as a search for technology assessment. Technology assessment is the institutionalized practice of studying and publicly deliberating on the broad societal impact of new and emerging technologies [13]. Technology assessment is not just academic thinking; it includes organized societal discussion and support for democratic political decision-making on new and emerging technologies [14]. For us, technology assessment "combines an awareness about potential

negative and positive effects of technological change with the belief or hope that one can anticipate these effects" [15].

Nanoethics has developed against the background and as a part of the critical reflection on nanotechnology. Like other fields in applied ethics (e.g., bioethics, agricultural ethics, or public health ethics), nanoethics is not pure philosophical ethics but an interdisciplinaryendeavor "to advance the examination of ethical and social issues surrounding nanotechnologies in a philosophically rigorous and scientifically informed manner" (in the words of the first editorial of the journal *Nanoethics* in 2007) [16]. And in doing so, nanoethics does not need to be a separate field of ethics, nor is it necessary to identify specific "unique" nanotechnology questions. In nanoethics, general ethical issues are linked to specific nanotechnological developments.

Various interdisciplinary approaches have been developed in nanoethics: methods regarding the engagement of citizens in the discussions on the impacts of nanotechnologies under the heading of upstream engagement [17], methods for bringing normative considerations into the development of the technology itself under the heading of value-sensitive design [18], methods for analyzing and weighing the societal aspects of risk [15], and finally comprehensive approaches to implementing responsibility in research and innovation under the heading of responsible research and innovation [19]. All these approaches have one thing in common: they seek for ways that help engineers, citizens, scientists, members of parliament, and people in governments, funding agencies, and NGOs to start a sensible conversation on nanotechnology and its impacts.

A peculiar aspect of ethics is that it is not neutral and descriptive when it comes to fostering a conversation of this kind. Ethics, and hence nanoethics, is a normative and prescriptive discipline. It is not primarily interested in describing the way things are empirically, but in prescribing how things ought to be [20]. The core of doing ethics is the belief that it is relevant to reflect on and argue about the way things ought to be. As stated in the introduction, the three functions of nanoethics (direction, protection, and organization) revolve around three normative questions: where to go and what to stimulate, what and whom to protect and empower, and how to organize. The normative answers to these questions are not "just" given by the way the world happens to be. When discussing possible answers, people put forward arguments to support certain choices. If we are to have a sensible conversation about these choices, facts are important but not enough: exchanging and reflecting on the different arguments is at least as important. And we might differ, of course, as regards the answers to these questions. Doing nanoethics, however, only makes sense if – without being blind to the reality of power structures, lobbying, and other influences on the way citizens and society make their choices – we strive for choices that are supported by the best possible arguments. Doing ethics thus means looking for the best possible arguments, including a critical analysis of those arguments, their structure, and their persuasiveness.

1.3 From nanosafety to innovation

Ensuring safety is an important element in gaining trust. From the moment nanotechnology development started to be organized in large-scale publicly funded research programs, one of the most pressing issues has been the question of whether the "nano" in nanotechnology (i.e., engineering material properties at the nanoscale) would itself be safe for human health and the environment. Nanomaterials exhibit unique properties compared with "normal" materials made of the same chemical substances. For example, whereas normal carbon does not allow for electrical conductivity, very small carbon nanotubes can be used as a new generation of electronic switches in ever smaller and faster computer chips. In longer lengths, these tubes can be used as lightweight but superstrong materials. However, in such lengths, carbon nanotubes might have the same properties as rigid fibers like asbestos. Bearing in mind that asbestos was once also touted as a miracle material and its large-scale use caused many early deaths, it is no wonder that the introduction of nanomaterials sparked a global debate among experts and NGOs on nanosafety and about what a precautionary approach to the safety of nanomaterials would look like.

Addressing the potential safety issues of nanomaterials is far from straightforward, however. First of all, carbon nanotubes comprise only a very small fraction of the many nanomaterials being developed, and only the long versions of these carbon nanotubes may pose the risk that small fibers exhibit in general when being processed. Other nanomaterials also have totally different uses, going as far as the protection of human health (e.g., nanoparticles for new cancer therapies). Both the novelty of nanomaterial characteristics and the many shapes and sizes in which nanomaterials can be used make the development of adequate safety testing a daunting task, bringing other discussions in its wake – for example, the large number of animal tests that would be needed for regulatory approval. Uncertainties about safety thus bring questions of direction, protection, and organization directly to the fore.

One such area is the organization of protection. There is a clear need to *consolidate* relevant knowledge from the growing number of scientific papers on nanosafety into regulatory requirements. At the same time, *innovation* in risk assessment methodologies is needed, to enable us to cope with the rapidly increasing range of materials to be assessed and to respond to the calls to reduce animal testing. However, the same innovations unsettle the process of standardization and consolidation. Furthermore, instead of "end-of-pipe" testing just before market introduction, both industry and the authorities would prefer early screening and the application of safe-by-design principles in R&D processes as far as possible [21]. The development of such approaches here requires close collaboration between the "innovators" and the "regulators." Such a *transformation* of public–private relationships brings with it new challenges in terms of building trust, sharing costs, checks and balances, and intellectual property

protection. Given that resources are limited, ethics with regard to risk is thus a question not only of safety levels for individual nanomaterials in specific contexts but also of the practical choices involved in trying to regulate current generations of nanomaterials, while anticipating future ones. The boundaries of existing institutional structures therefore need to be renegotiated and transformed.

Another area is that of choices related to balancing the various values that drive innovation. For example, society needs to transition to non-fossil energy production. That is why substantial budgets are being spent on nanomaterial research to enable the transition. Core challenges include the safety of these nanomaterials. Increasing the energy efficiency of solar panels or improving battery lifetime, for example, often involves the use of rather toxic materials, which present pressing safety problems when these products reach the end of life. Here, new value articulations (e.g., the transition to a circular economy, which demands that waste be turned into new feedstock) open new perspectives on the trade-offs between safety and sustainability [22]. There is consequently an increased need for holistic approaches, broadening the scope from Safe-by-Design (SbD) to Safe-and-Sustainable-by-Design (SSbD) principles and linking protection and direction in approaches for responsible research and innovation.

As this example makes clear, practical choices in innovation show the importance of opening up risk assessment and risk management practices. Proper governance of innovative processes and the balancing of safety, sustainability, and practical use need to incorporate expert-driven risk assessment in broader deliberative processes. Special consideration, therefore, needs to be given to issues of risk appraisal and decision-making under conditions of complexity, uncertainty, and ambiguity [15]. This sketch of an ethics of nanorisks shows that ethical reflection and societal discussion on the risk governance of nanomaterials needs to broaden out beyond sheer "protection" to include the dimensions of direction and organization. An ethics of nanosafety cannot confine itself to the responsibilities of experts to protect human and environmental safety; it needs to include the empowerment of citizens with regard to safety issues, as well as the concepts that guide innovation (e.g., the "cradle-to-cradle" approach) and practical issues regarding the organization of safety governance, citizen empowerment, and innovation for societal challenges.

1.4 From nanotechnology to NBIC convergence

Combining technologies in novel ways often drives innovation. Over the past few decades, the technological convergence between four technological revolutions has been creating a new technological wave. Known as "NBIC convergence" nanotechnology, biotechnology, information technology, and cognitive technology are propelling each other.

NBIC convergence signifies an increasing interaction between the life sciences, which have traditionally studied living organisms, and the natural or engineering sciences, which have traditionally studied and built non-living systems [23]. This merger is reflected in two bioengineering megatrends: "biology is becoming technology" and "technology is becoming biology" [24].

Inherent in the "biology is becoming technology" trend is the promise that living systems (e.g., genes, cells, organs, and brains) might be engineered in much the same way as non-living systems (e.g., bridges and electronic devices). This expectation is driven by the fact that the nanosciences provide more and more ways to measure, analyze, and intervene in living organisms. "Biology becoming technology" promises a major increase in new types of interventions in living organisms, including the human body and brain, as illustrated by cultured heart valves, bacteria with complete synthetic genomes, human germline editing, and deep brain stimulation.

The "technology becoming biology" trend entails the ambition of engineering properties we associate with living organisms (e.g., self-assembly, self-healing, reproduction, and intelligence) into technology. The "technology becoming biology" trend embodies a future increase in new types of bio-, cogno-, and socio-inspired artifacts, which will be used in our bodies and brains and/or intimately integrated into our social lives. Examples of bio-inspired artifacts are stem cells, hybrid artificial organs, 3D-printed artificial blood vessels, and synthetic cells. Humanoid or android robots, avatars, emotion detection, and AI are examples of cogno-inspired artifacts.

This new wave of technologies enabled by NBIC convergence radically broadens the bio-debate [25]. Technologies such as human germline editing and deep brain stimulation fuel the debate on human enhancement. Those types of interventions in the human body and brain force policymakers to anticipate new issues in the field of safety, privacy, bodily and mental integrity, and informed consent. Secondly, intelligent machines – from smartphones to automated cars, service robots, and augmented reality glasses – are able to detect and portray social and emotional behavior and shape our behavior. These intimate technologies, which are increasingly penetrating our privacy and social life, lead to new safety, privacy, data ownership and liability issues, and questions regarding the limits to the simulation of, for example, friendship and violent behavior [26]. Besides raising all kinds of societal and ethical issues, NBIC convergence challenges some of the basic concepts we use to understand ourselves and the world we live in [27]. The "biology is becoming technology" and "technology is becoming biology" trends are slowly but surely blurring the boundaries between living and non-living; sickness and health; technology and nature; human and machine intelligence; human and machine agency; and science, technology, and society. These types of conceptual uncertainties are putting the regulation of numerous existing social practices under

pressure. How to regulate AI, the development of killer robots, human germline editing, or virtual reality in a humane way?

If nanotechnology is indeed an enabler for technological integration, then it is clear that nanoethics needs to take this enabling role of nanotechnology in the convergence of technologies as its point of departure. We will illustrate the implications for nanoethics with the aid of three short examples.

1.5 From nanobiology to synthetic biology

One of the ways converging gets real is by combining nanotechnology with genomics, which leads to nanobiology. This is not the place to discuss the technical issues involved in this combination, but it seems clear that, combined with an engineering perspective on biology, it leads to the idea of synthetic biology. The essential feature of synthetic biology is the notion that the biological world is no longer a "given" but becomes an object of design, engineering, and human creativity [28].

This change of perspective opens a Pandora's box of ethical issues. It raises questions regarding the direction of synthetic biology: should we confine synthetic biology to smart biological systems for the specific production of important materials, or should we consider our ecosystem as an object for technical improvement [29]? Systematic agriculture and traditional breeding already give us enormous influence over the ecosystem; hence, it might be worthwhile to look at it more systematically and with more and better tools from a sustainability perspective.

Questions regarding protection follow directly from this perspective. It is not only important to protect humans against biological risks created by synthetic biology; the protectability of nature, ecosystems, endangered species, or biodiversity also becomes an object of deliberation and reflection. Fundamental philosophical questions regarding the moral status of non-human entities go hand in hand with practical ethical questions regarding the management of biological dangers and the role of a precautionary principle.

Synthetic biology intensifies the need for a discussion on the ethics of organization. Changing the biological outlook of the planet is by definition not a private issue. It is clear that at least some decisions regarding the development of synthetic biology go beyond the territory of individual freedom. How to reconcile this with the idea of academic freedom, or with a free market? How should we organize collective decision-making? What institutions can be helpful in setting collective goals and protecting individual freedoms and the environment?

If we take the role of nanotechnology in the development of synthetic biology seriously, it is clear that there are very few boundaries to the field of nanoethics.

1.6 From nanomedicine to human enhancement

A combination of nanotechnology with medical technologies is being exploited in nanomedicine. Issues in nanomedicine range from delivering precise quantities of medicine to precise sites in the body to replacing diseased organs with artificial (improved) artifacts. These developments can raise the same ethical questions as high-tech medical technologies in general, such as fairness and equity with respect to high therapy costs, or the treatment of so-called welfare diseases. Here, however, we focus on more radical questions involved in the step from nanomedicine to human enhancement, which follow on from the idea that there is no medical necessity to limit the goals of nanomedicine to restoring normal functioning. We focus on human enhancement because it is an extreme perspective that helps to clarify the issues at stake in nanomedicine. The essential feature of human enhancement is the notion that, with the aid of growing biomedical understanding, the human mind and body can be transformed into objects of design, engineering, and human creativity [30].

Human enhancement can be seen as the use of biomedical technology to achieve goals other than the treatment or prevention of disease. There are many different definitions of "human enhancement," however [31]. The discussion on these definitions is not "just" a game of words; it is a discussion on the proper framing of the debate, and the various definitions pre-structure different perspectives on the social and political appraisal of human enhancement [32]. The question of direction would seem to be hidden in these definitional discussions. The direction of human enhancement – improving human performance – is not new. "Existing enhancement technologies, like dietary supplements and hearing aids, are relatively uncontroversial. Other examples prompt more public discussion: cosmetic surgery, the use of drugs beyond their original medical settings, narcotics and doping in sports. These technologies in combination with prospected future enhancement technologies spur public debate on human enhancement" [30]. The discussion on the direction of human enhancement is also a discussion on what it means to be human. Is what it means to be human fixed, or is it open to our collective creativity?

But if "being human" is at stake in the discussion on human enhancement, then this raises the question of how to protect human vulnerability. There are two sides to protect human vulnerability in this context. The first is protecting individuals against harms and risks caused by the negative consequences of developing technologies. Being in control of the human body might be the dream of human enhancement, but for the foreseeable future, control is out of reach. Unintended, unforeseen collateral damage due to enhancement techniques that are still under development might pose risks for their users and can cause real harm. The medical profession and the health system generally have a strict professional ethic and governance in which the "primum non nocere" principle (above all, do no harm) is pivotal. A vital consideration when looking for and developing new medical techniques is the idea of proportionality: positive and negative chances need to be in balance. Balancing the risks and

benefits for people who are seriously ill and need treatment seems to be of a different order from balancing the positive chances of enhancement against the risks to someone's currently uncompromised health. But besides the questions of "Is human enhancement safe?" and "How safe should it be in order to be allowed?" there are also societal values at stake that need to be protected. A significant discussion that human enhancement provokes is that of justice [33]. How can human equality be protected if some have access to technologies that help them to enhance their intelligence, strength, or vitality? Improving individual performance is valued in our society, but not at all costs and not by any means. Doping is banned from competitive sports because it is considered unfair. But what about the use of drugs that are intended to improve focus and attention (e.g., Ritalin) by students during their exams? And do these practices create peer pressure: will improved results achieved by users pressure other students or co-workers into using similar drugs? A critical discussion on human enhancement relates to the idea that unnecessary changes to the body could be considered as a violation of human dignity or as a lack of respect for human life. A more positive perspective emphasizes the continuity between self-development and the quest for self-improvement through education, sport, or a healthy lifestyle and the use of human enhancement techniques. The goal of self-improvement is deeply embedded in human development, and the use of new means – in itself – changes little.

Finally, there is the question of organization. How should we organize the possible implementation of human enhancement? Is applying human enhancement technologies an individual choice by individual consumers, or should the choice be made more collectively? Collective decision-making is difficult because – as former colleagues of the Rathenau Instituut have written – "State-promulgated policies and religious movements that have been claiming a monopoly in defining 'humanity' have a rather dubious track-record. Still, new technological developments can have collective effects. To discuss and to re-think the consequences of enhancement in terms of their meaning for our self-perception is a necessary condition for a well-functioning democracy. But what space is left to start such a collective conversation?" [34]. They claim that, in a liberal society, the basic setup for decision-making on such a dazzling topic as human enhancement therefore seems to consist of two components: state-secured safety and individual choice. And although they realize that "this picture is a bit of a caricature. Nevertheless, it serves to make our main point, namely that notwithstanding the great benefits of having a liberal society, in its basic structure it might have insufficient space for public discourse to address questions on collective issues that cannot be dealt with on a satisfactory level by either state regulation or individual choice" [34]. And as we have argued elsewhere, it is doubtful that "the fora for ethical reflection and debate that are institutionally linked to the practices of professional health research and health care will be able to take up the challenge to explore the ethical issues raised by the developments outside the medical domain" [35]. Thus, nanoethics cannot evade the fundamental

questions of political philosophy: democracy, individual freedom, public goods, and collective decision-making.

The role of nanotechnology in nanomedicine in the development of human enhancement technologies confirms the conclusion of the section on synthetic biology (Section 1.5). If we take the development of nanotechnology as an enabling technology in the context of emerging technologies seriously, then there are very few boundaries to the field of nanoethics.

1.7 From nanoelectronics to artificial intelligence

Artificial intelligence (AI) already dates back to the 1950s, but it has gained momentum over the past two decades, especially in the form of machine learning and deep learning. This is due mainly to the increased collection and storage of "big data" and the growing processing power of computers. Both developments are driven by great advances in information and communication technologies, and in particular micro- and nano-electronics. AI is not just a single technology: it can better be understood as a "cybernetic system" that observes, analyzes (thinks), and acts, and can learn from doing so. It cannot therefore be separated from other digital technologies such as robotics, the Internet of things, digital platforms, biometrics, virtual and augmented reality, persuasive technology, and big data. AI can be seen as the "brain" behind various "smart" applications such as self-driving cars, military drones, and cognitive assistants. It therefore plays a role in many intelligent machines and is strongly related to the broad trend of digitization as cybernetization [36].

The development of digitization involves a wide range of social and ethical issues. Besides privacy and security, issues such as the control of technology, justice, human dignity, and unequal power relationships play a role. Human rights such as non-discrimination and the right to a fair trial can come under pressure as a result of the digitization (among other things using AI) of judicial decisions [36, 37]. The above-mentioned issues are all being identified and discussed in the worldwide public debate that has arisen about AI in recent years. In the wake of and through the AI discussion, the public debate about digitization – and therefore about nanoelectronics as the driving force behind it – has broadened and reached the political agenda. Thus, nanoethics – as an ethics of a crucial enabling technology – cannot evade questions of direction and how research funding can encourage responsible innovation.

One way to discuss responsible innovation in AI is by formulating orienting principles. Interestingly, the principles that have been formulated for AI in recent years are similar to important biomedical principles, such as beneficence, non-maleficence, autonomy, and justice [38]. In biomedical practice, these principles aim to guide medical interventions in the human body and brain. It seems that awareness has grown that

digital technology, in particular AI, intervenes in our lives in a fundamental way. As a result of the technological convergence we discussed above, digital technology is gaining fundamental impact on human life. And parallel to the need for bioethical reflection in the case of medical technology, AI needs digi-ethical reflection. Principles, however, are not sufficient to encourage responsible innovation in AI, because the practices in which AI is gaining importance differ fundamentally from physician–patient relationships in biomedical practice. An example is the discussion on the concept of meaningful human control. Is meaningful human control of autonomous AI systems possible, when these systems potentially make critical decisions (as in the case of killer drones or artificial judicial decisions) [39]? Another issue specific to AI is the discussion on the "right to meaningful human contact." In practices where human contact and interaction are crucial – for example, raising and educating children, caring for elderly people, and the interaction between governments and citizens – "meaningful human contact" is a key value that needs protection. Here, we see the importance of the second question on our nanoethics agenda: what to protect and who should be empowered to enable them to be protected or to protect themselves? Which features of human–human interaction constitute meaningful human contact need protection? How can we empower vulnerable groups such as children and elderly citizens against digital deception [37]?

As said above, principles alone are not enough. And there is no shortage of guiding principles. In recent years, we have seen a flood of ethics codes in the field of AI. The strength of these codes is that they are a result of collective awareness processes in various parts of society. Their weakness, however, is that the individual codes do not constitute enforceable rules. That is why the ethical question of organization is also important for these developments. In a democracy based on the rule of law, legislation ought to play a crucial role in the implementation of AI. The use of AI must comply with fundamental rights, including constitutional rights, and specific legislation such as the EU's General Data Protection Regulation or sector-specific legislation in fields such as health care or the transport market. The connection between innovation and public values must therefore also be pursued far more emphatically [40]. Innovation means not only technological innovation but also social, economic, and legal innovation.

1.8 Conclusion: The need for a broad nanoethics agenda

We are now looking back at over 20 years of social reflection on nanotechnology. Gaining legitimate trust is vital for the nanotechnology community. That is why nanotechnologists engage in public discussions, social engagement, and interdisciplinary nanoethical research. Justified trust needs to be built upon information and an open exchange of arguments. Looking at these interactions from an nanoethical

perspective means looking for the best possible arguments, including a critical analysis of those arguments, their structure, and their persuasiveness. This sets the context for the challenge to nanoethics in orientating societal reflection on the future of nanotechnology.

Ensuring safety is an important element for ensuring trust. That is why we looked more closely at the agenda-setting questions raised by the safety issues that nanomaterials evoke. But nanotechnology is much more than the creation of nanomaterials. Nanotechnology is a crucial enabling technology in many technological and scientific developments. It is, for instance, crucial in what has been called "NBIC convergence." NBIC convergence signifies increasing interaction between the life sciences and the natural or engineering sciences, between the perspective on studying and cultivating living organisms and the perspective on studying and building non-living systems. Looking at nanoethics from the NBIC point of view broadens our perspective. The transformative power of nanotechnology is such that there are very few boundaries to the field of nanoethics.

In this introductory chapter, we have argued that nanoethics involves reflection in three areas: direction (including what to encourage to achieve that direction), protection (including whom to empower in order to protect themselves), and organization. The first area, "direction," relates to our hopes and fears, which structure our reflections on the future. This is especially important for the ethics of research agendas: in what direction is research going? What problems need to be solved? This involves such things as the importance of new technologies in fighting famine, supporting health, or helping to achieve more sustainable ways of living.

As we have seen, new technologies emphasize the need to protect what is vulnerable (rights, identities, autonomy). Societal reflection on this topic is urgently needed when innovations and inventions enter the market: for example, the way new devices or structures influence human autonomy and developmental freedom, and how solidarity and human welfare can come under pressure from large-scale surveillance. Protection includes the empowerment of those that need to be protected. The examples of the importance of human contact and interaction in fundamental human practices such as raising and educating children, caring for elderly people, and interaction between citizens and government show that "meaningful human contact" is a key value that needs protection. But this value also shows the importance of the follow-up question: who needs to be empowered to actively protect this value? We need to reflect on ways in which humans in vulnerable situations can be empowered against digital deception.

The third issue that nanoethics needs to take up is that of organization. This focuses on the way we organize innovation and the way we institutionalize the ethical debates about innovation (meta-governance). Nanoethics reflects on the institutions and organizations that are responsible for setting the direction (funding agencies) and are designed to govern responsibilities (legal and voluntary regulation) and the way we legally structure the distribution of costs and benefits (liability, intellectual

and other property rights, and the role of companies). As we saw in the example of nanosafety, ethical reflection cannot confine itself to the responsibilities of experts to protect human and environmental safety; it needs to include the concepts that guide innovation, for example, the "cradle-to-cradle" approach. Safety issues are not confined to the actual risks of certain nanomaterials; they include safety problems when these products reach the end of life. Governance structures aim to transform the "end-of-pipe" safety question into an innovation challenge.

Nanotechnology has enormous transformative power. That is why doing nanoethics is not just making a calculation of the risks and benefits, and the distribution of those risks and benefits, somewhere in the development of a new product, device, or process. Doing nanoethics is developing orientation for continuous societal reflection and structures for societal dialogue about the direction, protection, and organization of nanotechnology. This is what has been done for more than 20 years, and during those two decades nanoethics has created and encouraged new perspectives on the relationship between science, society, technology, and governance.

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2 Is there a new technological imperative?

Abstract: The overall argument of this chapter is that the level of technological optimism in society leads to the technological fix being the first option considered for many problems and that this in turn generates a technological treadmill. Many, if not most, technological fixes cause new problems to which technological fixes are again applied. Fixing or alleviating problems caused by this human propensity for technological fixes creates a new technological imperative. This argument is then applied to nanotechnology.

Keywords: technology, privacy, imperative, nanotechnology

2.1 Introduction

We are mammals with similar vulnerabilities to other mammals and we inhabit the same world that they do. The natural environment is important for us just as it is for them. We are also herd animals like many other non-human creatures. We like living in groups and have developed various methods for cooperating so that the group can flourish. For us, technology is important in both the natural and social environments; in the former, for at least food and shelter and in the latter for communication among other things. We are technological herd mammals. This remains true even if we are made in God's image. Our focus here is on human technological mammals in the natural environment.

We begin by considering general issues of technological optimism, technological fixes, and the technological treadmill to see how these lead to a new technological imperative. The implications for nanotechnology within this structure are then outlined.

2.2 Technological optimism

Because we are technological mammals, we need technology not only to live well but in many cases, even to just survive. In the contemporary world, certainly in Western society, we are technological optimists in the way that we behave if not in what we say. "We" here is society in general. While concerns are raised about some technological developments and uses, these concerns seem to have little effect on the behavior

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of researchers, developers, businesses, and the general public. Any worries tend to be drowned out by almost adulation for the new and an unquestioning attitude that new technologies will make life better. The popular press lauds these new technologies and encourages us to buy and use them. A constant stream of new developments and products come onto the market, and the assumption is that all or most problems have technological solutions. The 5G technology will be many times faster than 4G and enable the Internet of Things, driverless cars, and the downloading of movies in seconds instead of minutes. New agricultural technologies will enable farming in deserts, and life spans will be increased further with new medical devices and procedures.

This claim of technological optimism has been challenged by some. Louis Rossetto, for example, recently wrote "It's Time for Techies to Embrace Militant Optimism Again." He argues that despite all of the great technological advances over the last 100 years we are "prisoners of unrelenting pessimism:"

> For the past 25 years, the world has only been getting better. People are healthier, wealthier, more educated, and living longer, better lives than humans ever have. [1]

He may be correct in believing that we are currently overly pessimistic but this might not be technological pessimism, or if it is, it does not seem to stop us developing, accepting, and using new technologies.

According to Alan Drengsen, from the industrial revolution on, the West has had strong elements of technophilia and technological optimism:

> Even as late as the nineteenth century, we find statements of unbounded optimism and complete fascination with the new technologies, with emphasis on the promise of a new world resulting from the coupling of science and technology. ([2], 81)

He believes though that this attitude is not so strong now that many people are aware of the dangers and risks of at least some technologies.

Kevin Kelly too thinks that we are no longer as optimistic about technology, certainly not as optimistic as we should be, because we have become somewhat disillusioned and do not always recognize the improvements of new technologies and focus too much on failures or dangers. However, according to him:

> The momentum of technologies pushes us to chase the newest, which are always disappearing beneath the advent of the next newest thing, so satisfaction continues to recede from our grasp. . . . But I celebrate the never-ending discontentment that technology brings. ([3], 11)

It is not human optimism that drives technological development, he thinks, but the technologies themselves; they have a momentum that pushes us, but it seems we are willing participants because we are not content to stay as we are:

> We are different from our animal ancestors in that we are not content to merely survive . . . this discontent is the trigger for our ingenuity and growth. (11–12)

Whether it is technological optimism or something else which drives us, clearly something does and more will be said about this after looking at a couple of areas where the awareness of dangers seems to have little effect.

Consider technology for monitoring and surveillance. We have been warned for many years, in the popular media, in literature, and in academic publications of the dangers. In a recent newspaper article, Matt O'Brien raises the problem of spying and privacy and security concerns with many new devices:

> All these talking speakers, doorbell cameras and fitness trackers come with the promise of making life easier or more fun, but they're also potentially powerful spying tools. [4]

In literature, George Orwell's well-known and prophetic novel, *1984*, was published in 1949 and Big Brother managed to keep an eye on everyone with technology that was primitive by the standards of today. More recently, Ben Elton's *Blind Faith*, published in 2007, has technologies much like the current ones, so gives a more realistic picture of what surveillance is possible now.

In the computer science and ethics fields, concerns about privacy and data use and security have been discussed at length for many years. Deborah Johnson examined privacy problems in computer use in 1985 [5] and since then there have been many others, including Jeroen van den Hoven [6], Helen Nissenbaum [7], Roger Clarke [8], and Shoshana Zuboff [9]. All raise serious real or potential dangers when governments, corporations, and others gather large amounts of information about individuals.

Despite these expressed dangers, people in general seem to be unconcerned by them. Certainly, regulations are put in place to protect privacy and personal data but the lure of the new appears to outweigh any concerns. O'Brien notes that

> the sceptics who raise privacy and security concerns can be easily drowned out in the flashy spectacle of gee-whiz technology. [4]

The situation is similar with artificial intelligence (AI) technologies. AI has seen a resurgence in recent years with applications discussed in a wide variety of areas [10]. This has been facilitated by large increases in computer power, due partly to developments in nanotechnology, vast amounts of data being collected from the online world, and developments in learning algorithms that have allowed machines to learn decision-making rather than needing to be programmed in detail as in early AI systems. Driverless cars have caught the imagination of many, and their benefits and problems are frequently raised. Medical applications are seen as important ways of making treatments and diagnoses more efficient, including in the current COVID-19 pandemic [11]. Other areas include finance with decisions on buying and selling shares among other things, in law, and as being an important component in monitoring and surveillance technology with data mining, profiling, facial recognition, and so on.

AI has caught the imagination of many but over the last 50 or so years numerous people have been worried about its impact on humans. One of the early critics

who was also one of the computing pioneers, Joseph Weizenbaum, first said in 1976:

> "all projects that propose to substitute a computer system for a human function that involves interpersonal respect, understanding, and love . . . are obscene." And their ". . . very contemplation ought to give rise to feelings of disgust in every civilised person." ([12], 268–9)

Weizenbaum's concerns are not so far removed from data mining and machine learning and facial recognition applications. The judgments made by these technologies regarding who might be a terrorist or financial loan risk, or if the face seen looks like that of some wanted person, should involve some interpersonal respect and understanding. Overall this can be seen as dehumanizing. Similar concerns were expressed by others, including Arthur Kuflik [13] and James Lenman [14].

More recently, Stephen Hawking [15], Elon Musk [16], and others have raised concerns about dangers with the increasing development and use of robots and development and use of autonomous weapons [17]. Rather dramatically, Nick Bostrom has even warned that "superintelligence [in machines] represents an existential risk to humanity" [18, 19].

Despite these concerns and suggestions for future research priorities [20, 21], there seems to be no appetite to change the direction of or to reduce the research, development, and use of AI. The benefits of continuing research and development are assumed to outweigh the dangers.

These examples suggest that, at least in these cases, it matters little what is said about dangers or risks, new technologies keep being developed, and people keep buying new products. Perhaps optimism is the wrong word for the development consumption of the new. If it is true that pessimism is rife these days, then perhaps retail therapy is a better explanation. Buying is a way to make one feel better, for a time anyway. We live in a consumerist society, so pressure to buy is constantly applied through advertising, nudging, and so on. And given that people keep buying, new products keep being developed.

Along with this desire for the new and novel is the belief, probably implicit, that most problems can be solved through technology, whether it be climate change, health, food production, or just about anything else. Whether or not we are optimistic about technology in general we do regularly turn to technology to solve our problems.

2.3 The technological fix

2.3.1 Arguments for technological fixes?

We humans have some serious limitations when compared with other living creatures. We are not very good at running, swimming, or climbing, do not have good

claws for fighting or digging, cannot fly at all, and our senses are just average it seems. Our intelligence, however, and the tools and technologies that have resulted from it give us an advantage over other creatures. As Sean F. Johnston notes, "Reliance upon technological solutions to address human problems is arguably a human trait" ([22], 620) and is almost certainly a necessary one. According to Frederick Ferré, technology is the "practical implementation of intelligence" ([23], 26). Developing and using technologies then could be said to be part of being human. This has always been the case. Australia's Indigenous inhabitants developed significant technologies, not only in order to survive but to live well in a civilization that lasted over 60,000 years. Obviously, spears and other tools were used for hunting but environment changing technologies were employed too. Fish traps of stones were built in rivers, and trees were felled and moved into position to make dams. These structures enabled them to have ample fish supplies to feed large gatherings of people [24]. Fire too was used very systematically to encourage animals to gather in areas where they could be easily caught and to promote the growth of particular kinds of plants and trees [25]. This reliance on technology which has always been present has, as Johnston argues, become more ubiquitous in recent times.

The term "technological fix" was first used by Alvin Weinberg in the mid-1962, according to Johnston ([22], 621) but says that the concept was around long before that [26].

The reason that technological solutions were attractive was that they are simpler that social solutions:

> I am increasingly impressed with what I call the "Cheap Techno- logical Fix" as a means of circumventing social problems. (Weinberg quoted in [22], 630)

Weinberg noted in 1966 that "Social problems are much more complex than are technological ones." "Social problems never had clear-cut solutions" but there is often a "crisp and beautiful technological *solution*" ([27], 7).

The focus of the technological fix here is a little different from our reliance on technology that was outlined earlier. The idea there was that we need to use technology because of our deficiencies, a fairly innocuous idea. The position advocated by Weinberg is that technological solutions are better because they are simpler than social ones. The problems too, of course, differ in complexity. It is one thing to solve the problem of digging holes by using spades instead of hands but quite another to solve the problem of climate change. The social solution of changing peoples' behavior is difficult, perhaps even impossible, while switching to nuclear power as a clean energy source looks relatively simple.

We can see two reasons here for the attractiveness of the technological fix. The first is that we need technology to survive and also to live comfortably and it is easy to move from the simple tools needed, like spades, to more complex technologies. If there is nothing wrong with the former, why should there be with the latter, we may

ask. The second is that these fixes are usually simpler than social solutions that try to change behavior. Johnston notes that a third attraction is also present:

> The notion of the technological fix also proved to be a good fit to consumer culture. Our attraction to technological solutions to improve daily life is a key feature of contemporary lifestyles. ([28], 48)

Making this link with consumerism is important. It shows relationships between various aspects of our lives that are related to technological optimism such as advertising, and attitudes to technology. It highlights the closeness between culture and technology.

Given that we humans regularly do turn to technology to help solve problems such as using refrigerators to keep food cold and tractors to plant crops, why should we be concerned about technological fixes? These examples, however, are not what people usually have in mind when they criticize the notion of a technological fix. The use of the term is mostly pejorative and is commonly used to criticize or raise concerns about certain technologies or its uses. Geoengineering to solve climate change problems and genetic engineering to ensure adequate food supplies are two examples of what are seen as technological fixes. Why is this an issue? What is wrong with turning to technology to help in solving problems? Some see no problem. Others, however, are worried by this technological solution approach.

2.3.2 Arguments against technological fixes

Dane Scott discusses a number of arguments against technological fixes and we will largely work within his framework [29]. The criticisms are divided into philosophical and practical.

The core philosophical criticisms relate to the notion of progress and to our relationship with nature. The first worry about progress that he notes comes from Leo Marx. Marx argues that "the dangerous idea of a technical fix" is based on a mistaken view of the relationship between science and culture. This is, he says, a

> lingering belief that a causal nexus exists between progress within science and technology and the general progress of humanity. ([30], 7)

This nexus, Scott believes, does not exist. From the fact that we might know how to control nature (through science and technology), it does not follow that we know how to control the social environment nor that the social environment can be controlled in the same way as the natural.

The second argument about progress relates to Thomas Kuhn and his account of scientific revolutions. According to Scott, "it is safe to say that after Kuhn it is no longer possible to hold an uncritical belief in scientific progress" ([29], 212). For Kuhn, there is no simple linear progression in science (apart from within paradigms), rather

one paradigm is replaced by another during scientific revolutions. Given the close relationship between science and technology, if science does not progress in ways that provide more answers to problems of physical reality, doubts are raised about the ability of technology to provide answers for social problems.

These arguments against the technological fix are not convincing. For Marx, no strong link exists between progress in science and technology, on the one hand, and the progress of humanity on the other. This may be true but it does not follow that technology cannot be useful in solving human problems. Technology after all is part of human culture, so it would be surprising if it were of no use in helping to solve problems in the social environment.

The argument based on Kuhn is also tenuous. The underlying thought seems to be that if we can no longer uncritically believe in scientific progress then we should no longer believe in technological fixes. But it is not clear why this is the case. While science might not progress in a purely cumulative matter, there is clearly still scientific progress. New paradigms provide better explanations than the ones that they replace, surely a sign of progress. There may be no simple linear progress according to Kuhn but there is progress nevertheless. Consider his well-known example of the Copernican revolution. The earth-centric Ptolemy system had numerous problems including extreme complexity and was eventually replaced by the heliocentric Copernican system. It too had its problems but had more explanatory value than its predecessor. This is clearly a kind of progress. If science can progress in this way, then there is some reason to have an optimistic view of technological progress.

The next philosophical objection mentioned by Scott concerns our relationship with nature. We will depart from Scott here and consider the argument of Eric Katz. His worry about the technological fix is with what he sees as "the destructive effect that it has on the natural environment itself" and how that affects us. He argues that we have an "*attraction to value* that exists in a natural world outside of human control" that is, we have an attraction to the value of the "wild." Attempting to fix or improve nature through technology reduces this value:

> Technology can satisfy human wants by creating the artifactual products we desire, but it cannot supply, replace, or restore the "wild." ([31], 266)

> The technological "fix" of nature merely produces artifacts for the satisfaction of human interests. ([31], 270)

Technologically fixed or modified nature has less value than does nature which is "outside of human control." Undoubtedly, many of us are attracted to that part of nature unaffected by humans or at least where there is no obvious human intervention. A couple of problems arise here though. First, it is not obvious why nature modified by humans has less value than the unmodified. One reason, plausible but difficult to formulate precisely, is that it has the capacity to "take us out of ourselves," to help us see ourselves as part of something much larger. We are just a

small part of the natural world, significant in our own eyes but not so significant in the big picture. As noted previously, we are reminded that we are mammals not so different from the kangaroos or deer that we may see in our environments. This will not convince everyone of course. Not all will have this feeling out in the wild and others will possibly be just as awestruck in more artificial environments. Another concern with Katz's view is that very little of nature is unaffected by humans. It has been argued that Australia itself is an artifact because even what is still considered nature has been modified by its Indigenous inhabitants over many tens of thousands of years, largely by controlled burning.

Arguments designed to undermine uncritical commitments to scientific progress and to technological fixes for nature are certainly worthwhile and it is valuable to examine progress and the relationship between humans and nature. However, none of this shows that technological fixes in themselves are wrong, just that we should not use them uncritically, something to which we will return.

Apart from the philosophical criticism, there are also practical ones. Scott discusses three: technological fixes do not solve problems, they create new ones and they preserve systems that should be replaced ([29], 215). Here we will comment on the first and third criticisms and leave the second for the next section.

As it stands, the first practical criticism is not accurate. Technological fixes solve some problems but depend on the way that the problem is framed. Scott discusses technological solutions to problems created by copper smelting in two US towns (215 ff). In both cases, emissions from the smelting were the problem and technological fixes were applied. According to Scott, whether or not the fixes were successful depends on the criteria used for success. They were a success in the sense that the immediate problems of the emissions were solved in the short term but were harder to assess if they provided longer-term environmental solutions. In simpler cases such as the streetcar example, where in order to stop passengers standing on dangerous outside platforms, those platforms were simply removed, and the success is not ambiguous [26].

The last practical criticism mentioned by Scott is that technological fixes can prolong systems that should be replaced. A good example, discussed by Spreng et al. is CO_2 capture and storage (CCS). The danger with this solution to carbon emissions is this:

> The temptation that CCS offers is the extension of the fossil-fuel era by perhaps a few 100 years. It is a technology designed limit emissions of CO_2 to the atmosphere, but it extends the period during which CO_2 is emitted. ([32], 853)

This is indeed a problem here but it is not necessarily the one in all technological fixes. Again the streetcar offers an example where this problem should not arise.

Spreng et al. also raise the problem of assessing the effects of a technology fix. These fixes must be assessed but:

> The large and finally insurmountable challenge of technology assessment is to compare the known problems a technology solves with the unknown problems it creates. ([32], 853)

This assessment must be done, they agree, but it is not an easy task and some wisdom is required.

2.3.3 Technological fixes: The real issues

Humans have always had to rely on technology, technological fixes if you will, to solve many of our problems. We could not survive in any other way. As already mentioned, it can be argued plausibly that technology is part of our nature. Instead of focusing on technological fixes in themselves, our focus should be on which technologies should be developed and used to solve which problems, how they should be used, what criteria are important for making decisions about development and use, and what are the likely effects of this development and use. The precautionary principle has an important role to play here and problems raised by dual use require examination. What technologies should be developed is a relevant issue because if a technology is developed, it almost certainly will be used, simply because it is there. What scientific research should be undertaken also needs consideration. Just as something will most likely be used if it is developed, something will most likely be developed if the research has been done and it is known how to develop it.

In summary, the argument here is that there is nothing wrong with technological fixes in themselves although it is dangerous to assume that all problems can be solved in this way. The importance of the topic lies in gaining a better understanding of which technologies should be used to solve which problems and how those technologies should be used.

Scott's second practical objection is that technological fixes create the need for further such fixes. We now turn to this.

2.4 Technological treadmill

Assessing the effects of a technology fix is difficult, as Spreng et al. show, and these fixes often create new problems and beget the need for further fixes, as Scott notes:

> As the second practical criticism points out, when one takes a wider and longer view, technological fixes generally delay, relocate, or create new problems. ([29], 216)

Alan Drengsen sees this as a defining feature of technological fixes:

> I call this attempt to repair the harm of a technology by modification, a technological fix. ([2], 260)

For him, using technology to solve a problem caused by the use of technology is what a technology fix is. This is a narrower use than is common but it does highlight the fact that one technological fix often leads to another. This is demonstrated well by Spreng et al. in their discussion of nuclear energy. Nuclear power stations solve the emissions problem of fossil fuels but create problems of the safe storage of nuclear wastes, which in turn requires a technological solution ([32, 2], 264). This is the technological treadmill.

Our optimistic view of technology leads to the technological fix; our first choice in solving problems is frequently, perhaps mostly, to turn to technology. But technology begets technology. The more technology that we have, the more that we need in order to solve problems created by previous technologies. The arms race is a good example. One nation develops a weapon that is better than those of its rival. The rival then attempts to develop an even better one or some new defensive weapon, and so on. The Internet provides a similar example. The Internet has given us unprecedented communication, entertainment, and other opportunities but relatively soon after it became widespread, hacking began, some of it for fun, and some for more sinister reasons. Computer viruses were created and spread to bring down systems and for other criminal activities. These in turn led to new security systems for computers and networks, which in turn led to more sophisticated viruses, and so on. Currently, this "warfare" is apparently being carried out by nations attempting to influence the politics and elections in other nations and in the attempts to counter this interference.

Not all treadmill cases are in this warfare category. Many technologies, regardless of how beneficial they are, have harmful side effects. Cars are a good example. They have brought many benefits but they are also instrumental in large numbers of injuries and deaths. In order to mitigate the risks, regulations stipulate how they should be driven and what safety features should be incorporated in their design. Additionally roads have been designed in ways to lessen accidents. AI technologies are now being used to develop driverless cars which, supposedly, will reduce the risk of accidents given the most accidents are caused by drivers.

An important case but less commonly discussed in the technology context concerns the natural environment and includes human health. The period from about September 2019 until the present (August 2020) has been an interesting time in Australia. First, we had unprecedented wild fires, which burnt an area of about the size of England and it is estimated to have killed or displaced up to 3 billion animals. It is generally accepted that climate change exacerbated the situation with extreme heat, drought, and storms. This climate change is at least partly a result of human technological activity, particularly connected with energy production that powers our many technological devices. A side effect of our use of technology has been to change the climate in a way that necessitates further technologies to fight and control wildfires. This is only one instance of the technological treadmill in this context. Another is to develop more technologies for renewable energy, for example, solar and wind in order to mitigate climate change.

The fires were followed by COVID-19, the second interesting event in this period. While the connection between this virus and technology may be more tenuous, strong evidence exists of a link between human activity and viruses moving from animals to humans, particularly the Hendra and Ebola viruses and SARS, which like COVID-19, is a coronavirus. Loss of habitat through deforestation and fragmentation of forests and climate change can result in movement of species to areas less suitable, higher density, more interaction between different species, and closer contact with humans. This can lead to spillover of viruses to other species including humans. Animals with higher stress levels are more susceptible to viruses, something that these habitat changes make more likely [32–37].

It may seem to be something of a stretch to see the technological treadmill here and somewhat outside the scope of the philosophy of technology. When we consider how large-scale deforestation occurs and how modern agriculture is conducted it begins to look more obvious. Land clearing on a large scale requires technology, commonly in the form of heavy equipment such as bulldozers, trucks, and tractors. Modern farming too relies on advanced technologies. The use of these technologies changes the natural environment in ways that increase the risk of diseases moving from wildlife to humans. When this spillover does happen, more technologies, particularly medical ones, are required, as we are seeing in the current research on vaccines or a cure for COVID-19. Earth-moving technologies can beget the need for medical technologies.

What follows from the technology treadmill? First, very careful technology assessment is required before a technology fix is applied to a problem. This might lead to the use of a different technology be used or to a non-technological solution. The second concerns responsibility for solving the problems caused by the previous use of technology. We look at this in the next section.

2.5 Technological imperative

The technological treadmill, the need to constantly develop new technologies to solve problems caused by previous ones, seems to imply a technological imperative. In order to find out if this is the case, we first need to see just what the technological imperative is.

Various concepts of the technological imperative occur in the literature. Eike-Henner Kluge gives a clear definition from health care although not with which he agrees:

> one might almost argue that medical informatics is the poster child of the technological imperative in health care delivery – if it is technically possible, then it should be done irrespective of the social, ethical or legal considerations. ([38], e1)

Unlike this account, most assume that using the technology will be for the good as can be seen in a common one in the computer industry:

> new technologies are inevitable and essential and that they must be developed and accepted for the good of society. [39]

This is a little ambiguous itself. The idea that new technologies are inevitable looks like a form of technological determinism, in which case there is no need to say that they must be developed; it is inevitable that they will be. Which ones are developed of course may not be inevitable. Putting this aside, however, the important part is that there is an obligation to develop and use them because it is for the good of society.

This ambiguity is shown clearly here:

> The doctrine of the technological imperative is that because a particular technology means that we *can* do something (it is technically possible) then this action either *ought* to (as a moral imperative), *must* (as an operational requirement) or inevitably *will* (in time) be taken.
> (Hasan Ozbekhan quoted in [40])

Another view is similar to Marxist technological determinism:

> A technological imperative means that the form that society takes is determined by the needs of the technology instead of the needs of the people within the society. [41]

For Arnold Pacey, the imperative shows nothing inevitable about technology but rather something about people. It is

> The lure of always pushing toward the greatest feat of technological performance or complexity which is currently possible. ([42], 79)

Antrea Herrera has a similar view. Technology in the form of hashtags on social networks creates:

> a technological imperative to publically name one's sexuality.

However,

> This technological imperative would not exist apart from the desire to engage in communities of similarly stigmatized individuals. ([43], 320)

The imperative is enabled or afforded by the technology but is produced by the desires of people.

Apart from the Marxist interpretation, all the other accounts involve a human element. The technology must or should be used and where it is claimed to be inevitable that inevitability is because someone at sometime will develop or use it. Here, the technological imperative will be used to mean that it is imperative – that is, vital or urgent – that technology is developed and used for particular purposes. This is the sense in which it is used by David B. Hertz when he says that it is imperative that engineers are given the skills to deal with the total environmental problem ([44], 105).

"Imperative" is used here in the sense that it is in "It is imperative that I exercise more." A technological imperative is an imperative that a technology is developed and used to solve or alleviate a problem. It is often also used in a more general sense where it is said that the technological imperative is to develop technologies to the greatest extent possible, on the assumption that this will be for the good of society.

Apart from technological imperatives, there are also social and moral imperatives. Given the integration of technology into our culture, these three imperatives are not completely distinct. Many social imperatives, say, to provide adequate health care for all, are going to involve technological imperatives, in this case, to develop medical drugs, vaccines, and so on, and there is a moral imperative to do this. These three imperatives will not always occur together but for our purposes here those instances will not concern us.

The technology imperative then is the moral imperative to develop and use technology for the good of society, but it is stronger than this. Because of past human activities, particularly those involving technology, many problems have been created especially for the natural environment. It is imperative that we develop technologies to fix these in ways that do not lead to yet further problems. This would be a step toward jumping off the treadmill.

This new imperative is based on what Thomas Pogge calls *intermediate* duties. These duties are stronger than positive duties to do good but are weaker than negative duties not to cause harm ([45], 34). If I come across someone injured who needs help, then it is good if I help him. This is a positive duty. If, however, the person is injured because of some action of mine, then my duty to help is stronger; it is an intermediate duty.

The new technological imperative then is this: we have an intermediate duty to future generations to develop and use technologies that provide solutions to problems created by previous technologies. In what follows we will focus on imperatives related to the natural environment.

2.6 Nanotechnology and the technological imperative

The argument so far is about technology, in general. The focus now will be on nanotechnology, specifically on issues related to the environment and climate.

2.6.1 Nanotech optimism

There is a general optimism about technology, or so it was argued at the beginning of this chapter. Not everyone is optimistic but among consumers, researchers, and

developers, any pessimism or expressed worries are largely ignored. Optimism for nanotechnology, at least amongst consumers, is less obvious, simply because nanotechnology is less obvious and also still relatively new. Nanotechnology is largely an enabling technology, that is, it enables or enhances other technologies so is mostly hidden from view. But even if it is largely hidden from view, some optimism is displayed about nanotechnology-enhanced products. Bernard Marr in an article entitled "7 Amazing Everyday Examples of Nanotechnology in Action" talks of "exciting new solutions and products." The enhanced products that he mentions are sunscreens, clothing, furniture, adhesives, coatings for car paintwork, tennis balls, and computers [46].

2.6.2 Nanotech fix

Nanotechnology can play a role in many technological fixes and not just in tennis balls and the others mentioned by Marr. Here, we will consider just a few, all of which are related in some way to the natural environment, namely, issues with the environment itself, agriculture, energy, wildfires, and pandemics. The latter two will be looked at in more detail in the following section.

First, the natural environment. It is not surprising that the natural environment is important for humans. We are mammals and that is where we evolved. It is the source of our food and our raw materials, so a healthy environment is to our advantage, not only for the material things that it supplies but also for our physical and mental well-being. And the more biodiverse it is, the better [47, 48].

Nanotechnology can or potentially can provide technological fixes for a number of environmental problems. Novel sensing and monitoring technologies can help in detecting pollution and disease, selective adsorption on nanosorbents, nanomembrane separation, and environmental nanocatalysis can all help in environmental protection and remediation such as removing contaminants for soil, water, and air. Environmental remediation relies mainly on using various technologies (e.g., adsorption, absorption, chemical reactions, photocatalysis, and filtration) for the removal of contaminants from different environmental media (e.g., soil, water, and air) [49–51].

Agriculture is closely related to the environment, so many of the applications of nanotechnology are the same or similar, for example, air and water purification, pesticides and monitoring of pesticides and plant pathogens, remediation for pesticide, and soil degradation. There is also potential for crop production, diagnosis, and plant breeding [52] and for fertilizers [53].

Given problems with climate change and the role of energy production and use the generation of greenhouse gasses, sustainable and clean energy is one of the most urgent areas for technological solutions. Nanotechnology is being utilized in improving solar cells for solar energy and improved the efficiency of energy use storage and distribution [49, 54, 55].

Various applications of nanotechnology related to energy are summarized in the following quotation:

> Nanotechnology is applied to various aspects of renewable energies. By applying nanotechnology, the efficiency of PV/T [photovoltaic/thermal] systems will improve due to higher heat transferability of nanofluids applied for heat transfer. In addition, PV modules can be improved by applying nanotechnolgy in their structures and materials. In fuel cell technologies, nanotechnology has different advantages such as fuel cells with lower cost and higher efficiency, distribution, and storage of hydrogen fuel; nanocatalysts are used in biofuel industry to improve their performance. In wind energy, materials with higher durability and lower weight are achievable by applying nanotechnology. ([56], 1404)

These three application areas (the environment, agriculture, and energy) have all been related to ways of protecting or improving the environment. The next two are concerned with technological fixes for problems that are at least partly a result of previous environmental issues including climate change caused by the use of technologies. Technological fixes for wild fires and some health issues are part of the technological treadmill.

2.6.3 Nanotech treadmill

Climate change resulting in higher temperatures, dryer conditions, and extreme weather has played a role in the recent disastrous fires in Australia and in California. Nanotechnology can play a role here in a couple of areas. One is clean and renewable energy as we have just seen. Hopefully this, together with protections of the environment and improved agricultural methods, will have a beneficial effect on climate change in the longer term.

Nanotechnology can assist in fire safety in a number of ways. It helps in the detection of fires with more sensitive smoke alarms that can detect particles at the very start of a fire. Fire-resistant nanocoatings can increase the strength and durability of materials to better withstand heat which can be useful in the protection of lives and property. Improved fire retardants can assist in fire suppression [57].

As stated earlier, the natural environment has benefits for our well-being but as we saw in the previous section, environmental degradation or even just change can have serious consequences including increasing the potential of virus spillover where viruses from one species can move from one species to another, including humans.

Some of the potential of nanotechnologies is outlined here:

> First, nanoparticles (NPs) can offer alternative methods to classical disinfection protocols used in healthcare settings, . . . Nanotechnology tools to inactivate SARS-CoV-2 in patients could also be explored . . . nanomaterials could be used to deliver drugs to the pulmonary system . . . the concept of “nanoimmunity by design” can help us to design materials for immune modulation, . . . In addition to disease prevention and therapeutic potential, nanotechnology has important roles

> in diagnostics, . . . In summary, nanotechnology is critical in counteracting COVID-19 and will be vital when preparing for future pandemics. ([58], 2; see also [59])

2.6.4 Nanotech imperative

As we said earlier, we have an intermediate duty to future generations to develop and use technologies that provide solutions to problems created by previous generations often but not necessarily through the use of their technologies. This is the new technological imperative. This imperative applied to nanotechnology then is to develop and use nanotechnologies to provide solutions to previously created problems. This requires some explanation. Two considerations are relevant here. One is the seriousness of the problem and the other whether it was caused by human activity. Tennis balls losing their bounce might be a problem for tennis players on occasion but it cannot be considered to be a very serious social issue. Changing balls regularly can solve the problem. Even if the only solution lay in nanotechnology, it seems of little importance compared with alleviating harms of wildfires or finding a treatment or vaccine for COVID-19 or other pandemics. Here, the seriousness of the problems seems to be enough for decision-making regarding solving problems.

There is another aspect to the seriousness criterion. The seriousness of a problem might not always show the full extent of the responsibility or the strength of the duty to attempt to alleviate or solve it. The cause of the problem can also be relevant and here intermediate duties come into play. If human activity was part of the cause, then the duty to solve it is stronger. It does not follow that problems that arise naturally through no human activity do not deserve attention. Injuries from natural disasters such as earthquakes, for example, are a legitimate source of research into and development and use of nanotechnology. The argument is merely that there is a stronger duty to try to solve some problems than others. Consider these two cases. In one, an earthquake causes a landslide that buries a village resulting in a large loss of life and injury. In the other, the landslide is the result of coal mining with the same consequences. In both cases, as much as possible should be done about alleviating the suffering but in the second there is a level of responsibility on those who caused the tragedy that is absent in the first. Applying this reasoning to the environment, wildfire, and pandemic case, where human activity has played a role in increasing the likelihood of wildfires and pandemics through environmental damage, an intermediate duty is created. The technology imperative based on this involves trying to fix the environmental damage that has been caused by humans and alleviating the harms caused by the consequences of this damage. The nanotech imperative is to employ that technology for the good of the environment and to overcome the harms caused by its destruction.

As we have seen, nanotechnology has an important role to play in fixing or alleviating the problems previously mentioned, and it is important that research and development continues in those areas. What must not be ignored though are the potential

risks with certain nanoparticles, both for human health and for the environment. It is imperative that research into those risks gets as much attention as research into benefits does [49, 60–62]. If it does not, this is just another step on the technological treadmill.

2.7 Conclusion

We are technological mammals. Technology enables us to survive and to live well and to flourish. Because we are mammals the natural environment is also essential for our survival and flourishing. Unfortunately, our use of technology has often led to environmental changes, including changes to the climate, that are not ideal for the types of creatures that we are. The "Terrestrial turn in philosophy of technology" [63] would lead to more integration of philosophy and ethics of technology, and the environment should be embraced. The new technological imperative, including the nanotech imperative, is to keep a focus on those problems created by humans with technology, especially environmental problems, and to try to solve those, hopefully in ways that do not generate the need for further technological fixes – that is, an intermediate duty that we have to future generations. Like all mammals, we can only survive and flourish in a particular kind of world.

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Part II: **Advancing nanoscience initiatives and ethical concerns**

Marcel Van de Voorde and Michael Vlerick

3 Nanotechnology: Societal impact and ethical considerations

Abstract: In this chapter, we offer an introduction to nanotechnology, highlighting the big impact of these tiny things, and we reflect on its ethical implications. Firstly, we argue that nanotechnology is no mere hype and substantiate this with an overview of its applications in medicine, consumer products, and industrial products. Secondly, we discuss the harms nanotechnology might cause to health and environment and argue that the development of nanoproducts and applications should therefore be regulated. Thirdly, we take on societal issues following from the development of nanotechnology, such as economic and social (in)justice, potential violations of privacy, and autonomy and unethical applications. In the face of these ethical issues, we argue that there is need for transparency, interdisciplinary panels concerned with "nano-ethics" and institutions of democratic control. Finally, we offer a series of concrete recommendations in the face of this promising and disruptive technology.

Keywords: nanoscience, picotechnology, regulation, intellectual property rights, democratic control

3.1 Introduction to the nanoworld [1]

Nanoscience is the study of phenomena and manipulation of materials at the atomic and molecular scales. Properties at this scale differ significantly from those at a large scale.

Nanotechnology is the design, characterization, production, and application of structures, devices, and systems by controlling shape and size at the nanometer scale.

Nanoscience broke through in January 2000, when former US President Bill Clinton launched the US National Nanotechnology Initiative. The whole world followed the United States and today nanoscience has become one of the most important research topics worldwide. In the twenty-first century, nanotechnology is predicted to spawn the next industrial revolution, together with artificial intelligence and robotics.

In order to imagine 1 nm – a unit at the nanoscale (Figure 3.1) – it is useful to compare it with 1 m, a readily imagined unit at the macroscale. A meter is a billion times larger than a nanometer. If we shrink the distance from the Earth to the Moon (~360,000 km) by a similar amount – that is, 1/1,000,000,000 – we get a mere

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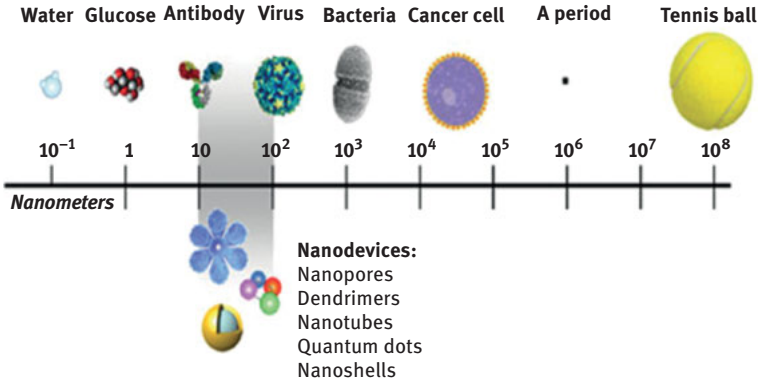

Figure 3.1: Visualizing the nanoscale.

36 cm (Table 3.1). If we do the same for the radius of the Earth (~6.400 km), we get 6.4 mm.

Table 3.1: Units and *subunits* value in meter.

1 millimeter (mm)	0.001	10^{-3} m
1 micrometer or micron (μm)	0.000001	10^{-6} m
1 nanometer (nm)	0.000000001	10^{-9} m
1 picometer (pm)	0.000000000001	10^{-12} m

As we will argue in this chapter, nanotechnology has the potential to revolutionize (the quality of) human life. In Section 3.2, we describe the breakthroughs in and potential of nanotechnology. In Section 3.3, we discuss the potential harm of nanotechnology to human health and the environment and offer solutions. In Section 3.4, we take on the societal issues and ethical dilemmas it raises. Finally, we conclude with a series of concrete recommendations.

3.2 Revolutionizing human life?

3.2.1 Nanotechnology: Is it hope or hype? [1]

Nanotechnology has captured the imagination of scientists, engineers, and the public alike with its promise to revolutionize a broad range of technological applications. In particular, its potential for health care was of huge direct interest. The initial

enthusiasm was tempered somewhat by recently raised concerns about potential adverse effects of nanotechnology on health and environment. Nevertheless, governments and funders never withdrew their support and so the fears of the public were somewhat allayed. Admittedly, some of the enduring buzz surrounding nanotechnology may be due to the incentive experts have in keeping up this enthusiasm in order to generate novel funding streams.

What is not in doubt, however, is that there are also legitimate reasons for this enthusiasm. Scientific research shows us that both bulk and surface properties change at the nanoscale in ways that are not at all predictable from the macroscale. Recent developments in nanotechnology bring us on the verge of creating entirely new material properties, properties that could never have been imagined earlier.

The increasing number of high-quality publications attest to the discovery of new properties and new potential applications. All of these previously unimaginable breakthroughs and advances in scientific understanding came about through the intriguing concept of the nanoscale. Moreover, the instant public recognition of the potential of nanotechnology (and the funding following in its wake) boosts the further development of nanotechnology and the extraordinary market opportunities following in its wake.

As pointed out, in order to justify the funding enhancement, researchers and technology developers highlighted the many societal benefits of nanotechnology in their early work. These were certainly justified, well thought out, and peer-reviewed. What appeared to be harder to estimate correctly was: (i) a realistic timescale for the development of these innovations and (ii) what parallel, enabling technologies would be needed to harness nanoparticles. Our conventional way of looking at advances in the development of materials did not equip us well to make these "crystal ball" predictions.

The fact that we massively underestimated the time it takes to develop nanotechnology innovations is the core reason why some now question the entire enterprise. This cycle of bullish optimism followed by pessimism when the promised results are not delivered in time is inherent to many new areas of research and development. But the global, multifaceted potential impact of nanotechnology has accentuated this cycle, creating higher and more urgent expectations . . . and bigger disappointment.

So, after two decades of intense research, are we forced to conclude that it was a hype based on empty promises? Certainly, some of it was. However, the fact that we have not (yet) achieved what we promised at the outset does not amount to making empty promises. It is not so much a question of "if" many of these promised breakthroughs will happen, but "when" they will happen. It is a matter of timescale. There is nothing deceptive about the physicochemical discoveries we made and the tangible technologies they enabled us to develop. Indeed, as is the case at the molecular scale, nature definitely has a lexicon for operating at the nanoscale. So, there is something for us there to both understand and exploit. What is missing for the moment is our leveraging ability.

Major breakthroughs in a subset of the field could well accelerate the development of nanotechnology in general and change the perception of the field. We are witnessing the beginning of such breakthroughs in cancer research and in research on tropical diseases. This shows the multifaceted nature of nanotechnology. It is not just another branch of science, but a scientific universe in itself. It requires us to rethink our existing tools and methodologies.

Moreover, the practical needs that nanotechnology applications could address have not gone away. We still need to reduce the usage of scarce materials, to make devices less obtrusive (whether on a jet airplane or inside the human body), to create stealth structures to improve therapeutics, to improve imaging, to manipulate small structures reliably, to accelerate information processing, to enhance microprocessor performance, and so on.

A common past mistake has been to assume that once a basic structure is in place or that a fundamental phenomenon has been observed, the next step of harnessing it would be more or less straightforward. The opposite is true. This last crucial step is always more difficult and requires an interdisciplinary effort that we have not always been able to deliver. Moreover, devising practical nano-enabled technology is perhaps somewhat less glamorous than doing the fundamental research (and it can count on less champions).

But breakthroughs have been made. A prime example of highly successful nanotechnology is in the area of synthetic biology, in which nanostructures have been assembled and utilized. The question we face is how we can use our understanding in this field to make similar breakthroughs in other fields. Moreover, the undeniable fact that direct technological successes are limited for now does not change the fact that the paradigm shifts the field has engendered have been of immense value. The knowledge that we have gained, we owe to the buzz that has been created around nanotechnology. Now, we must set the scene for a next realistic and productive phase.

3.2.2 Should we wait for picotechnology?

Scientists are already exploring the picodimensions, one thousand times smaller than the nanodimension. In the context of this volume on nano-ethics, it is useful to mention picotechnology. If only to give an idea of what is coming in these revolutionary times, picotechnology will engage length scales that will be particularly challenging to study, let alone to exploit. Advances in the resolution and sensitivity of noncontact analytical tools – especially those based on electromagnetic radiation – provide an insight into what may become possible at this new molecular-scale frontier. Atomic-scale topological and positional discrimination will become possible, both of free structures and the structure within the solid state and at the interface.

An example of this is synchrotron radiation, which provides both positional and ultrafast dynamic resolution. At the opposite scale, a force microscope uses picoscale surface interactive forces for structural resolution. The ultimate picotechnology will be far removed from the nanoscale. It will enable us to focus on matter in much more fine-grained way than our current "statistical" averaging of large-scale molecular and atomic populations.

The picoscale is thus not entirely representative and would have to be linked somehow to the classical Boltzmann hierarchies if it is to be used in the "real" world. Properties would also have to be correlated with the inevitable fast molecular and cluster dynamics seen at the picoscale. The value of picotechnology will be in the better understanding of matter it yields and the bridging between the molecular (chemistry) and the macroscale. Practical outcomes are difficult to predict at this stage. Awaiting picotechnology as an advanced variant of nanotechnology does not seem warranted. An exception to this is that picotechnology might enable us to fashion materials with unprecedented properties.

So, in summary, while picotechnology might yield new products, its benefit lies first and foremost in enhancing our understanding of matter. This might in turn help to improve our fashioning of nanomaterials in particular and harness the nanoscale for practical applications in general (especially through the analysis of nanostructure subcomponents). For instance, the current assumption that nanostructures in a given population are similar because of a facile structural similarity may well be revisited through improved analysis by picotechnology methods.

Picotechnology is thus neither a substitute nor an advanced variant of nanotechnology. Rather, it is a tool to better understand the nanoscale. To simply await the advent of picotechnology and to expect it to succeed where nanotechnology failed is misguided.

3.2.3 Nanotechnology applications

The basic principles of nanotechnology, such as synthesis, processing, properties characterization, and modeling, are outside the scope of this chapter – we gladly refer you to other sources [1–3]. This section focuses on the revolutionary developments and applications of nanotechnology.

Nanoscience and nanotechnology have a very large number of potential applications. It is safe to assume that everybody will be faced with it one day in one form or another: be it in the domain of industry, health care (medicine, dentistry), energy and transport, administration, economy, or architecture, in the house, in the hospital, in the factory, in the car, in the office, and so on.

Scientists and engineers are using techniques at the nanoscale to create new materials and products that will increase human standards of living and help to tackle some of the most important global challenges, including

- (even) more powerful portable electronics with more capabilities and storage capacity;
- medical techniques to perform operations with procedures that are much less invasive (the so-called injected surgeon);
- novel drugs that are more effective and have fewer side effects;
- filters for producing clean drinking water in the developing world, and for cleaning up industrial pollution and toxic chemicals worldwide;
- sensors to provide detailed information on the environment, aiding with a wide range of tasks, from irrigation of crops to pollution monitoring in cities.

Examples of applications are:

- *In medicine* [1], nanoparticle-based vaccines may one day provide permanent immunity to infectious diseases such as common cold, influenza, and covid by being constantly adaptable to new strains.
- Artificial replacements of body tissues such as skin, muscle, tendon, and even organs produced by nanoscale fabrication mimic natural processes and structures.
- Microscopic devices containing a host of nanotechnology functions to seek out disease provide detailed diagnosis, and even undertake surgery or drug delivery.
- Rapid blood/urine testing using "laboratories-on-a-chip" to give near-instant results to a doctor without having to wait days for samples to be sent to a distant facility for processing.
- Novel coatings were applied to teeth in order to protect the enamel against decay by changing the chemical interaction with the saliva (Figure 3.2).
- *In consumer products* [2–5], smart textiles with nanodevices built into the cloth will provide functions as diverse as medical sensing, temperature control, monitoring of air quality, and even energy harvesting for charging mobile devices. Moreover, stain resistance of cloth can be greatly enhanced by nano-enabled coatings.
- Nanoscale etching of a surface with a laser can affect the reflection of light in a way that creates vibrant colors on a metal surface without using any dye.
- Anti-aging cosmetics use active ingredients that are encapsulated in nanocarriers, stabilizing them and enabling penetration through the epidermis.
- The current generation of smartphones could become even thinner and will swap strength and stiffness for flexibility, being able to be folded or rolled like paper for easy storage. More memory and functionality will be available through advances in nanoscale fabrication.
- Nanoscale effects will enable the future generation of "quantum computing," with algorithms based on probabilistic outcomes rather than the absolute results given by conventional computing. At this stage, the possibilities are still uncertain but potentially extremely exciting.

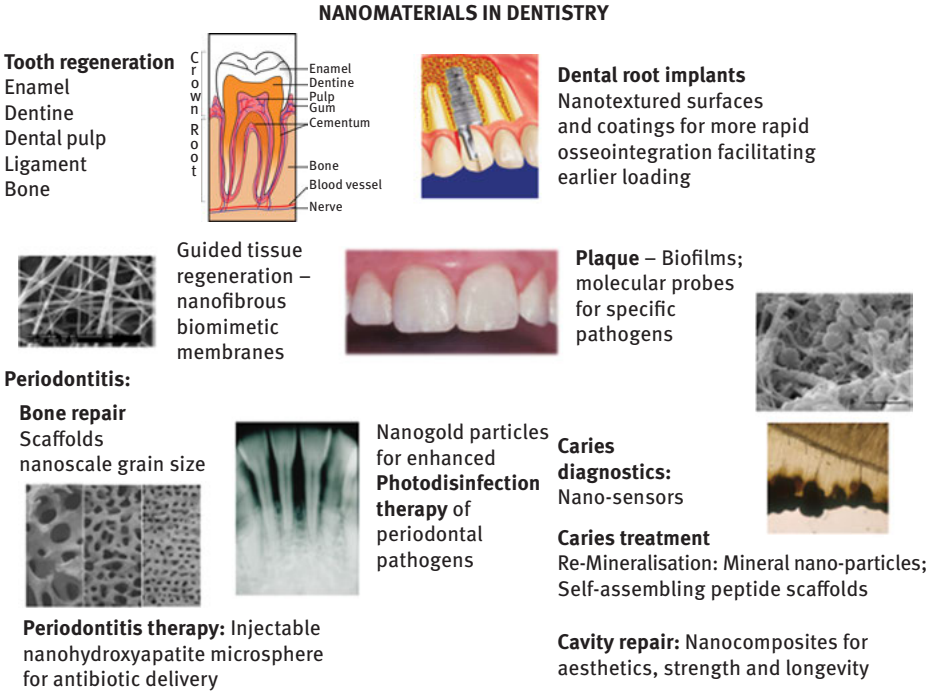

Figure 3.2: Nanomaterial potentials in dentistry.

- Nano-sensors can be integrated into food packaging to detect bacteria and provide a visual warning if the food is spoiled; or alternatively whether fruits or vegetables are ripe and ready to eat. Nanomaterials can be used to keep foods fresh for longer. Nanotechnology systems can also be integrated with block chain technology to provide the integration of detecting, locating, tracking, and remotely controlling food products to increase efficiency and security of food transportation.
- Sensor networks based on nano-sensors can be used in crop fields to provide localized information on water, sunlight, and the delivery of fertilizers and pesticides, offering a high level of control to farmers to deploy chemicals only where they are needed.
- *In industrial applications* [6], nanomaterials can have unique catalytic properties, drastically reducing the process complexity of and the energy required for the synthesis of important chemicals.
- Nanomaterials hold the key to successful carbon capture and storage, and the recycling of carbon dioxide back into fuels such as methane.
- Nano-strengthened materials can be used to produce lightweight alloys for cars, allowing reduced fuel consumption. It also allows for the fabrication of tires with better grip in wet conditions.

- Electrode materials for rechargeable batteries can be greatly enhanced through nanotechnology, reducing weight and improving performance in the next generation of hybrid and electric vehicles.
- Paints can use nano-fillers that will prevent fading and even provide self-repair for small scratches. Nano-coatings can provide scratch resistance, dirt repellence, and automatic control of lighting for window glass.

3.2.4 Revolutionizing (the quality of) human life

The idea that nanotechnology has the ability to drastically change the world is most probably the main reason why nanotechnology is often referred to as a "disruptive" technology. As pointed out above, these big promises attracted big attention. The number of areas that could be revolutionized by nanotechnology are mind-boggling. They include health care, information and communication technology, energy and transport, environment and climate change, and security and safety. Nanotechnology has the potential to revolutionize our everyday life with nano-foods, clothing, cosmetics, and cleaning products, *and* to solve major world problems such as global warming, environmental damage, access to clean water, public health, poverty, and protection against harmful bacteria and viruses and even against terrorism and crime.

On the other hand, we cannot exclude that nanoproducts harm human health and the environment, as reported by certain toxicity studies. These risks are a source of major concern. Unsurprisingly, some people view nanotechnology as something out of (scary) science fiction. They view it as an invisible technology, potentially lethal in the form of biological weapons, which could profoundly invade our privacy and inadvertently damage our bodies. In the next two sections, we discuss the threats posed by nanotechnology.

3.3 Potential harm to health and environment [7, 8]

3.3.1 The threat of uncertainties

Alongside the benefits of nanotechnologies, we must of course pay attention to the possible risks to human health and the environment, along with the societal and ethical issues it raises. In most nanotechnology applications, the nanoparticles or nanostructures are entirely inert and are constrained within a larger device. However, when the technology relies on nanoparticles, we must take into account the possible consequences of a release of these particles in our environment (and into our bodies) [7, 8].

Nanoparticles can enter the body through inhalation, ingestion, or through direct contact with the skin. Nanoparticles may lead to toxicity or disease. They could cause inflammation, by interfering with the normal operation of body or organ chemistry, or even lead to the generation of cancers. Figure 3.3 shows the diseases that are associated with exposure to nanoparticles.

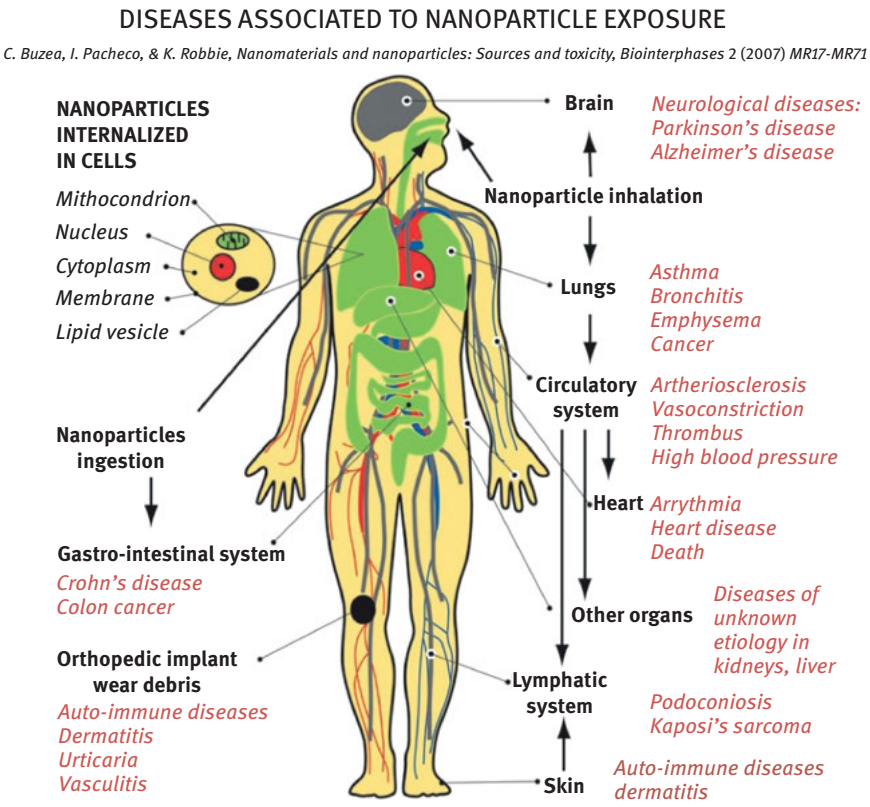

Figure 3.3: Main routes of entry of nanoparticles into the body and some resulting disease possibilities (right part).

3.3.1.1 Entry by inhalation

Once inhaled, nanoparticles are either simply exhaled, or can be deposited anywhere in the respiratory tract from the nose, mouth, and larynx, down to the bronchi and alveoli of the lungs. This could lead to the exacerbation of asthma symptoms, cardiovascular adverse effects, and possibly carcinogenicity.

3.3.1.2 Entry by contact

Intact skin can effectively block the penetration of micro- and nano-objects. However, if the skin barrier is compromised by injury, sunburn, or skin disease, nanoparticles may diffuse through damaged or weakened skin and enter the bloodstream.

3.3.1.3 Entry by ingestion

Nanoparticles can be ingested directly (e.g., with food and drink) or indirectly (e.g., through the nose due to postnasal drip). Once in the digestive tract, the particles can be transported into the circulatory system.

At present, we only have limited understanding of the human health and safety risks associated with nanotechnology. Public health agencies are actively conducting research on the potential adverse health effects of unintended exposure to nanoparticles. At this point, we cannot exclude that the use of some nanoparticle products has unintended adverse effects. For example, silver nanoparticles used in socks as an antibacterial coating that reduces odors may be released when washed and then flushed into the wastewater stream. There they may destroy bacteria, which are critical components of natural ecosystems, farming, and waste treatment processes.

Given these potential harms, nanotechnology should be closely regulated by governments during the initial stages of its introduction into the marketplace. This is no easy task. We must weigh off benefits against (mostly unknown) risks [10]. We must also be aware that it is virtually impossible to eliminate all risks.

3.3.2 The need for regulation [9, 10]

The growing manufacturing of nanotechnology products and their commercialization calls for the development of a regulatory framework to avoid harming people – both workers with nanomaterials and the consumers of nanoproducts – and the environment. This framework should be developed not only on a national scale by national governments but also on a supranational or even global scale by institutions such as the European Union and the United Nations [10]. Given the scientific complexity of nanotechnology, this should be done in close collaboration with scientists, toxicologists, and industrial players [9, 10].

In the workplace, guidelines and procedures should be developed to protect exposed workers as much as possible. When it comes to everyday consumers, no substantial harm to their health has been detected, but we must remain vigilant. We cannot exclude with absolute certainty that people are not or will not be intoxicated by nanoparticles.

The regulation of nanotechnology should satisfy different criteria [3, 10]:

- We should strive for the harmonization and standardization of regulation on a global scale since nanotechnology has a global impact. First steps in this direction are being taken, with the European Union and the United States attempting to harmonize the regulation of nanomaterials.
- A sui generis regulation should be developed for all categories of nanomaterials. Nanomaterials can have significantly different characteristics than the bulk form of the same material. Many regulatory agencies have not yet devised specific regulations for the use of different nano-sized versions of the same substance.
- Nanoproducts should be labeled: All nanomaterials in substances, mixtures, and so on should be clearly indicated in the labeling of the product. Today, this information is often lacking.

The importance of (more) research can hardly be overstated. At present, we do not have sufficient understanding of nanomaterials. In order to have a better understanding of the risks involved, which in turn is necessary to draft appropriate regulation, we must have a better understanding of nanoparticles.

The European Union and the OECD in collaboration with many national – for example, US-National Science Foundation – and international bodies – for example, International Standardization Office in Geneva – have been working for years to develop guidelines for risk assessment of nanoproducts and technologies [3]. These efforts must be ramped up now that more nanoproducts are finding their way to the market.

Nanotechnology, however, does not only come with health and environmental risks, but also raises a host of societal issues. In the next section, we discuss these issues and suggest ways of addressing these.

3.4 Societal issues and ethical dilemmas [9, 11–13]

Nanotechnology does not only call for regulation because of the risks it poses to human health and environment. This disruptive technology also has the power to radically transform human societies. We must ask ourselves, what kind of world are we creating? As we will discuss below, while nanotechnology and its applications could have massive benefits and radically improve the human condition, they could also increase economic and social injustice, decrease privacy, and have a host of other morally undesirable effects.

Therefore, the development of nanoscience and nanotechnology should not be left to engineers and nanoscientists alone. It is of utmost importance that experts in the social sciences and humanities and the public at large are involved. Developments in nanotechnology should therefore be transparently communicated and

closely monitored. For this purpose, scientists, engineers, and industrial players should work closely together with ethicists and social scientists *and* the public should be informed and consulted.

We must also realize that the ethical issues raised by developments in nanotechnology are not fixed. They will change over time with the development of new insights and applications. Moreover, global problems such as environmental problems and health issues (e.g., pandemics) also evolve over time and require new solutions and regulation. What is beyond any doubt, however, is that nanoscience and technology has the potential to revolutionize human life (and the lives of other species) and will therefore continue to raise important ethical questions. What is needed is an ongoing ethical debate involving all relevant experts and stakeholders (more on this below) [9, 10, 12].

In addition to protecting human health and the environment, we must be vigilant that nanotechnology does not exacerbate (and ideally reduces) economic and social injustice. We must also protect human dignity and autonomy in the face of nanotechnology-enabled privacy eroding technologies. Great power, as they say, comes with great responsibility, and nanotechnology has the potential to provide us with great power . . . so we must take our responsibility and develop this disruptive technology in an ethically desirable way. Nanotechnology can and should increase the well-being of all stakeholders.

3.4.1 Economic and social (in)justice

In a morally perfect world, all stakeholders or possible beneficiaries would have equal access to nanotechnology applications. In the real world, it is very likely that at least initially nanotechnology will benefit wealthy nations and individuals (substantially) more than their poorer counterparts. Wealthy nations have the necessary infrastructure and can muster up the necessary investments to develop nanotechnology applications. Developing nations do not, or at least not to the same extent, and risk missing out on these innovations [3, 6, 8].

In fact, third world countries have already been disappointed when it comes to nanotechnology. With the emergence of nanotechnology, 20 years ago in the United States, developing countries had great hopes that it would accelerate their economic development. Due to a lack of scientific and technological infrastructure, however, nanoscience and technology never took off and the applications that were developed in industrialized countries were for the most part not made available to developing countries.

A major obstacle, in this context, is intellectual property rights or patent systems. Intellectual property rights threaten to make nanotechnology applications unaffordable and thus unavailable in developing countries. While the rationale of patents is to incentivize the development of new applications – by giving a time-

limited monopoly on the production and commercialization of products developed in-house – it is unclear whether this actually is the case when it comes to nanotechnology applications. Out of fear of missing moneymaking patents, competing firms are incentivized to file for many and broadly defined patents. Often, these firms cannot or will not develop these patents themselves, but they hope to cash on the development of their patent by other developers. This in turn might make it less, not more, attractive to develop the said applications [14]. The current patenting system, we believe, should be revised. In addition to creating economic injustice by making useful applications unavailable in poorer regions, it seems to be missing its primary target, which is to promote innovation.

In any case, intellectual property rights are likely to increase economic injustice between the developed regions and the developing regions of the world. The latter stand to miss out on many applications, which could increase their wealth and well-being. This is especially problematic given that nanotechnology applications could offer solutions to important problems of developing nations, such as the purification of water, energy production, efficient food production, and customized health solutions.

Finally, at the speculative end of things, nanotechnology – together with other cutting-edge technological developments such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene editing – has been linked to human enhancement. By manipulating molecular structures, nanotechnology could in principle be used by humans to enhance their appearance, physical strength, longevity, cognitive capacities, and others. Applications targeted at delivering such enhancements raise a long list of ethical issues and dilemmas.

Among those ethical issues is the realistic possibility that the commercialization of such applications would exacerbate social inequality. If access to these applications is limited to the wealthy (who can afford these "treatments"), this could create a huge gulf of unequal opportunities and outlook in life between the rich and the poor. In addition to having less means, the latter would also find themselves at the losing end when it comes to their biological endowment. This in turn would make it very hard for them to aspire to a better future, since they could not compete in the job market with luckier cognitively enhanced people.

In short, with respect to the possibility that nanotechnology negatively influences economic and social inequality, we believe the following moral imperatives apply:

i) Nanomaterials and nanotechnologies should, as much as is realistically possible, be made available to everyone in the world. This is more than a *moral* imperative for wealthy nations. A wealth gap between rich and poor nations negatively affects those rich nations because it leads to mass migration to wealthy regions, which can be profoundly destabilizing for those nations [15, 16].
ii) Nanotechnologies should be developed to target specific problems faced by developing countries and made available to these countries in order to enhance the standard of living and the prospects of people in these regions.

iii) The development of nanoproducts in industrialized countries should not have an adverse effect on wealth and economic prospects in developing countries. This could be the case if new nanoproducts developed in industrial countries outcompete existing conventional products manufactured in developing countries. In this case, compensations should be made and those technologies should be made available to the developing countries in question (as pointed out above).

3.4.2 Privacy and other ethical issues

Nanotechnology could revolutionize health measurements by implanting microchips or biosensors in (human) organisms. This could lead to a marked improvement of human health (and to more efficient managing of chronic diseases such as diabetes). However, such technological developments may well be co-opted for surveillance and personal information gathering purposes. This raises a host of privacy issues [17, 18].

Can we use personal data for scientific research? Could these data be shared with insurance companies? More extremely, we can imagine that all humans have a nanosensor implanted, which tracks their every movement and activity at all time. Michael Mehta [17] has coined the term "nano-panopticism" to describe a society in which nanosurveillance technology has created a "panopticon": a context in which everybody is "watched" and monitored at all times.

While the latter scenario is manifestly undesirable, we cannot simply dismiss any surveillance with the aid of nanosensors as immoral. People living a healthy lifestyle would benefit from having their health data accurately measured and sent to an insurance company which could in response lower their premium. Moreover, many people would probably agree that if we can detect the preparation of (and therefore prevent) heinous crimes and terrorist activities, we would be better off. But how far are we willing to go and what is the price we pay for increased security? These are hard questions that will become ever more poignant as the technology develops.

In addition to privacy issues, the development of nanotechnology raises other ethical issues. Given that nanotechnology lends itself to a very broad range of applications, it will come as no surprise that it can be used for ethically undesirable or at least questionable purposes. In particular, it could be used to design weapons and military apparel ranging from highly protective armor to miniature nuclear bombs. Ominously, a sizable part of the US funding of the development of nanotechnology, emanating from the National Nanotechnology Initiative, goes toward the development of such military applications.

Another ethical issue worth mentioning is animal suffering in nano-experiments. In order to test the safety of nano-medicines, materials, and products, experiments are performed on animals. Given the rapidly increasing production and commercialization

of such medicines, materials, and products, animal testing is likely to go up. In an overview of such experiments, many were described as being "moderately to severely distressful to the animals" [19]. This raises an important ethical dilemma: how much – if any – animal suffering is justified for human benefits?

3.4.3 Solutions: Interdisciplinary debate, transparency, and democratic control

In order to avoid these societal woes and ensure that nanotechnology enhances the human condition, we need to reflect on its desired development. As pointed out above, with the power to transform our world, we must constantly ask ourselves what world we want to create. The development of nanotechnology applications should not be left to nano-scientists and engineers, let alone to industrial players responding to economic incentives. Social scientists and philosophers have an indispensable role to play in guiding the development of these disruptive technologies.

3.4.3.1 Interdisciplinary debate [3, 9]

Technological innovation and ethics are age-old allies. New technologies raise a host of important ethical issues such as the potential harm and the economic or social injustice they may cause. These risks and potential woes, of course, are no reason to dismiss the development of new technologies. Technological innovations are the drivers for the improvement of standards of living throughout history. We should not stop innovation – quite to the contrary! – but we should remain vigilant to the possible harm they may cause.

As pointed out, these ethical issues are prominent in the development of nanotechnology. This follows from the enormous potential impact of nanotechnology on the world we inhabit. Nanotechnology, some have argued, could hand us the power to radically reshape our world by modifying the very structure of natural materials. While this is still very speculative, we cannot exclude that it will one day be a feasible endeavor. So how are we to reshape our world? Or rather, how are we to decide how we are going to use these disruptive technological innovations?

We believe this crucial question calls for an ongoing debate bringing together experts from a broad range of fields. In particular, experts in the exact and applied sciences and experts in the social sciences (economists, sociologists, psychologists, anthropologists, etc.) and humanities (philosophers of science, ethicists, etc.) should join forces. We need platforms and think tanks that bring together nano-scientists and engineers, on the one hand, and social scientists and philosophers, on

the other hand. Their task is to give direction to development of future innovations and ensure that these developments benefit all stakeholders.

It is vital that these experts deliberate together. Too often today these two worlds remain isolated from each other. Nanoscientists and engineers work on advancing nanoscience and its applications and philosophers reflect on these developments from the sideline. This is problematic for two reasons. Firstly, the philosophical reflection often does not reach the scientists and engineers and so it misses its goal of steering the innovative developments in a desirable direction. Secondly, the philosophical reflection is somewhat disconnected and therefore poorly informed about what is actually happening in the lab. To remedy this, we should organize permanent interdisciplinary think tanks. Today, these are for the most part lacking. Finally, of course, in order to be effective, there must be proper channels through which these interdisciplinary deliberations are communicated to the policymakers (on the national and international levels) who make up the regulation.

But in addition to experts in a variety of fields, the world citizens themselves – the ultimate stakeholders – should have their say. Democratic control – or rather input by the stakeholders – is important for two reasons. Firstly, it gives the necessary legitimacy to the policy or regulation proposed in these think tanks and/or adopted by the governmental and supranational bodies (such as the EU and the UN – see above). Secondly, having the input of a diverse group of people is likely to lead to better policy [20, 21]. More on this important second point below.

For there to be efficient democratic control and input from the population, three conditions must be satisfied. Clear and objective information must reach the population. The population – or at least a representative sample of the population – must reflect on this information and on desirable policy. Finally, there must be proper channels so that their conclusions or views reach the policymakers.

3.4.3.2 Transparent information

The first condition (objective and clear information) requires a high degree of transparency from scientists, engineers, and other experts and industrial players involved. This is not always the case. The most important reason why information may be biased or withheld is a conflict of interest [10]. Such a conflict of interest may lead companies producing nanoproducts or applications to underplay the risks involved. The same goes for scientists and engineers who are on the payroll of these companies and policymakers who are funded or otherwise influenced by lobbying parties with a vested economic interest. In the past, parties with a conflict of interest have acted as "merchants of doubt" [22] to prevent precautionary measures against smoking, lead pollution, and environmental degradation.

We must therefore remain vigilant that industrial players and their spokespersons do not withhold or distort information about their products. Today, labeling

information on nanoproducts is often missing. This is problematic. The consumer has a right to know what products they are consuming, together with an objective estimation of the risks involved. This, of course, is no easy feat given the high degree of uncertainty that possible harm would occur (and calls – as pointed out above – for more research urgently). Nevertheless, the available information should be communicated in a transparent way.

3.4.3.3 Democratic control [10]

Democratic control can be exercised in different ways. While a lengthy discussion of democratic tools and institutions is beyond the scope of this chapter, we would like to bring a promising tool – that has been gaining momentum worldwide over the last decade – to attention, the so-called citizen councils.

Traditionally, national democracies are "representative" or "indirect," meaning that the decision-makers – the ones drafting policies and laws – are elected by (and represent) the people. The people exert control to the extent that they vote for those representatives or parties that propose policies that they (the people) believe are desirable. When they are disappointed in elected representatives, they can express this by not voting for them at the next election. This traditional democratic system has a lot of merit. It often leads to policy that is acceptable to the majority of the population. The condition of course for efficient democratic control is – as pointed out above – transparent information on policy proposals and the issues at stake.

Nevertheless, representative or indirect democracy has an import shortcoming. As Fishkin [23] has pointed out, it leads to "rational ignorance." When you have one vote in millions, you are not incentivized to take the trouble to inform yourself in-depth on the issues at stake and the policy proposals advanced by different politicians and/or parties to tackle these issues. This is especially relevant when it comes to complex matters such as policy regulating the development and commercialization of nanoproducts and applications.

A promising alternative democratic tool, in this context, are citizen councils [10, 23–25]. Such councils are composed of a representative sample of the population (often assembled by sortition). After being thoroughly informed by experts, they deliberate with the aim of reaching a high degree of consensus around certain policy proposals. Citizen councils have the added advantage that they can be organized on local, regional, national, supranational, and even global level. Given the importance of coordinating national policy when it comes to nanotechnology (see above), this is an important feature. Ideally, policy and democratic control would emanate from the global level. After all, we all have equal stakes in the development of nanotechnology.

An often-voiced criticism of citizen councils and other forms of direct democracy is that laypeople are not equipped to deal with complex issues. According to this

view, we should leave it up to experts. Social experiments with citizen deliberation, however, show that they often lead to thoughtful proposals even on complex issues [21]. In fact, research shows that a diverse lot of laypeople often outperforms a small group of experts. As Hong and Page [20] put it forcefully, "diversity trumps ability."

3.5 Conclusion

Mnyusiwalla and colleagues [9] claimed almost two decades ago that we must close the gap between the development of nanotechnology and the ethical reflection on its societal implications. Today, their call is more relevant than ever. Nanotechnology has the potential to revolutionize human life and so we must guide its development to ensure that it benefits all stakeholders. For this, we need sui generis regulation to protect human health and the environment – without robbing people of the many benefits these innovations bring [10] – and we need an ongoing debate between experts (from various fields) *and* between citizens guiding the policymakers.

In short, this debate should be:

- Critical: based on transparent information and expert estimations.
- Thoughtful: leading to creative solutions.
- Inclusive: including not only experts but also citizens and taking into account the interests of all stakeholders (both human and non-human, present and future generations).
- Respectful: admitting of divergent opinions and views, with the aim of reaching proposals that are widely accepted.

Given nanotechnology's extraordinary economic and societal potential, it would be unethical to attempt to halt its development. It holds the promise to substantially improving human (and non-human) well-being. But this progress and innovation must be thoughtful. As is the case for many breakthroughs in technology, we cannot exclude harmful applications. We must therefore proceed with caution, but proceed we must.

What is needed is an interdisciplinary field of "nano-ethics," together with transparent communication and democratic input. First steps have been taken, but more remains to be done. We cannot allow ethical reflection to lag behind technological development. It is our joint responsibility to make nanotechnology a force for good and create a better world.

Below, we end with a series of concrete *recommendations*:

1. Sui generis regulations of existing nanoproducts and applications should be drafted. These regulations should be internationally harmonized. More research should be done to have a better grasp of possible risks.

2. There needs to be transparent information on existing nanoproducts and applications. In particular, the labeling of nanoproducts should be accurate and clear.
3. The development of military applications of nanotechnology should be strictly limited to purposes of security and defense.
4. Interdisciplinary "nano-ethics" panels should be erected with the task to analyze present and future developments and formulate recommendations for the policymaker.
5. The next generation of scientists and engineers should be educated in the promises and perils of nanotechnology (and other promising disruptive technologies). A multidisciplinary training in "nano-ethics" at universities worldwide would contribute to this.
6. Institutions of democratic control of the development of nanoproducts and applications should be erected. Citizen councils are especially suited for this purpose.
7. There should be proper channels to connect the output of those interdisciplinary panels and the institutions of democratic control with the various national and supranational policymakers.
8. We must take particular care to protect economically disadvantaged states and people. They should not be the victim of developments in nanotechnology (either because they have no access to products and applications or because the development of these products and applications in developed countries hurts their economy). The development of nanotechnology should contribute to increasing social and economic justice.
9. The scientists and engineers at the cutting edge of research and development should be aware of their moral responsibility. They should communicate transparently about risks and benefits of existing products and about (the implications of) their latest findings and projects. This transparent information should be directed at other scientists, policymakers, and the public at large.

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4 The nanotechnology transition

Abstract: Nanosciences and nanotechnologies are concerned with the study, manufacture, and use of objects that have at least one dimension (1D) between 1 and 100 nm. Compared to objects on our scale, new physical phenomena can be observed at these dimensions because quantum effects can appear. It turns out that particles can behave like corpuscles or waves depending on the conditions. This leads to unexpected effects (quantum effects) such as the existence of discrete energy levels in atoms or molecules, particle tunneling through a potential barrier, and the existence of spin which is an intrinsic property of particles allowing to classify them into bosons or fermions that obey different quantum statistics (Bose–Einstein and Fermi–Dirac). We briefly introduce this new physics that is useful to understand what happens at the nanoscale because classical mechanics is not always applicable, and it is often necessary to use quantum mechanics. Nanomaterials are essential to many applications; we present, as an illustration, the new forms of carbon that have outstanding physical and chemical properties. Ethics is an important aspect that must be taken into account when developing nanotechnology applications. We discuss the difference betweendogmatic ethics, which slows down progress, and pragmatic ethics, which takes advantage of this new technology to increase the well-being of populations while being careful of unnecessary excess. We examine a few areas where nanotechnology plays an important role: health care, information technology, defense and security, and nanotoxicity. We discuss the fact that most of the progress done to protect citizens against various threats can also be used to spy, monitor, and control them. This is clearly a critical issue that has to be thoroughly considered in democratic countries.

Keywords: nanotechnology, nanomaterials, quantum effects, dogmatic ethic, pragmatic ethic, health, defense, security, nanotoxicity

4.1 Introduction

Depending on the person and also on the applications, nanotechnology can be considered a source of good or bad. But this is also true for any technology. However, we must remember that the world is neither white nor black. The advantages and disadvantages of applying nanotechnologies must be assessed. If we find that the advantages far outweigh the disadvantages, we can use this application as long as other criteria are met (economic, environmental, safety, etc.).

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This chapter is a short introduction to nanotechnology [1–4]. A few areas are briefly discussed as they relate more specifically to ethical and safety issues. These subjects will be fully developed in the rest of this book by several authors.

4.2 Size domain

By convention, the nanotechnology field concerns the manufacture or manipulation of objects with at least one of the dimensions between 1 and 100 nm. One nanometer (1 nm) is an exceedingly small distance since it corresponds to one billionth of a meter or one millionth of a millimeter. To figure out what a factor of a billion represents in everyday life, compare the case of one person who has $1 on his bank account and another who has $1 billion!

Let us see how the size of a few living or inert objects is relative to the range of lengths included in 1 and 100 nm. About 1 nm is typically the length of 7 touching gold atoms placed in line. The diameter of a strand of human DNA molecule is about 2.5 nm. The average diameter of coronaviruses (among them the SARS-CoV-2 that we face and that leads to the Covid-19 disease) is about 125 nm. Other viruses have typically a size of 200 nm. These are visible under the electronic microscope. Bacteria have, in the average, a size in the range of 3,000–4,000 nm. They are visible under the light microscope. A red blood cell has a size even larger, about 7,000 nm. The diameter of a human hair, which can be seen with the naked eye, is in the range of 80,000–100,000 nm.

4.3 Nanoscience and nanotechnology

Nanoscience is studying the properties and structure of materials and objects that have at least one of their dimensions in the range 1–100 nm. Nanoscience tries to understand the basic mechanisms, find theoretical explanations, and develop models. Nanotechnology deals with the practical techniques to design and manufacture objects and nanomaterials at the nanoscale to get new applications and devices.

Roughly speaking, the measurement of the properties of a quantum dot and the calculation of the energy levels is relevant to nanoscience while the manufacturing of gold nanoparticles where a drug has been grafted to the surface in order to treat cancer is more a concern to nanotechnology.

4.4 Nanotechnology is already widely used

Microelectronics is a domain of utmost economic importance. Microprocessors are present in many daily devices, and memories are more and more necessary for large-scale data storage. This is illustrated by the fact that more transistors are produced every year than rice grains are harvested in the world.

Figure 4.1 shows the evolution of the technology node in the semiconductor industry as a function of time. The technology node refers to a semiconductor manufacturing process and is related to the smaller feature size that can be etched on a silicon wafer. The smaller the feature size, the more transistors you can put on the wafer allowing to manufacture increasingly powerful microprocessors. Another advantage is that the energy consumption of the microprocessor decreases for a same information treatment power. However, it is also more difficult to evacuate the amount of heat produced because the heat density produced becomes large as the size of the transistors become small. In the figure, we see that the limit of 100 nm has been reached at the beginning of the century and that this field has entered the nanotechnology area.

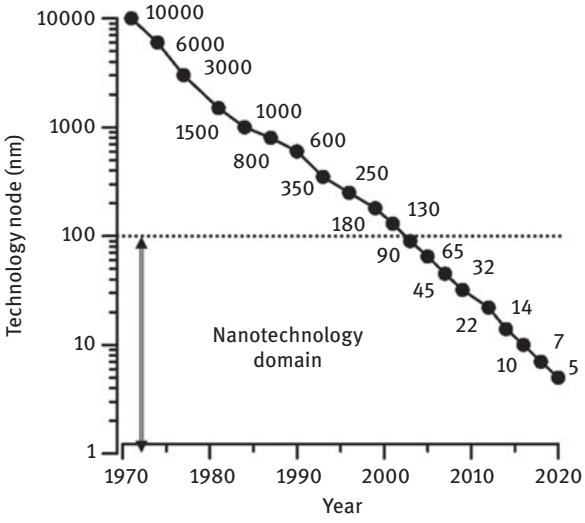

Figure 4.1: Evolution of the technology node in microelectronics as a function of time. Data from Wikipedia.

4.5 We can “see” and move atoms

In order to work at the nanoscale, it is necessary to have instruments allowing observe samples with accuracy better than the nanometer. An important breakthrough in the domain of observation was made by Gerd Binnig and Heinrich Rohrer who invented, in 1981, the *scanning tunneling microscope* (STM). They were working at the IBM-Zurich in Switzerland and received the Nobel Prize in Physics in 1986 for this achievement. The STM is based on the tunneling effect and allow to “see” individual atoms after a proper information treatment. With this device it is not only possible to see atoms, but it is possible to move them from one place to another on the material provided it is a conductive or a semiconductive material. In 1986, the atomic force microscope, invented by Gerd Binnig, Christoph Gerber, and Calvin Quate, was able to work on insulating surfaces too.

The ability to see details at the nanoscale is essential to develop nanotechnology applications. It also allows to understand the basic mechanisms taking place in the nanosized range.

4.6 Our macroscopic world

The macroscopic or classical world is the world in which we are living. We are surrounded by objects that we can see, touch, move, and so on. Classical physics has been developed to understand and describe this world. In the classical world, we have *particles* that have a mass and their energy is localized in space. A molecule of dioxygen is an example of a particle. We have to deal also with waves which, on the contrary, have energy delocalized in space. Visible light or radio waves are examples of waves.

The motion of a macroscopic object such as a coin, a car, or a planet can be described using classical mechanics. A classical particle is determined by its position (three components in our space) and its velocity (also three components). Classical mechanics says that if we know the initial position and velocity of a particle and the field of forces that operates on it, it is possible to calculate its dynamical evolution as a function of time (trajectory). Classical mechanics is a deterministic theory. It turns out that most of the classical variables such as the velocity, the energy, or the temperature to only cite a few, are continuous variables. For example, we can vary the speed of a vehicle from zero to its maximum value. When we drive from one point to another, the distance from the start varies also in a continuous manner.

Waves have a different behavior. They are described by a wave equation, which is the solution of a partial differential equation with boundary conditions. An important consequence of that is that the macroscopic variables are not always continuous. For example, the sound waves generated by the vibration of a

guitar string are periodic and depend on the nature and the length of the string. Only one frequency, which means one energy, and its harmonics are generated, and we have not all sound frequencies (white noise).

4.7 The microscopic world

Matter is made of atoms. It can be single atoms, or they can be arranged in molecules. It turns out that it is impossible to understand and describe atoms or molecules using classical concepts only. It has been necessary to introduce a new theory to do so: quantum mechanics. Quantum mechanics is the appropriate theory to describe the microscopic world, that is, typically in a dimension range of 1 nm and below. An atom is made of electrons and a nucleus. Quantum mechanics is necessary to describe both atomic and nuclear physics.

A classical particle is determined by its position in space and velocity vector. During its evolution under a field force, the particle follows a trajectory. In quantum mechanics, the notion of trajectory breaks down. All the information on the particle is contained in its wave function, which is the solution of a partial differential equation with boundary conditions: the Schrödinger equation. Because of the mathematical form of the Schrödinger equation, several quantities such as the energy of an atom, for example, are not continuous but discrete. One says that the energy levels of the atom are quantized.

An important consequence of quantum mechanics concerns the issue of measurement. In classical mechanics, it is possible to measure simultaneously the position and the velocity of a particle with a precision that is only limited by the measuring tool. This is not the case in the microscopic world where quantum mechanics must be used. While a classical measurement is deterministic, it is probabilistic in quantum mechanics. If we measure the position of a particle, we can just give the probability that it is at a given position. Furthermore, it turns out that it is not possible to measure simultaneously the position and the velocity of a particle with an infinite accuracy. This is known as the *Heisenberg uncertainty principle*.

4.8 Fermions and bosons

Matter is made of atoms and molecules, which are in turn made of electrons and nucleons. Although they are not (because they are made of quarks) nucleons can be considered as elementary at the level of atoms. A particle has spatial degrees of freedom corresponding to its position but also intrinsic degrees of freedom, which are independent of its spatial position. The *spin* is such an intrinsic degree of freedom. It behaves like an angular momentum and can only take discrete values in

units of $\hbar$. All particles existing in nature have a spin. In units of $\hbar$, it can be either an integral spin (0, 1, 2, . . .) or a half-integral spin (1/2, 3/2, 5/2, . . .). Particles with an integral spin are called *bosons*, while particles with a half-integral spin are called *fermions*.

An electron, for example, has a spin $S = 1/2\ \hbar$. It is a vector. Since it behaves like an angular momentum, the projection of the spin on an axis, the z-axis for example, can only take two values: $S_z = -1/2\ \hbar$ and $S_z = +1/2\ \hbar$. These projections are often referred to as *down* and *up* in atomic physics.

Photons have a spin $s = 1\hbar$. In principle, there should be three projections on the z-axis. However, because the speed of the photon is always equal to the light velocity in any frame of reference relativity theory predicts that we can only observe two projections in the real world: $S_z = \pm 1\hbar$. They correspond to the two states of the polarization of light. However, the third projection $S_z = 0\hbar$ corresponds to virtual photons, those that are exchanged in the electromagnetic interaction.

At the microscopic level, particles are indistinguishable. Depending on the nature of the particles, *fermions* or *bosons*, an assembly of particles behaves differently. Fermions obey the *Fermi–Dirac statistics*, which states that two particles cannot be in the same quantum state (*Pauli's principle*). Bosons obey the Bose–Einstein statistics, which states that as many particles as we want can be in the same quantum state.

4.9 Wave–particle duality

In the macroscopic world, there are particles and waves. A particle always behaves like a particle and a wave behaves always as a wave. At the microscopic level, things are different. A particle can behave under some conditions as a wave. For example, electrons or neutrons behave as a wave if they have the proper kinetic energy and diffract on a crystal. You can also observe interferences in a young experiment, a typical behavior for a wave.

Waves can also, under certain conditions, behave as a particle. This is the case in the Compton or photoelectric effects. Compton effect occurs in gamma detectors used in medical imaging measurements, for example. The photoelectric effect is the basic mechanism used to produce electricity from sunlight in photovoltaic cells.

The French physicist Louis de Broglie was the first to point out the duality between waves and particles. According to this hypothesis, a wave is associated with each particle and the corresponding wavelength is known as the *de Broglie wavelength*. Louis de Broglie was awarded the Nobel Prize in 1929 for his discovery of the "*wave nature of electrons*."

4.10 Quantum tunneling

If a classical particle impinges on a potential barrier, it bounces back but does not go through it. It can only pass to the other side if its kinetic energy is larger than the top of the potential barrier. If the kinetic energy is smaller than the top of the barrier, a particle cannot penetrate it and the barrier region is forbidden to the particle.

However, we know that a classical wave can partially go through the potential barrier even if it has energy below the top of the barrier. In the forbidden region, an evanescent wave is formed with a decaying intensity. If the potential barrier is not too thick, a wave with a smaller amplitude emerges from the other side of the barrier. This effect is called tunneling and is observed, for example, with microwaves.

At the microscopic level, a particle can behave as a particle or a wave depending on the conditions. Therefore, tunneling can also be observed if certain conditions are fulfilled. Consequently, there is a certain probability that a particle tunnel through a potential barrier. This has been observed experimentally for particles such as electrons, protons, or neutrons, for example. The wave–particle duality leads to quantum tunneling. This phenomenon is the basic mechanism used in the STM that allows to see and move atoms on a surface.

The probability that a particle tunnel through a potential barrier depends on the kinetic energy of the particle compared with the height of the barrier and on the thickness of the barrier. It is easier to tunnel through a barrier if the kinetic energy of the particle is close to the top of the potential barrier. The tunneling probability also increases as the width of the barrier decreases.

4.11 Surface versus volume effects

Any object has a volume and a surface. It is made of materials. If the object is of macroscopic scale, the bulk properties of the materials are often those that play the major role in the properties of the object. It turns out that, as the size of the object decreases, surface effects become more and more important compared to volume effects. For example, it is difficult to burn a lump of aluminum. However, if the lump of aluminum is ground into a small powder, it burns easily.

To back this up, consider a small cube with a side of 1 cm. The volume of the cube is 1 cm^3 and the surface area is equal to 6 cm^2. If we cut this cube into nanocubes with a side of 1 nm, we get 10^{21} nanocubes. The total volume of material remains the same, but the total area is now equal to 6,000 m^2. By doing this operation, the ratio between the surface and the volume has increased by a factor 10^7. Therefore, surface effects become predominant.

The main point to remember is that, at the nanoscale, surface effects can become dominant over volume effects. This amplifies the reactivity.

4.12 Nanomaterials

All objects are made of materials. Materials play a key role in the development of society. Indeed, as said by E. Kobayashi, from Panasonic, "those who control materials control technology." For an industry, mastering new materials gives a clear advantage over its competitors.

Nanomaterials are an essential part in the development of nanotechnology. There are two ways to classify them.

The first classification focuses attention on the external dimensions of the object. If one of the dimension (1D) is smaller than 100 nm, it is considered that we have to deal with a 1D nanomaterial. This is the case of ultrathin films that have a thickness smaller than 100 nm. A two-dimensional (2D) nanomaterial is one in which two dimensions are smaller than 100 nm. It is the case of carbon nanotubes, for example. If we have an object with three dimensions (3D) that are smaller than 100 nm, we have a 3D nanomaterial. Nanoparticles belong to this category.

A second classification focuses attention on the dimensions of the nanostructures that are embedded within a macroscopic object. It considers that a dimension that is smaller than 100 nm is not relevant. Therefore, a nanoparticle is a 0D object, while a carbon nanotube is a 1D object because it has only 1D that is larger than 100 nm. An ultrathin film is, in this classification, a 2D material. A macroscopic material containing no nanostructures is just a 3D material.

4.13 Natural nanomaterials

Nature has made nanomaterials for specific applications. A natural nanomaterial is a nanomaterial belonging to the mineral or living world for which no human modification or processing has been made. Man tries to mimic natural nanomaterials to develop artificial nanomaterials with the same properties. There are many examples of natural nanomaterials. For example:

- Lotus flower leaves have self-cleaning property. Nanomaterials have been developed to mimic this property to manufacture surfaces that remain clean and dry. This is the case of self-cleaning windows or waterproof clothes.
- The gecko is a small lizard which can cling to any surface at any orientation. It can do that on almost any surface (smooth, rough, wet, dirty, etc.). To achieve that, there is a strong adhesion to the surface due to many tiny hairs located on the sole of the feet of the gecko. The interesting thing is that the adhesive mechanism is

reversible, and this is the reason why the gecko can walk on the surface. An application using nanotechnology to mimic this mechanism is a reversible surgical Band-Aid that can stick on the skin of a patient and can be removed without pain.
- The silk of a spider web is also a natural material. It has a strength of about 5 times greater than that of steel and can be stretched up to 10 times its initial length. Developing nanomaterials that mimic the silk of a spider web has potential applications in several fields (sport equipment, automobile, aeronautics, defense, etc.).

Because of their high performance in the applications where they are used, natural nanomaterials are a good model to develop artificial nanomaterials with outstanding properties.

4.14 When should we develop nanotechnology?

It is not because a new technology is available that it is worth developing applications based on it. Using a new technology is only interesting if:
- it offers new possibilities;
- it decreases the cost of an application compared to the use of an existing technology; and
- it improves the possibilities of an existing technology at the same cost or at a reasonable increase of the cost.

The appearance of new possibilities is of course more appealing, but the two other points should not be neglected as well.

4.15 Top-down and bottom-up approaches

There are two ways to build nanostructures or nanomaterials: the *top-down* approach or the *bottom-up* approach.

In the top-down approach, a nanostructure is built by removing matter from a bulk material and adding extra material at some step of the manufacturing. To take an analogy, this is the way followed to carve a figurine from a block of marble or granite. When the figurine is finished, some part of its surface can be covered with gold leaf, for example. The top-down approach is the natural evolution of macroscopic manufacturing aiming to manufacture smaller and smaller objects.

In the bottom-up approach, the idea is to build a nanostructure starting from atoms and molecules and organizing them. This is the way followed by nature to build complex structures. The problem in this approach is that the number of atoms and molecules contained in a nanostructure is large and it would take too much

time if the organization of the constituents is done one by one. Fortunately, self-organization processes can be used to do that.

4.16 Carbon: A major material

The chemistry of carbon compounds is dominated by organic chemistry. Organic compounds have a huge importance in the living world and inert objects or materials surrounding us. Until 1985, only three crystalline forms of carbon were known: graphite, diamond, and lonsdaleite (a diamond with a hexagonal lattice rather than a cubic lattice).

In 1985, R. Curl, H. Kroto, and R. Smalley found a new crystalline form of carbon: *fullerenes*. The smaller member of this family is the buckyball or buckerminsterfullerene (C_{60}) which is a hollow molecule containing 60 atoms of carbon arranged according to a shape similar to a soccer ball with 20 hexagons and 12 pentagons at the surface. It is a truncated icosahedron. C_{60} is the first member of molecules called fullerene made of carbon atoms only. They all have a hollow shape (sphere, ellipsoid, tube) and an even number of carbon atoms (C_{60}, C_{70}, C_{76}, C_{78}, C_{84}, C_{60}, . . .). The scientists received the Nobel Prize in Chemistry in 1996 for this important discovery.

In 1991, S. Iijima discovered nanotubes of carbons which are cylindrical tubes with a few nanometers wide and length ranging from below the micrometer to several millimeters. They can belong to two different families: single-walled carbon nanotubes and multiwalled carbon nanotubes, which are made up of several concentric single-walled nanotubes. The end of the nanotube can be open or closed.

In 2004, A. Geim and his collaborators isolated a new allotrope of carbon: *graphene*. It is a monolayer of carbon atoms packed in a honeycomb lattice. K. Novoselov and his collaborators first manufactured graphene by peeling a graphite crystal with an adhesive tape. A. Geim and K. Novoselov received the Nobel Prize in Physics in 2010 for "groundbreaking experiments regarding the two-dimensional material graphene."

Formally, carbon nanotubes can be considered as one or more sheets of graphene that are rolled up in concentric cylinders.

4.17 Ethics

Ethics is a philosophical concept linked to morality. The latter may differ in certain respects from one civilization to another. It is basically the question of estimating what is good or bad. At the professional level, an ethical approach makes it possible to define a code of good behavior in the moral sense of the word. For an individual, it is a set of moral principles governing his behavior. For a technology, an ethical approach ensures that it does improve human condition and does not harm the people.

The purpose of ethics is to indicate how human beings should behave and act among themselves and with the surrounding environment. Ethics must guide human action to decide when the individual or society is faced with a conflict of values.

An ethical approach consists in thinking about the values that are guiding and motivating the action that one carries out in a particular field. It is not a question of science but of evaluating whether the technologies developed are useful or not to society. It is about weighting the pros (that are useful for the society) and cons of a technology or an application. Indeed, each application of a technology can be used to do good or bad. There is no technology or application that does only good or bad.

An ethical approach is based on the conception that a society can have of the good and of what is right, which makes it possible to improve the human condition. There are ethical issues in any new scientific discovery. This is also the case as far as nanotechnology is concerned. Some people find great advantages in the applications while other people focus on the potential dangers.

4.17.1 Dogmatic ethics versus pragmatic ethics

The German economist and sociologist Max Weber (1864–1920) distinguished between two types of ethics: the ethics of conviction and that of responsibility. In the ethics of conviction, it is a question of forbidding or imposing something without worrying about the consequences. The ethics of responsibility is on the contrary to consider the consequences of a choice.

Today, we could rather speak of *dogmatic ethics* and *pragmatic ethics*. The dogmatic ethic wants to ban some technology on scientifically unfounded arguments. The pragmatic ethic is based on a general framework taking care of the morality of the civil society concerned but, when one has to choose between several solutions, the one which is really feasible is chosen, thereby a technology that is irreplaceable at the present knowledge is not banned (Figure 4.2).

We can illustrate the problem of a dogmatic ethic on two examples in the electricity production domain.

The fight against climate change has become a global goal. We must reduce our CO_2 emissions, which can be done in the electricity supply domain by reducing our consumption of fossil fuels. Many states like Germany or California want to do that while banning nuclear energy and developing intermittent renewable energies (wind and solar photovoltaic). Accordingly, they have shut down some nuclear plants or planned to do so. It is a dogma since a nuclear plant does not emit CO_2 in operation. The problem is that wind and solar photovoltaic are intermittent energies. When there is no wind or no sun, or when these resources are too low, it is necessary to quickly start coal or gas plants to supply electricity to the consumers. These fossil fuel plants emit CO_2. The consequence of replacing a nuclear plan by windmills and photovoltaic panels is to increase CO_2 emissions, which is contrary to the initial objective. To solve

this problem, Germany is building new coal fire plants and relies heavily on the importation of electricity from the neighboring countries.

In August 2020, in California, the weather was very hot but there was no wind. Air conditioning was needed at these temperatures and required electricity to operate. The Sun could provide it in the middle of the day, but it declined afterward and set around 7 pm when the inhabitants still needed electricity to power their air conditioners. Despite the start-up of gas-fired power stations (which emit CO_2), production was not sufficient and electricity cuts were necessary. As neighboring states also needed electricity, California could not import. The application of dogmatic ethics (reduction and shutdown of nuclear power plants) has led to this situation as well as a sharp increase in the price of electricity and an increase in CO_2 emissions.

There are currently movements against nanotechnology. Before banning these as part of a dogmatic ethic, it would be good to study, depending on the fields involved, whether the advantages do not greatly outweigh the disadvantages.

4.18 Health

People are living longer today than a century ago. For example, in France the life expectancy which was about 50 years in 1900 has now reached more than 80 years in average (men and women). The increase in living standards, the development of hygiene, prevention, and the existence of increasingly efficient health care, thanks to technology that has played a major role in increasing the life expectancy of people. While it is important to increase life expectancy, it is even more important to increase life expectancy while staying healthy. Nanotechnology can provide pertinent answers in the health-care domain.

Health care can be summarized in a simple way as *test*, *treat*, and *repair*.

Test corresponds to the *diagnostics* domain. The trend is to use more and more noninvasive or minimally invasive techniques to get information about the human body (analysis and imaging). This includes biological, physical, and chemical analyses, and imaging techniques.

Treat consists of treating the patient's symptoms with medication (therapeutics). It is important to deliver the right quantity of a drug at the right place and at right time while minimizing side effects.

Repair: because people are living longer and longer, and parts of their body get damaged or no longer function properly. Accidents can also lead to significant damage or irreversible injury. Surgery, implants, grafts, and regenerative medicine are then particularly useful in treating patients.

Nanotechnology can provide solutions in these three areas. For example, in the diagnostics area, nanoparticles can be efficient imaging agents. Gold nanoparticles are used to detect colorectal cancer, iron oxide nanoparticles coated with dextran

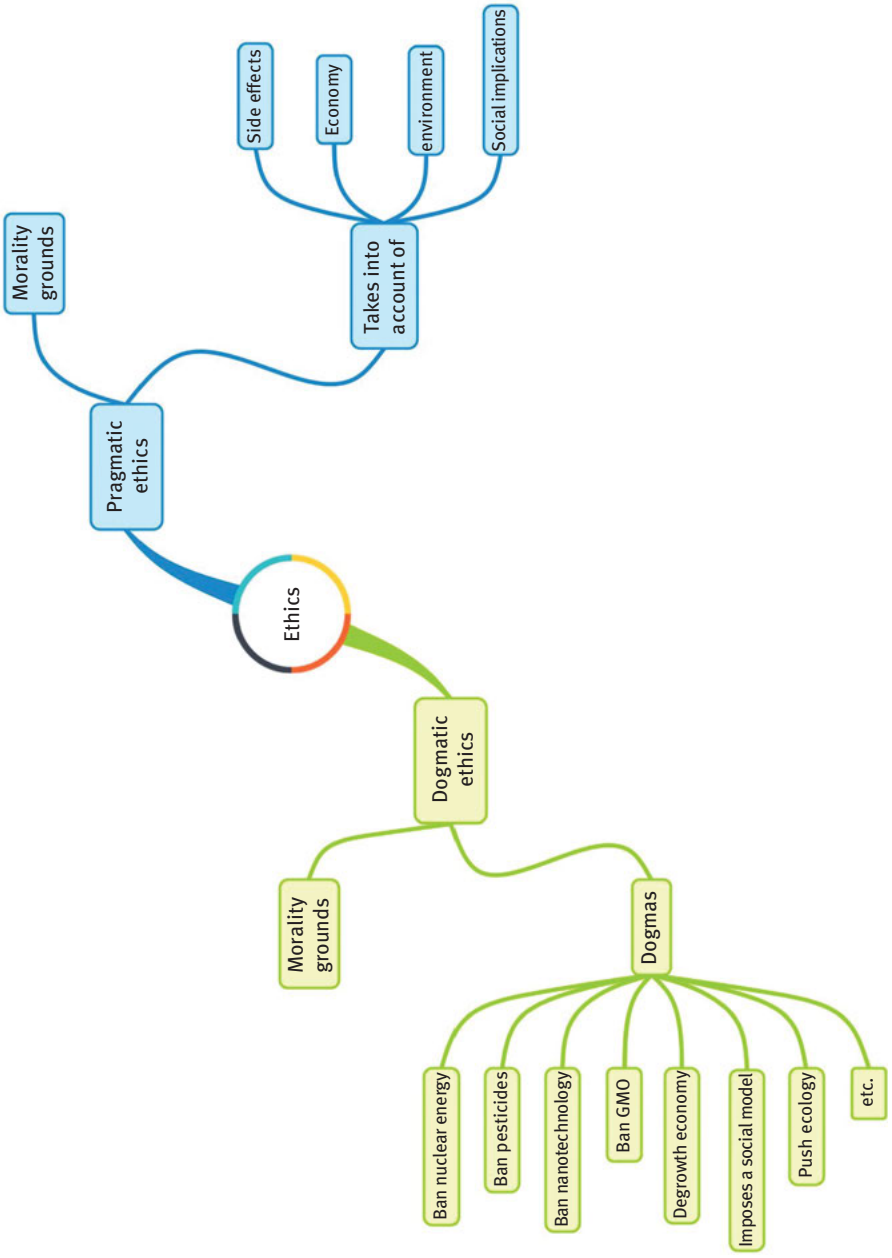

Figure 4.2: This mind map tries to represent the difference between pragmatic and dogmatic ethics. Some of the dogmas are indicated but they all are not applied necessarily at the same time.

can target lymph nodes, and so on. Nanotechnology is also involved in biochips, lab on chips, and cell on chips.

Nanotechnology provides more efficient targeted delivery and gives the ability to reduce drug quantities while getting the same or better results. Nanoparticles can be functionalized with drugs or encapsulate drugs that can be delivered on demand, thanks to an external signal. Nanotechnology contributes to develop dedicated treatments and pave the way to personalized medicine.

Regenerative medicine is a part of health care that is in full development. It concerns people born with serious deficiencies, accidents leading to serious damage of the body, diseases such as cancer leading to important bodily damage such as the removal of a breast in breast cancer, aging populations with parts of their body becoming less and less efficient or inefficient, and so on.

Besides these positive effects, there can be a temptation to misuse the possibilities given by nanotechnology to medical applications that are not in agreement with ethics. For example, the use of drugs for illegal applications (drug addiction), the use of plastic surgery to change the physical appearance of criminals, the cloning of individuals, and so on, it is also an ethical problem to restrict health care for financial reasons.

4.19 From microelectronics to nanoelectronics and molecular electronics

We have already quoted the fact that microelectronics is now developing components that have some of their dimensions in the nanometer range. This concerns in particular microprocessors and memories. The driving force of the evolution of microelectronics is *smaller*, *faster*, and *cheaper*. Using lithography in the range of 1–100 nm to manufacture components is therefore a natural evolution of microelectronics.

Reducing the size of the components can change the properties of the objects because quantum effects appear. In this case, they do not provide the same functionalities for which they were initially designed.

It is also possible to develop quantum circuits in their own right. This is the area of nanoelectronics. One of the goals is to develop single electron transistors. Because the thermal noise can be large at room temperature compared with the signals generated or required by the single electron transistor, it is necessary to operate at extremely low temperature. The mechanism of *coulomb blockade*, which is a pure quantum effect, gives the ability to precisely control the flow of a single electron.

Quantum dots can now be manufactured with a specified size. The energy levels of a quantum dot are quantized, and the energy-level separation is inversely proportional to the size of the dot. Since this energy difference is related to the wavelength of electromagnetic radiation, a quantum dot can absorb or emit light at a wavelength

that depends upon the size of the dot. Therefore, it is possible to design quantum dots emitting or absorbing light at a given wavelength. This tunability gives the ability to adapt this technology to a wide variety of applications.

In conventional electronic devices, the transport of electrons and holes is creating a current that is used to treat digital information. The use of the spin of the electron, which is a quantum property of this particle, and its charge opens a new area: *spintronics* or *spin electronics*. The *giant magnetoresistance*(GMR) discovered in 1988 by A. Fert in France and P. Grünberg in Germany, who were awarded the 2007 Nobel Prize for this discovery, is based on a stack of materials of nanometer range thickness. The stack contains alternating nonmagnetic and ferromagnetic layers. The electrical resistance of the device strongly depends on the orientation of the relative magnetization in the ferromagnetic layers. Memory storage and magnetic field sensors are examples of applications of the GMR.

Although the wavelengths of visible light are in the range of 380–780 nm, it is possible to control light by physical properties or chemical properties of nanostructures or by their spatial structure. This corresponds to the field of *nanophotonics*. Nanotechnology is concerned by antireflection coatings, Bragg mirrors, and so on. Quantum well lasers have also been developed for more than 40 years. We can also quote photonic crystals that are artificial periodic nanostructures creating a periodic dielectric function. This creates a photonic band gap, which means that only a range of wavelengths can be transmitted by the medium. Bragg gratings are an example of a 1D photonic structure. They can be used to check the structural stability in dams.

So far, we have described devices that can be manufactured using a top-down approach. Another possibility is to build nanoscale devices using a bottom-up approach starting initially from atoms and molecules. This corresponds to *molecular electronics*. It is of course impossible to do that by manipulating single atoms or molecules because it would require a tremendous amount of time since a nanodevice is made up of an exceptionally large number of elementary constituents. However, it can be done for systems containing a small number of atoms or molecules. It is, for example, possible to build a molecular wire using an organic conjugated molecule. In this case, the π-electrons are delocalized over the whole chain. A molecular diode can be made by associating a conjugated molecule that is a donor of electrons, a molecule containing σ-electrons only, playing the role of a spacer, and a conjugated molecule that is acceptor of electrons. One of the difficulties of such elementary components is to establish electrical contacts with the molecule.

Conductive polymers are usually easy and cheap to manufacture. While conventional polymers are good insulators of electricity, conjugated polymers are conductive when they are partially oxidized or reduced by doping. Polyacetylene was the first conductive polymer synthesized and investigated by A. J. Heeger, A. MacDiarmid, and H. Shirakawa in 1977. They were awarded the Nobel Prize in Chemistry in 2000 for this discovery. Polyacetylene is an intrinsically conducting polymer and its electrical conductivity is increased by a factor of 10^8 by oxidative doping with iodine. They

have several potential and real applications such as organic photovoltaic panels, biochemical sensors, organic LEDs, and electrochemical capacitors.

A bottom-up approach can be used if a self-organization of the molecules is possible. This is the case with Langmuir–Blodgett films or self-assembled monolayers. Self-organized methods are necessary to build nanoscale devices from a large number of molecules at a reasonable rate.

The goal of microelectronics, nanoelectronics, and molecular electronics is to build powerful and cheap devices to treat information. A very large number of applications are possible. The question of ethics comes into play when choosing the application.

Using information technology for facial recognition, for example, poses an ethical problem. It can be used not only to search for criminals or terrorists but also to monitor individuals who have nothing to be blamed for. The line between the search for criminal activity and mass surveillance is not easy to define. Abuse and misappropriation of information are possible, which can harm individuals. All this requires in-depth reflections to separate what concerns the protection and spying individuals. Indeed, it is impossible to guarantee that information obtained on a citizen will not one day be divulged or hacked. This can be for advertising purposes but also to classify individuals into categories that will allow the state to act against some of these categories in the future. It is certainly dangerous that in the long term everything about you is known, such as tastes, habits, purchases, trips, and relationships, and this is often better than yourself. Indeed, you certainly do not remember that you were buying an item 2 years ago at 2 pm in a shop located at 50 km from your home.

The recording, storage, and use of this information for purposes other than the search for criminals are against individual freedom. This surveillance is more and more possible and easy, thanks to more and more efficient information processing systems, smaller and smaller electronic components, and to the collapse of their cost. Nanotechnologies are fully contributing to this evolution. While a million transistors were worth the price of a house in the 1970s, it dropped down to the price of a sheet of post-it 30 years later and is worth even less today.

As the recording information, its storage, and processing are an irreversible development, it is important that ethical questions are addressed in this area and try to define what is positive or negative regarding individual freedoms.

4.20 Defense and security

Defense and security of a country and its population are of great importance. These activities are ensured by both the military and the civilian security forces. Defense and security encompass anticipation, detection, and response to threats to the country and to its citizen. Defense equipment is becoming more and more technological, and information and communication systems play a more and more important role in this area.

However, the means to ensure the safety of citizens can also be used to suppress movements frowned upon by the government or to help it stay in power. The question of ethics is then of little weight compared to the interests involved.

Nanotechnology contributes to the defense and security area either by improving existing technologies or by introducing new ones. The main areas of nanotechnology that can be used for defense are information and communication systems, energy, material science and manufacturing, mobility, weapons, and life science.

The current trend is a dual use of technologies which can therefore be used both in the civilian and military fields. In the past, the military field was able to develop its own technologies. But these quickly became obsolete and their maintenance in the future uncertain, all at an extremely high cost. On the contrary, the civilian sector is developing very rapidly, thanks to a much larger market. Technological developments are faster and cheaper. Some of the components can then be used in the military field at much lower cost. It is also possible to select among the civilian components, those which have the best quality.

Homeland security is becoming an increasingly important concern for the population. Terrorist attacks are difficult to defend against. Anticipating, preventing, and dealing with these threats are not an easy matter. The different steps to deal with terrorist attacks are:

- Anticipating an attack requires fast information and data processing systems to extract weak signals related to a threat. At this stage, nanotechnologies contribute on several levels as we have seen above. However, the technology is far from being sufficient and must be supplemented by human intelligence resources, which also rely on miniaturized systems (some of which use nanotechnologies) to obtain information.
- Detection is essential to prevention. Sensors and analytical detection techniques are needed to detect explosive, chemical, biological, radiological, and nuclear threats that are prepared. Nanoparticles and nanomaterials are already available for sensors to detect toxins and biological agents.
- Protecting people, infrastructure, and equipment during and after an attack requires several varieties of measures to be taken. Proper clothing might be required in case of a biological, chemical, or radiological attack. These protective clothes should be lightweight, durable, and at a reasonable cost. Nanocomposites can be useful to meet this demand. Incorporation of nanomaterials, nanotubes, or inorganic fullerenes in concrete or steel alloys can reinforce their structure against ballistic objects, explosions, or earthquakes. Nanocoating can also be used for surface protection and improve the fire resistance of the bulk material. An electromagnetic attack can destroy information systems, electronics, communication systems, and so on. An electromagnetic shielding can prevent that, and conductive polymers can be used.
- After an attack, it is necessary to identify the authors, capture, or neutralize them. Identification systems are based on fingerprints, DNA, iris, facial identification, and

so on. A number of identification techniques rely on nanotechnology which can improve the identification method or provide new possibilities of identification. Nanotechnology will also be useful in forensic analysis of evidence.
– After a terrorist attack or a natural disaster such as fires, floods, cyclones, typhoons, tornados, earthquakes, or meteorite fall, repairs must be made. Decontamination might be necessary in biological, chemical, or radiological attacks. Nanoparticles and nanomaterials can be used as decontamination agents.

Ethics comes into play in the use of the applications to homeland security. Most of the tools developed can also be used to spy on and control an ordinary citizen who has nothing to be blamed. These technologies, which can include nanotechnology components, can be used not only against terrorists but also against any person who represents a danger to the government. In a democratic country, these diversions of the initial goal can be partially prevented by representative bodies of civil society. However, in authoritarian regimes, they can be fully exploited by government to control people and reduce liberties. With the Covid-19 pandemic, we have an illustration of the use of these technologies in several democratic countries to reduce the freedom of citizens.

4.21 Nanotoxicity

Nanoparticles and nanomaterials are now used in many applications. The materials involved have often a much larger reactivity at the nanoscale than at macroscopic scale because they have a much larger surface of interaction. The question of the toxicity of materials is therefore an important issue for the consumer and the manufacturer.

It is worth making a difference between the notions of *hazard* and *risk*. A hazard is a potential source of damage to a person, people, an equipment, or an organization. Climbing is a dangerous sport but if you do not practice it there is no risk of a climbing accident. A risk is a real damage that you could encounter if you are exposed to a hazard. For example, if you practice climbing, you have some probability to get an accident. We speak most of the time of probability because the risk is often uncertain. Efforts should be done to reduce the risk, but zero risk does not exist. Furthermore, even doing nothing is often dangerous. The advantages and disadvantages of a given application should be evaluated before using this application at large scale.

There are naturally occurring nanoparticles produced by forest fires, volcanic eruptions, dust storms, and so on. In high concentration, these nanoparticles can induce serious health problems. These nanoparticles can travel far away and can be found in each breath we take and in the drinking water. Other less violent natural processes can produce nanoparticles. Most of these natural nanoparticles have a low human toxicity at low concentration.

We have to face anthropogenic nanoparticles that are produced as a side effect of human activities (exhaust pipes from diesel vehicles, smoke from cigarettes, emissions from coal-fired plants, etc.). They can significantly increase the risk of cardiovascular events.

Engineered nanoparticles are produced on purpose: thousand tons of titanium dioxide, silica, black carbon, and so on, hundreds of tons of nanoparticles of metal, carbon nanotubes, and others. Unlike anthropogenic nanoparticles, engineered nanoparticles are designed to remain stable and not aggregate into larger particles. Cosmetics is an area where engineered nanoparticles are often used.

The main problem of nanoparticles is their ability to enter the organism and translocate within it. Within the organism, they can cross physiological barriers such as the blood–brain barrier or the air–blood barrier in the lungs. They are also able to travel through the circulatory systems (blood circulatory or lymphatic system). Some nanoparticles can even enter inside cells and induce damage.

The toxicity of nanoparticles depends on several factors such as their concentration, size, shape, and physical and chemical structure. This is still an open area of research since the extrapolation of what we know from particles of large size or bulk materials cannot be done. When manufacturing nanoparticles or nanomaterials, it is easy to have devices protecting employees.

The exposure to nanoparticles can be direct or indirect. In a direct exposure, the consumer is in contact with nanoparticles on purpose. This concerns, for example, cosmetics, clothes, food packaging, and drugs. In the case of an indirect exposition, the consumer is not intended to be in contact with nanoparticles. However, the consumer can be in contact at a low concentration from the degradation of the object, during its use or at the end of its life.

4.22 Conclusion

Nanotechnology is slowly diffusing into other existing technologies meaning that we have a smooth nanotechnology transition. In most applications, hybrid systems are developed, which combine classical technologies and nanotechnologies. The aim is to improve the performance of already existing devices, to lower costs, and sometimes to introduce new functions.

There are very few Complete nanotechnology systems. However, there are nanometric-sized objects that allow simple operations to be carried out. This is the case with nanoparticles that can be used alone, such as gold nanoparticles, or functionalized. Molecules such as C_{60} can protect drug molecules located within C_{60}. They can also be grafted at their surface with active molecules and serve as vector particles to reach a target such as cancerous cells. They can carry a payload that

can be liberated by external signals (such as an electromagnetic wave, a magnetic field, etc.) when the target is reached.

The question is whether an application is useful to mankind or whether it is useless or harmful given the moral values of the society in which it is developed or used. These moral values may vary by countries and civilizations. In most cases, it is quickly possible to estimate whether the advantages of nanotechnologies outweigh the disadvantages. However, there are applications where there are almost as many disadvantages as advantages. These cases require ethical thinking. There are also applications that can be diverted from their original purpose to be applied for fraudulent purposes. This does not mean that we should turn away from this technology, but it must be overseen. A minority of people may find the use of nanotechnology unnecessary while the majority consider it useful. In this situation, it often happens that the opinions are based on arguments that go beyond scientific knowledge. An ethical analysis is then necessary to try to make progress in the reflection.

Today, in Western societies, fear merchants have an important influence and are widely supported by the media because they are a source of buzz: trains that are late are more interesting as information than trains that arrive on time! Westerners are currently sick of being too happy and they have a sympathetic ear to fear merchants who use the precautionary principle, ecology, and many other ideas to ban nuclear energy, pesticides, nanotechnologies, and so on. They are also pushing to introduce sometimes unrealistic standards and regulations that undermine the competitiveness of the European industry. If Europe follows this path, particularly in the field of nanotechnology, it will only play a minor role at the international level in the future.

Finally, is it important to realize the increasing importance of dogmatic ethics compared to pragmatic ethics represents a danger for society because it can lead to nonoptimal solutions or even counterproductive effects for society. This means also less high-end jobs.

Books where the reader will find complements as well as references are listed under References.

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Jean-François Hochepied

5 Technological revolution, societal counter-revolution?

Abstract: While nanomaterials have allowed the emergence of new products and new technologies, their development and dissemination have started to raise societal concerns. Delusional promises, carelessness about health and environmental issues (at least until recently), poor concern about education of people paved the way to societal overreactions and even complotism, making industrialists to withdraw some nanoproducts or deny their "nano" characteristics. At the same time, even the definition of nanomaterials is a delicate subject and the difficulties in estimating the risks are a colossal scientific challenge in metrology and toxicity. If these scientific and technical difficulties are perceived as signs of incompetence or manipulation by populations or industrialists, the market for nanomaterials and nanotechnologies could collapse under the effect of a societal counter-revolution. Only a large-scale initiative for nano-education will enable knowledge-based decision-making for the regulation of nanoproducts, with the consent of citizens.

Keywords: nanotoxicity, conspiracy theories, metrology, societal acceptability, education

5.1 Introduction

Controlling the development and assembly of various materials at the nanometric scale has allowed the development of nanotechnologies and the appearance of innovative nanoproducts in almost all industrial sectors. The added value of these products can result from the significant improvement in the functional properties of the previous product (e.g., batteries) or in its lifespan (nanocharges in tires), new functionalities (e.g., flame-retardant properties for polymers), or miniaturization (nanoelectronics). These products can take advantage of the purely dimensional effect of size reduction (increase in the specific surface area of catalysts, nanoparticles entering cells for nanomedicine, etc.) and/or exploit the new physical properties (optical, magnetic, and electrical). Some products can also be specific at the nanoscale (carbon nanotubes, fullerenes, etc.) without equivalent on a larger scale. Many products have thus integrated nanomaterials and have had an industrial destiny because the added value exceeded the additional costs of adapting processes and means of characterization or quality control. At the two extremes in terms of complexity (and production

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costs), on the one hand, we find low-cost nanopowders produced at high tonnage (silica, titanium dioxide, etc.), most often intended to be formulated in processed products (paints, cosmetics, etc.), and on the other hand, complex nanodevices such as those of nanoelectronics. Even if we can identify a certain number of successes resulting from this nanotechnological revolution, we must remain aware of the possibility of a societal counter-revolution, justifying the need for nano-ethical approach.

5.2 Products from the nano-revolution

In the category of nanoparticles, a distinction should be made between (1) simple particles, of fairly common materials, produced industrially with large tonnages (carbon black, silica, titanium dioxide, etc.), and nanoparticles that are more expensive to produce (nano silver and carbon nanotubes) but which have succeeded in having an industrial reality due to less quantity requirements to guarantee the desired functions and the added value to the products that contain them (antibacterial function of Ag, nanoelectronics of carbon nanotubes), and (2) complex particles often made up of several interfaced materials (in the form of core–shell or heteronanostructures) in order to combine the functionalities of each material (functionalized nanoparticles for medicine, etc.). Simple nanoparticles have widely diffused in everyday products, including food products. The use of nanoparticles in paints and coatings makes it possible to obtain depolluting, bactericidal or antiviral surfaces. Within a matrix, nanoparticles can provide remarkable properties. Thus, the incorporation of simple nanoparticles more or less agglomerated, in polymer matrices, even at relatively low charge rates, has considerably improved their mechanical properties or their resistance to wear (nanosilica for tires), their resistance to fire, and barrier effects (packaging). Certain suspensions of concentrated nanoparticles have shown surprising properties opening the way to clever applications. We may cite one of the oldest nanotechnological product, ferrofluids, invented in the 1960s. These are concentrated suspensions of superparamagnetic nanoparticles behaving like a magnetic liquid, and found applications making profit of their static or dynamic behavior in the vicinity of magnets: seals for hard disks, mechanical dampers, lubricants, and so on. Interestingly, some applications used a cooling effect based on the sharp temperature dependence of nanoparticle magnetic properties. Nowadays, the general family of nanofluids arouses a keen scientific interest for applications exploiting their energy storage properties in the case of nano-enhanced phase change materials, or the exacerbation of heat transfer in the case of “simple” suspensions.

The chemists have also succeeded in developing multimaterial nanoparticles, which can thus combine different functions (magnetic catalysts, for instance) or take advantage of the interfaces (junctions) between the two materials (charge separation in (photo) catalysis, for dye-sensitized solar cells, and more generally for all

energy conversion systems such as batteries or fuel cells). The applications of these sophisticated particles in environmental remediation, pollution control, solar energy conversion, and nanomedicine are often still in the making, but their industrial reality is undoubtedly not very far away. In addition to these nanometric particles, nanoporous materials also come within the scope of nanomaterials. They can benefit from their high specific surface area in catalysis and also from the confinement of gas in nanometric (open) pores in thermal insulation (Knudsen regime): aerogels (in particular of silica) exhibit thermal conductivities of the order of 15 mW/mK at atmospheric pressure while that of air is 3 times higher.

Finally, nanometric (multi)layers can be obtained by different techniques (physical vapor deposition, chemical vapor deposition, atomic layer deposition, spin coating, dip coating, etc.) and spatially controlled not only in thickness z but also in the x and y directions to draw the desired structures (nanolithography), with applications, for example, in nanoelectronics. It should be noted that "simple" multilayers of nanometric thickness of different materials make it possible to have interesting mechanical (very high hardness of superlattices) or optical properties (optical filters).

Thus, in a wide variety of fields, the specific properties at the nanoscale have been exploited in numerous applications, improving the properties of materials or giving them new ones.

5.3 The other side of the coin

After a phase of enthusiasm for the study and exploitation of the properties brought by the nanometric scale, with its procession of promises, a phase of societal concern has set in. It results from the combination of overly optimistic announcements about the benefits of nanotechnologies, which sometimes take a long time to materialize, and difficulties in assessing health risks.

5.3.1 A "revolution" slower than expected

Since the year 2000, the reference year corresponding to the establishment of the National Nanotechnology Initiative by Bill Clinton under the leadership of Mihail Roco, some hoped-for advances have fizzled out, which puts the impact of the nano-revolution into question, and the prospective on the evolution of nanotechnologies (in terms of successive generations: passive nanostructures, active nanostructures, nanosystems, and molecular nanosystems) imagined at the start of the 2000s has been reassessed several times, each time shifting the expected date of emergence of the most advanced nanosystems [1].

Where are the nanomachines imagined by Eric Drexler [2] 35 years after his book *Engines of Creation – The Coming Era of Nanotechnology* and 30 years after

Nanosystems? Some promises of "nanorevolution" have collided with harsh industrial reality. Nanotechnology is no more in its infancy and cannot be content with selling dreams, and results are not all success stories. People have been working on cancer treatment by hyperthermia with magnetic nanoparticles for more than 20 years [3], and we are still waiting. Nanotechnologies are also no exception to the laws of the market. Thus, certain technologies, as brilliant or revolutionary as they are, have not succeeded in breaking through even if the performances are improved regularly. We can cite as an example the case of dye-sensitized solar cells invented by Michael Grätzel [4] some 30 years ago, which must be satisfied with a relatively modest market size when compared with the global photovoltaic market.

5.3.2 Undermined confidence

5.3.2.1 Nanotoxicity issues

Alongside certain disappointed hopes or delayed deadlines for advanced nanotechnology products, much simpler nanoproducts very quickly invaded certain markets with relative recklessness about their possible specific toxicity, especially in the case of nanoparticles introduced into food products to change their texture or visual appearance, such as silica or titanium dioxide. The recent awareness by consumers of the existence of nanoparticles in food products has caused a stir in many countries. Under societal pressure, many manufacturers then removed nanoparticles from their formulations, which proves in passing that they were not essential. In October 2020, the European Parliament objected against the authorization of titanium dioxide as a food additive in the name of the precautionary principle and the observation that children were the most exposed [5]. There are other forms of exposure to nanoparticles, against which it is more difficult to guard. By wear or degradation of certain materials or coatings, nanoparticles can be dispersed in the atmosphere or the environment, with possible reconcentration phenomena by living organisms. As soon as researchers' attention was drawn to "nanotoxicity," in particular, by the article by the Oberdörster trio in 2005 [6] or that of Andre Nel et al. in *Science* in 2006 [7], scientific articles devoted to this new field have multiplied and their impact has supplanted those describing new properties or syntheses of nanomaterials, to the point of justifying the creation of a journal only devoted to this subject ("nanotoxicology" in 2007). Due to their size, nanoparticles may easily penetrate living organisms by inhalation or ingestion and enter the cells, eventually accumulating there, risking disrupting their functioning by dissolution and release of species with a high local concentration, or by surface interactions. While much attention has focused on carbon nanotubes, it quickly spread to large tonnage particles (SiO_2, TiO_2, etc.) to which workers on the production site – especially if the latter is in a country where health standards and workers well-being are not a priority – as well as consumers are potentially exposed. Due to the

variety of toxicological approaches in vitro (choice of cell lines, particle dispersion and contacting protocols, choice of end points, etc.), the lack of standardization of tests and insufficient characterization of particles tested in many studies, the multiplication of the results has generated more confusion than certainties. In any case, it has become a tendency to assert that nanoparticles were "toxic," in particular by in vitro tests, even if the doses were unrealistic. Incidentally, acute toxicity is tested much more (for obvious practical reasons) than long-term effects. In addition, the descriptors of nanoparticles being very varied, it quickly became clear that it was impossible to test all the existing particles and statistical approaches (quantitative structure–activity relationship) QSAR tried to take over [8], but the studies are particularly demanding in terms of descriptors (measured or calculated) of particles and endpoints. Beyond a tendency saying that overall the toxic effects depend more on the chemical nature of the particles than on dimensional descriptors, there is no formula allowing to assert a level of particle toxicity according to these multiple descriptors. In addition, the toxicity of certain nanoparticles could be greatly linked to molecules capable of being adsorbed on their surface, during their journey to human cells (cocktail effect or Trojan horse), increasing the complexity of the subject. Thus, unlike the classic toxicology of molecules defined unambiguously by their structural formula, it is not possible to define the toxicity of "nano-TiO_2" or "nano-Ag." So, even if apparently no nanoparticle found in everyday consumer products seems to be particularly dangerous for health compared with the many pollutants to which we are exposed daily, this very complex situation fuels concern and the application of a precautionary principle is not surprising, which led, for example, to the previously mentioned ban of TiO_2 in food products. In addition to human health, a growing societal concern encompasses the environment, especially since the phenomena of reconcentration can occur in living organisms, plants, or animals, then consumed by humans. In this context, it is obvious that if the introduction of nanoparticles in products is limited to an aesthetic benefit or comfort, the risk is less acceptable. In this regard, the case of silver nanoparticles is very interesting. Their antibacterial effect must be weighed against their potential toxicity. If they are sprinkled on a teddy bear, many parents will rightly be reluctant. If it is a question of avoiding bad smells by wearing socks or sports clothes, one can also wonder if it is worth it since the silver particles will be gradually dispersed in the environment after washing. On the other hand, in a hospital environment, the benefit will probably be greater than the risk, especially if, in addition to bacteria, the silver nanoparticles have an effect against viruses.

5.3.2.2 Conspiracy theories

At the other end of the spectrum, one might think that "nanotechnologies" such as nanoelectronics do not cause health concerns, contrary to high tonnage products stuffed with nanoparticles liable to be released unintentionally during use. However,

they are exposed to another risk that should not be taken too lightly. The extreme miniaturization of sophisticated, intelligent, or remotely controllable objects "naturally" opens the way to conspiracy theories. Perhaps, the most recent and entertaining is the one concerning Bill Gates' alleged "nanochips" in vaccines [9], but conspiracy theories have been with nanotechnology for a long time, as fans of the X-files series probably remember [10]. It is one thing to fear that inert toxic nanoparticles accidentally enter your body, it is quite another to fantasize that "smart" or remotely controlled nanoparticles are inoculated into you not for medical purposes (diagnosis or therapy using nanoparticles) but to spy or control you, and this agonizing fantasy feeds abundantly conspiracy theories about vaccines. Another famous example of a conspiracy theory based on nanotechnology is the alleged presence of nanothermites in the towers of the World Trade Center during the 9/11/2001 attack. This theory must have been appreciated by the fans of the genre since it was repeated after the fire at Notre-Dame de Paris in April 2019, showing all the same in passing the existence of a conspiratorial "culture" (if we dare say!) spanning the decades. One may smile about all this, but scientists would do well to be concerned about the breakthrough of conspiracy theses and more generally the rise of obscurantism in supposedly "enlightened" nations. It should also be borne in mind that scientists are not always irreproachable and can themselves feed – voluntarily or not – certain anxiety-inducing and/or conspiratorial theories; for example, Drexler's gray goo [11], a scenario in which self-replicating nanomachines would consume the entire world.

5.4 The time for nano-ethics

Thus, nanoproducts can arouse the distrust of citizens, suspecting their leaders of incompetence when it comes to the health or ecological impact of nanoparticles, or of totalitarian thoughts when it comes to nanotechnologies. In order to avoid the tearing of society between scholars and citizens, the time has therefore come for a knowledge-based nano-ethics. This nano-ethics is expressed in a particular way depending on whether one is a researcher, an industrialist, a political leader, or a simple citizen.

5.4.1 Nano-ethics for researchers

In the first line, researchers are expected to be guided in priority by a strict scientific ethics. Researchers cannot dispute that the nano wave of the 2000s, which brought a lot of public and private funding, led to a certain overbidding of promises and a tendency to publish as quickly as possible under the pressure of the competition. If this has spurred certain advances in nanotechnology, there have also been controversial results and even outright scientific fraud to an unprecedented level, as in the case of

"Schön scandal," so famous that it is even entitled to a Wikipedia page [12]. It is noteworthy that this scandal concerned hard sciences (nanoelectronics), with many fake articles published in prestigious journals. Of course, scientific fraud is not a phenomenon specifically linked to the field of nanotechnologies, but it is a greater temptation in "hot" fields. In any case, scientific fraud is a long-term poison that could be very harmful in a climate of societal mistrust of nanomaterials, since the confidence in published scientific reports should be the cornerstone of a knowledge-based nano-ethics.

5.4.2 Nano-ethics for industrialists and decision-makers

Manufacturers, for their part, cannot avoid including health and environmental concerns in their products containing nanomaterials any longer, starting with knowledge of the risks relating to their release during use, and worrying about the recyclability of their products such as nanocomposites, batteries, or electronic devices. Beyond the objective of improving performance in use, life cycle analysis must be integrated into the innovation process.

At all levels, for industrialists, political decision-makers, and citizens, the issue of nano-education is critical to allow the restoration of mutual trust. The role of the researcher will be decisive so that the choices of industrial and political decision-makers are supported by science, with the confidence of the majority of citizens. This task is particularly difficult, as shown, for example, by the fiasco of the debate on nanotechnologies in France in 2010 [13]. Manufacturers need to better understand the nanoparticles they use as an ingredient in the products they manufacture. To do this, they must initially be at least aware of the nanoparticulate form of some of their raw materials, which must therefore be clearly identified as such. This implies definitions, standards, statements, and rules shared by all, as well as an appropriate nanometrology. Unfortunately, these points are not at all obvious when one thinks back to the difficulties only to agree on the definition of nanomaterials [14]. Most of the definitions are based on an arbitrary limit (100 nm), which has no particular significance from the point of view of physical or toxicological properties, while implying an appalling complexity in nanometrology to declare that powders (the simplest of substances) are in the nanoparticulate form or not when, unfortunately, their size distribution crosses this border. The intervention of a second arbitrary limit on the respective fractions on both sides is then required in order to give a verdict. The huge metrological problem is that there is no quick method to achieve this: indirect methods (dynamic light scattering for example) are representative of the sample but do not allow reliable access to the size distribution (when, for example, the distribution is not monomodal, when the shapes of the particles are anisotropic or when there are agglomeration phenomena), and the direct methods of individual measurement of the particles (electron microscopy) are extremely precise but expensive and time-consuming. As a conclusion, the definition of nanomaterials is

arbitrary and nanometrology is complex (and disputable), whereas the obligation to declare that some products contain nanoparticles is not desired by manufacturers knowing the risk of societal distrust. Such a situation paves the way for never-ending hairsplitting legal issues about the declaration of nanoparticles in products. This is where an industrial nano-ethics is expected to overcome the temptation to circumvent the declaration of nanoproducts.

5.4.3 Nano-ethics for citizens

For their part, whatever their age and social condition, citizens cannot spare the effort of acquiring a minimum of scientific culture; otherwise, they will be the prey of conspiracy theories, and the societal acceptability of nanomaterials is clearly at stake. We must not forget that the politicians are those who make the laws and can therefore decide to ban or impose nano-objects, and that the vote of someone who believes that the Earth is flat [15] counts as much as a Nobel Prize winner's vote. Without a widespread nano-education initiative, there will be no nano-ethics.

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6 The evolution of nanoscale research: Lessons learned and questions asked

Abstract: When it became widely understood that the rapid growth of knowledge and investment in nanotechnology could beneficially impact society, large numbers of scientists and developers were attracted into the arena. In time, the conversation began to transform from seeing nanotechnology only as a universal good to also considering that the nanoscale might impact the animate universe in radical new ways. There then arose a remarkable phenomenon of growing concern, controversy and, ultimately, a degree of fear in the public conversation. While some of these fears are now seen as excessive, there were genuine reasons for caution. In this chapter, we examine what can be learnt from our experience at the nexus of research, regulation, and policy development during those years. The chapter deals with the evolution of the nanosafety debate, focusing mainly on the distillation of what was learnt during the course of events so that the key messages can be passed on to future generations. The readers are asked to consider ahead of time what arrangements society should have in place so that those confronted with rapidly evolving (technology based or technologically resolvable) scenarios with considerable impact on society are well placed to face the challenge.

Keywords: nanotechnology, nanosafety, nanomaterials, biology, morals, ethics

6.1 Introduction

The writing of this chapter is timely, for it comes at a time when the first and most basic phase of nanoscale research is concluding [1, 2]. Our knowledge of nanoscale science and technology has grown to a point where we can now aim to reach a deeper understanding of the field and to pursue more far-reaching achievements. It is a good time to reflect on the past decade and a half, and examine what can be learnt from our experience of research, regulation, and policy development. These thoughts originate from our active interest and involvement in all aspects of nanoscience from research and discovery, to technology and policy throughout these critical years. We hope they will help newcomers interpret how we arrived at our present position in nanoscience.

More significantly, we hope the insights may be useful for future science and policy leaders who are confronted with areas outside of nanoscience, where new

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and untested technologies are rapidly impinging on the animate and inanimate environment, and society at large. We should stress that such rapidly emerging impacts on the equilibrium of society do not need to emerge only from the man-made (or modified) material universe. They may also emerge from qualitative step changes in the capacity of information technology, as in artificial intelligence and deep learning approaches. Moreover, humans may not be the only actively developing actors. We live in a permanent competition–collaboration state with microorganisms (including pathogens), many of which we have been screened from for eons by physical and -biological barriers. If the many elements of modern life cause these ancient defenses to weaken, then society itself could be challenged.

Such scenarios as we envisage here share many similarities. Science is at the root of the beneficial advances, or the solution to the challenges. However, understanding and mitigating any potentially undesirable impacts of innovation on society also requires technical and scientific knowledge to make progress. And, as a consequence of rapid development, the state and limits of that knowledge are (at that moment) insufficient to face the challenge. These scenarios anticipate a limited period of warning time during which society has a chance to prepare for outcomes that could involve new and emerging risks. Time won with foresight may be of the essence in finding effective solutions, and the preparation we have made beforehand and the earliest steps we take to address the problem are of critical importance. To face such challenges, we require a conceptual framework that enables societal systems-level preparedness. Taking into account the widespread and multidimensional impact, such a framework must be intersectoral, going far beyond science, involving institutions, policy, governments, and people.

Thus, the challenges that surrounded the rapid emergence of nanoscience and technology, and the perception of potential society-wide risk are in many ways an excellent test case and learning environment for the future. It was in some respects a "near miss" because many of the worst fears were not realized, but to those that lived through it, all of the elements were there to make it feel real at the time. That experience highlighted many aspects that in a more complete "crisis" would also be expected to recur.

We should be aware that nanoscience is still evolving and there is more to learn. For that reason, many who have labored and continue to labor in the field, seeking to understand and systematize the vast body of knowledge and practice that the nanoscale has unleased, may feel some different instincts to those presented in this chapter. Here, we will not seek to represent any sectoral view directly, though it may be helpful to see those views reflected, because that is also an aspect from which we can learn. For instance, those individuals and institutions charged with the responsibility to create a framework of regulation that will both protect and promote trust in technology within society may have at times felt their legitimate efforts hampered, and feel that their experience was, and still can be, frustrating. Others may have felt that key sectors of society were (and remain) slow to fulfil their obligations and assist the process.

Others may look back and feel vindicated that their predictions of "no great alarm" were more correct than not and bemoan the loss of momentum caused by such concerns. All of these are legitimate reflections of the experience of our generation.

Here our purpose is to take a step back and reflect more deeply on the experiences, and their meaning and portent for society in the future. The observations we make here are made from a purely personal perspective. While we feel they represent a broad and informed consensus on all that was experienced and achieved, they do not represent any body, or institution, and are presented with the humbling recognition that we are yet only a little way along the path of what nanoscience and technology will one day become. Perhaps this chapter's most valuable contribution is to pose key questions to society, not so much about nanoscience, but about the question of rapidly emerging risk. It is not our role to give all of the answers to those questions, but we hope that the value of this chapter will be found in the wisdom of the questions it raises.

While at the time of writing there are many society-wide threats, none seem outside our current or imminent control. Several including the current COVID-19 pandemic (while at this time seemingly manageable) do reinforce the central premise that society may be dysregulated quite profoundly by rapid onset of crises that were not foreseen. The question we pose asks whether, during this period of relative calm, there is room for all sectors of society to find ways of improving the arrangements to deal with the questions we faced and continue to face in our generation? To be useful, the question must be posed to and addressed by all actors in such a scenario, including those who in the heat of the moment of previous "dry runs," appeared to find themselves in implacably opposed positions.

We cannot know what is ahead of us. By now the issues of machine intelligence, massive data, synthetic biology, and many other integrative technologies are becoming well known. So, here we should also ask whether our systems can deal with the as yet unknown and unimagined. Thus, there remains time to rethink some of the present arrangements for dealing with rapidly emerging society-wide threats (or fears). For instance, while prudence and balance necessarily reside in the institutional and intersectoral checks and balances that (by construction) promote debate between interests, these all have a high cost in terms of time and resources. They rarely assist the scientific process. Will the future allow the recrafting and improvement of these systems? Could the processes, leaderships, relationships, and even the workflow between their different elements be modified to lower these costs? Are there options that facilitate the creative and innovative energy of humanity to build on platforms of safety and economic viability from the beginning?

Most would probably agree that for this discussion to be valuable to those that follow, an honest and clear reflection on the issues of safety, regulation, and ethics in nanotechnology as they appeared at the time is required, rather than only to reflect on our understanding of the outcomes. We also need to take into account how adjustments have already been made, and ways in which researchers, policymakers, regulators, and society as a whole have grown since the first days of nanoscience. And rather than

assigning blame for aspects that were ineffective, we should better question what the experience could teach us in the development of alternative strategies for the future.

6.1.1 Setting the scene: Beginnings of the nanosafety discussion

Future readers of this chapter will appreciate the feeling of concern felt by those close to the question of nanosafety and the atmosphere of "near crisis" generated in the public domain and the press. The phrase "perfect storm," coined and widely used during that period, described the huge and growing scientific and technological activity combined with our lack of knowledge of the potential health and safety issues. Even those with more measured views, and who perhaps believed the atmosphere of crisis was premature, recognized the genuine and scientifically -based origins of the concerns. Future readers should recognize the pervasive feeling of confusion and uncertainty that infected thought and action. Some vocal proponents felt justified in holding positions based on the belief that nanostructures were (or were not) safe. Others likely felt they benefited from the attention that the controversy supported. Some had a growing feeling of unease that society was perhaps not consciously making informed choices, and rather was "sleepwalking" into the future. Those who knew the most were the least confident of their knowledge and tended to say less. Above all, and we shall see why shortly, no one knew who (institutionally) they could fully rely on, to make balanced judgments. As time went on, trust further eroded. This is hardly an attractive scene, but it should be considered typical for the types of new risk scenarios we envisage.

Importantly, it should be noted that many individuals, organizations, industry sectors, institutions, policy makers, and politicians acted honorably and sought to make good decisions. Thus, ours is not a simple story of right and wrong, or simple answers to simple questions. This story concerns the much deeper and durable question of how society can simultaneously protect itself from harm and from overreaction to fear, especially when those fears are not unreasonable considering the scientific knowledge of the day. Our discussion recognizes that unforeseen and uncontrolled hazards could profoundly harm humanity, but that overreaction to unwarranted fears leads not only to lost opportunities but may also lead to very wrong outcomes in which no one is well served. The abiding challenge is to balance these issues during, rather than after, the perceived crisis.

6.1.2 The strategic positioning of nanotechnology: Success or failure?

At the time of writing, many consider that nanotechnology has yet to achieve the very high expectations that were set for it. It is often overlooked that a lot has been achieved, and it has quietly advanced society in all sorts of ways. There are many

modest and slowly growing applications in fields ranging from technology to food, diagnostics, and medicine, but we have not seen the radical and rapid impact on society that some felt to be imminent. Early expectations were largely set by an intrinsic dynamic of "overselling" the immediacy of outcomes, and grossly underestimating the time and substantive understanding required for true success.

For those of us that delved earliest and deepest into the scientific investigation at the nanoscale, the experience and evolution of opinion was quite different from the popular view in the field. We were excited by the science but tended to be critical about the rapid and radical beneficial impact on society. As years have passed, our growing insight has led to growing confidence that many radical and positive changes from nanotechnology are yet to come. For us, the nanoscale story has just begun. At the time of writing, we are convinced that information content and information density are important elements that will characterize future nanostructures. Key advances are about to initiate a new threshold in the biological complexity and potential for subtle mechanisms of biological regulatory action of nanostructures. It will be necessary for many sectors to find the fresh energy and resources to make good on these advances, but we believe that nanotechnology will ultimately achieve the very large ambitions it promised in the beginning.

6.1.3 What is a nanomaterial?

Before going any further, it is useful to comment on what a nanostructure is, and how it came to be defined. To some degree, the answer has always depended on the detailed circumstances, application, and the purpose of the question. Indeed, for many questions of scientific and technological interest, there is no canonical size at which particulates "become" nanomaterials, and most properties behave in a rather smooth manner across the size range. Our experience suggests that particles of some tens of nanometers behave qualitatively differently even to those of many hundreds of nanometers. We will discuss what these size differences within the nanoscale itself may mean for biological interactions of particulates later in the chapter as this underpins many safety considerations.

Here, we only need to consider that nanoscale structures were viewed as potentially acting qualitatively differently both in living organisms and the environment to their macroscopic counterparts. That recognition inexorably led to the prospect that these materials would need to be regulated as a distinct class from their macroscopic equivalents. From there it became clear that it was necessary to have some sort of formal (potentially legal) basis for the definition of a nanomaterial. The details of how nanomaterials were ultimately defined in different jurisdictions in most respects reflect differences in tradition or legal framework. In substance, however, the intention and broad outcomes were comparable and constituted a rational response to the challenge [3–5]. In 2010, the Scientific Committee on Emerging and Newly Identified Health Risks

(SCENIHR, an independent committee providing advice to the European Commission) provided scientific input on elements to consider when developing a definition of the term "nanomaterial" for regulatory purposes. The SCENIHR opinion *Scientific Basis for the Definition of the Term "Nanomaterial"* was subject to a public consultation. Following this, in a report published on December 8, 2010, the SCENIHR concluded that the size is universally applicable to nanomaterials, is the most suitable measure, and that a defined size range would facilitate a uniform interpretation [6]. The definition was based on the numbers of structures in a population within a given size range and a lower limit was proposed to be 1 nm and an upper limit to be 100 nm.

At the time, this definition appeared somewhat arbitrary to many both in science and industry. However, it was inevitable that such a definition would be required in the context of standardization and regulation. Some in industry feared that a definition would stimulate unwarranted fear about nanomaterial safety and "outlaw" the nanosized domain. However, few thinkers then (and certainly not now) considered this formal size definition suggested any safety threshold. And it did promote deeper investigations into a new size range that certainly deserved attention. Possibly, it also helped calm and structure the thinking so that one could at least envisage ways of managing the future, and importantly, its application has been sensible in general. Still, future readers may also consider whether this definition would have been so easily and wisely applied if serious acute nanohazards had been ubiquitous.

6.1.4 The uniqueness of the nanoscale in living systems

To appreciate why size matters it is important to go back to the foundation of the hypothesis that the living universe could be affected differently by nanostructures than structures of other sizes. Early on, it was clear that biological processing of nanoscale objects occurred by quite different processes than those of smaller molecules or larger particles. In essence, whatever they were made from, nanostructures adopted some biological identity and were then "read" by quite unique cellular processing mechanisms [7–9]. Indeed, today, we understand much more about the key information-rich machinery that is driven at the nanoscale and by which biology communicates with itself (whether between cells or at a system level, such as the immune system) [10, 11]. That is the size range where, for example, extracellular vesicles communicate significant amounts of information between tumor cells and the immune system. It is there that the battle between tumor growth and patient survival is partly fought with a stunning degree of subtlety that we are only now beginning to understand [12, 13]. Indeed, as our knowledge grew, we are now even more aware of the remarkable sophistication and distinctiveness of nanoscale biology, which is emerging as a frontier of scientific knowledge. If we are correct (and future readers will be able to determine that), then that is a story that is destined (over coming years) to make some of those much -discussed step changes in medicine.

6.2 Early intuitions on nanoscale biology and the early role of science

As it became clear that man-made nanostructures adopted a biological identity from their surroundings via their "biomolecular (protein) corona", it was evident that these structures would not act like conventional chemicals [10]. At that point, two possible broad future outcomes became obvious. Either man-made particle–biomolecular structures could become a sort of "grit" in the biological machine, becoming a viable and quite exceptional safety concern. Or we would learn to master these nanoscale complexes and they would open up a whole new frontier in which we could intervene in biological messaging, and thereby cure diseases, possibly in a qualitatively novel manner. Both views certainly had substance.

Nevertheless, more cautious thinkers cautioned against immediate and simplistic scientific conclusions. While the knowledge on the exposure to natural environmental nanoparticles suggested no compelling evidence of a dramatic and acute safety hazard, it was evident that longer-term exposures could produce subtle health effects. There was, for us, also an "intuition" that the very fact that engineered nanostructures acquired a genuine biological identity meant that the defenses built over eons of biological evolution to defend against natural nanoscale threats may well be deployed against this apparently new engineered threat, possibly in ways that we had not fully appreciated. These growing intuitions (later to become hypotheses) suggested the presence of endogenous nanoscale biological protection mechanisms that paralleled the organ defenses that degrade and thus limit harm from toxic chemicals. We may pause here to note the difficulty in which responsible scientists found themselves in these early moments. It now seems certain those early ideas were the correct paradigm, but how could one justify injecting these "intuitions" into such a seemingly urgent discussion? We will further discuss this fundamental dilemma for scientists later in the chapter.

The emerging field of "nanomedicine" was similarly impacted by such considerations. Those same suspicions of natural nanoscale biological defenses implied that gaining access to the key biological communication pathways (the strategy to revolutionize the development of medicines) may not be as easy as was supposed. Certainly, these ideas suggested the need to evolve deeper insights into how such protective mechanisms worked, in parallel with phenomenological observations of the consequences of bringing nanostructures in contact with biology. In the atmosphere of growing concerns about nanosafety, such deep mechanistic studies were underemphasized, and the development of that field was also impacted, and progressively drifted from its original concept with quite significant consequences.

One significant point that future thinkers should consider is that, at the time, individual scientists, when called upon to discuss such questions or advise in the public interest, were presented with profound ethical and practical questions to which the answers have not yet been found. We have alluded to the fact that responsible

scientists found it unjustifiable to make comments based on their intuitions, even though they are those intuitions that form the basis of hypothesis-driven research. The problem goes deeper than that. Science carries with it a tradition and legacy that values thoughtful analysis and caution in interpretation that tends to limit strong or premature conclusions. The only option for the most knowledgeable and balanced scientists was therefore to clearly signal the knowledge gaps. On the other hand, we know well that, against a voluble barrage of certainty based on "belief," or "facile scientific conclusions", excessive silence leads to a vacuum that is soon filled. There are still no certain roadmaps to deal with this dilemma for scientists at the interface with policy. To date, scientists have found that only the pathway of careful analysis and interpretation creates durable understanding. In the interim they have no option but to rely on personal judgment to decide the degree to which they can fill that vacuum when called on to act on behalf of society.

Science is a great bastion of honest thought, and its honor must be protected for the good of all. Certainly, not all science is reasoned and ethical, and some during this period contributed to the problems. However, it will interest the general reader to know that the best science is intrinsically balanced and cautious. It is not to be feared by any sector of society. It will rarely promote irresponsible risk, nor lightly destroy its own pathways to knowledge by propagating unwarranted fears, unless they clearly signal danger. It is sustained by a deep moral and ethical framework that makes it intrinsically honest and trustworthy both by construction and tradition. Unfortunately, it is also quieter than other forces in such emerging scenarios, and existing ethical frameworks in science do not deal well with the question of "filling the temporary vacuum" of uncertainty at moments of crisis.

6.2.1 Growing concerns about the safety of nanomaterials

As the situation matured, the justifiable safety concerns and considerations fed into much more complex dynamics at the scientific, technical, political, and public interface. Cautious and reflective discussion between science, institutions, and policymakers led to a universal acceptance that there was a new issue that had to be dealt with. Even with hindsight, few would question that conclusion and the prudent steps that were taken to begin scientific, regulatory, and policy investigations. For instance, early on great efforts went into the adaptation of chemical safety testing methods for new nanoscale technologies. That was right and proper, and although the cooperation between the different sectors was sometimes hesitant, confused, and even grudging, some of those efforts will have a lasting value. Indeed, there will still be much to do there as nanotechnology reaches new thresholds, albeit at new levels of sophistication and more nuanced questions than in those early days.

Universally (and unsurprisingly), good leadership was at the core in all that was successful. Issues that are always with us (wavering from objective truth, a desire for

personal and institutional recognition, or resources) have greatly amplified potentially negative implications at such moments, and may profoundly undermine the objective. On the other hand, clear messages to promote an engagement across sectors that is honest, fruitful, meaningful, and cooperative requires leadership that is both strong, decisive, and sufficiently balanced to merit the trust of all.

Here then lies one of the profound dilemmas of modern society in situations where technical issues collide with the policy world in moments of crisis. There may appear to be no neutral, authoritative, and honorable force capable of providing that leadership. Even institutions acting on behalf of the public interest may be claimed to be biased in some manner. While this may be an unfair conclusion, the absence of such a neutral party is problematic. Furthermore, even with goodwill, the absence of institutions with authority to compel cooperation means that conflicts will be settled partly by competitive political dialogue and competing subjective arguments. That then was the outcome for the nanosafety field. There are many costly overheads to this approach, and no guarantee of an ideal outcome. Future readers may question if there are alternative approaches.

The alternative for society could be a form of neutral (but generally scientifically aware) arbitration that, while lacking the power to make decisions on any issue, could prescribe powers to enforce cooperation, reasonable disclosure of relevant information, and reasonable actions between all parties. In this type of scenario, where the issues are neither right nor wrong, the solutions not self-evident, and where all parties must in the end cooperate to find the best outcome, such a form of arbitration is one possible approach. The instruments were not available to our generation for these ideas to be tested. Indeed, possibly there was no identifiable institution that was perceived as sufficiently disinterested, or possessing the necessary powers to act in that role. If society believes that the potential for rapidly emerging overwhelming threats should be addressed, it will be important that such questions be discussed thoroughly. The issues are complex for society, and the creation of such bodies also carries risks. Before any actions are taken, thinkers across many domains should consider very deeply the complex implications for such arbitrated solutions. Now is the right time for that reflection.

Within the nanotechnology dialogue we began to see the emergence of tensions and differences of opinion between different institutional, regulatory, industrial, policy, and non-governmental stakeholders. All of the different actors had legitimate concerns and points to make, and given the differences in interest, many interactions were remarkably honorable. That is a point to which we will return later. While some found aspects of the discussions frustrating at the time, with hindsight one can see that many of these events were quite natural and healthy, and certainly unavoidable in the existing systems. Future leaders charged with responsibilities in such complex scenarios with limited knowledge may improve and streamline the processes whereby prudent caution and excessive fear are balanced. However, unless they find qualitatively new approaches, they may be wise to accept that responses to such urgent challenges

are not always simple. Possibly it is within the process itself, rather than only through the outcome, that the meaning of "ethics in practice" is revealed.

It cannot be denied that the often -fractured nature of simple nanomaterial testing approaches that evolved within the academic community were sometimes more confounding than helpful. These were often driven by a natural desire and excitement by many scientists to engage in something important and "topical," where new sources of funding could be expected. In turn, this sometimes led to poorly designed experiments, carried out with limited background, sometimes generating quite incorrect results that generated unwarranted fear across society. These further inflamed an exaggerated fear that was fed by a range of human factors and dynamics, with such results being widely quoted in the press. Nevertheless, readers should understand that these events were occurring against a backdrop of warranted caution, and there was no simple and rational basis on which to reject the claims out of hand. Those that doubt this assertion should look back at our description of "the uniqueness of the nanoscale in biology." We were in uncharted scientific territory, with no identifiable right or wrong, or simple and fast answer. The injection of confused science into this framework of legitimate concerns and complex dialogue was unhelpful for all of the interested parties, and most particularly for the public good. We shall reflect later on the detrimental impacts on society.

Lest those future readers misunderstand this point, we stress that the public dissemination of such claims was hardly avoidable. For ethical journalists, it could hardly have seemed proper to suppress even the most worrying reports, unless there were compelling reasons to do so. And, as we have shown, scientists with more insights and knowledge hardly knew what to say. Certainly, they could not deny that we had legitimate concerns, only that they were different ones from our more excitable peers. That is a hard message to clarify and communicate in the public domain.

6.2.2 The importance of trust in science

Consequently, a profound question arose for our societies, not just for the question of nanosafety but for the status of science itself. In whom do we trust at times of potential hazard and doubt? Scientists, scientific advisors, and the regulatory and other institutions they support are essential and hold a sacred trust to the truth, but cautiously and conservatively expressed. In the heat of excited debate and confusion, where so many conflicting human dynamics are at work, it seems only the word of science will ultimately be trusted, unless discredited. The injection of poorly conceived scientific opinion, therefore, represents a serious risk for society. If science is discredited, then society itself risks an impasse, for which there is no ready solution. Certainly, if conflict is based on substantive scientific issues, then it is essential that all be heard. However, ill-founded debate based on shallow or opportunistic science risks more profound distrust in science itself. Scientists wishing to leave an honorable legacy

in this arena will be wise to keep firmly to ancient principles of scientific substance, independence from external motivations or indeed from their own ego or interests. Their reflective independence holds the key to finding an honest resolution between the different stakeholders that is safe, prudent, and pragmatic.

The thoughtful reader may have noticed that, so far, fundamental, mechanistic, and hypothesis-driven science has not yet made much of an appearance in our story. Truly the pace of events and tendency to favor fast, fashionable answers made it difficult for those ancient and reliable values to take root and grow strong. Still, they began to be heard.

6.2.3 The durable values of the scientific method and fundamental research

One of the quite remarkable outcomes of the more fundamental scientific investigations that began to evolve around these safety questions is worth recording here. It tells a tale of the durable value of persistence in the execution of excellence in scientific method. It also reinforces the ultimate value of fundamental scientific investigation to complement applied scientific studies, even where the issues seem very practical and where hard-pressed leaders could mistake the need for speed in getting answers and force a focus only on established, quick pathways. Both are essential components of a strategy, and while it is possible that we did not achieve the right balance between these in facing the nanoscale controversy, our institutions had the wisdom and maturity to recognize that need.

The observation that fundamental science is the required basis not just for technology, but for safe technological development has long been recognized. However, it has been and will continue to be questioned in each generation as some may conclude that resources are best committed to apparently more immediate and practical applied priorities. While the focus on more practical expression of the nanosafety question grew at a breath-taking pace, there persisted an effort to look at the growing body of poorly designed "nanoparticle testing" claims of acute hazard with a more critical eye. In parallel, more fundamental efforts were made to understand what was really happening at a deeper scientific level. At first it was not fully appreciated that the fundamental understanding of the principles would not just guide long-term conclusions and policies of nanosafety but would also be the key to auditing and clarifying the fears and controversies surrounding the claims of "acute nanotoxicity." Phenomenological (purely observational, for example, "testing") science, while an essential component in this arena, is always more prone to simple error in some way. It was purely the chance of specific technical issues that (on this occasion) led to overestimation of naïve toxicity. It is very easy to trust weak science because it gives us the answer we seek, if it becomes pliable to our way of thinking. The implications are evident.

Here is not the place to discuss the technical reasons for these confounding reports, but a small example will possibly illustrate the issues and unexpected levels of misunderstanding that can occur. Many scientists in the field were familiar with the simple idea of dissolving chemicals in the low to zero protein mixtures used to culture cells, and then, to expose the cells to such mixtures to see the outcome. The proteins they added were simply to feed the cells during the experiments and usually had limited functional relevance. Over many decades, this very simple experimental setup had provided (and still does provide) rapid insights into the biological responses of small molecules. The critical difference here was that nanostructures should have been envisaged more as abundant surfaces. In growing cells on a surface, the imperative is more to prevent excessive surface forces from disrupting the cells [14, 15]. Thus, in the absence of a clear picture of the role of the biological milieu coating the surface and creating the biological identity, the simple laboratory experiment of dispersing particles in low protein "solvents" created surfaces that damaged the cells.

Of course, there is much more depth to that story now. However, the key issue is that, at the time, teams of scientists used paradigms of dispersion that damaged the cells, which caused immensely complex and novel forms of toxicity. In reality, no such effects could be observed (nor ultimately ever were) when the matter was fully resolved in the real world [16]. However, this simple misunderstanding (and others of similar vein) when combined with some of the more subtle and nuanced studies of hazard created a whirlwind of confusion and exaggerated reports. As we shall see, this is one place where more fundamental science intervened and corrected the discussion.

6.2.4 Fundamental and structured investigative science is drafted into the debate

In parallel to the growing fears of nanotechnology, a new dynamic within the scientific community also began. Some scientists who were closely involved in the problem early on became increasingly convinced that the most worrying reports being widely circulated were not genuine. They became progressively aware that nanoscale biological interactions may elicit far fewer acute toxic effects than one might have expected from such new processing pathways. Indeed, we were unable to reproduce many of the claims of serious acute toxicity.

Our challenge was how to act. This was clearly a diversion from the more long-term interest in developing the field for medical benefit, but it hardly seemed possible to stand aside in the light of these events. There began the self-assembly of a team of concerned scientists from around the world which was initially named the International Alliance for Nano-EHS [17]. They began to share their doubts about the reality of the more extreme claims and arranged the first "round robin" interlaboratory studies to mutually check their results [18, 19]. While the legitimate concerns of this and other similar groups focused on the honor of science, they simply

lacked the resources and capacity to exercise these plans at the required level. Insightful policy leaders recognized the need, and practical resolutions, though haphazard, were found to support such efforts [20]. Due to the lack of suitable international funding frameworks at that time, these activities were separated within Europe, the United States, and other countries, and that was hardly desirable. Still, whatever their imperfections, it was those studies that began to unravel the flaws in the early research that had generated the acute toxicity results [21, 22]. Future readers and policymakers should take careful note that these corrective efforts were, at the beginning, based on small numbers of people that recognized early on the emerging dangers of erroneous science, not just for nanotechnology, but for the integrity of science. Their efforts were late, halting, and fragile. A profoundly important lesson for society to reflect upon is how, with such high stakes, it came about that counterbalancing arguments in science were so fragile.

6.2.5 Lessons for future scientific leaderships

To make sure the message is clear for those reading this commentary in later years, we stress that the different opinions that existed as to what constituted good, correct, or necessary activity by different scientists, policymakers, funders, and other decision-makers were largely held honorably and with conviction. Even those espousing quite radical outcomes of acute toxicity in many cases had a legitimate (albeit mistaken) technical basis for their views. More importantly, it was simply not possible for the media and general public to decide who was right and who was wrong in such scientific disputes. Indeed, in retrospect, it could be easy to forget that some of the more exaggerated scientific views and claims appeared to be the most audible, highly credible, and mutually supportive. Here, we simply stress that the availability of a pool of capable and balanced scientists to counter wrong directions in science cannot be taken for granted. We are convinced that suitably focused and strongly based fundamental science is a powerful counterbalancing force to errant science. Its tradition confronts, probes, and investigates all threads of observation, and seeks to connect the knowledge into a general understanding. It is a bulwark against facile conclusions and this is an important message for future funders.

Future leaders may reflect deeply on the fact that the scientific community is sufficiently diverse and necessarily unfettered. Still, that also means it can quickly generate and pursue “fashionable directions” that, in later years, appear to be ill judged and are not necessarily easy to self-correct quickly. Cold fusion and polywater are just a few examples that span some decades. Many of us involved in the nanosafety question were initially confused at the unfolding of events, as we watched the “center” of science (as we perceived it), and a whole technological development become endangered by being led down an erroneous and unnecessarily destructive path. And we found that our fledgling initiatives to preserve the integrity of science were already

on the "back foot." We imagined (wrongly) that the mainstream actions of society would avoid this outcome, and ours was merely a footnote to other actions. In effect, we had misunderstood the situation. Science was the "honest broker" to which others looked for guidance. Other sectors viewed each other with caution or so lacked sufficient mutual confidence they were unable to initiate action. The established organs of respectable science that lacked the fast-paced knowledge to meaningfully assist, and while honorably seeking to intervene, were quickly side-lined by the rising clamor. It was left to science to correct itself, and science was not prepared for that task at such short notice. What was left was an unfunded assembly of thoughtful scientists that (in expressing balanced and cautious views) was in danger of representing the margins of the dialogue. Truly, events had moved rapidly.

If these events signal a deeper structural problem with the evolution of the scientific enterprise, particularly how it is funded and maintained, then that is a question society may wish to consider more deeply. Certainly, the human and economic costs of undoing scientific errors that are widely reported and believed in the public domain are significant for all concerned. The "righting of the scientific ship" when controversies appear also involves great societal interests. However, it is appropriate that all consider how the almost imperceptible changes in the scientific ecosystem in recent decades impact on the deeper structure and values of science itself. The issues include the need for short-term scientific funding and the overwhelming pressures for scientists to draw immediate attention and recognition to obtain that funding. While we have shown that such factors may have distorted the whole nanotechnology enterprise, these experiences also lead us to question how science can sustain its roots in integrity and trust in the future.

Many will consider that the current trends fail to promote the best science, lead to unhealthy overselling, and weaken focus on durable outcomes. While some of these practices are universally lamented, in the unique role science plays during periods of unexpected and emerging societal risk, we see a more profound problem. During those times, the long legacy of integrity and drive for truth embodied in the scientific tradition is a critical resource and safeguard for society. The question is whether these values are sustainable in the current framework. The nanotechnology experience may be just a small but early warning. Leaders may now wish to reflect deeply on the implications of a world in which competition for resources drives scientists to behave in ways antithetical to the common good, and a world in which there are no trusted arbiters of scientific and technical outcomes. Society itself may have a larger role to protect the fabric of science, as one of its most precious resources.

Meanwhile, the confused dialogue on nanosafety was not the only consequence. As we noted earlier, the central observation that endogenous nanoscale objects could access the key strategic niches denied in conventional therapeutics was always part of the great strategic goal of the nanoscale medicines. The events around nanosafety changed focus away from fundamental understanding of the defense mechanisms that were frustrating these ambitions, and in turn that changed the destiny of the first

decades of nanomedicine. At first almost imperceptibility, the focus on the larger achievements shifted, and became more an effort to deliver drugs in nanoscale capsules. That was a worthwhile venture, but it was unlikely to sustain broad interest in nanoscale therapeutics. Ultimately, it was those promises of radical innovations that would have made a radical shift in our capacity to innovate in therapeutics that had underpinned the exceptional support for the "nanomedicine enterprise," and as the light dimmed, so did the support. Not all of these events were visible at the time, and many genuine and energetic efforts were made by responsible leaders to act well and with the understanding of the period. Another message to the future then is that the cost of ill-considered directions and scientific enterprises is not just in the objectives themselves (e.g., nanosafety) but in the "opportunity cost," and in terms of lost focus, resources, and the drive to develop a nanomedicine that would attract great investments.

6.2.6 Lessons for future academic leaderships

Now it is time for the university, not just as a scientific resource, but as a core of reflective thought to appear on the stage of nanotechnology history. We have seen that teams of independent scientists that were required to unravel the controversy were (sensibly and unavoidably) recruited from universities. Still, the overall role of academia during these times deserves a deeper kind of consideration that distance and reflection can provide. Most will now agree that during the early years too much emphasis was placed by academic scientists in the field on naïve testing of nanomaterials, executed in university environments where there was insufficient experience or resources. To begin with, it was not evident that even the best (then known) testing methods would yield meaningful answers. Worse still, universities were not the right forum for this kind of work. We have seen how those arrangements fed into erroneous scientific directions and excessive claims of risk. This outcome was purely an accident in how nanoparticles were assessed. Reflective leaders from all sectors should note carefully that any scientific arrangement that is capable of creating broadly incorrect results can hardly be relied on to catch the subtle and substantive danger. This then is not a question of "sides" of a scientific argument, but at root, the appropriate level and framing of the scientific endeavor. Ineffective framing that locks in early on is hard to undo and can be positively a danger in itself.

In the aftermath, it is easy to critique these events based in university environments, but that would be a mistake without understanding the drivers for these events. Thus, one may question why, in our generation, the very academic environments that excelled at generating insights and traditionally had acted as reflective and cautious guides to the future could have followed such a narrow and uncritical pathway. Most will appreciate that academia, because of its position, risked a lot in reputation by making exaggerated claims and failing to critically assess the situation as it unfolded.

Even now we cannot be sure if we have fully appreciated the extent of lost confidence and trust in the academic enterprise engendered by these outcomes. Yet, we hope that readers will appreciate that it was only natural that funding would be directed at apparently urgent questions, and it was unavoidable that the available pool of scientists largely resided within the universities. For reasons discussed earlier, the academic pressure to find resources accounts for the rest. There were no exceptional dynamics underlying these outcomes, and the outcomes are now encoded into the academic funding and support ecosystem. Efforts to improve some of these mechanisms have been undertaken in the succeeding years, but those have not substantially changed the internal dynamics within academic science.

There were, however, other far-reaching outcomes that shaped the whole nanotechnology enterprise in ways that were not evident at the time. For instance, many of the best scientists who could have contributed to advancing the understanding of nanoscale biology were not fully motivated to do so because they distrusted the shape of the growing university endeavor as they believed it lacked substance and was fueled by short-term funding interests. Their absence left a vacuum, and efforts to investigate the fundamental principles of nanoscale biology were, for a time, overwhelmed.

In framing funding strategies, these potential implications for the university were only evident as time went on. Sincere efforts were made at the early moments, particularly by a few key policy-funding leaders, to make correct judgments. It was not always clear how much freedom the existing framework of science organization and funding allowed them, and their seniority may have limited time and energy they could expend on specific arenas. Still, what progress was made was driven by good leaders who had an entrepreneurial breadth of vision and clarity of purpose, and sufficient depth to appreciate the relevant aspects of science. Such people are unique assets in a critical moment, and they are not as exchangeable as general (and equally outstanding) managers are in such moments. In future, it may be necessary to consider whether the existing lines and systems of management and organizational responsibility are appropriate when there are significant time-sensitive or otherwise critical issues that affect all of society to be dealt with. That observation will come as no surprise to senior executives, but it is remarkable how easy it is to forget well-known things when science and technical tsunamis hit.

6.2.7 Institutional, sectoral, and policy reactions

Seen in the afterlight of the controversy about nanosafety in those years, and against a backdrop of as yet very incomplete uptake of the technology into industry and society, some of the early policy actions around safety issues could be read as overreaction. On the contrary, our view there is that the steps taken were prudent, proportionate, and justified. There were and still are (albeit now more subtle and confined) credible scientific reasons to expect distinctive biological outcomes on

the nanoscale. With the prospect of widespread exposure to these new structures, it was barely responsible to have done otherwise than act. We may ask, of course, if the worst fears had been realized, would we have been prepared? Those closest to the responsibility to manage such questions may still doubt that enough was done sufficiently quickly.

Nonetheless, those that seek lessons for the future should also recognize that our system of institutions and governance sought to execute their roles with distinction. At the time, some may have seen their reactions as excessive or ineffective. However, one needs to stand back to understand more deeply the issues to fairly represent our institutions and systems of checks and balances. The European Parliament expressed strong concerns about the lack of preparedness [23], the European Commission responded by efforts to make reasoned policy [24], and dedicated agents of policy attempted to codify those policies into practical frameworks. These questions were handled at the highest levels in the United States, again by highly committed and effective leaders. Appropriate action was taken in China, and significantly, there was dialogue between all major economies. Whatever the shortcoming of the machinery as it then stood, we cannot say it failed to act.

Industry, like science, is much too varied a sector for a single outcome or assessment. Some sectors of industry made reasoned progress. Some, fewer, took proactive positions of ethical leadership and left an abiding respect in those with whom they came in contact. Those of us who have experienced this outcome will recognize the hint of a future alternative to the mainstream of events that eventually pertained. Again, individual leadership played a significant role. Some mistook the moment, and resisted scrutiny, and withdrew into "beliefs" that were loudly stated. It was fortunate for all that; on this occasion, some of those beliefs were not incorrect. Some in industry, perhaps being uncertain of their position, were frozen with uncertainty. Some critical observers even believed there was a desire to delay useful outcomes. Future industry leaders, entering into such a situation, will need to reflect deeply on their role. They will require quite exceptional strength of leadership for they have to make some of the most conflicted decisions. If wise, they will not risk appearing to "begrudgingly" cooperate and engineer constant delays. Delay is a tactic, not a strategy. Alternatives should be found. Such leaders will, if our experience is representative, feel under attack, sometimes unreasonably so. Some attacks may even be based on erroneous science. Scientists, and society at large, may reflect if it is fair (or efficient) for society to leave them to face unwarranted and ill-founded attacks themselves.

It may also be useful for those most essential non-governmental organizations that honorably and independently seek to defend the public interest to carefully consider the lessons learned. Future leaders and champions of such organizations will do well to recognize that confounding exaggerated conceptions of emerging risk with a more nuanced and cautious scientific approach serves no long-term interest, least of all that of the public. We have argued that such outcomes can skew a more realistic and important focus, and delay investigation of potentially real threats posed by new

technologies. We also cannot measure whether a more cautious approach to the science by such organizations would have reduced unmerited polarization between the sectors, that polarization possibly making it harder to get to the truth. On the other hand, some certainly felt that without the great effort to make these issues seem serious in the public, the interest and attention would shrink, and even legitimate concerns would not be examined. Such are the overheads of a system of checks and balances applied to (in principle) "fact-based" societal issues.

More profoundly, such non-governmental organizations have a natural role (in some way analogous to that of the universities) to speak their truth independently of governments and institutions. They play a lasting and immeasurably valuable "backstop" role for society. It is therefore essential that they (like scientists) act proportionately and preserve the public trust so that their capacity to warn is undiminished. Like scientists in our generation, not every step was taken by non-governmental organizations to protect that trust and prestige. Having a backstop may one day be important for us all.

We now briefly move forward to the present and summarize the overall outcome and current status of the scientific research endeavor.

6.3 Modern understanding of scientific principles governing nanoscale biology and nanosafety

We now see that the original concepts of biological nanoscale processing provided the right longer-term insights. We have noted that original thinking was deflected by the overwhelming focus on acute toxicity, though that is now righting itself. We understand more deeply how, over eons of exogenous nanoparticulate challenges from pathogens to dusts, biology has evolved very complex layers of nanoscale recognition that are able to assign a biologically meaningful identity to even the most complex nanoscale objects. Indeed, biology pays so much attention to this size scale because that is where much of its information is passed and where it requires greatest security. The original aspirations were not wrong in thinking that, if we could control these, we would do something qualitatively new in biology and medicine. This required time and redirected focus to recoup.

As noted earlier, this special processing at those size scales evolved strong and ancient protections against nanoscale threats. While nothing in safety is guaranteed, and all requires caution, this also gives us hints that we might look for dangers in the subtle evasion of those mechanisms. That is because history shows that unresolved protective mechanisms that do not have an exit strategy may turn the cell against itself in ill-controlled ways. At the time of writing, we are seeking to consciously challenge these mechanisms and "test the defenses" to understand them better. This appears a promising direction to detect subtle hazards.

Of course, while interpretation of epidemiological evidence is fraught with dangers, it is worth considering. Currently, for example, we are investigating in great depth the potential role of immune dysregulation in all dusts, man-made, environmental, and especially complex-shaped non-degradable particles released from industrial processes. Our attention is increasingly focused on very narrow classes of shape (Figure 6.1), which could perhaps be considered the nanoscale equivalent of very specific toxic chemicals in the background of a much broader range of inert particulates, for which we have at present no real evidence of hazard [25, 26]. This description should send several clear signals to those concerned with nanosafety. Firstly, it is necessary to really go deeply into the mechanisms to identify risks. Secondly, while superficially some of these remarks may appear to dampen safety

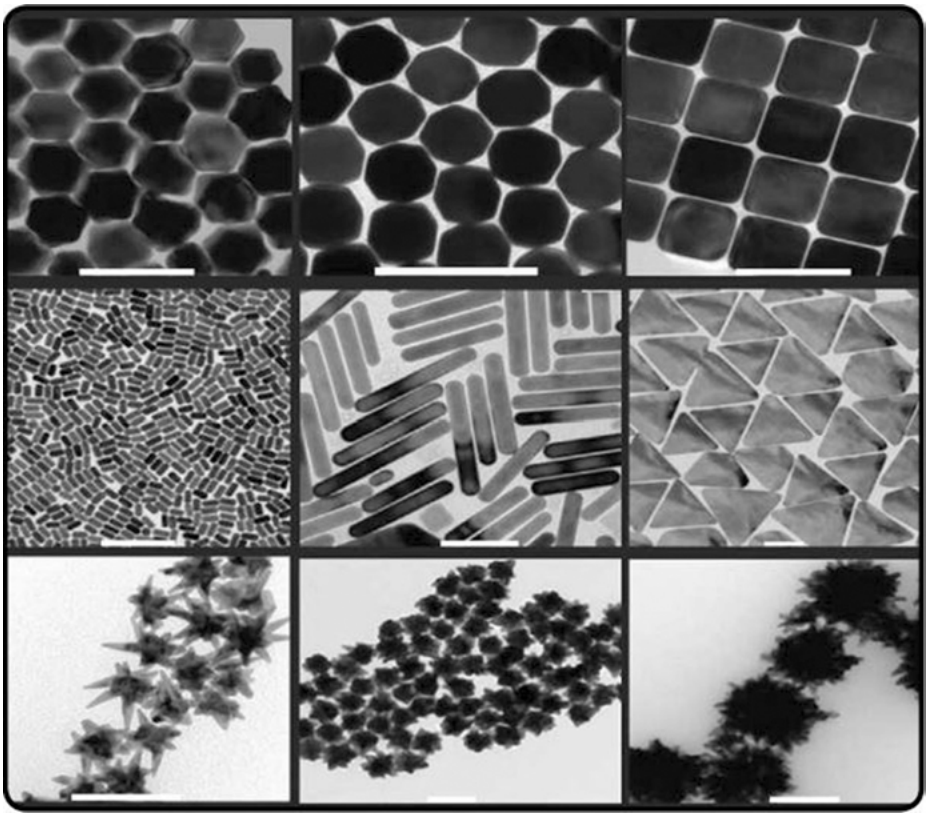

Figure 6.1: Library of anisotropic gold nanoparticles: transmission electron microscopy micrographs by Željka Krpetić, Qi Cai, and Jennifer Cookman (CBNI, UCD). Originally published in the open-source report: Science for Environment Policy. Assessing the environmental safety of manufactured nanomaterials. In-depth report 14 produced for the European Commission, DG Environment by the Science Communication Unit, UWE, Bristol. 2017. Available at http://ec.europa.eu/science-environment-policy [25].

concerns for nanostructures, it is not a license to pollute. The widespread dissemination of non-degrading or slowly degrading waste, such as plastic particulates, that wears or weathers into numerous different particle types can never be a good choice for society. Within that vast pool of particulates, it now does seem likely there will be some that have an impact on health. It remains to be established just how significant this effect is. This means that the process of understanding, capturing, regulating, and monitoring nanoscale waste, debris, or indeed entirely new structures is just beginning. It will take the remaining time at least from this generation before that is firmly under control.

Readers will observe, however, just how far this picture is from the concerns about widespread risk arising from a naïve and innocent biology being presented with nanostructures, how different the truth turned out to be from those initial fears, and how necessary it was to take risks seriously at the scientific level, not just operate old scientific machineries and follow well-worn paths.

We believe that the most radical outcomes we may now expect in the nanoscale world are the applications of nanoscale biological recognition and identity in human health. While we are still early on in our efforts, we have now measured the significance of the mechanisms of key information-rich message-passing biological machinery, which we earlier illustrated with the example of extracellular vesicles communicating between tumor cells and the immune system. We are now certain that breaking into those messaging systems will provide us with immense therapeutic power. It will allow nanoscale medicines to break away from simple applications of drug delivery to qualitatively new scientific and medical developments. Many practical outcomes will be possible as a consequence. Our ability to safely use nanostructures to deliver foreign RNA as vaccines against COVID-19 while meeting with some success around the world, is comparatively so much less efficient than the virus they seek to defeat because, unlike the virus, we are not systematically capable of overcoming endogenous cellular defense mechanisms [27].

The predictions we make here are different from those made in the past. They are based on accumulated knowledge of great depth. And, significantly, we now have in our hands the first, albeit primitive, concrete examples that achieve some outcomes that have eluded us for decades. We feel certain that these achievements are now within reach. Experience shows, though, that it would be unwise to predict how quickly these can be brought to practical fruition. This chapter attempts to lay out durable messages and understanding. Future readers will be able to see how these issues unfolded. For present readers, it is more important to recognize that our endeavor is moving again, quickly.

6.3.1 Morals and ethics in the context of modern science and society

We who lived through these experiences are sometimes asked how they impact the broader question of moral and ethical considerations. It is possible that this chapter will stimulate those more professionally qualified, such as moral philosophers, to engage with such questions. Their legacy, depth, and understanding are needed, among all of the other actors who have appeared in this chapter, if we are to truly advance society. For what it is worth we offer a more informal perspective here. It seems to us that the fundamental moral issues are quite well defined and potentially answerable, providing one shares certain basic concepts. At root, we address great scientific and technological developments (or science- and technology-addressable events, such a breakthrough pandemics) that have the potential to harm us all, ultimately equally, and, with the right decisions, there is the potential for great benefit over time. We hold it axiomatic that there exists a moral imperative for all to act appropriately to protect ourselves, our world, our children's future, and the future of humanity. Surely, upon reflection every part of society, every interest, will acknowledge that. One suspects that this may be the place to start any significant and deep dialogue about the future because that is the last point at which we are likely all to agree.

Ethics, how morals are transduced into actions or conduct, is quite another matter. We emphasized several times that ours is not a story of simple rights and wrongs in ethical codes. Almost every line of this chapter is suffused with the challenges and complexity of the ethical dilemma presented by these great "new risk" challenges, complicated more by the pace of events, and the confounding evidence and views being presented from so many directions. Underlying all of our discussion, the thoughtful reader will recognize the message that even if modern science and society leave our moral framework secure, our understanding of our responsibilities and modes of action is now dated. Our systems, and the ethical frameworks they support, while not incorrect, are simply not designed for the kinds of challenges they now face. They are "bunkered" into silos of independent thought, action, and ethics that, in isolation, seem appropriate, but collectively fail to address rapid societal challenges.

For example, if we take academia (for that we know best), one must ask the questions directly: What have we learned from the "near miss" of nanotechnology? Where do we see an evolving concept of ethics that address the issues described here? What has fundamentally changed to moderate irreconcilable pressures on young scholars to jump onto a "band wagon" that feeds panic and fails to address risk? It would seem to an (albeit incompletely qualified) observer of these events that many of the key domains of thought, scholarship, and planning are "absent without leave" in these issues. At the time of writing, there appears little reflective thought being dedicated to our need for joined-up and rational frameworks of action, systems of values and ethics, to respond to these critical overarching events that will continue to confront us. It will

be necessary for all of society, including its leaders, to reflect deeply on these questions if, when the moment comes, we are to be ready.

6.4 Conclusion and questions that remain for future consideration

We conclude this discussion by summarizing some of the more specific questions that we feel merit consideration. While many of these questions are posed with a specific background and experience of the "near miss" of nanotechnology, they are broadly applicable to our present and future circumstances. Certainly, at this point in the evolution of nanotechnology it would not be necessary or effective to implement some of the wide -ranging changes discussed here. Therefore, our comments should be understood in the context of the future.

First, should the process of dealing with the question of safety as a response to radically new developments that involve technology and science be reordered? There may be opportunities for minor adjustments such as "safety by design" where that is feasible, and as technologies mature, that should become almost an automatic principle. However, peering into the future, we foresee that radically innovative technologies could introduce new kinds of risk. Furthermore, other society-wide threats requiring mobilization of science and technology will emerge in different contexts that may require a more joined-up approach than we currently possess. The great lesson we have relearnt is that to protect human society and simultaneously support a free and unfettered human passion for invention requires us to have systems and people in place ahead of the events, or those events will control us. Effort to frame those systems while trying to address the emerging risk is simply not feasible, and our efforts were incomplete. We were rescued by the fact that no widespread application of a very harmful technology occurred.

There are many elements required for such a system of early warning and response to society-wide threats. However, at their core must be science and technology itself. One of the key lessons we have learned is that any rising arena of risk must be analyzed deeply scientifically very early on. This means its conceptual foundations, governing principles, and mechanisms must be uncovered from the beginning, rather than wait until we are forced only to deal with examples in crisis. In our generation, we inverted the order of these events because there was no choice – we were not prepared. Is it conceivable that thought leaders can be formed into teams (international think tanks) ahead of time to carry out explicit serious and deep research on the principles long before they materialize, allowing knowledge to mature into practice? Could such "new risk" teams be drawn together on a grander scale so they learn overarching principles from each other and do not reinvent the process each time? As we write we see that perhaps the last opportunities to implement such ideas in artificial intelligence,

convergent-synthetic biology, pathogenic species breakthrough, or "percolation" pandemics are likely to occur in the next few years. Could any of these lead to such unexpected and dramatic challenges to the scientific and technical status quo that would dysregulate society itself? Are we as a broader society prepared at the systems level?

Such suggestions are made easier than realized because of realities on the ground. Still, while competition may be a fundamental and necessary dynamic, perhaps the way competition is manifested is not. Would it be wise for future leaders of industry to reflect on how they can make such a broader societal innovation and workflow (that also considers safety) work for, rather than against, them? It was in our generation, and likely will remain in future, a non-trivial problem for industrial competitors to engage in frameworks of advanced research that impact whole arenas, while remaining competitive in their own activity. However, we have also seen that failure to deal with this tension does not have a useful outcome. We should support such efforts. Surely it is not in society's best interest to see industry, as major generators and distributors of wealth, health, and well-being, to be left on the "back foot", if that can be avoided. Could far-sighted industry leaders, with sufficient resources, security, and confidence in their own status find the way forward for this key sector of society?

If we really wish to innovate whole joined-up systems of safe development, the question of how nations and blocks of nations will engage is also critical. From the perspective and experiences of this generation at least, much can only be successfully achieved with global cooperation at the scientific, technological, and policy levels. However, readers will recognize that at the time of writing the world appears to be becoming less susceptible to international outcomes. While it is not the role of even the most broad-minded scientist to advise political leaders on what is (and what is not) feasible in their arena, it would be wrong for those with the experience of our generation not to remind all that many problems are hard to solve in isolation from others that create or share those problems. Perhaps here also the expression of competition is not as immutable as we think.

We have said much about the role of academia, surely enough to suggest the need for reflection within our own house. However, as with much of this discussion, we as academics ourselves alone are unable to address these questions. Which leader of an institution will be able to tell their young colleagues to reserve their search for sparse resources, and instead keep only to the ruthlessly hard-fought arenas that fund fundamental research? Which academic director will be able to advise those young colleagues that they should not appear on television and adopt a position that perhaps overly exaggerates, excites, and stimulates some topic but they should instead go to the laboratory and fight the battle there? If science and technology are the root stock of our wealth, health, and development, should not society take a hand? Competition in science as with all else is important and beneficial, but could its present mode of expression create pressures that could undermine the very fabric of science, and all that it stands for? These questions should be asked now.

Those of us who witnessed the efforts to master, systematize, and render rational the nanoscale arena will recall being impressed both by the quality, integrity, and dedication of those at all levels charged with the responsibilities in their different domains. The facts are that many of these efforts are barely recognized, especially after the events. This is far from the experience of successful actors in other areas. As it happens, these individuals do not have the right that some scientists took to themselves to popularize their current beliefs, and they often work in quiet obscurity. In fact, some of these remarks apply to the finest right across all the domains, from science, industry, and non-governmental organizations. Whether the present arrangements will allow society to continue to draw forth talented and dedicated people remains to be seen. To some this may seem like a minor point, besides the others, but our generation has relearnt the importance of having the right leaders and individuals in offices both high and low when technology- and science-driven system-wide crises arise. That durable need for the highest qualities of courage and settled judgment of individuals in the relevant roles will not diminish.

What then are the lasting messages? Certainly, it was never the purpose of this chapter to address all of the important questions outlined above. We hope instead to have asked some of the right ones. Perhaps, we should leave the reader with the point that the benefits and risks entailed by or resolvable by technology are no longer confined to our village, our city, or our country alone. Perhaps therefore, it is worth considering whether the issues raised by the pace and scale of such new opportunities and potential risks can still be effectively dealt with using ways of thinking and systems that evolved to confront more isolated and limited circumstances. And to ask if there are better pathways for human development that open new avenues of progress for humanity and our earthly home.

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7 The synergistic ethics interaction with nanoengineering, dentistry, and dental engineering

When choosing something worth doing, never give up and try does not disappoint anyone.

Sir Prof. Harry Kroto (1939–2016)
Winner of Nobel Prize in Chemistry in 1996

7.1 Introduction

7.1.1 The genesis of the study: A few personal comments by Leszek A. Dobrzanski

I have been friends with Prof. Marcel Van de Voorde for over a quarter of a century. I respect him for numerous initiatives and activities, including the White Paper [1]; the Bologna initiative to standardize three-cycle studies in Europe and many other initiatives for a united Europe and its inhabitants; the edited 15-volume encyclopedia of nanosciences and nanotechnologies [2]; and a research book on Engineering, Medicine, and Science at the Nanoscale [3]. Therefore, I was not surprised by his next initiative to organize a team of authors and edit a book on ethical issues in nanotechnology, or even in modern science in general. However, I was surprised that he had just invited me to this elite group of authors. I am not a philosopher; I do not deal with ethics professionally. It was my most significant doubt. But . . .

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I am a Catholic, brought up on Christian traditions and in the spirit of helping everyone with whom Fate has come into contact with me. It is impossible not to quote here the words that the family home instilled in me and which I try to pass on to my children and grandchildren. This thought was beautifully formulated by the former Polish Minister of Foreign Affairs, Prof. Władysław Bartoszewski "It's worth being decent . . . " [4]. The late Fr. Prof. Józef Tischner, whom I had the honor to meet personally years ago, formulated this thought in more detail as follows: "Our main concern in our world is: to escape the evil that is now threatening us, to achieve the good that can be achieved here and now" [5]. For 50 years, I have been actively involved in science, research, training engineering, and scientific staff. I have written dozens of books and hundreds of scientific articles, published scientific journals, organized dozens of international scientific conferences, and been active in scientific councils of various scientific institutions and publishing houses. I have been a professor for 25 years. I have held numerous honorable academic positions, including Dean, Vice-Rector of two Universities, Deputy Director of a Scientific Institute, and for three years been the Director of a Scientific Center in a private institution. I have a lot of experience. I have worked with thousands of people in many countries. I have always tried to be dignified when thinking of other people. I had dozens, if not hundreds, of discussions with the late Professor of Philosophy Jacek Rąb and my longtime Secretary and Master of Philosophy, Katarzyna Gołombek. I cannot undertake a research dissertation on ethics but can present a research essay on this subject. Prof. Marcel Van de Voorde convinced me, and I took up this job, dedicating it to him, my friend, for his 85th birthday.

And here is a place to explain the adopted motto of this study. I had the honor of meeting Prof. Harry Kroto. I even thought that one day I would be able to invite him to Poland. Unfortunately, we didn't make it, because Fate wanted otherwise. So, guided by his words, I try to do this task in the best possible way to meet all expectations.

To cooperate in the preparation of this work, I invited a team of co-authors with whom I have been collaborating for years in the field of issues related to the implementation of the new scientific discipline "Dental engineering," in the creation of which we have our joint participation.

7.1.2 Purpose of the study

So what is the problem we have to analyze? In this chapter, we want to combine ethics as the leading subject of this book with what has been occupying our attention, time, and skills for several years. We will combine it with nanotechnology and dental engineering, as well as with dentistry, to which this engineering activity is subordinated. These are the issues that we have devoted ourselves entirely to,

especially in the last three years, working at the ASKLEPIOS Science Center in Gliwice, Poland. Figure 7.1 shows symbolically three possible variants of connections between these branches of knowledge and professional practice. These are the three possible concepts:

Figure 7.1: Allegorical representation of the three concepts of the interconnection of ethics, nanotechnology, dental engineering, and dentistry (a) through the medieval deity Światowit with four faces combining four points of view in one head, (b) through the Chinese censer with three legs and a shaped lid, (c) through three linden trunks fused at the base with a common root.

1. Equivalent connections between these four areas, pictured by Światowit as "World's Owner," a Slavic deity worshipped primarily in the twelfth century by the lost tribe of the Polabian Slavs – Ranów, who lived on the island of Rügen in the Arkona castle; the statue depicts a deity with four faces, each looking in a different direction, symbolically representing four parts of the world, combining four points of view in one head;
2. The relationship in which the ethics joins other areas, such as heavily arched openwork cover with four brackets in the form of elephant's head and a lion figurine Chinese lying at the top of the Chinese censer tradition dating back centuries, made at the turn of the century as cast bronze in the shape of a spherical vase on three animal legs, with scarecrows at the base; and on the belly, it is decorated with relief with two pairs of dragons holding a fireball, with ears with dragon heads on the sides and a belt with a meandering pattern around the top edge;
3. or, finally, connections in which other areas grow out of ethics as the basis, as in the case of small-leaved linden, in which three large trunks grow from one common root.

The current state of views and knowledge in each of these four thematic areas will be successively discussed in the remainder of this study. It will be done to accept any of these concepts.

This study aims to provide a general description of nanotechnology, dentistry, dental engineering, and ethics, and to define the interrelationships between these areas and to indicate their development prospects concerning the current requirements of the present day.

7.2 General characteristics of dentistry and dental engineering

7.2.1 The scope of conservative, endodontic, and periodontal treatment of diseases of the oral cavity

Modern dentistry is mainly concerned with the functioning, pathologies, and treatment of teeth, periodontium, tongue, mucosa, and other tissues of and around the oral cavity, as well as the temporomandibular joint. These issues are detailed in [6]. Oral health is an essential part of those activities covered by the United Nations in the Sustainable Development Goals [7] for the protection of health and the extension of human life. It is an essential aspect of health protection, given the fact that oral diseases directly or indirectly affect or cause many systemic diseases and complications. Treatment of these diseases result in incurring high costs, absence from work, and requiring social insurance funds, and also disability benefits. The problem increases with the life of the individual suffering from oral diseases, which has a significant impact on a broad scale [8]. P binding oral health has a positive effect on the economy by reducing the burden on the health-care system and insurance. For obvious reasons, the problem is particularly worsening in the low-income and lower middle-income countries of the LIC/LMIC.

The most widespread diseases of the oral cavity include caries, periodontal diseases, and partial or complete toothlessness. Caries, as a bacterial disease, has long reached a pandemic scale and affects approximately 3 to 5 billion people worldwide [9, 10]. Relatively recently, it has been recognized that periodontal disease has reached the size of an epidemic, which has been recognized relatively recently. The problem affects about 50% of adults worldwide, and about 83% of the entire world's population experience periodontal bleeding [6] during their lifetime. These diseases usually eventually require tooth extraction, resulting in edentulousness. Toothlessness harms food consumption, and indirectly on many other dysfunctions of the body, regardless of the reduction in aesthetic values and self-esteem of patients. Oral diseases, including caries and periodontal diseases, and toothlessness which after some time is an inevitable consequence of both of these

diseases, have an impact on the general health of patients affected by these diseases through the risk of numerous systemic complications. In the current situation, it is therefore unacceptable to neglect or even ignore this group of diseases not only by the governments in individual countries, but also by the patients themselves, from prophylaxis, through treatment of oral cavity diseases to treatment of severe systemic complications in the most severe cases. These include complications of caries, including abscess and stroke, coronary artery disease, endocarditis, bacterial pneumonia, rheumatoid arthritis, nephritis, osteoporosis, premature delivery, and loss of infant birth weight, and even death [11–16]. The cause of numerous complications and systemic diseases may also be a direct disease focus associated with periodontal diseases in the oral cavity. These diseases include, among others, stroke and dementia; diseases of the lungs, kidneys, cancer of the mouth and pancreas [17–22]; diseases of the circulatory system; cardiovascular diseases including heart failure; and ischemic disease including hypertension [23–28]. Chewing dysfunction caused by toothlessness causes the inability to grind food and the inability to chew, which affects, among others, cerebrospinal fluid-related migraines and headaches, pains in the cervical spine, obstructive sleep apnea, and mood disorders; in the elderly they also adversely affect the hippocampus in the temporal lobe of the forebrain [29–35] and related spatial memory disorders and episodic conditions, worsening of multiple sclerosis, dementia, and Alzheimer's disease. They can also be the cause of stroke, pneumonia and respiratory tract infections, some cancers, including large intestine and oral cavity, gastrointestinal diseases, oesophagus and gastrointestinal tract, duodenum, pancreas, insulin resistance, diabetes, kidney disease, rheumatoid arthritis, and adverse pregnancy outcomes [36–48]. The measure of the adverse effect of these diseases is the DALY index, which expresses the total number of life-years lost as a result of premature death or damage to health as a result of trauma or disease, compared to 100,000 inhabitants [49]. The maximum values of this indicator occurring anywhere in the world are 48 years in the case of caries, 160 years in the case of periodontitis, and 300 years in the case of toothlessness [50]. These indicators do not take into account systemic diseases caused by oral diseases but relate directly to individual conditions.

Generally speaking, there are several specializations in dentistry, including conservative dentistry, endodontics, periodontics, prosthetics, and implantology. The most common treatment is conservative treatment, which consists in the preparation of carious lesions by drilling and subsequent reconstruction of the hard tissues of the tooth. The prepared cavities, especially of large teeth, are currently most often filled with the indirect method, using a system of inlays, onlays, and overlays as well as crowns produced in the center of manufacturing prosthetic elements based on impressions prepared by a dentist. These filler posts are most often made of ceramic materials, including porcelain, but also gold or composite materials, or gold and ceramic alloys [51, 52]. They are assembled by the dentist using bonding types of cement. Traditional direct filling of carious cavities, adequately

prepared by a dentist, is entirely performed in a dental clinic. Various materials are used for the fillings, including composite usually of tooth color, silicone and silicophosphate types of cement and compomers [53] or glass ionomer (GIC) types of cement which are typically used as temporary fillings. It is the dentist's responsibility to select this material properly. Thin layers of photopolymerized composites are applied after a thin primer, or a binder is applied directly to the prepared teeth. After the composite is partially cured with a light beam of the appropriate wavelength, the final formation and polishing of the surface take place. Coupling agents such as silane are used to enhance the bonding of the resin matrix and the filler particles. Amalgams in which mercury is the main ingredient can also be used as dental fillings. By 2030, amalgam fillings will be withdrawn entirely from use in the European Union [54, 55]. In the United States, the FDA considers amalgam safe for adults and children over six years of age [56]. As amalgams are widely used in many countries against the poorest social groups, this poses a serious ethical problem. Given that such use is mainly determined by the relatively low cost, other aspects including aesthetic considerations, are ignored as criteria for selecting this material, and it could be considered a violation of the Human Rights Convention [57] on the grounds of discrimination or social exclusion.

The damage to the dental pulp and the accompanying pain caused by caries bacteria requires endodontic treatment [58–60]. Preparing the tooth to remove the dental pulp in the entire canal system, drilling and disinfection after shaping, and then filling with a replacement material replacing the living tissue will ensure the best hermetization of the root canal system. The most critical factor determining the success of endodontic treatment is the tightness of the anastomosis between the dentine and the material that tightly fills the root canal, to enable the further functioning of the tooth in the oral cavity. Composites with a polymeric polyester resin matrix with inorganic fillers can be used as the filling material. Due to the polymerization shrinkage, in such cases leakages may occur at the border with the walls of the root canal, making the treatment ineffective. Today, root canals are often filled with gutta-percha [61–66], which consists of 18–22% pure β gutta-percha, 59–75% zinc oxide, and 1.1–31.2% barium and strontium sulfate or other compounds as well as 1–4.1% wax and other polymers. The use of gutta-percha requires the use of a sealant based on synthetic resins each time. Gutta-percha is applied with cold and thermoplastic condensation methods or in the form of a powder with a sealant and nanosilver particles.

Periodontal diseases, that is, the dental suspension apparatus, are clinical severe problems in the field of oral diseases worldwide. The immediate cause of the periodontal disease is the disruption of host-microbial interactions near the gingiva due to the deposition of plaque and tartar, as a result of coalescence and biofilm accumulation of complex bacteria, coupled with an immunoinflammatory mechanism and other risk factors [67]. These risk factors of the periodontal disease [68–71] are modifiable, which offers modern dentistry an opportunity to treat them.

Periodontology concerns the treatment of periodontal diseases, which is always preceded by comprehensive diagnostics and proper planning of the procedure. The four-stage treatment [72, 73] begins with the hygienization phase and the initial treatment phase. It includes the appropriate non-surgical treatment phase and, alternatively, the surgical treatment phase when nonsurgical treatment has not brought satisfactory results, and the disease is severely advanced. The last stage is maintaining the condition of periodontal tissues achieved in the previous phases of treatment for many years. Untreated, periodontal disease causes loss of attachment and destruction of alveolar bone [74] and can also lead to tooth loss. Sometimes all teeth should be removed, even at the age of 40. Apart from periodontal diseases, the causes of tooth extraction include both caries and iatrogenic causes arising during its treatment. Dental extractions require prosthetic and/or implantological treatment.

7.2.2 Examples of nanoengineering applications in dentistry

Nanotechnology refers to the collection of various techniques and methods for the production of multiple products or their components at the level of single atoms or particles with linear nanometric sizes of 1–100 nm in at least one direction. Nanotechnology is one of the fundamental areas of science in the twenty-first century, mostly decisive for technological and economic progress and, in general, for the progress of civilization [75–80]. Research is used to design and manufacture nanoscale structures with new properties and cover the basics of understanding and shaping matter in the nanoscale [81] and the application of this basic knowledge in innovative activities [82]. Thanks to the development of nanotechnology, many products with unexpected properties and properties previously impossible to achieve with other methods and technologies have been produced. Nano-objects and nanomaterials of interest to nanotechnology are classified according to their characteristic dimension in one, two or three directions. Nano-objects can have three dimensions at the nanoscale, including nanodots, or two, such as nanofibers, nanorods, and nanotubes, where the nanotubes are hollow, or one external dimension in the nanoscale, such as nanoplate or nanoribbon [83].

One of the most extensive application departments of nanotechnology is currently the medical industry, which uses nanoelements, including for the analysis and treatment of long-term diseases such as heart disease and cancer [84]. The increased use of nanotechnology in medical diagnostics and device fabrication is currently driving the global nanotechnology market strongly. Biological processes, the production of organic molecules and cellular mechanisms at the nanoscale are at the heart of innovation in health care and medicine and have enabled implantation devices, biosensors, imaging technologies, and nanoscale therapeutics. Drug delivery systems, especially for cancer treatment, and non-invasive surgical technologies, have a significant market share. A wide range of nanotechnology applications

in health care is related to health care resulting from chronic diseases associated with an ageing population. The use of nanocoatings in healthcare and medicine is increasing [85]. All signalled issues are described in more detail in [6].

Due to the subject of this chapter, special attention has been paid to the application issues of nanotechnology in dentistry. Nanodentistics is a multidisciplinary research area that involves the application of new nanomaterials, nanotechnologies, and nanodevices, including nanobots, for the diagnosis and treatment of oral diseases. These issues are covered by numerous scientific and research activities, although many of them are still in the conceptual phase. Nanomaterials have been used in multiple products, e.g. for oral hygiene. A new discipline that has been named nanodentistry [86, 87] and this concept was introduced by Robert A. Freitas Jr. in [88], continuing his extensive research into nanomedicine in general [89, 90]. Nanodentistry [91, 92] includes innovative solutions in the diagnosis of diseases, therapy, and prevention, which fundamentally change the possibilities of maintaining oral health using nanomaterials [93, 94], biotechnology [95–97] with tissue engineering and based on nanotechnology, sophisticated oral health diagnostic and therapeutic tactics. Numerous activities and research work within the innovative paradigm of solving the problems of traditional dentistry aim at the use of biocompatible nanostructured materials for the development of a new generation of advanced clinical methods for effective oral hygiene. There are two main trends in nanodentistry. In the first stream, they include solutions implemented in clinical practice, or at least subjected to in vitro tests, for practical applications from toothpaste and anti-caries specifics, fluids for rinsing dental canals, filling composite materials used in endodontics, as well as binding materials and impression materials used in prosthetics. The increasing clinical application prospects in various fields of dentistry have nanodiamonds (NDs) [98–100], graphene and graphene nano family (GFN), sometimes also enhanced by the presence of growth factors. Graphene and graphene family of nanomaterials (GFN) may be applied to implants of titanium alloy and unusual effectively contribute to improving the properties of titanium and its alloys, to induce osseointegration by binding of biomolecules, and in animal studies confirmed harsh promote cell proliferation and accelerates differentiation of an osteogenic rat bone mesenchymal stem cells (rBMSCs) [101]. A multiphase nanocomposite with graphene and GFN can help prevent implant-induced infections. Graphene-based nanomaterials increase osteoconductivity, osteogenic differentiation and biomineralization [102]. A thin layer of GO and silver nanoparticles on a titanium substrate, obtained by depositing graphene oxide GO on the surface of titanium with numerous carboxyls, hydroxyls, and carbonyls with a negative charge favoring easy association with the positive Ag ions in an aqueous solution, and the layer obtained in this way is characterized by antibacterial properties, for example, against S. mutans and P. gingivalis [103]. There are real possibilities of using graphene and GFN in combination with titanium dental implants, bone regeneration membranes, resins, types of cement, and adhesives as well as for teeth whitening

treatments [104]. Electrophoretic deposition of GO and chitosan (CS) on hydroxyapatite-titanium substrate promotes improved deposition, proliferation, and differentiation of BMSC cells and better osseointegration of the implant after implantation [105]. Although hydroxyapatite (HA) exhibits a slow biological mechanism of interaction and low strength cannot be widely used, electrophoretic deposition of GO gives a chance for broader use of hydroxyapatite (HA) coatings [106]. Dental pulp stem cells (DPSCs) can be obtained relatively easily from extracted teeth [107]. Graphene and/or GFN-assisted stem cells seem to be applicable to restore missing teeth together with periodontal tissues [108]. More details on this issue are possible to find in [6]. The second group of activities in the field of nano-dentistry deals with study solutions that may appear to be almost science fiction issues, rather than engineering or medical facts. Unique and visionary concepts are the intention to develop and manufacture dental nanobots, which have become known as dentifrobots. One of their possible versions is a nanorobotic dentifrice in the occlusal area [88] that is deactivated, for example, if swallowed [109]. Dental nanobots could also be useful for relieving the pain associated with dentine hypersensitivity [110–112] or for quick tooth positioning [113], and to selectively seal dental tubules using natural biological materials [92]. Other details on nanodentistry are provided in [6]. Indeed, further progress of research in this area will bring a series of discoveries and solutions, both theoretical and practical, that will allow them to be implemented in everyday clinical practice in maintaining oral health and dental care over time.

7.2.3 The scope of dental engineering and implantological and prosthetic treatment

The consequence of both caries and periodontal diseases, as well as damage to the condition of the teeth, caused, for example, as a result of sports, communication, work accidents, and some developmental defects are the necessity to extract teeth. To avoid severe complications in the general health condition, mentioned previously, in each case, it is necessary to have a prosthetic reconstruction, which also requires the insertion of implants. In unusual cases, prosthetic restorations can be made on adequately prepared the patient's teeth. Details are provided in [6].

Prosthodontics, also known as dental prosthetics is part of stomatology, "pertaining to the diagnosis, treatment planning, rehabilitation and maintenance of the oral function, comfort, appearance and health of patients with clinical conditions associated with missing or deficient teeth and/or oral and maxillofacial tissues using biocompatible substitutes" [114]. The scope of dental and prosthetic treatment, which usually includes complex cases, includes full oral rehabilitation, oral implant surgery, occlusion functions, congenital disabilities of the dentition, disorders related to the temporomandibular joints (TMJ), including the planning and fabrication of various prosthetic restorations.

A surgical dental implant, also known as an endosseous implant, attaches to the bone of the jaw or mandible to support the dental prosthetic restoration, including crown, bridge, prosthesis, and facial prostheses. Enormous progress in the field of implantology and dental prosthetics has been made in the last few decades. Undoubted breakthrough in this field of the cylindrical dental implant with a helical surface and stabilization of the implant in the bone secondary to the biological process called osseointegration were made by PI Branemark [115–119]. Since then, the implants are usually screwed into an adequately prepared hole in the bone procession and may be loaded after 4–6 months of osseointegration. There are also other techniques for placing implants, for example, by hammering with a unique accessory [120]. After osseointegration is completed, the abutment can be mounted using the abutment screw, on which the prosthetic restoration is placed. The crown is assembled to the abutment using a small screw or dental cement, which is a suitable polymeric material. Fixed bridges or removable dentures can also be mounted on dental implants.

It is also possible to integrate the abutment with the implant. Immediate implantation procedures are also performed, combined with immediately preceding tooth extractions.

Also, small-diameter dental implants, also known as orthodontic micro-implants or micro-screws, are used, referred to as temporary anchor devices (TADs), to be inserted into the jaw bone as orthodontic anchors. TAD implants require removal after treatment and are therefore not fully osseointegrating.

Contemporary interventionist dentistry is closely related to the current level and state of engineering, resulting from the development of the industry. The developing industry with its productive, economic, spatial, and social functions is the basis of global prosperity and is included in the sustainable development economy. Economy 4.0 [49] closely related and inspired by the current stage of the industrial revolution Industry 4.0 [121–124] (Figure 7.2).

Numerous details were given in the author's work, together with a full, extended holistic model of Industry 4.0, composed of six intelligent components (Figure 7.3).

This model assumes the leading role of people. The basis of the model is the technological plane, which includes four complimentary components, including engineering materials designed following the Materials 4.0 methodology, technological processes of product production involving many technologies and, among others, additive technologies, technological machines enabling the implementation of these technological processes. The fourth component in the technological area is the cyber-physical CPS system, to which the presented Industry 4.0 model initially was unjustified in the source works [121–124]. The idea of Industry 4.0 is reflected in the area of dental engineering by the concept of Dentistry 4.0 [121–132], which is an essential determinant of the current level of clinical possibilities offered by modern dentistry. Clinical activity, according to the Dentistry 4.0 standards, is closely related to advanced engineering activities in the area referred to as

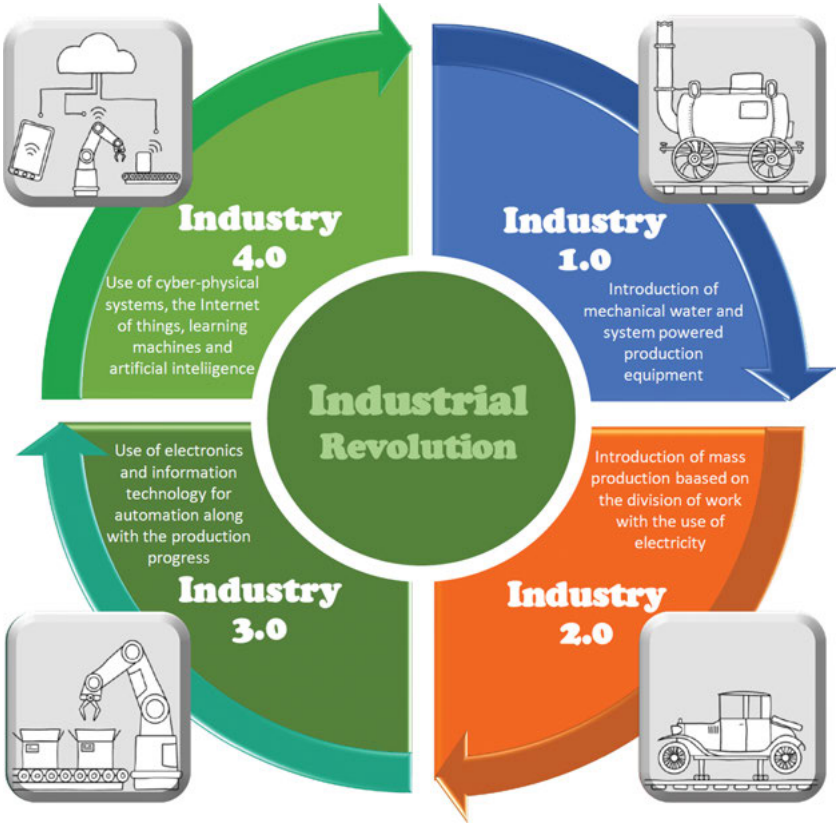

Figure 7.2: General diagram illustrating the four stages of the industrial revolution.

dental engineering. These activities include engineering design, including the structural design of prosthetic restorations and implants and dental implant-scaffolds using computer-aided CAD methods, using Cone beam computed tomography (CBCT) imaging of the patient's dentition and a virtually reproduced image of soft and hard tissues in the oral cavity, material design using advanced engineering materials, including with the required biocompatibility and technological design with computer-aided CAM production and the use of additive technologies.

Figure 7.4 shows a diagram of Dentistry 4.0. The current stage of Dentistry 4.0, described along with this newly introduced concept in these works, is characterized by advances in cloud computing, 3D imaging using CBCT, data manipulation and personalized additive technologies, the so-called 3D printing. The work [131] presents modern relations between a dentist and a dental engineer, whose cooperation and joint planning and implementation of tasks in the field of diagnostics with the use of CBCT and individual treatment planning and design of a prosthetic restoration with surgical templates. Usually, the selection of an appropriate prosthetic restoration is

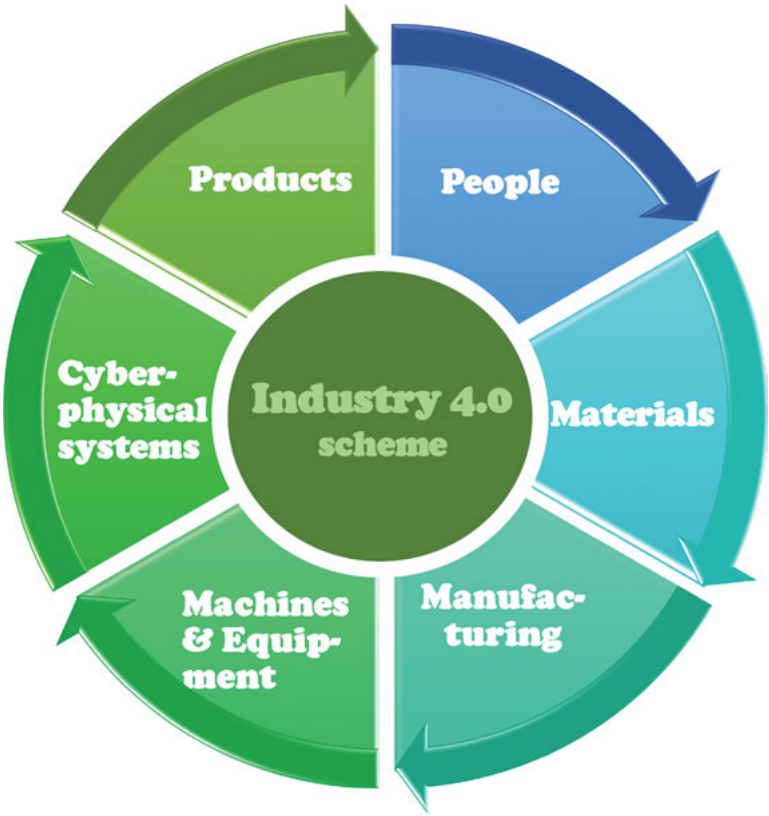

Figure 7.3: General diagram of the Industry 4.0 model showing the relationship between the individual components.

individually designed based on the diagnosis of the condition of the patient's teeth damage made using the conical tomography (CBCT) method. The authors of this chapter, together with representatives of other centers, actively participate in the research and dissemination of this diagnostic method and the development of digitization of dental diagnostics [131, 133–162].

The scope of dental engineering includes issues related to dentistry, material engineering, material process technology [163–166] and manufacturing engineering, including additive technologies [167–172] including computer-aided design and production CAD/CAM [134, 173–181] along with computer-aided medical imaging, issues of tissue engineering [174, 182, 183], as well as information technology, automation, and robotics, including means of production, machines, and technological devices involved in the processes of manufacturing prosthetic restorations and implanted devices, as well as in medical procedures during procedures performed by dentists. Medical imaging is an integral part of the entire approach, and

Figure 7.4: General diagram of the Dentistry 4.0 model showing synergistic relations between dentistry, dental engineering and materials engineering.

the system created on this basis, including with the use of intraoral [184–187] and extraoral [188–190] scans, and especially computed tomography with the CBCT cone-beam [135–140, 191] necessary for treatment planning and designing implants and prosthetic restorations. The relationship between dentistry and engineering issues is therefore apparent and therefore, a natural element of the current development stage of Industry 4.0. At the previous stage, which can be called Dentistry 3.0, and as mentioned earlier, the most essential attribute of real progress was the progress in conservative dentistry and the implementation of dental X-rays of patients [192]. In the implementation of the assumptions of Dentistry 4.0, as well as in the performance of the tasks of the engineering community and its humanistic mission toward society in general, material issues play an essential role. This technological level, apart from materials with the material design stage achieved, Materials 4.0 requires the use of appropriately computerized, robotic and automated machines and technological devices as well as various manufacturing processes, including additive

manufacturing. As a result of many trials and experiments as well as many years of research and application experience in dental prosthetics, many materials are used, practically from all groups of biomaterials. The most commonly used metal materials used in the manufacture of implants and scaffolds are titanium and its alloys [174, 182, 193–204] as well as niobium and tantalum and their alloys. For dental applications, moreover, cobalt alloys [205–214] and precious metal alloys are also used. Light metals, also possible to be used for implants and non-biodegradable scaffolds for dental purposes, include Mg and its alloys [215].

Concerning the mentioned metal alloys, various manufacturing technologies are used, including casting, production with powder metallurgy methods, machining, and they can also be successfully used in additive manufacturing, including SLS/SLM technology. Additive manufacturing of AM is increasingly used in dental prosthetics [168, 180, 216], and to metal prosthetic restorations mainly selective laser sintering (SLS), also called selective laser melting (SLM) or DMLS (direct metal laser sintering), which in fact, they apply to the same process when sintering occurs with a liquid phase [217]. Models, as well as removable and temporary prosthetic restorations, are made by stereolithography from polymeric materials.

For the production of porous scaffolds and implant-scaffolds, medical, including dental implants, additive technologies are most often used in conjunction with prior CAD/CAM design as competing with casting or machining [218–223]. To make additive elements from metals and their alloys and other construction materials, charge materials in the form of liquids, rolled materials, thin fibres and most often powder is used. In medicine, additive technologies are used to manufacture scaffolds for the implantation of living cells into the body [215, 224, 225], models of dental implants and bridges [167, 169, 226], individualized implants of jawbones, hip joints, and skull fragments [227–234]. This purpose is achieved by electron beam melting [221, 235–239] and selective laser sintering/melting (SLS/SLM) [219, 221, 240–249] of various groups of engineering materials, mainly metals and their alloys, and implants and implant-scaffolds produced in this way allow for osseointegration [250] to connect the implant to bone. The method of procedural benchmarking of the dendrological matrix of technology values [251, 252] showed that additive technologies are unrivalled to other technologies in these applications.

At the present stage of Dentistry 4.0 there is a huge share of robotization and digitization [141, 253] and the growing importance of computer-aided CAD/CAM design and manufacturing in the field of dentistry and dental prosthetics in the last decade [131, 134, 142–146, 254]. Reports on this topic appeared in many other publications, given for example here [147, 255–259], which reported the use of SLS selective laser sintering, although sometimes different names were used for the technologies used, which did not differ from the mentioned process.

Tissue engineering issues are of significant importance in the Dentistry 4.0 stage. The process of osseointegration is associated with the implantation of each implant. However, actions are taken to accelerate this process and shorten it from 4–6 months

to a much shorter one. Various works are carried out in this direction, including own. In many clinical applications, scaffolds are used to spatially locate stem cells in selected places in the body, as well as using carriers to transport these cells, independent of pure cell therapies when they are introduced into the bloodstream [260–269]. Scaffolds can be rigid with a porous structure, in which osteoblasts are inhabited. At the same time, in the case of soft tissue therapy, microporous mats made of polymer or carbon nanofibers can be used to colonize with fibroblasts [270]. The need to introduce cell therapy methods in dentistry was included in the works [174, 182, 193]. Scaffolds must meet strength requirements and provide an appropriate environment for cell proliferation and growth [268, 271]. The task of scaffolds is also that in their pores, as part of cell growth, the process of their vascularization takes place, which guarantees development and survival [272–275].

The avant-garde area of regenerative dentistry in the field of Dentistry 4.0 are implantable skeletal products with surfaces of a metal porous or ceramic skeleton, possibly covered inside the pores with biocompatible ceramics. It is a new generation of the implant-scaffolds used for implantation in dentistry [175, 176, 198–200, 276–279]. In the case of introducing into the pores of such created implant – scaffolds of natural autologous cells, for example, osteoblasts, engineering, and biological materials are obtained as a new, special group of composite materials that can be implanted into the human body, for example in the form of a root part to replace lost teeth. The mentioned materials and devices are continuously researched and developed. Such implantable devices include:

- an artificial part consisting of a microporous rigid skeleton produced by the additive method of Selective Laser Sintering SLS, for example, from titanium, cobalt, or magnesium alloys, in which biocompatible layers, for example, TiO_2, Al_2O_3 or ZrO_2, by atomic method, can be applied to the inner surface of the pores layers deposition ALD and for example antibacterial continuous silver nanolayers or islands,
- and a biological part, consisting of living cells filling the pores of the microporous backbone of engineering materials.

Due to the type of matrix, these are rigid materials.

Suppose other materials are used to create a porous matrix, for example, polymeric or carbon nanofibers. In that case, the flexible biological engineering materials are obtained useful in the treatment of soft tissues, for example, in dentistry [280, 281].

Installation of the implant requires the production of holes in the bone strictly designed depending on the model of soft tissues and, above all, bones virtually reconstructed by a dental engineer based on a set of images from CBCT and then appropriately designed and produced additive technologies in the center of designing and manufacturing prosthetic restorations. The detailed division of tasks of the center for the production of prosthetic restorations and the dental office following the expectations of patients, regarding implant treatment by the concept of Dentistry

4.0 is covered by the target scheme of horizontal and vertical integration in intelligent centers for designing and manufacturing prosthetic restorations along with an example of a technological line. The implementation of a system corresponding to Dentistry 4.0 in a given dental clinic cooperating with a well-organized center for designing and manufacturing prosthetic restorations is accompanied by minimizing the costs of designing and manufacturing personalized prosthetic restorations with disproportionately higher quality, precision, and manufacturing tolerances than those produced conventionally.

The intelligent interaction of value factors, that is implants and prosthetic restorations as a product, machines and manufacturing devices, and people in various areas of integration, including marketing, procurement, supply and sales, and services constitute networked production integration systems. Due to the nature of production, the design and production centers of prosthetic restorations cooperate with many dental clinics, which, after diagnosing patients on their own, send electronic images obtained using the CBCT along with other necessary information about patients and patient IDs. Cloud computing is more and more often involved in communication and data exchange between individual dental clinics and the center of designing and manufacturing prosthetic restorations. Information obtained in this way from various dental clinics provides opportunities of CAD design methods for each patient, using highly specialized software restorations necessary to use models and surgical templates an enables the dentist implantologist implementation of the procedure. The information obtained is also the basis for production planning on CNC machines, SLS additive production machines, ALD coating machines for porous restorations or implants, as well as with the use of robots. Design and manufacturing centers for prosthetic restorations increasingly include intelligent input and output logistics. Meeting the standards as mentioned earlier, Dentistry 4.0 fully corresponds to the dental version of a smart factory organized following the current stage of the industrial revolution, Industry 4.0 [50].

The presented solution ensures a significant improvement in the business efficiency of the center for designing and manufacturing prosthetic restorations. The use of digital technologies allows reducing the production costs of some prosthetic restorations in the Dentistry 4.0 standards by up to 70% compared to conventional methods [192]. The benefits of Dentistry 4.0 also include significant growth and a more integrated network of providers and patients. The implementation of this concept, however, requires the employment of highly qualified engineering staff. The investment costs of computer software and technological machines necessary to implement this idea are incomparably higher than in the case of using conventional technologies. Conventional devices and technological machines are even several dozen times lower than those used in the implementation of the Dentistry 4.0 idea.

7.3 Ethics

7.3.1 General characteristics of ethics

Ethics with a name taken from the Ancient Greek language from the word ἦθος ethos "custom." Descriptive ethics (aetiology) [282] examines the essence of good, moral behavior, questions about humanity, and our nature. It describes various ethical systems that arose in different historical periods and other communities and the essence and reasons for shaping them. Normative ethics (deontology) [283] deals with norms; that is, obligations and criteria for evaluating actions and their justification, and maybe individual or social. Metaethics [284] deals with theory and method, dealing with the logical analysis of the language of ethics and its methodology, it examines the logical structure of normative expressions, their consistency, logical status, ways and correctness of justifications of various assessments, and norms. Critical ethics is closely related to metaethics, covering the sociology of morality, the psychology of morality and the semantics of morality, dealing with ethical theories, concepts and examining their validity, and thus examining assessments, norms, personal patterns, ideals, and ways of justifying them as data, but without evaluating them.

As in each subsection of this study, a few words should be devoted to the historical retrospective. In the case of ethics, this task is complicated, because the development of philosophical thought, and ethics, in particular, is inextricably linked with the development of human civilization. It is impossible to generalize this topic in a study with a limited essence, but only the most essential elements can be highlighted.

Ethics is derived from Socrates and Plato, but as a science, it was established by Aristotle. Referring to Plato (424/423 BC – 348/347 BC), it should be noted that he already focused primarily on the issue of virtues and happiness. Following his teacher Socrates, he recognized that the soul is the center of what is most human and proper to man. The soul is responsible for reasoning, desire, and anger, which is the basis for the internal distinction of its parts responsible for individual functions, and its proper functioning is the path on which a person can reach the highest happiness. In Plato's ethical reflection, virtue is equated with knowledge of what is termed ethical intellectualism. The ability to act right is therefore determined by the knowledge of what is good, just, pious, brave . . . Since the soul is what is divine in man, it should rule and subjugate the body. Plato, therefore, believes that the soul is responsible for reasoning and knowing the truth and for the good and virtuous conduct of man or, on the contrary, for his iniquity and injustice. The perfection of action in the framework of the assigned goals and functions is ensured by the virtues (valor) of the human soul. Their meaning is related to the activity proper to the soul, which is simply life. The question of how to achieve a

good life, therefore concerns the virtues (valor) of the soul. Plato divides the soul into three parts, assigning to each of them a corresponding virtue (valor):

- intellectual, responsible for reasoning (logistikon), whose virtue is wisdom (sophia), consisting in the reign of reason over the whole soul and its parts,
- lusty, responsible for desire, and desire (epithymetikon), whose virtue is prudence, moderation (sophrosyne) consisting in subordinating to the lusty factor of ruling and guiding reason,
- angry, responsible for human temperament (thymoeides), whose virtue is bravery (andreia), consisting of persistence and constancy in what the reason will determine, despite all the opposites.

Intellect is the part that should rule the rest, and therefore temperament and desire should be subordinate to it. The fourth virtue, related to the soul as a whole, is justice (dikaiosyne) consisting in the internal harmony between all the soul's faculties.

Aristotle (384 BC – 322 BC), a student of Plato, developed a critique of Platonic ethics. He was the creator of a philosophical system different from Platonism and equally coherent, which strongly influenced European philosophy and science. He initiated the philosophical current called Aristotelianism, which had many forms in different epochs. The Christian variety of Aristotelianism called Thomism was established in the thirteenth-century as a philosophical and theological doctrine of St. Thomas Aquinas (ca. 1225–1274) and is still considered the official philosophy of the Catholic Church. Aristotle's ethics was developed through practical observations and resulted from his theory of being. He understood good and virtue (areté) as striving to improve his form, that is, the soul, and achieving its optimal form appropriate for a given individual is a determinant of permanently achieved happiness and virtue (eudaimonia). Good, therefore, is a subjective concept and is an individual value, not an absolute value, because it depends on many different factors. Since human souls are unique, something good for one person does not have to be good for someone else. Seeking to make everyone happy at once by creating an ideal state is therefore impossible. It leads to the opposite effects of making everyone unhappy, in which he was radically different from Plato. Aristotle also disagreed with the equation of good and knowledge of ideas. His theory of the soul shows that every human being grapples with the natural conflict of the desires of the flesh and the rational assessment of the situation by the rational part of his soul. Virtue, therefore, cannot be acquired permanently through the simple acquisition of knowledge, for it can only be obtained through a continuous and effortless process of overcoming one's desires. Morality is, therefore, following the dictates of reason, instilled by education or as a result of one's own thoughts. Hence, wisdom in the absence of willpower does not guarantee virtue to man, while a strong-willed uneducated person may be more virtuous. At the same time, Aristotle distinguished virtues into dianoetic (intellectual) resulting from experience and ethical (moral) resulting from habit.

The intellectual virtues include the reason (phronesis) and wisdom (sophia). Ethical virtues are included in the so-called golden mean, between the two defects which are excess and deficiency. Among the ethical virtues, the highest is justice, which can be separating when there is a just distribution of goods and equalizing when wrongs are compensated. The general basis of righteousness is the friendship that constitutes the human community. Other virtues, such as tactful wit, are somewhere between clownishness and crude, and courage is found between audacity and cowardice. None of the virtues is inborn, as they are naturally acquired and developed through habit. The moral attitude (hexis) of a person arises, therefore, as a result of the practice of life, and thus exercise, habituation, and learning, and toward the morality of the environment, and not only as a result of reasoning. Man's conduct in order to achieve happiness as the highest good and final goal requires following the principle of the golden mean determined by reason. It is impossible to approach morality too wholly and strictly ignore the desires of the flesh. In addition to acquiring knowledge, the soul should also develop the ability to control lust through willpower, courage and reason. In life, individuals find themselves between two extreme and unattainable adversities; that is, the superhuman virtue inherent in deities and the bestiality inherent in animals. Aristotle believes, however, that there are such proceedings as adultery, theft, and murder in which the golden mean cannot be found because these are wicked acts.

Behind the choice and view presented in work [285], one can briefly explain the history and development of ethics, starting from Plato and Aristotle, through Christian moral thought, the precursor of which can be considered Plato, including the works of Martin Luther, and writers including Niccolò Machiavelli, Montesquieu, Edmund Burke, Immanuel Kant, David Hume, Georg Wilhelm Friedrich Hegel, Karl Marx, Søren Kierkegaard, Arthur Schopenhauer, and Fryderyk Nietzsche. Among the twentieth-century philosophers in this study are mentioned GE Moore, John Dewey, and RM Hare. Such an approach was met with various reception. On the one hand, it was recognized that it presented moral concepts that change with changes in social life, and therefore it was denied that there is one subject of ethical research. This book was also considered impressionistic and at the same time exposing original beliefs about the state of moral concepts. It was also regarded as provocative and not so much historical as an essay on the history of ethics. There were other critical elements. In general, the issues are complex and multi-threaded, so in such a short study as this one, it is challenging to address the historical problems in more detail. However, some historical references will be cited later in this chapter.

The modern division of ethical theories was made by the late Prof. Rudolf Carnap [286] due to the scope of moral norms (objectivist and subjectivist), due to the source of moral standards (naturalism, anti-naturalism, and emotivism) and due to the assessment of people's behavior (motivism, effectiveness, and nominalism). In the latter case, good and evil are treated as undefinable primary concepts. What is in accordance with the dictates of this system is good. Therefore, neither the motive nor the

effect matters in the moral evaluation of an act, but only its compliance with the moral imperatives. Undoubtedly, I. Kant [287] had a significant influence on the development of the theory of autonomous ethics, the ethics of duty, prompted by reason, assuming that man is a thinking and free being. For man lives in a world of nature, where he is determined and at the same time in the world of his own mind, where he is free. The categorical imperative states that one should act as if one would like the principle of such conduct to become a general law. Man cannot be treated as a means because he is the subject and goal of this action.

Ethics, similarly to aesthetics in the scientific sense, are branches of axiology, that is, the branch of philosophy dealing with the study of values, in the case of ethics – moral values [288]. In practical terms, ethics includes research into the concepts of practical reasoning, which have good, right, duty, freedom, rationality, and ethical valor. Ethics, in general, consists of the study of morality and the development of thought systems that allow moral principles to be derived from them. Evolutionary psychology holds the view that race, and perhaps even more generally human civilization, has survived, among other things, thanks to morality. The inner sense of good and distinguishing it from evil favored coherent human actions, guarding them against threats and favoring survival. The level of human moral development includes six consecutive stages, although the possibility of a seventh or eighth stage has been considered [289]. These stages can be classified as:

Level A. Premoral level,
- Stage 1 – Orientation to punishment and obedience,
- Stage 2 – Naive instrumental hedonism,

Level B. Morality of conventional conformism,
- Stage 3 – Morality of maintaining good relationships to gain the approval of others,
- Stage 4 – Morality upholds authority,

Level C. Morality of the adopted moral principles,
- Stage 5 – Contract morality, individual rights and democratically accepted law,
- Stage 6 – The morality of the individual rules of conscience.

The presented concept of principle-oriented morality is oriented toward justice, which associates it with stereotypically male thinking. At the same time, in feminist ethics, moral feelings with a focus on “care” are essential [290, 291]. In turn, one should not underestimate the possibility of genuine moral feelings and the real moral agency associated with it, even in very young children [292].

Morality [293] should be understood as a normative social system comprising norms and principles, formally constituting a set of directives that are not sentences in a logical sense. Therefore, their truth cannot be proved or denied. Within the culture, various normative systems coexist, most often overlapping only partially or even divergent. These include, apart from moral norms resulting from religion professed by

an individual or society or imposed by a recognized philosophical view, also legally permitted standards of conduct or rules set by moral law resulting from the socialization process in a specific community, even local, including professional. Ethics deals with the meaning and origins of these moral normative systems and the investigation of the underlying philosophical premises, the study of the impact of morality on people and the analysis of the effects of its absence. Empirical ethics assesses the impact of morality research and its relevance to ethical thinking and the formulation of boundaries between the world of facts and the world of norms and components affecting human moral actions and ethical orientations and is related to the new concept of "moral intelligence" [294]. The value of an act may be assessed depending on the approach, in ethics of bravery for virtue, in deontological ethics toward duty, and in consequentialist ethics taking into account the consequences and responsibility.

There is, however, a difference between morality, customs and law, even though some of the moral, social, and legal norms are even the same. Failure to comply with the moral standard is associated with a feeling of guilt, breaking the moral standard is accompanied by a feeling of shame, and violating legal norms usually requires punishment in addition to guilt. The difference between these normative systems comes down to the answer to a different question, often in an almost identical case. In the system of moral norms, the question is "What is wrong to do or not to do," in the system of moral standards, in turn, "What should be done or not done," while in the legal system "What must not be done or not done," of course, in this case, under penalty of punishment. Someone else plays the role of the judge in each case. In matters of morality, answers must be given to oneself by the professed ethical and philosophical system, including the religious view, when in the case of morality, the environmental opinion decides. In the field of law, decisions are made by an officially established court representing the socio-political system in a given country. The considerations are undertaken in this study concern the first of these concepts, and therefore the moral imperative, which determines the behavior of an individual. Moreover, these are deontological considerations of practical ethics [295], understood as the ethics of duty, in practice related to human professional activity. Therefore, one can speak of medical, legal, engineering, managerial, business, and social deontology, including teaching, psychology, and others.

7.3.2 Ethics in medicine and dentistry

An essential part of practical ethics is bioethics, dealing with problems related to biology and medicine, including euthanasia, issues of treatment or its omission, genetic modifications, transplants, cell cultures, choice of treatment methods, shaping the approach to health and diseases and the health policy of the state, but also in the field of human relations with the living world and animal husbandry. The subject of this study is obviously related to this issue.

The term medical ethics is widely used in the world, first introduced in 1803 by the English physician Thomas Percival [296], and its development became the basis for a code of ethics issued in 1847, then refined in 1903, 1912, and 1947 [297]. The inspiration of the so-called Western medical ethics dates back to antiquity, such as the Hippocratic Oath of the fifth century BC. Recent studies indicate that it is most likely the handwriting of Hippocrates himself, written between 420 and 400 BC [298]. The ethical importance of the oath decided that its influence has survived from antiquity to today. During its 1948 convention in Geneva, the World Organization of Physicians developed a modern version of the oath – the Geneva Declaration, which was then amended in 1968, 1983, 1994, and 2005 [299]. A characteristic feature of the oath and other writings of the Corpus Hippocraticum [300] is the search for ethical principles for the medical profession. In the earlier Codex of Hammurabi, King of Babylon (1792–1750 BC), only the punishments and rewards that await a doctor for his work were mentioned. The cure involved the payment of 10 shekels of silver to the physician, and his hands must be cut off for having caused his death," a bilingual Greek and Latin text of which was published in Frankfurt in 1595. This oath was made by physicians in antiquity and laid the foundations of today's medical ethics and the final words of this oath in translation from the original [301] read as follows: "I swear to Apollo the physician and Asclepius and Hygea and Panacea and all gods and goddesses, taking them as witnesses that according to my strength and the judgment [conscience] of this oath and I will keep this written agreement. (. . .) If I keep my oath and do not violate it, let me prosper in life and art, and fame for all-time among all people; and if I break it and betray it, let everything the opposite will touch. " In the fifth century developed a code of medical ethics Formula Comitis archiatrorum [302]. In 1815. UK Parliament passed a law Apothecaries Act, and in 1847 year, the American Medical Association adopted a code of ethics [303]. The development of liberal theory and procedural fairness in the sixties and seventies caused that bioethics developedin the 1980s [304]. From the 1970s onwards, the importance of ethics in modern medicine grew in importance, related to, inter alia, the dissemination of institutional bioethics committees to evaluate research on humans and animals and with the participation of human cells, hospital ethics committees, increasing the scope of educating physicians in the field of bioethics, expanding the role of physician ethics, and integrating ethics in many curricula in medical schools [305].

The dispute over the need for codes of professional ethics has been going on among ethics for a long time. Supporters of the ethics of rules consider it necessary to codify moral norms. In contrast, the supporters of situational ethics deny the need for the functioning of codes, considering conscience as the only instance deciding dilemmas. Therefore, there is still a dispute about the scope of regulations of ethical codes, and even the need to create them, because on the one hand there is the will to regulate all possible moral dilemmas in the form of extensive ethical codes, and on the other hand, the belief that such a well-educated social group

knows what to do and it does not need external prompts. It may seem sufficient that an appealing message and the reference in the codes of ethics to the conscience of representatives of medical professions and to be content with pointing out the virtues that characterize each practitioner of this profession, boiled down to the following four [306]:

- compassion, that is, concern for the welfare of others and the ability to empathize with others (the patient);
- prudence, that is, constant and insightful insight into the situation, understanding, and sound judgment, which are the basis of decisions made, excluding personal sympathies, extravagances, and fears;
- ability to reciprocate trust and care for removing symptoms of a multi-faceted crisis related to this issue;
- integrity that is healthy, integrated, responsible, and integrated moral character and fidelity to professed norms.

On the one hand, there are ready-made solutions, in the form of code passed on verbally or in writing from generation to generation. On the other hand, there is a vision of a free man, unlimited by any imposed orders or prohibitions, who, by nature, goes toward good. Such a person does not need any codes. Each of these variants has a long tradition of ethical thought. Everyone also has their supporters and staunch opponents. The ethics of codes, as the followers of postmodernism want today, are a relic of a bygone, modernist era, where everything was standardized and penalized. "Great Narratives" also involved formalized morality. Today, the ethics of codes no longer meet social needs. Nevertheless, the codes still exist, and there is even a tendency to widen the number of areas of life regulated by them.

The development of codes of professional ethics seems necessary, in the case of professions whose performance requires respecting values that are particularly valued socially, in which, in general, moral qualifications are as important as professional qualifications [307]. It concerns for example the areas as follows:

- health and life (medical ethics),
- freedom (lawyer and judge ethics),
- personality shaping (teachers ethics),
- of broad social significance (scholar's ethics).

The unique nature of the work of medical professionals seems to justify the codification of the rules governing the activities undertaken, due to:

- irreversibility of the consequences of medical decisions and actions,
- entrusting the doctor with secrets and the most personal and intimate matters,
- the need to undergo unpleasant and dangerous treatments and allow them to be performed by loved ones,
- social authority to decide about human life, the right to inflict wounds (surgery) and the restriction of personal freedom (infectious and mental diseases) [308].

There is also the problem of who should develop a code of ethics in force in medical professions, whether the doctors themselves should do it, or whether it should be given to them by those who do not practice this profession. The analysis of these and other identified and emerging bioethical problems in social, historical, and cultural contexts belongs to the domain of cultural bioethics, distinguished by Daniel Callahan [309] in his traditional division. It might seem that such a task should not be performed by doctors, because it may be at the expense of patients, were it not for the fact that every doctor knows that sooner or later he will become a patient. In the system of organizing society, defined as "risk culture," it is the consequence of natural human inclination, and so the culture is endangered by itself [310]. Despite this, even if it may seem that some provisions protect the doctors themselves, the patient always remains the beneficiary, which speaks in favor of a professional opinion on this matter by the medical community.

A typical pattern used in the analysis of medical ethics is a culturally neutral and straightforward approach to ethical issues in health care, based on four complementary moral obligations called "four at first sight principles" (Figure 7.5) [306, 311]. These rules include:

- respect for autonomy [312, 313] – the patient has the right to choose a method of treatment or to refuse it,
- charity [314] – the physician should act in the best interest of the patient,
- harmlessness [315] – Latin "*primum non nocere*" in order not to cause any harm to the patient by treatment and "usefulness" to do more good than harm,
- equity [316] – in the distribution of limited health resources and decisions made about who will receive what treatment, especially deficit treatment.

Figure 7.5: Scheme of the four first sight principles.

These frameworks provide a fundamental moral language to help physicians and healthcare professionals make treatment and health-care decisions while reflecting on the moral aspects involved.

In all circumstances, physicians are ethically obligated [317] to respect human rights as enshrined in the Universal Declaration of Human Rights (1948) [318] in Europe, the Convention for the Protection of Human Rights and Fundamental Freedoms [319] concerning medicine in The Convention for the Protection of Human Rights and Dignity of the Human Being concerning the Application of Biology and Medicine (1997) [320]. Nevertheless, there may be a conflict between individual standards of autonomy and personal human rights concerning solidarity and social justice, as is the case in Anglo-Saxon countries, including the United States, when in European countries more attention is paid to the egalitarian nature of health care and greater participation free of charge health services [321, 322].

The principle of informed consent in the field of ethics requires that the patient or an adequately authorized person must be fully informed about the potential benefits and risks of choosing a treatment and understand them. Of course, the patient also has the right to informed refusal. The value of informed consent is closely related to the importance of autonomy and truthfulness. The associated confidentiality is part of the traditional values of medical ethics, building the trust between physician and patient so necessary in treatment. Three groups of arguments support the observance of confidentiality of information about the patient and his health problems [306]:

- consequentialist arguments: patients honestly disclose the facts and submit to testing because they trust that doctors keep information entrusted to them confidential,
- arguments based on the right to autonomy and privacy: disclosing authorized information and facts exposes the patient to danger, loss of friends and relatives, emotional imbalance, discrimination, loss of job;
- arguments based on fidelity: an obligation to keep one's word that is based on clear and implicit promises.

In some countries, however, some laws deal with exceptions to the principle of confidentiality and medical confidentiality, and the ongoing discussion suggests that it needs to be nuanced [323]. It also requires a high degree of caution in disclosing any examples of treatment of patients on the Internet, even in general discussions, as it may be a cause of violation of the principles of medical confidentiality and informed consent [324]. Doctors should not allow a conflict of interest to influence medical judgment, and doctors must avoid such situations. Without going into details, doctors should not take undue benefits, including financial ones, for example, by using the persistent or unnecessary treatment, forcing drugs due to corrupt ties with suppliers, overstating the cost of medical services, etc.

There are, however, some additional aspects to consider when providing medical attention. They include the so-called double effect; that is, two effects caused by one action. The introduction of this principle is attributed to St. Thomas Aquinas [325]. Sometimes it is permissible to cause damage as a side effect in connection with the achievement of the intended good outcome. However, it is unacceptable to cause such damage if it is only to achieve the same good result.

A physician deciding to inject a large dose of morphine into an incurably ill patient is unacceptable, as it will accelerate and lead directly to the death of this patient. However, it is permissible for a physician to administer a seriously ill patient the same dose of morphine if the intention is to alleviate the suffering and pain of the patient, even if he realizes that he is hastening the death of the patient. It is, therefore, a combination of the principles of benevolence and harmlessness.

Ethically complex problems include conflicts between autonomy and benevolence/harmlessness when patients do not accept treatment according to doctors in the patient's interest. The conflict of the patient's interests with his well-being can be solved in various ways. However, Western medicine obeys the wishes of a mentally competent patient who makes his own decisions, even if doctors judge that the patient is acting against his own interests. Many other societies put patient benefits over patient autonomy.

There are also other severe aspects of medical ethics, such as the acceptance of ambiguity in medicine, euthanasia, for which there is no agreement that the principle of harmlessness excludes the practice of euthanasia. However, this view is dominant in many countries, where it is considered a criminal offense [326].

Despite the widespread adoption and acceptance of the approach to ethical issues in health care in the form of "four at first sight principles," discussions about the need for professional ethics continue, including questioning such a need. Usually, in the argument for maintaining them, the traditions of the profession and the general humanistic and culture-forming nature of the profession's ethics are raised, which indicates its participation in the achievements of humans. A wide discussion was undertaken, among others in 2001, almost 20 years after the formulation of the "four at first sight principles," [327] in a series of articles on "The Internal Morality of Medicine." [328–333] The universality of the subject matter does not make the problem and the opinions presented at that time obsolete, even though the following years bring new problems, such as the current global COVID-19 pandemic caused by the SARS-CoV-2 virus and discoveries in the field of medicine. The best proof that 20 years later and exactly 40 years after the publication of the basic work [327], in which the "four at first sight principles" had just been formulated, another series of articles entitled "Celebrating the 40th Anniversary of Principles of Biomedical Ethics: Essays in Honor of Tom Beauchamp and James Childress." [334–343] The dilemma posed in 2001 required a decision whether medical ethics is part of general ethics and is part of its part, which is bioethics, or on the contrary, it is created by representatives of medicine as independent of other specific ethics and is not part of a more general theory.

According to the view contained in [333], medical ethics is a reasonable proposition to solve the contemporary health dilemmas of humankind, which may be influenced by bioethics, which is part of the culture that led to its formulation [333]. With the opposite assumption about internal morality (medical internalism), four different approaches can be distinguished, that is:

- essentialism, when the standards of medical ethics derive from the idea and sense of practising medicine [329];
- the concept of "necessary practical conditions" when moral standards are derived from the conditions of practising the medical profession;
- historical professionalism, when doctors set standards of practice and professional ethics for doctors;
- internalism of the evolutionary perspective, when professional norms are creatively evolved over time in interaction with external moral norms [330].

Other positions include liberalism assuming the existence of relationships similar to market regulations between patients and medical staff, which, depending on the political trends currently in a given country, lead to mutually contradictory and often unstable pro-social tendencies, which seems to be better from an ethical or pro-market reform point health service.

This special edition of The Journal of Medicine and Philosophy, commemorating the 40th anniversary of the "Principles of Biomedical Ethics" by Tom Beauchamp and James Childress, highlights the key role that this book has played in not only creating the research and application area but also having a huge impact on scientists and practitioners in fields ranging from bioethics, clinical ethics, and research ethics through philosophy, theology, and public order to medicine, nursing, and social work. The bioethical framework – commonly referred to as "principled" or "four principles approach" is perhaps the most popular in biomedical ethics today. Even critics of principlism [334] appreciated the most inspiring virtues and achievements expressed in this work, among them:

- innovation and novelty,
- involvement in cooperation and interdisciplinary work when it was not considered fashionable in the authors' native disciplines,
- the ability to create a moral framework that is accessible and attractive enough universally for use by academic bioethicists, clinical ethicists, research ethicists, health-care professionals, students, policymakers, and laypeople;
- intellectual humility, honesty, openness, and respect;
- ecumenism and authenticity in seeking truth in many competing views, rather than rejecting them.

It was emphasized [343] that, despite the passage of time, the views of the authors did not change significantly. However, with time, due to the ongoing discussions, polemics, and criticism, some arguments were strengthened. The paper [332] presents a

clear and well-documented overview of the principles in this field, including the "four at first sight principles" – respect for autonomy, no harm, benefit, and justice – along with some more detailed principles, including truthfulness, privacy, confidentiality, and faithfulness. Different sets of the bioethical principles and rules overlap to a great extent, although some have significant consequences. The principles of respect for persons and charity may seem almost identical to the principles of respect for autonomy and charity. Still, in reality, they are very different and have significantly different implications. Like Rebecca Walker [341] also Robert Veatch [332] puts the principle of respect for persons over the principle of respect for autonomy and includes the latter in the former. The division of "usefulness" into positive and negative, that is, benevolent and harmless [332], has been criticized [343] as it is actually "charity" divided into "positive charity" and "utility." In the [343] approach, the principle of not hurting others, more precisely the principle of not killing others, does not become a rule or rule based on consequences, just as a lie that leads to believing what is false (consequence or effect) does not make truth out of it principles of consequentialism.

In work [341] it is suggested to abandon the principle of respecting autonomy and replace it with the principle of respect for people who can perform sufficient work independently and thus avoid the need to refer to other principles, such as justice or specific rules such as privacy and confidentiality. Similarly, this paper presents a proposal for collaborative decision making (SDM), which ignores the authority of patients and potential study participants in the decision-making process. It is, therefore criticized in [343]. The work [338] takes into account specification and balancing, and above all the lack of the theory of value because in the absence of such a theory, principledism is inadequate and cannot be solved regardless of the description of human well-being. The necessity of a value theory focused on human well-being is emphasized to define the principles of benevolence and nonevil, and the lack of specification of functions to eliminate or reduce conflicts with principles and rules. Weighing and balancing moral principles and determining which should prevail in conflict situations also requires a theory of value, arguing with the two-pronged approach to balancing that cannot succeed without a theory of value. This approach, however, contradicts the pluralistic approach in the development of "principled" or "four principles approach" [343]. In the next work [339] the attention is focused on the discussion of virtues and the theory of virtue, both conceptual and normative, and how to introduce them into the problems of practical ethics. However, an ethical theory in which virtues are fundamental neglects duties, rights, and social needs. However, taking into account theories based on obligations and rights, the opposite is assessed of reductionist theories, which by denying virtues essential status allow only rights or obligations to have a fundamental position [343]. Equally criticized is the view that there is no strong reason to identify basic concepts and issues in normative ethical theory, both in general and in specialized sub-areas such as medical ethics. The idea promoted by various theorists,

as well as morality and moral theory shows that either virtues or duties or rights are the only ones out of the three that can be considered fundamental [343]. Work [337] deals with the description of universal morality, and the norms expressed in the "approach of the four principles" are objectively derived from universal morality, and the moral authority they carry exceeds that of the norms that constitute particular morals, although their moral authority may serve those they govern. It means that well-constructed individual morals are morally authoritative in their respective domains. On the other hand [343], all people involved in morality not only know it but also accept the meaning and importance of generally applicable rules, including:

- not lie,
- not steal,
- not punish the innocent,
- not kill or harm others,
- keep promises,
- respect the rights of others.

No specific moral lifestyle that does not meet the standards of universal morality can be qualified as morally acceptable. Thus, it is not necessary to repeat some of the basic principles of any acceptable morality, and that does not mean that they do not apply to cultures, groups, or individuals. Thus, the origin of moral norms for the medical profession or any other profession does not differ fundamentally from that of the norms of general morality. Common morals have authority in all communities, while individual morals are authoritative only for specific groups [343].

In work, [340] attention was paid to the theory based on moral agency, so that everything that is a moral subject has moral status, while everything that is not a moral subject does not have moral status.

The subject of this study concerns the issues of dentistry. So the question arises. Are ethical issues medically different from those in dentistry? Even though dentistry is a part of medicine, there is a specificity on the one hand of this profession, and on the other hand, relations between dentists and patients and, in general, a separate organization of work, and thus the entire system of dental services. As a rule, these services are provided by many scattered small clinics, most often in the private hands of dentists. It points to the need to combine two, perhaps not contradictory, but different deontological approaches of practical ethics – medical and business, which dentists must reconcile.

Similarly, as in the case of general medicine, there are a few basic at first sight Principles of ethics regarding dentists and dentistry. Following the Code of the American Dentist Association, all the principles adopted in medicine, in general, are taken into account and add one more, which is considered auxiliary there. The five at first sight principles of dental ethics are as follows: patient independence, harmlessness, charity, justice, and truthfulness (Figure 7.6). The

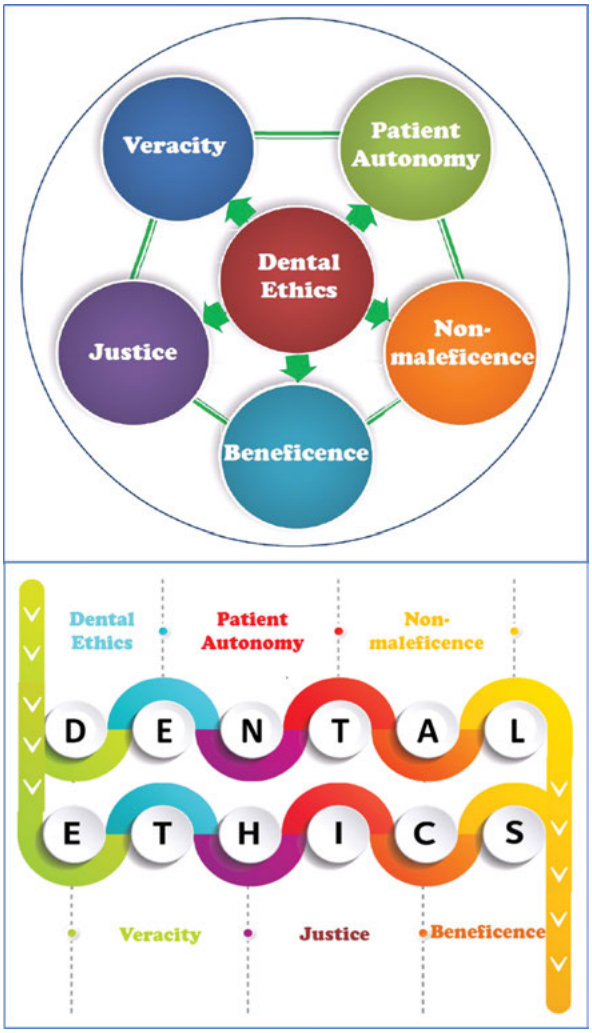

Figure 7.6: Diagram of the five at first sight principles of dental ethics.

rules are equivalent, and they can also overlap. The remaining side aspects are analogous to those in general medicine [344–347].

Although dentistry is a branch of medicine, perhaps even considered to be somewhat autonomous, it can be argued that in the modern world, the ethical awareness of dentists has developed faster than that of doctors in general. For example, in the United States as early as 1866 [348] at a meeting of the American Dental Association, the Code on Professional Ethics was formulated for the first time. There was an adaptation of a document established 25 years earlier. Revisions were made in 1880 and successively in 1899 with significant modifications made in 1922. It was determined

that dentists should proceed "in accordance with the Golden Rule." At the same time, the obligation to report on other doctors who are "illegal, corrupt, or dishonest conduct" was introduced and it was recommended that dentists be active "whose prime purpose is service to humanity." While the latter finding does not raise any objections, the former can be viewed as ambivalent. Ethics, including professional ethics, should be strongly motivated as an internal imperative, not because of fear or fear of being denounced by a colleague. Changes were made in 1944, removing the first obligation. In 1955, 1958, and 1960, the set of Principles of Ethics was introduced and modified [349, 350]. Changes were introduced in the following years, and the latest version of the ADA Principles of Ethics and Code at Professional Conduct is dated in 2018 [351]. The Principles of Ethics have become a model, either official or unofficial, for dentists in many countries, regardless of the arrangements made in them, or especially where such documents have not been established in those countries.

However, we are ready to share to some extent the critical view presented in [352], where it was suggested at the beginning of the 1980s that an act drawn up by a professional association cannot take into account all ethical expectations, as it lacks a general reference to the requirements of society. It may be aggravated by the fact that apart from moral aspects, there are also intellectual requirements and organizational issues. Our reservations to all documents of this type, including ethical requirements and prohibited or even prohibited activities, especially those subject to disciplinary or criminal sanctions, make each of these documents a legal act, even a non-moral one. These documents can, of course, be prepared very professionally, and that is why this is not what our doubts concern. The law, or even the mores, are entirely different orders than the ethical system, which was mentioned earlier. Ethics is inside you, and the law is simply to be followed. It is a fundamentally different motivation, which we have already written about while discussing etiological aspects. Indeed, this approach has a positive effect on raising the general level of health services, in this case, dental services. Still, there are unclear doubts as to how much this is actually due to the increasing ethical level of each dentist. If we are optimistic that dentists will accept the principle that "this is not done, Mr Friend," it is shaping the practice, but not ethics. The actual classification of phenomena is determined by the statistical distribution of motivation in the group of dentists in each country, and possibly by the predominance of any of these three motivations. Of course, the activity of all professional organizations, associations, and chambers of doctors is very beneficial and certainly meets the ethical requirements. Still, no statutes, codes, or regulations can essentially replace ethics in the actions of individual people. The sum of one-person behavior determines the ethical level of a given environment.

7.3.3 Ethical aspects of engineers' activities

From the issues discussed in this chapter, it is essential to refer to another aspect of practical ethics, which is undoubtedly the ethics of the engineering profession in general and in the field of dental engineering in particular, so closely related to dentistry and medicine in general. Dentistry issues 4.0 are closely associated with tasks in the field of dental engineering, so it is evident that there are also ethical obligations in this area resulting from the profession of an engineer. The professional engineer, especially in close cooperation with the health service, has high social expectations. The mission of this profession is to design and manufacture a wide range of products, goods in general and services that meet the numerous needs and expectations of society. The content of aspects of this activity is associated with a far-reaching impact on the state of the climate around the globe and the local situation of the natural environment. These are the issues of exploitation of natural resources and waste management, pollution of the atmosphere and the environment with toxic substances, dust and gases, and noise reduction. The issue concerns the safe operation of various products and structures, the reliability of products and technologies, as well as concern for the maximum limitation of the harmfulness of the impact of products on the health of individual people, as well as concern for people's well-being, which is measured by the delivery of the most commonly used goods and products. The particular scope is the provision of numerous products to improve human health as well as to extend human life. Continuous technological progress, including reaching the stage of development of the technical revolution Industry 4.0 and the related stage of Dentistry 4.0, on the one hand, puts more and more demands on the engineering staff, and on the other hand, places at the disposal of society more and more worldly goods and products that meet the increasing needs and requirements [353].

The philosophy of technology has gained a permanent position in the philosophical sciences. Technology plays an essential role in modern society as an economic and cultural force. The philosophy of technology [354] as a discipline has emerged successively over the past two centuries. At that time, the focus was mainly on the humanistic philosophy of technology [355]; that is, the influence of technology on society and culture, and not technology itself, accepting the primacy of humanities over technology. A branch of the philosophy of technology has recently emerged, dealing with the practice of designing and creating artifacts, including artificial processes and systems. The nature of the things thus created. This branch of the philosophy of technology does not apply to the humanities and social sciences. Still, it is related to the philosophy of science and the philosophy of action and decision-making [354].

The development of technology ethics as a sub-discipline of philosophy dates back to the beginning of the twentieth century, which results from the instrumental perspective of technology, assuming that technology desirably increases human capabilities. The thesis about the neutrality of the instrumental vision of technology

indicates that it is a neutral instrument used in a good or bad way, which is not accepted by many philosophers [356–360]. The conceptualization of technology determines the scope and program of technology ethics as:
- a political phenomenon [73, 361–364],
- social activity [365–368],
- a cultural phenomenon [369–373],
- professional activity (engineering ethics) [374–376],
- cognitive activity [377, 378].

In the second half of the twentieth century, there is a departure from technological determinism, assuming that technology is a spontaneous and autonomously developing phenomenon as a result of choices made, which is accompanied by a release from ethical reflection on technology in favor of specific technologies, and even phases of technology development. Technology ethics is, therefore, empirically interested in the succession of various technologies and the activity of engineers and the technological process [354].

It was assumed that engineering, like medicine, is a profession, although the definition of the profession is still controversial, so it is described by a set of features:
- is based on specialized knowledge and skills that require extended learning,
- is performed by an authorized and relatively narrow group,
- assessment of professional competences may be performed only by persons practising this profession,
- serving society is the ideal to provide society with useful and/or socially valuable products, services, or values,
- the ethical standards underlying professional practice are derived from or are related to the socially accepted ideal of the profession (Figure 7.7).

Engineering ethics covers actions and decisions that are collectively or individually made by practising engineers [379]. Engineering ethics has been developed since the 1980s, initially in the United States. Detailed ethical issues of interest in engineering ethics include [374, 375, 380, 381]:
- professional duties of engineers, including, for example, codes of ethics for engineers,
- the role of engineers toward managers,
- competences,
- honesty,
- signaling irregularities,
- concern for safety,
- conflicts of interest.

However, it is estimated that this scope is narrowed down and requires extension [382, 383]. Significant ethical aspects include the way of organizing the entrusted

Figure 7.7: Diagram of the features of the profession of an engineer.

tasks, which is not taken into account by the traditional micro ethical approach, just like it ignores the issues of the impact of technology on society and decisions regarding technology, which does not take into account, for example, technological, is to focus on developing the ethics of specific technologies. It is related to computer ethics [384–388], including robotics, artificial intelligence, machine ethics, and algorithm ethics [389–393], ethics of biotechnology [394, 395], ethics of architecture and town planning, [396] and nanoethics [397]. There are also examples of even more detailed ethics on nuclear energy [398], nuclear deterrence, [399] and geoengineering [400]. There are real doubts as to whether a specific pursuit of newly created fields of applied ethics is purposeful as new engineering specializations are created and developed. Although each of them could raise their own new philosophical and ethical problems, there is no certainty that this requires the creation of separate ethical sub-disciplines. The argument for creating such a state, however, maybe they need to use the specialist knowledge of a given technology and interaction with non-philosophical experts in this area, which may also favor the development of ethical knowledge as a result of such interactions, as well as the impact resulting from the combination of engineering ethics with a cultural and political approach. For example, the emergence of both the ethics of computer engineering and nanoethics was contested on the assumption that neither computer engineering nor nanotechnology generates new ethical problems [401, 402].

On the other hand, the newly created fields of ethics are classified as applied ethics, related to the application in these cases of theories, norms, concepts, and methods of moral philosophy. However, general standards and moral methods can

be too broad and are not suitable for direct application to the ethics of specific technologies. Hence, any new aspects relate only to the improvement or at the most reformulation of standards, concepts, and methods, which does not exclude novelty in some cases. In the case of biomedical ethics [306] or computer one [403] respectively, more detailed than general normative standards were formulated, but due to the degree of generalization respectively biomedical or computer issues regarding privacy and property are still useful in various, and not only specific, issues of ethics. New areas of ethical application include the fact that research and technological development are not performed by individuals, but take place in human networks [404]. Aspects of broader importance for many new technologies include the analysis of the social and ethical effects of creating new technologies and the uncertainty of reacting to such situations. Anticipatory ethics is a way of solving such issues [405], which is a part of the new interdisciplinary field of responsible innovation ethics [406].

Technological development, as most philosophers of the technology believe, is goal-oriented, so that technological artifacts serve specific purposes and do not serve others effectively. Technological artifacts, their functions and objectives conceptually related to each other do not ensure the full value-neutrality of technology. There is no unequivocal interpretation of the value of technology, although some philosophers believe that technology can have moral agency. Thus, technologies can function morally autonomously and can be morally accountable for their actions. Such a debate began with the initiation of computer ethics [407–410], and its review is contained in [411]. Typically, authors who claim that technologies having moral subjectivity require redefining the notions of agency and its relation to human will and freedom [410, 412, 413]. Unfortunately, in such circumstances, the morally significant differences between humans and technological artifacts may blur, leading to a risky generalization that technology is morally relevant.

Consequently, it could be considered that technology is somewhat value-laden, which, respectively, enables or, on the contrary, limits various human activities and the achievement of human goals. Technologies, however, can be value-laden other than through the attribute of moral agency [414–417]. Nevertheless, some authors consider technology to be a very physical structure and therefore, to be value-neutral and so, may be used well or badly [418]. One of the specific areas of moral agency and technology is the design of intelligent artificial agents [419]. Doubts about the need for the technological design of full ethical factors are given in [392], and in [393] reported that the main problem is not so much designing artificial factors that function autonomously and interacting with the environment, but ensuring the appropriate ethical sensitivity of such machines.

Accountability is at the heart of the ethics of technology. It is the central imperative, and as discussed in [420] argued that, for the first time in history, humanity is capable of destroying the earth and itself. It was a pessimistic assessment of the assumption of responsibility by engineers for the technologies they developed in traditional philosophy and the ethics of technology. The issue was treated in a general

way, thinking that engineers valuing technology were not able to control it and take responsibility for it [357].

The dispute begins with the concept of liability. The emphasis can be on the forward-looking or virtuous nature of assuming responsibility, and focus less on blame [376, 421]. Other retrospective concepts of liability emphasize, on the contrary, accountability and reprehensibility, even reaching the legal concept of strict liability, in which the condition of knowing the weakness is weakened [422]. Three perspectives for assigning responsibility in engineering have been distinguished based on:

- merit,
- rights, and
- consequentialism.

It seems that the perspective of consequentialism, using the perspective concept of responsibility, has the most substantial impact on engineering [423].

However, engineers are believed to play a paramount role in ensuring the safety, health, and welfare of society, as reflected in many codes of ethics for engineers, including probably everyone in the United States [computer philosophy]. The enumerative scope of responsibilities of engineers is reduced to three categories of responsibility toward:

- the profession and its honest and competent performance,
- employers and clients,
- community and society as a whole.

Many engineers take responsibility in all three of these categories [376]. However, freedom of action, knowledge, and causality as conditions of individual responsibility mentioned many times in the philosophical literature cannot be met by engineers. Hierarchical or market constraints often force engineers to behave in specific ways, preventing them from taking responsibility for their career decisions. Various studies have therefore highlighted these aspects, and the difficulties encountered [424–426]. The long chain of engineering activities, from research and development of technology to its practical application, and the accompanying chain of many people involved, also make it difficult or even impossible to meet the causality condition. The underlying problem with assigning individual responsibility to engineers in a collaborative environment is, therefore, the problem of many hands (PMH), once introduced in [427] concerning public officials. The solution of International Humanitarian Law (IHL) may be a procedural approach [428] related to Rawls's model of reflective equilibrium, designing institutions that help to avoid it or virtuous behavior in organizations [429].

At the design stage, there are many options for selecting and shaping technologies, taking into account, for example, the impact on human health and shaping the surrounding environment, which places particular emphasis on the ethical aspects of design. In the use phase, technologies are already given, and possible negative

social consequences may be impossible to avoid or even fix. In work [430], it is stated that the most modern design takes into account the value for various values and fields of application. Taking into account the ethical nature of design consists, for example, in:

- value-aware design (VSD) in a systematic way in computational ethics [431],
- design for X in engineering to incorporate instrumental values, including maintainability, reliability, and cost,
- designing for sustainable development,
- inclusive design to make projects accessible to the entire population, including for example people with disabilities and the elderly [432],
- affective design [433], to create designs that evoke positive emotions in users and thus contribute to human well-being.

A conflict of values may accompany design in the event of an intention to integrate values with the design, because, for example, the safest car, due to its weight, probably cannot correspond to the idea of sustainable design. There is, therefore, a contradiction between striving for the best design features of a car and safety and sustainability. Traditional engineering methods for resolving such conflicts consist of a trade-off between design requirements, cost-benefit analysis, and multi-criteria analysis. These methods, however, have methodological problems [434, 435]. In [436] various alternative methods of solving value conflicts in the design are given by:

- setting thresholds (satisfactory),
- value reasoning,
- innovation,
- variety.

Technological risk, as one of the traditional problems in the ethics of technology, entails both ethical aspects as well as epistemological and theoretical-decision issues [437]. Among the various definitions, the usual assumption is that risk is the product of the probability of an undesirable event and its consequences, [438] and is expected to be as minimal as possible. Therefore, risk reduction is an important goal of technological development, and codes of ethics usually place engineers responsible for designing safe products and reducing the risks associated with their operation. However, there are no secure technologies and products, so achieving such a goal is not always possible, and sometimes it is even undesirable from a moral point of view. The products may have a higher price, their operating costs may be higher, they may be more inconvenient to use, or they may be less durable. From an ethical point of view, the second stage of risk assessment is the most important. However, the first stage of risk assessment already includes evaluation elements, including the sequence of risk assessment [439]. The third step concerns risk management. Morally significant is also the selection of evidence to determine the risk and the

possibility of making mistakes. The type I error consists in determining the risk when it does not exist. In contrast, the type II error refers to the situation when it is defined that the existing risk will be considered non-existent. Avoiding type II errors appears more ethically essential [439, 440]. In such a case, a technological hazard may occur. It is resulting in the risk of loss or damage to the health of users and the general discomfort of the society. There are different ways of assessing risk [441], and although the naturally occurring risk may sometimes be unavoidable, it may not be morally acceptable. It is doubtful to determine the acceptability of the risk of one technology by comparing it with the risk of another technology, in a situation when both cannot be considered alternative to the decision necessary to take [442]. Benefit-risk analysis can be a different approach to risk assessment, and the essence is to compare the risk with the benefits of a given activity using various criteria [443]. Risk is only acceptable if the cumulative benefit of the exposure outweighs the total risk, which is the probability-weighted disadvantage of the results [444]. The third approach is risk acceptance by those who bear the risk, provided that they are made aware of the risks involved. Expecting informed consent from a large number of people simultaneously affected by this risk usually fails as it is impracticable and may, therefore lead to a stalemate [444]. Alternative risk assessment methods were also proposed using philosophical and ethical arguments, for example, based on a philosophical critique of current practices [439] or taking into account emotions in the assessment of risk acceptability [437] argues for the role. Exposing anyone to risk is only permissible if it is part of a fair social system of risk-taking working in its favor [444]. Of course, this creates legitimate moral dilemmas, such as who benefits from risky activities, and whether the sharing of risks and rewards is fair. There is also an opinion that it is exaggerated to focus attention on risk in technology ethics, if only for the reason that anticipating risk in the absence of knowledge about the operational behavior of the product is burdened with the lack of premises for reliable evaluation. Therefore, it has been proposed to introduce the new technology as a social experiment with consideration of the situation in which such actions are morally permissible [380, 445]. Other ethical concerns are that the assessment only covers health and safety effects, disregarding social or psychological impact, and this lowers the moral value of the risk assessment performed [446].

7.4 Recapitulation and final conclusion

7.4.1 General discussion

Caries is one of the most underestimated and most common infectious diseases. Its rapid, modern development is most often caused by inadequate oral hygiene, the consumption of large amounts of sugar and the lack of frequent check-ups by the

dentist, genetic conditions, insufficient fluid balance caused by excessive effort, diseases, like anaemia, diabetes, and various other diseases, as well as frequent use of drugs such as diuretics, antidepressants, and antihistamines. Risk factors also include lifestyle, systemic and environmental factors in the development of caries, thus including it in the group of modern civilization diseases, which also have ischemic heart disease and type 2 diabetes. Lactobacilli and streptococci are responsible for the development of caries, wreaking havoc throughout the body. Because of them, in many organs, the so-called infection defocuses, when the original focus of infection is diseased teeth or tissues surrounding them. Caries and gum disease cause headache and sinus pain, heart diseases including myocarditis, endocarditis, heart attack, glomerulonephritis, gastric ulcer, liver, lung, arthritis, optic neuritis, corneal disease, brain abscess, inflammation meningeal lesions, skin lesions, promote premature birth and low birth weight in infants, and increase the risk of diabetes. Some of these diseases can be life-threatening, cause septic shock or even be a direct cause of fatal sepsis, which is rare, but medical statistics record such cases. Caries intensively promotes periodontitis, which is a chronic disease that most often occurs in adults and is the second cause of tooth loss, next to caries. If left untreated, it can lead to gum recession, tooth mobility and loss, and the bite loses its original function. It causes chewing dysfunction, speech disorders, and gastrointestinal complications. Periodontal disease can also be a risk factor for high blood pressure, nosocomial pneumonia, cardiovascular disease, atherosclerosis, diabetes, cancer, stroke, and even Alzheimer's disease. It can also cause premature birth and low birth weight. Holistics in dentistry is an approach to dental problems from a holistic point of view. It covers the relationship between the condition of the teeth and the functioning of other systems and the occurrence of diseases. In the current situation, it is difficult to rule out the coincidence of caries and periodontal disease with COVID-19 disease caused by the SARS-CoV-2 coronavirus. Medicine does not currently know the answer to this question.

Underestimated caries and gum disease not only lead to tooth loss but also to dementia, as seen in toothless seniors who have been found to develop dementia, which is three times more common than their peers who have some or all of their teeth. It is most likely related to inflammation resulting in tooth loss, which can negatively affect the brain, as well as a change in diet due to missing teeth and deficiencies in essential nutrients that negatively affect the work of the nervous system. It has been found that there is a link between the loss of the ability to chew hard food and the failure of cognition that characterizes Alzheimer's disease. It is evident that the lack of teeth causes malocclusion and causes serious gastric diseases, apart from aesthetic considerations. Toothlessness can often be a direct cause of shortening human life and is even a predictor of mortality, mainly from cardiovascular causes. Missing teeth cause coronary plaque formation and aortic hardening, increased susceptibility to electrocardiographic abnormalities, heart failure, ischemic heart disease, hypertension, and stroke. Comorbid associated with toothlessness include certain cancers, diabetes, insulin-dependent diabetes, kidney disease, and

rheumatoid arthritis. Diseases of the stomach, gastritis, duodenal ulcer, pancreatic diseases, including neoplasms, as well as neoplastic lesions of the oesophagus and upper gastrointestinal tract, are common. Mood and neurocognitive disorders, obstructive sleep apnea, cervical spine pain, migraine and headaches may appear, which are directly caused by malocclusions due to tooth loss, which determine the metabolism of the cerebrospinal fluid. Malocclusion and chewing dysfunction cause functional and morphological changes in the hippocampus in the temporal lobe of the forebrain. They harm the hippocampus in the elderly and cause associated spatial and episodic memory disturbances, as well as aggravate the symptoms of multiple sclerosis and increase the risk of general dementia. The improvement of chewing conditions as a result of implantological and prosthetic treatment prevents the dysfunction of the hippocampus.

In a favorable situation, caries and periodontal disease may directly contribute to the patient's death. Nevertheless, tooth extraction is often unavoidable, which, although allowing for immediate problem solving, creates further problems. The consequence of extracting even one tooth is an imbalance in the stomatognathic system, which, in the absence of any component, ceases to function efficiently. Both caries and periodontitis can even lead to complete toothlessness. As a result of tooth loss caused by caries and periodontal disease, implants and prosthetic restorations including bridges and crowns should be placed.

Sick teeth or their complete cancer is therefore not only a loss of aesthetic value, as many thought, and is associated not only with some discomfort associated with eating difficulties, but also the cause of many diseases throughout the body caused by chewing dysfunction or the lack of it. This state of affairs, therefore has a huge impact on the health welfare of societies on the one hand and puts enormous pressure on the social security and healthcare systems of all countries on the other. There are no statistical data to directly assess how the treatment of caries, periodontitis, and toothlessness affect the economic effects resulting from the need to treat diseases of the oral cavity, which is most likely to be determined in direct terms. In contrast, the significance of the systemic complications presented above for the social costs related to the treatment of these diseases, costs of rehabilitation, costs of sickness absenteeism at work, and disability benefits paid by the society are so difficult to identify as difficult to determine. Undoubtedly, this poses huge ethical challenges to the entire dental community, as reducing the negative effects of oral diseases on a social scale has a health significance for the entire population and significantly affects the economic condition of individual countries. This scope of ethical responsibility for the effects of the health of the oral cavity, due to numerous systemic complications, extends to entire national health systems and doctors of various specialities. There is no doubt that the basis of all behavior of dentists and physicians are the four basic ethical principles that apply to physicians in general, including respect for autonomy, charity, harmlessness and justice, in the case of dentists, extended to truthfulness as the

fifth main principle regarding the patient's health, resulting directly from the Hippocratic oath, which is made in an appropriately modified form by every dentist and doctor of any other speciality before starting his professional activity. It is worth noting that the duty of a dentist and any physician of a different thing is continuous education to offer the patient diagnostics and therapies at the highest possible level at any time. It is an ethical duty of a dentist to professionally cooperate with a center for the design and manufacture of prosthetic restorations with extensive knowledge of the current advanced design and manufacturing capabilities using avant-garde computer-aided methods using all the benefits of computerization, robotization and automation, as well as additive and advanced methods of refining the surface properties of the manufactured prosthetic restorations. t is not without significance that the ethical obligations of dental engineers working closely with dentists are of particular importance, mostly because of the possibility of direct assistance to sick patients. Among the ethical duty of engineers there is the obligation of being an expert and possessing skills and high competencies recognized in a professional environment, to serve the public by providing valuable products and value and respect of high standards deriving from the ideals of the profession of an engineer. The ethical obligations of dental engineers, in addition to the honest and competent performance of their profession, also include moral responsibility toward employers and clients as well as the community and society as a whole. Undoubtedly, ethical risk analysis and assessment of its acceptability are fundamental.

It is often necessary to implement avant-garde technologies, the use of which is in the critical health interest of the patient. In light of the discussion in this chapter, incurred in this case is an acceptable risk because the total benefits outweighed the full exposure risk and introduced new technology as an experiment, which actions are morally permissible. Not using the available technological possibilities in such a situation and in any therapeutic case must be considered an ethical tort of the dentist. Similarly, the assessment of not using the avant-garde and currently available materials, incredibly filling materials, and using instead traditional but morally obsolete materials during conservative and endodontic treatment, or the use of inappropriate pharmacological agents, must be strict. Undoubtedly, one of the ethical delicts in this respect is the omission of the achievements of nanodentistry to the extent possible for the common application. All these aspects relate to the ethical delicts to implement the achievements of the current development stage of Dentistry 4.0. Conscious or even unconscious omission of these achievements should be considered a serious ethical breach of the dentist, in extreme cases suggesting the need to eliminate the dentist, which harms patients from the possibility of providing health services.

The ethical obligations of dentists now include the use of tissue engineering achievements that can be applied in dentistry and the related research achievements regarding new designs of implant-scaffolds and biological-engineering materials.

The general problem of respecting the findings of the so-called ethical codes considering that, in general, the duties of every person, including the dentist, can be classified into three mutually exclusive orders: ethical, environmental, and legal. The code, although called ethical, is in essence the closest to the legal order, especially since almost every sanction is provided for in the form of disciplinary liability of a dentist and a doctor of any other specialty, in the form of codified rules. The authors of this chapter would like to point out again that ethical motivation is always a moral imperative. In every situation, it results from the dentist's inner conviction about his duties. The more natural it is to comply with the provisions of the code of ethics, the higher the ethical level of the dentists' community is, and this is what determines the increase in the quality of health-care services experienced by patients.

A severe general problem of modern dentistry concerns its role in modern societies. A serious dispute takes place in this case, seemingly on professional topics, but it is ethical in fact. In an important series of articles [9, 10], it was emphasized that the current approach to treating diseases of the oral cavity, especially caries and periodontitis, requires a radical change. The total was criticized in the work model called. Western dental care consists of specialized and technologically more advanced treatment, which, in the authors' opinion, includes the Dentistry 4.0 stage. Hence, it is believed that it is necessary to re-evaluate both the assessments and the prevention activities concerning the entire world population [447, 448]. It is an apparent ethical dilemma because it could mean that either those who heal the effects or those who try to prevent the disease act unethically or both. Not only that, in work [449] and during a large world conference, there is a statement that the goal of dentists is "drilling, filling and billing," which casts a shadow on the entire dentist community. The justification for such actions is allegedly meeting the requirements of wealthy patients who expect expensive procedures, which often do not concern treatment, but only the satisfaction of empty aesthetic expectations, such as dental prosthetics. It is impossible not to notice that the problem is not only local diseases of the oral cavity, but mainly very numerous systemic complications occurring in the absence of dental treatment, or even against it. It is estimated that humus affects 3.5 to 5 billion of the planet's nearly 8 billion inhabitants. Caries can be the cause of numerous systemic diseases mentioned above, and even the patient's immediate death, which can be reduced or even eliminated by correctly performed endodontic treatment. Likewise, periodontal disease has also reached epidemic proportions, although it has only recently been recognized in this way. They are the most common inflammatory conditions, affecting nearly 50% of adults in the world, and can lead to complete toothlessness if left untreated. Up to 83% of the population develop some degree of gingival bleeding during their lifetime. Periodontal diseases, like caries, are the direct cause of many long-term systemic diseases and complications. Partial or even complete toothlessness is an inevitable consequence of the

diseases mentioned above of the oral cavity, mainly caries and periodontitis, and it is also a direct cause of numerous systemic diseases.

In the opinion of the authors of this chapter, the evaluations are as much one-sided exaggerated, as far as simultaneously unethical, even though it was developed by a group of eminent world authorities in the field of dentistry. It has not been supported by sufficient research evidence. Of the well over a million dentists in the world [450], of which there are nearly 450,000 [451] in Europe, and about 200,000 [452] In the United States, the vast majority certainly performs their tasks following the imperative moral and medical principles and the current state of knowledge. Therefore, it is difficult to agree with such formulated assessments, which openly violate the foundations of general human ethics and the professional ethics of dentists. It is not true that treatment of the effects of the disease is unnecessary and therefore, unethical.

On the contrary, it is the moral duty of every doctor, including dentists, to provide medical help to every patient who is affected by the disease. It is not true to say that prevention is possible in all cases on the simple principle that "if I knew I would fall, I would sit down." There are many causes of these diseases, and, of course, it is impossible to limit ourselves to prevention. It should be done with all firmness and consistency. However, it should be firmly stated from an ethical obligation that regardless of the effectiveness of these actions, all available measures should be taken to limit the very harmful effects of oral diseases. There is no alternative here. It has been reported that the history of oral diseases is almost as long as the history of human civilization. The hundreds of thousands of years of statistical evidence show that it is naive to think that the currently introduced prophylaxis, even if it could be done, will radically remove these common diseases on a global scale, significantly since the current advancement of these diseases in the 5–14 age group does not differ much, except for edentulousness, from their prevalence in the entire population. The problem was analyzed in great detail in the Authors' own study [11], generally proving that the concept of substitution of all dental therapies, including Dentistry 4.0, by universal dental prophylaxis, is absurd. Spreading such opinions also contradicts the principles of human ethics and the specific aspects relating to medicine, dentistry, and engineering set out in this chapter.

Quite unexpectedly, this year a completely new aspect of the ethical attitudes of dentists has emerged, although ENT doctors and anesthesiologists, and even ophthalmologists and their assisting medical staff were in a rather similar situation. The work of these groups of doctors takes place in the patient's respiratory tract. The dentist must inhale the patient's exhaled air along with the bioaerosol. The transmission of this coronavirus takes place even with normal breathing [453], the virus can survive up to several dozen hours. Its incubation time is usually five or six days, but can be as long as fourteen days or longer [454]. Therefore, it is necessary to apply special protection measures, as one infected patient, infecting the dentist, will infect several hundred to one thousand patients and their families during the

incubation period [11]. It is this extraordinary situation that has disrupted health care virtually all over the world. Treating patients for infectious diseases in hospitals, into which many other medical facilities have been transformed, has practically been abandoned in many countries, or at least the treatment of patients suffering from other diseases has been severely limited. In the case of dentistry, dental associations obligated dentists to postpone scheduled procedures. In many countries, including the United States, European Union, and Brazil, the governments have recommended dentists a "stay at home" and "do nothing" strategy if they are not to be infected [455–459]. This is where a huge ethical conflict emerged. Dentist, stop treatment or use PPE. It is the implementation of a defensive STOP strategy (systemic, technical, organizational, personal), which is now universally applicable, does not eliminate the SARS-CoV-2 virus, but ensures passive protection of the patient and isolation of the dentist and medical personnel from the infected environment. As a result, dentists ceased to function normally, completely in defiance of the Hippocratic Oath. The situation is systemic and affects thousands of dental clinics around the world. This violates to a greater or lesser extent all dental ethics, laws protecting workers and patients, and human rights in general, especially in terms of improving the quality and length of human life.

To overcome these problems, our team developed a decidedly offensive SPEC strategy (system, prevention, efficiency, cause) [11], which led us to a new breakthrough technical solution that eliminates the mixture of clinical aerosol and pathogenic respiratory bioaerosol of the patient by negative pressure for complete inactivation and effective decontamination in an appropriately selected set of devices [6, 11, 50, 456]. In this way, the root cause of the ethical conflict was removed and a technical device useful in clinical practice was provided.

The paper [11] presents a model of sustainable development of dentistry, containing three mutually complementary elements. The developing methodology of treatment, combined with the computerized and robotic stage of Dentistry 4.0, uses computer-aided design and production of CAD/CAM as well as additive methods of manufacturing prosthetic restorations and implants. For design purposes, diagnostics based on medical imaging with the use of CBCT cone beam computed tomography as well as intraoral and extraoral scanning are necessary. Oral prophylaxis should be developed very widely, and dental care should reach the poorest social strata in many countries. These theses deserve full support and deserve implementation in terms of an egalitarian approach to prophylaxis and dental care. However, this view cannot be an antinomy of the achievements of dentistry in terms of treatment and the achieved stage of Dentistry 4.0. The third direction in the development of dentistry, ensuring sustainable development, is the widely understood safety of doctors and dental staff. The dentist performs all dental procedures in the patient's respiratory tract, and each infection of this patient with pathogenic microorganisms exposes him to direct infection, for example, with the SARS-CoV-2 coronavirus, which is a direct threat to life. The dentist must be safe

when doing his job, and more importantly, he must feel safe. It is therefore necessary to strive for an even development of each of the elements of this model, that is, Advanced Interventional Dentistry 4.0 AID 4.0, Global Dental Prevention GDP and the Dental Safety System DSS, imaged by the tetrahedron (Figure 7.8).

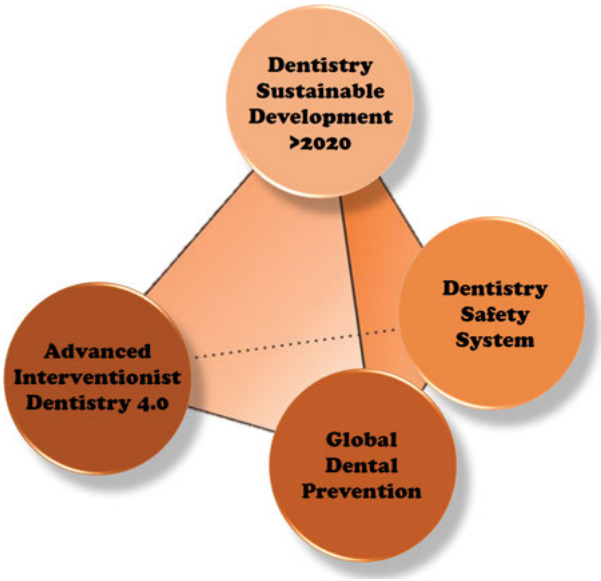

Figure 7.8: The model of modern Dentistry Sustainable Development DSD and the relationship diagram between Advanced Interventional Dentistry 4.0 AID4.0, Global Dental Prevention GDP and the Dental Safety System DSS [11].

Of course, many more details are covered in this chapter. The goal of this development of DSD, which characterizes nanotechnology, dentistry and engineering in general, was to thoroughly analyze aspects related to the daily practice of each physician in the field of interventional dentistry, in order to reach large masses of patients, covering about 2/3 of the entire world population, as well as preventive measures concerning almost 8 billion people. It is necessary to return to the question posed in the introduction, and to Figure 7.1, which symbolically presents three possible variants of connections between the title sections of knowledge and professional practice. Thus, whether the symbol is Światowit with four faces, or ancient Chinese censer standing strong on three legs, or finally three-trunk huge linden with a common root. After reading this chapter, the answer seems obvious. All activities are strictly dependent on ethics, including those related to dentistry and nanodentistry closely related to it, arising from nanotechnology, as well as dental engineering, a relatively young engineering discipline, without the development of which it is difficult to imagine the modern development of dentistry, especially following the standards of Dentistry 4.0. It is ethics and

the general ethics, as well as medical and dental ethics supported by engineering ethics, that underlie this activity. Thus, the symbol of all the activities described here is a small-leaved tri-trunk lime tree. The fact that this symbol is a living thing, the historic tree also indicates that the necessary moral imperative is respect for the natural environment, respect for ecological principles, both in terms of the selection of materials, and a responsible attitude regarding the implemented technologies and the eco-cycle in terms of obtaining raw materials and the economic waste and elimination of local emissions of post-production waste. The symbolic model of these interrelationships is presented in the form of an inverted tetrahedron (Figure 7.9).

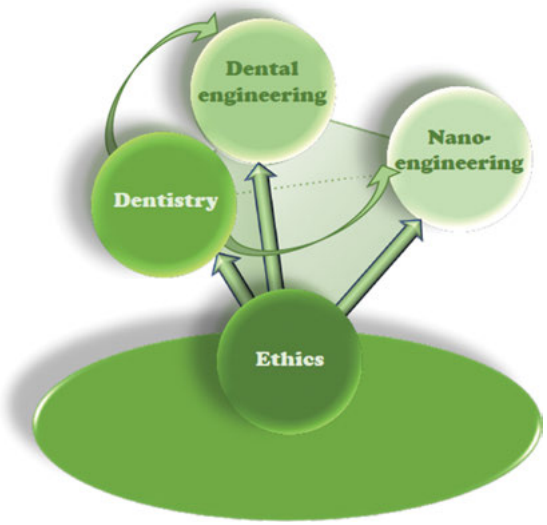

Figure 7.9: The model relationships between ethics, dentistry, dental engineering, and nanoengineering.

7.4.2 General conclusion

The general conclusion of this chapter can be a quote [460] written by Montesquieu (Iwie Charles Louis de Secondat, Baron de La Brède et de Montesquieu 1689–1755, French philosopher and lawyer, freemason, a writer, and the days of the Enlightenment, a foreign member of the Stanisław Academy in Nancy), with whom the authors of this chapter identify themselves fully:

> ***If you don't carry rules of morality in your heart, you won't find them in books.***

It undoubtedly applies to the dentist community, doctors in general, engineers, and all people of goodwill. The point is that all actions taken should be in line with the moral

imperative of decent people, which was mentioned by Prof. Władysław Bartoszewski. It is crucial that the group of people who can be included in it should be as large as possible and it is crucial that we will never be outside of this group of decent people.

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Judith Tanori and Amir Maldonado

8 Nanoscience and nanotechnology: Ethical implications for Latin American scientists

Abstract: In this chapter we reflect on some ethical implications raised by nanoscience and nanotechnology for scientists working in Latin America. Even if ethical concerns are universal among scientists, the social, economic, and cultural peculiarities of each region should modulate the response given to them. Most countries in Latin America are underdeveloped or in a developing situation. A considerable part of the population lives under the poverty line and near half of the labor force works in the informal economy. The science budgets are low. More scientists are needed. In addition, the countries in this region do not have full regulations for nanomaterials production, use, and disposal. Considering this situation, it is necessary that Latin-American scientists get involved and promote the beneficial applications of nanotechnology avoiding or minimizing adverse effects for humans and the environment. They must practice high quality science and take advantage of all possible collaboration opportunities. They need to follow the new developments in nanoscience and nanotechnology (novel materials and techniques, new regulations). They must also contribute to the training of young scientists with an ethical vision of their work. They should also contribute to reduce gaps in science related to income and gender. Latin American scientists must also engage in communicating science to the general public. If necessary, they should even participate in advocacy campaigns seeking to establish better regulations and evidence-based public policies. In the history of the region there are numerous examples related to the exploitation, production, handling, or disposal of materials that can give valuable insights into positive and negative consequences of science and technology. There are also very positive examples such as science fellowship programs or the discussion and implementation of the concept "university social responsibility."

Keywords: Latin America, Scientists, ethical issues, Nanoscience, Nanotechnology, regulations, Nanomaterials

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8.1 Introduction

The advent of nanoscience and nanotechnology in the last few decades has brought the need to analyze and respond to profound ethical issues. Each day the world population is witnessing the availability of new commercial products or processes based on the properties of materials at the nanoscale.

It is clear that nanomaterials applications have the potential to improve the quality of life of humankind. However, there is also concern about the possible adverse effects of our daily exposure to these materials that are increasingly pervasive in foods, drugs, cosmetics, coatings, home appliances, and many types of commodities.

As with any other materials applications, the release of nanotechnology products should be preceded by strong evidence that they are not harmful either for our health or for the environment. Laws and regulations define and establish public policies that rule over these matters.

As all citizens, scientists must obey and follow national and international laws and regulations. In addition, the scientific activity has its proper ethical guidelines to which scientists are committed. These ethical standards are most of the times stated by professional or academic organizations.

All these issues apply to scientists worldwide; the scientific ethical codes should have the same elements everywhere. However, local singularities around the world give rise to significant differences that affect the work of scientists in several places. For instance, the social and economic asymmetries between the richest countries in the Northern hemisphere and poorer countries in Latin America, Africa, and Asia are the source of particular ethical requirements in the latter; they should also modulate the collaboration between scientific groups in both kind of countries.

In this chapter we reflect on these issues from the perspective of scientists working in Latin-American universities. In the first place, we comment on some of the ethical challenges brought forward by nanoscience and nanotechnology. Then we discuss some Latin-American particularities that in our view are relevant when analyzing those ethical issues. We then make some comments on local regulations related with nanoscience and nanotechnology and recall some historical examples that could give some insight into our subject. Finally, we weigh in on some ethical implications in research and science education in our countries.

8.2 Nanoscience and nanotechnology: Ethical issues

Ethics deals with the human notions of “right” and “wrong.” It attempts to understand and guide our moral choices. The ethics of science is a branch of knowledge that seeks to establish a set of acceptable scientific practices; it is concerned with the consequences of scientific discovery and development.

In that sense, the ethical issues raised by nanoscience and nanotechnology are quite similar to those posed by material science and technology. When an application is devised for a known or a new material, scientists and engineers should also foresee, investigate, and avoid or minimize adverse effects. The history of science has numerous examples of situations where materials with promising properties have also negative counterparts that substantially condition the way they are used. One can think for instance of the cases of radioactive materials and of asbestos.

In the case of nanomaterials, the very feature that gives rise to a very large amount of potential applications is also the source of possible negative consequences. In fact, the difference between materials in the nanoscale as compared to the bulk lies in their size. When materials have some dimension in the nanometer range their electrical, optical, thermal, mechanical, and/or magnetic properties are different because of the influence of boundaries or interfaces. In addition, their exposed surface can be huge and for this reason they can display an enhanced catalytic activity. The size and properties of nanoparticles are suitable for interaction with biological materials and cell internalization.

In the last decades a great variety of nanomaterial synthesis methods have been proposed. Among them one can include the sol-gel technique, spray pyrolysis, thermal decomposition, synthesis in microemulsions, etc [1]. Nanomaterials are cheap to produce and can be cast in zero- (nanoparticles), one- (nanowires, nanorods), two- (sheets, layers, coatings), or three- (nanophases) dimensional structures.

Because of their availability and novel properties nanomaterials have a lot of beneficial applications for humankind. Just to mention some of them one can count:

1. Nanomaterials have the potential to contribute to fight against water shortages by providing useful systems for wastewater purification and atmospheric water harvesting.
2. They could also play a role in the reversal or containing of global warming by allowing the efficient use of clean energy sources.
3. Smaller and more powerful electronic devices are positively impacting every aspect of our daily life: cooking, entertainment, communication, education, health, etc. Combined with connectivity these devices allow the new possibilities brought by the internet of things.
4. Nanomaterials have also great potential in medicine. They make possible the design of new drugs or treatments. Biosensors ease health monitoring and disease control [2].

These are just some of the applications of nanotechnology. However, there is also a less optimistic counterpart. Listed below are some risks that we can foresee.

1. Nanomaterials pose risks to human life and health. If they persist in the air, soil, and water, particles can be introduced into the human body through the respiratory tract, the skin, or the digestive system causing toxic effects to cells [3]. They

can also alter the equilibrium in the human microbiota which potentially can compromise our wellness.
2. Nanomaterials could cause damage to the environment due to their high reactivity and ability to interact on a molecular scale with inorganic and organic chemicals. They can pollute soils, water resources, and the atmosphere, and can interfere in the normal functioning of biological cells and living organisms [3, 4].
3. Due to the great potential of nanotechnology to be used in regenerative medicine and genetics, development in this area can lead to human enhancement which could lead to social inequities [5].
4. Nanotechnology could have an influence on the loss of privacy due to the highly efficient and miniaturized electronic devices and sensors that are readily available [5, 6].
5. Nanotechnology in conjunction with other emerging technologies is promoting rapid and enormous changes in humanity. The progress is so rapid that sometimes our societies cannot positively adapt at the same speed. This could lead to critical issues with civil liberties [6].

With the increase in the use of nanotechnology, the production of nanomaterials now reaches a few thousand tons per year. This is the case of materials such as silicon dioxide, cerium dioxide, silver, and titanium dioxide [7]. It is well known that nowadays polymeric materials in the form of plastics and microplastics are dispersed in great quantities and in an uncontrolled way provoking environmental problems [8, 9]. In order to prevent a similar situation with the unwanted release and dispersion of nanomaterials, it is necessary to regulate them. Actions should be taken in order to forestall that new materials reach the atmosphere, soils, and natural water bodies. If this is not possible, the released quantities should be minimal. This implies the need of designing strategies, processes, and regulations for the controlled final disposal of nanomaterials.

The dispersion of nanomaterials in the atmosphere causes an increase in the quantity and variety of suspended particles that will enter the airways of various living beings, including humans. The uniqueness of this situation is that, due to their size, particles with a high specific surface area, with great chemical reactivity and the capacity to interact at the molecular level can be hazardous to biological cells [3, 4]. The biological risks of nanoparticles are related to the interaction they can have with cells. In Figure 8.1 we illustrate some possible mechanisms for the case of silver nanoparticles [10]. These particles can be active outside the cells. However, depending on their size they can also internalize and be active inside the cell. In both cases, the nanoparticles can release silver ions (Ag^+) which generate reactive oxygen species (ROS). The ions and the ROS can impair cell function. In addition, silver nanoparticles can accumulate in cell membranes and they can also bind to membrane protein. Thus, they can alter the function of proteins, membranes, and even DNA [4, 10].

The dispersion of nanomaterials in natural water bodies could cause damage to living organisms. In fact, nanoparticles, mainly metallic ones, have the ability to

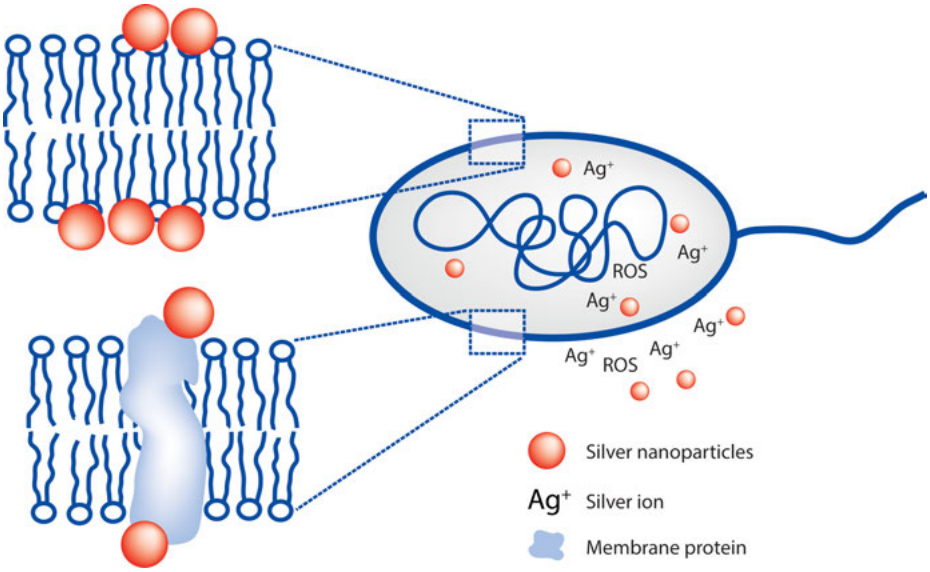

Figure 8.1: Nanoparticles can impair biological cell functions by different mechanisms. For instance, silver nanoparticles can release Ag^+ ions and generate ROS outside and inside the cell. These chemicals can affect proteins, membranes, and DNA. The nanoparticles can also directly bind to membranes (upper left) and to membrane proteins (lower left) thus affecting their functions. Note that this schema is not at scale (adapted from [4]).

interact with cell membrane proteins: they can bind to thiol groups of some amino acids. The nanoparticles can disturb the normal protein folding and therefore its functionality. Furthermore, nanoparticles have the ability to aggregate around biological membranes and even internalize into the cell. In the case of metallic nanomaterials, oxidative stress reactions occur, leading to cell dysfunction and degradation [4, 10].

The presence of nanomaterials in soils affects the organisms living there. Depending on the type of nanomaterial, their chemical and physical interactions could cause slight mortality in soil microorganisms. In some cases, they can also affect the reproductive capacities of these organisms with impact on subsequent generations [3]. All these effects can distort the natural cycle of recovery and nutrient production by vegetation. In addition, since plants have the ability to absorb nanomaterials, this may lead to transfer them in the trophic chain [11].

We have a new world of materials to explore when reaching the nanoscopic scale. Besides the beneficial applications of nanomaterials, they can have negative impacts on the environment and on living beings. It is thus very important to observe and to be aware of all the facets this new field of science and technology offers us.

8.3 Latin American singularities

Ethical concerns like those previously described should be universal among nanoscientists. However, there are singularities in every region in the world that shape the focus of interest regarding the ethical implications of nanoscience and nanotechnology. These singularities may vary from region to region and with time. In this section we will comment on some peculiarities in Latin America that are relevant in this subject.

The first thing to say is that Latin America is a large subcontinent from Mexico in the North to Argentina and Chile in the South. Countries in this region share common roots and a similar history. Most of the inhabitants speak Spanish or Portuguese, two relatively close languages. From a cultural point of view Latin America can be considered a unity. Their resemblant past has led Latin American people to similar present-day circumstances.

From the point of view of economy, the countries in this region are underdeveloped or in a developing status. The main economic activities still belong to the primary sector, although there are countries with some development in the secondary sector. There are a few strong Latin American industries, although many foreign companies have established themselves to produce in these countries due to the attractiveness of natural resources and low wages.

The exiguous industrial development has an important consequence for science and technology. The budget in this sector is very low (Table 8.1). In Latin America, investment in R & D accounts for less than 1% of the Gross Domestic Product (GDP); the exception is Brazil where this number is 1.3%. These figures should be compared with those of developed countries, where R&D spending is in the order of 2% of the GDP or more [12].

On the other hand, there are very few companies with Latin American capital that have research laboratories. The share of R&D spending by the private sector in developed countries is of the order of 60% or more (Table 8.1) [12]; this percentage in LA is much lower. For example, in Mexico, private participation in spending on science and technology is of the order of 23.7% [13]. This situation makes R & D expenses in the region to depend fundamentally on government budgetary plans. Scientists do not have access to industry funds nor are they fueled by problems stemming from industrial activity.

Undoubtedly one of the biggest problems in Latin America is inequality. According to recent figures, 184 million people (30.2% of the population) live below the poverty line [14]. Although the unemployment rate is of the order of 8% (WB), the informal economy has a great weight in the region. According to the International Labor Organization, around 50% of the labor force does not have a formal job [15]. Therefore, these people are not entitled to the corresponding social or labor benefits nor they pay the associated taxes.

The situation of poverty makes many Latin Americans see their future compromised. This is particularly reflected in the sciences since a large part of the youth

Table 8.1: Science budget as percentage of the GDP, scientists per million inhabitants and share of business sector in science expenses for several countries. Sources of the data: United Nations Educational, Scientific and Cultural Organization (UNESCO) [12],and (*)Organization for Economic Cooperation and Development (OECD) [13].

Country	% GDP	Scientist per million	Share of business sector (%)
Australia	2.2	4,532	56.3
Canada	1.7	4,541	–
China	2	1,089	–
Denmark	2.9	7,310	63.8
France	2.3	4,233	63.6
Germany	2.9	4,320	67.7
Japan	3.4	5,328	77.8
Korea	4.3	6,826	78.2
United Kingdom	1.7	4,227	–
United States	2.7	4,205	71.5
Argentina	0.6	1,206	–
Bolivia	0.2	163	–
Brazil	1.3	87	–
Chile	0.4	427	–
Mexico	0.4	260	23.7*

population cannot continue their studies or do not study in appropriate conditions. Budgets for science education are insufficient. The number of scientists is relatively low. For example, in developed countries the number of scientists is of the order of 4,000 (or more) per million inhabitants (Table 8.1). This figure is much lower in Latin America where countries have fewer than 1,000 scientists per million inhabitants (the exception is Argentina) [12]. Approximately 8% of the world's population lives in Latin America. However, 3.7% of the world's researchers live here [12]. It is clear then that it is necessary to increase the number of scientists in the region.

One consequence of the low number of scientists is that scientific questions have a limited space in public discussion. The average level of scientific literacy of the population is low. This is particularly undesirable when it comes to proposing, discussing, approving, or enforcing new regulations or legislation. The population does not have the tools to participate in the necessary debates and is susceptible to the influence of false information and fake news. In a context of globalization, this

is particularly important since our countries must harmonize their regulations with the most advanced economies.

Latin American scientists have the ethical imperative of contributing to increase the cultural level of the population. At the same time, they must influence local governments in order to have best budgets for science, technology, and education. And at the same time, they must contribute to create wealth from science-based companies.

Given the state of affairs, Latin American scientists must promote and take advantage of collaborative actions. First, between groups in the region in order to optimize resources and solve problems with social or economic impact in the region. But they must also take advantage of collaboration with groups of scientists from developed countries.

Scientists in this region must also contribute to eliminate the disparities that exist within the Latin American scientific community. For instance, there is a resource gap between research groups. Fortunately, there are institutions that enjoy reasonable funding, comparable to research groups in developed countries. However, there are many other institutions whose funding is insufficient to carry out scientific research and to train the required scientists. It is necessary to create programs to better finance science: establish new research groups with appropriate equipment and budget.

Finally, it is important to mention that it is also necessary to combat the gender inequality that still exists in the Latin American scientific community. Although there are more and more women scientists, the gap is still noticeable, especially in head and management positions. In fact, a recent bibliometric study found that in nanotechnology papers published by Latin American scientists from 1997 to 2015 only 25.78% of authors were women, as compared to 56.48% of men (the gender of 17.74% of the authors was not identified) [16].

8.4 Regulations in Latin America

As we have seen, Latin America has a certain number of peculiarities that impact scientific and academic activity in the region. These singularities are also reflected in the laws and regulations prevailing in the subcontinent. In the field of nanotechnology, regulations are in the earlier stages. The countries with more advances in legislation are Brazil, Mexico, and Argentina. Other countries are taking the first steps.

The main commercial exchanges of the Latin American region are carried out with the US and the EU. Numerous products that incorporate nanotechnology are available in Latin American countries. In Brazil, Mexico, and Argentina dozens of national and international companies use nanomaterials. They either produce them or import them from other regions. However, in Latin America, most of the population does not know what nanomaterials are and what nanotechnology is. People generally have no notion of how this technology is driving important developments

in medicine, foods, clean energy, electronics, agriculture, etc. Likewise, they are not aware of the risks that nanomaterials and nanotechnology can imply. On the other hand, regulations for the use of nanotechnology are incipient in the area.

Brazil is the country with the greatest development of nanoscience and nanotechnology in Latin America. It has also the greatest development of associated infrastructure. Regarding regulations, in Brazil there is no established regulatory framework; some proposed bills have been rejected. A bill was recently proposed before the Brazilian Senate, the bill PL 880/2019. It seeks to institute the legal framework for nanotechnology in that country in order to foster socioeconomic development and promote international cooperation in the field. Likewise, the proposed bill considers "the need to adopt an advanced model of legal, environmental and sanitary security in the management and use of these supplies"' as well as aims to address the related ethical, legal, and social implications. This bill received the favorable opinion of the Constitutionality and Justice Commission of the Brazilian Senate, CCJ, and it is currently in process [17, 18].

In the case of Mexico, the second country in the region regarding economic and scientific development, there is still no integrated legal framework for the regulation of the use of nanotechnology and nanomaterials. There is also no draft law to be submitted to legislation, nor are there official Mexican standards (abbreviated as NOM) of mandatory observance. The country's regulations in this area are limited to the definition of Mexican standards (abbreviated as NMX). These definitions provide a guide for the necessary interactions between producers, consumers, scientists, engineers, workers, organizations, and the general public. They also state definitions and concepts according, in most cases, to the technical specifications issued on the matter by the international standardization organization (ISO). Currently there are 16 approved Mexican standards related to nanotechnology [19].

The situation is similar in Argentina. The advancement of nanotechnology was promoted through a decree of the country's executive power (decree 380/2005), which led to the formation of the Argentine Foundation for Nanotechnology. There is no legal framework for the use of nanotechnology defined by the legislative bodies. Instead, it is the Argentine Institute for Standardization and Certification (IRAM) who prepares and issues the standards. To date, Argentina has four standards related to the physicochemical characterization of materials on a nanometric scale, specifications of nanoobjects, as well as management and risk assessment of nanomaterials. These standards coincide with some of the Mexican standards emanating precisely from the International Standardization Organization (ISO) [20].

Other Latin American countries such as Chile, Uruguay, Cuba, Colombia, Ecuador, and Bolivia have initiated the development of nanotechnology. Their efforts include the training of professionals in the area and the development of infrastructure.

Latin American countries should be prepared for the increasing use of nanomaterials and nanotechnology in everyday life. In order to address the processes and protocols required for controlling nanotechnology and to solve the problems of the

region, scientific and technical development must be achieved. The managing of the final disposal of nanomaterials is a major task that should involve all scientists and citizens at different levels of responsibility. The knowledge and perception of the population about nanotechnology will allow the use of nanomaterials and products based on this technology to be received with greater confidence. These elements should lead to an efficient participation of the population in the strategies and protocols for the final disposal of nanotechnological materials and products.

This is the status of regulations on nanotechnology in Latin America. The subject is still evolving. It is expected that in some years the resulting regulations will provide a framework for the research and the commercial use of nanomaterials.

8.5 Past experiences

Past events can also shed some insight on the ethical implications of scientific activity in Latin America. There are positive as well as negative experiences. We can cite many cases, but we will limit ourselves to a few that illustrate our subject.

Among the positive examples we can cite the vast program of fellowships for graduate studies that the Mexican government funds since several decades ago. This program has allowed thousands of young students to obtain a master or a PhD degree in science in institutions in Mexico and around the world. The program has contributed to an increase in the number of scientists in the country. Most of them now work in Mexican universities or research centers. With no doubt this is a successful program that should be maintained since it contributes to the increase in the scientific literacy of the Mexican population.

A second positive example is related to the importance that the concept "University Social Responsibility" has acquired in recent years [21].This term derives from one conceived to think about the human, social, and environmental impacts of private companies: "Corporate Social Responsibility" [22]. Briefly, we can say that when an institution considers its social responsibility, it takes into account all the impacts it can have on individuals, society, and the environment. In this way, universities can minimize their negative impacts and optimize the positive consequences of their actions. This constitutes an ethical imperative to which many Latin American universities are now committed. It is still early to make an evaluation of results on this topic. However, the discussion that has been generated in the concerned universities has led a large number of professors and researchers to reflect on these issues.

On the negative side, the history of asbestos production and export is an example of a situation regarding materials that should have been developed in a different way. Since the 1980s the production and use of asbestos has been discouraged in order to prevent several diseases. Many industrialized countries have since then banned the utilization of this material. However, Latin American countries are lagging behind in

asbestos related regulations. Even today most of the countries on the region still allow the use of asbestos; only Argentina, Chile, Uruguay, Honduras, and Brazil have banned it. Well after it has been banned in several countries, Mexico continued to import asbestos and export asbestos-containing products; the imports dropped from 35.3 tons in 1992 to 26.1 tons in 2000 [23]. And even today Brazil is one of the larger asbestos producers in the world [24]. Without a doubt, it is up to scientists to guide society and governments on the consequences of using this material. It is also their responsibility to advocate for harmonized regulations specially, with the countries that have advanced the most on this issue. The history of the process that led Canada from being an asbestos exporter to banning it can be very illustrative. In this process, part of the scientific community played a decisive role in helping to disseminate information to the general public. They have also participated in crucial advocacy campaigns [25].

A second example related to a technological activity that has left some negative consequences in Latin America has to do with the mining boom. For different reasons, both economic and technical, in the last decades mining exploration and exploitation has drastically increased in many countries in the region. Undoubtedly this has brought benefits to the area (jobs creation, new sources of income and wealth, etc.) but it has also had its adverse counterpart. The expansion of mining has brought environmental (pollution, spills), economical (weakening of other areas of the economy), and human (loss of land in communities) problems. For example, in Mexico it is estimated that the highest proportion of toxic waste such as heavy metals comes from the mining activity [26]. A few years ago, the tension between communities and mining companies gave rise to around 79 conflicts in 18 states of the country [26]. Although it is a complex and controversial issue, it is desirable that scientists get involved in situations like this to reduce or eliminate the negative consequences of such a lucrative activity as mining.

Examples such as those discussed here, which have had positive and/or negative consequences, provide valuable experiences to guide the ethical performance of nano-scientists and nanotechnologists.

8.6 Conclusions

Nanoscience and nanotechnology pose the same ethical challenges to scientists in Latin America as elsewhere. However, the history and the social and economic singularities of the region must somehow modulate the response given to these challenges.

It is clear that Latin American scientists must first of all do quality science, with the best international standards. Considering the low budgets, it is necessary to them to take advantage of all possible collaboration opportunities. This should be done both with scientists from developed countries and between groups in the region or with groups from other less developed countries. To optimize resources, it is necessary

to take full advantage of new technologies. For example, using video-conferencing, remote collaboration projects can be developed, or virtual scientific meetings organized.

Scientists in the region must continually keep up-to-date in their field. This implies not only knowing the scientific developments (novel nanomaterials and techniques) but also the new regulations in other countries. In scientific research, the beneficial applications of nanotechnology must be found, but one must also think about avoiding their possible adverse effects.

A very important issue is the training of new scientists. It is urgent that Latin America have more researchers per capita. And it is also necessary that they have an ethical vision of their work. At the same time, the community must contribute to reduce social inequalities. For instance, young people should be able to study, regardless of their social position; it is also necessary to eliminate gender gaps.

Last but not least, nanoscientists and nanotechnologists must make their knowledge known to general audiences. They must contribute to increase the scientific literacy of the population. This will help to create a more informed public opinion. If necessary, scientists should engage in advocacy campaigns seeking to establish better regulations and evidence-based public policies. With integrity and their quality work, scientists will gain the credibility necessary to contribute to the improvement of life in their countries.

Ethics deals with the notions of right and wrong. Scientists must reflect on these questions to act accordingly. And with this in mind, they will surely contribute to obtain the best of nanoscience and nanotechnology, learning from the past and the present to put aside their negative effects as much as possible. That is some of what we need to build a better world.

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Mohan L. Verma

9 Engineering marvels with nanotechnology

Abstract: After a drastic improvement of new tools and techniques, there has been a technology explosion in the last few years for patterning of materials in different dimensions at the scale of a nanometer (nm), which is one-billionth of a meter. The technology to create and manipulate things at an nanometer scale provides vast opportunities and challenges in almost all disciplines of science and technology. Nanotechnology is the subject in which, paradoxically, you first have to assume small to think huge and occasionally, make big to make small. In the coming years, there would hardly be any aspect of our lives where this science would not make an impact. Nanotechnology and biotechnology are anticipated to have an impact on nearly all sectors of society [1]. This chapter deals with some vital techniques and tools used for the preparation of nanomaterials (NMs) in its various dimensions along-with their uses in mainly nanoelectronic devices. This chapter starts with the definition of nanofabrication with a top-up and top-down approach to NMs preparation. The advanced technique of 3D nanoprinting of materials has given special focus in the context of its recent technological applications. For surface and nanobiological patterning and characterization, scanning tunneling microscope and atomic force microscope techniques are explained from its basic mechanism. Further, the designing and applications of 2D NMs in its different forms (hybrid/heterostructured, MXene) have been explained. Deoxyribonucleic acid nanotechnology is an important part of this chapter. The applications of NMs in optoelectronic/nanoelectronic devices and the density functional tools and techniques for the designing and characterization of the NMs have also been introduced at the fundamental level. This chapter is concluded with the Ethical and Social Implications of Nanotechnology.

Keywords: nanoengineering, nanofabrications, MXene, 2D materials, STM, AFM, density functional theory, material modeling, 3D nanoprinting, nanoelectronics, molecular electronics

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9.1 Nanoengineering and nanofabrication

9.1.1 What is nanofabrication?

Nanofabrication implies the creation of artifacts whose scale is in the nano-domain. The term fabrication is borrowed from macroengineering. The microelectronics industry makes use of fabrication to describe the advent of complex, highly integrated circuits. It is a procedure of choosing materials of the desired properties, depositing them, and patterning them in a sequence of steps designed to create a built-in circuit. To meet the challenge of shrinking components in microelectronics, new equipment and strategies are continuously being developed. Component sizes that had been in tens of micrometers grew to become single-digit micrometers, and then thousands of nanometers and went down up to a few tens of nanometers, the vicinity they stand today. As a result, what used to be called microfabrication was rebranded as nanofabrication, even though the governing principles have remained if the fact is told the same. Nanofabrication can be further divided into three foremost well-established areas of thin-film, lithography, and etching [2].

9.1.2 Top-down versus bottom-up nanofabrication

Manufacturing of substances at the nanoscale involved in growing of nanoparticles (NPs) and nanostructured materials. The nanofabrication techniques of materials are divided into two primary categories: "top-down" and "bottom-up" methods. A top-down strategy corresponds to produce nanostructures preferable for the synthesis of thin films and NPs with the desired characteristics starting from bulk materials and decreasing their dimension preferably larger than one 100 nm. The most frequent top-down method of fabrication involves mechanical grinding and etching techniques (viz. chemical etching and mechanical etching) [3]. Other top-down approaches consist of lithography techniques mainly scanning probe lithography, nanoimprint lithography, and block copolymer lithography [4]. On the other hand, the bottom-up, or self-assembly, approaches to nanofabrication use chemical or physical forces working at the nanoscale to assemble primary units into large structures. It principally involves the growth of single atoms and molecules of size much less than 100 nm. "Bottom-up" approaches begin with a chemical reaction delivering the metal atoms followed or accompanied by using managed aggregation of atoms into particles [5]. Figure 9.1 is the schematic representation of *top-down and bottom-up approaches for the synthesis of NMs*.

The nanofabrication methods can also be divided into three more categories: (1) physical techniques frequently rely on a "top-down" approach by subdividing some bulk (precursor) fabric into smaller units. (2) Chemical techniques, in which the NMs are synthesized from nucleation and growth of recursor species and (3) organic

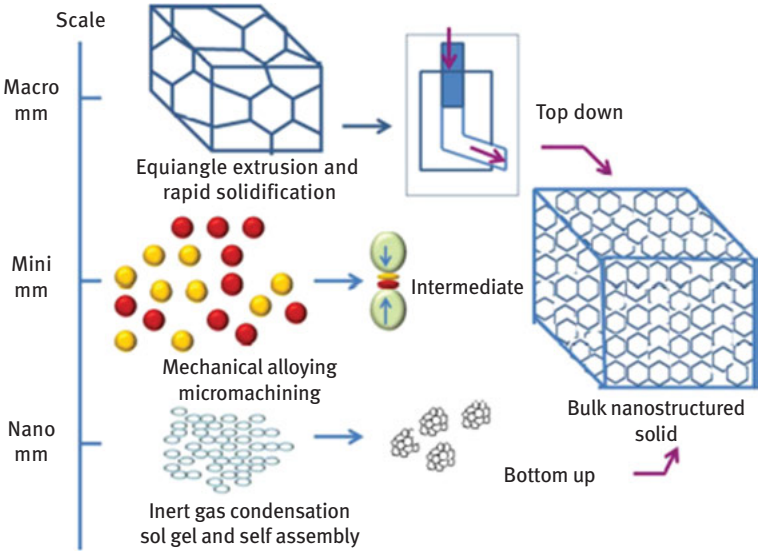

Figure 9.1: Top-down and bottom-up approaches for the synthesis of NMs.

methods: in which the NMs are synthesized through the bioactivity of some microorganisms and plants. Due to its low-energy necessities and low costs, the production of NPs via organic approach is established to be the promising greener method that approves synthesis in aqueous conditions [6–8].

9.1.3 3D nanoprinting

Three-dimensional (3D) printing is the construction of a 3D object from a CAD model or a digital 3D model [9]. The term "3D" printing can refer to a variety of strategies in which material is deposited, joined, or solidified under computer control to create a 3D object [10] with the material being added together. The creation of a 3D printed object is completed using additive methods in which an object is created by way of laying down successive layers of material until the object is created. Each of these layers can be viewed as a thinly sliced cross-section of the object. 3D printing is the opposite of subtractive manufacturing which is slicing out/hollowing out a piece of metal or plastic with a milling machine. 3D printing allows you to produce complex shapes with the use of less materials than common manufacturing methods. In the 1980s, 3D printing strategies have been viewed as suitable solely for the manufacturing of useful or aesthetic prototypes [11]. As of 2019, the precision, repeatability, and material range of 3D printing have extended to the point that some 3D printing methods are considered manageable as an industrial production technology. One of the

key advantages of 3D printing is the capability to produce very complicated shapes or geometries that would be otherwise impossible to construct by hand, consisting of hollow components or parts with interior truss buildings to reduce weight [12].

9.1.4 Nanopatterning of surface and STM

A scanning tunneling microscope (STM) is not an optical microscope, it is a device that obtains pictures of the atoms on the surfaces of materials. STM works by detecting electrical forces with a probe that tapers down to a point solely a single atom across. The development of the family of scanning probe microscopes started with the unique invention of the STM in 1981. Gerd Binnig and Heinrich Rohrer developed the first working STM. STM works by scanning a very sharp metal wire tip over a surface. By bringing the tip very close to the surface and employing an electrical voltage to the tip or sample, we can photograph the surface at an extraordinarily small scale – down to resolving individual atoms. As schematically shown in Figure 9.2, the STM follows three main principles. The first one is the quantum mechanical effect of tunneling, which allows us to "see" the surface. The second principle, the piezoelectric effect, allows us to precisely scan the tip with angstrom-level control. A typical piezoelectric material used in scanning probe microscopy is PZT (lead zirconium titanate). Lastly, a feedback loop monitors the tunneling current and coordinates the current and the positioning of the tip. The mechanism is shown schematically below. The tunneling is from tip to surface with the tip rastering with piezoelectric positioning, with the feedback loop retaining a cutting-edge set point to generate a 3D photograph of the electronic topography

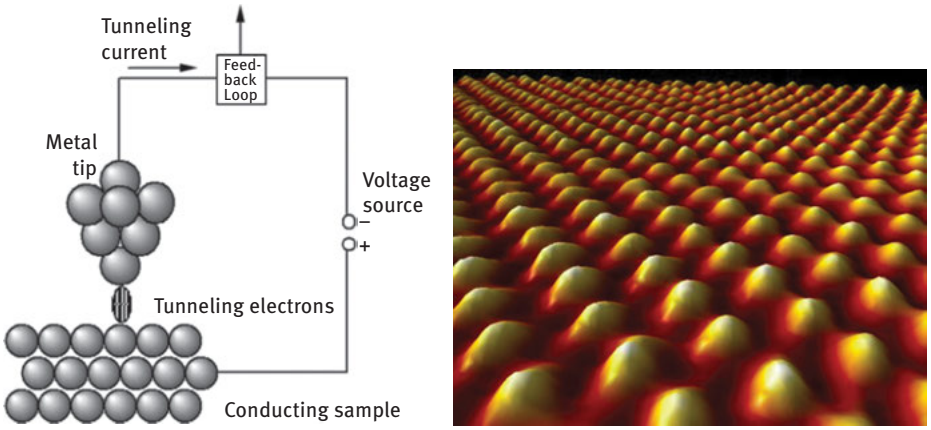

Figure 9.2: (a) Schematic of scanning tunneling microscopy with a feedback loop and electron tunneling and (b) 3D-rendered scanning tunneling microscope image of atoms.

The STM has applications in molecular science. It is used to move atoms individually, as well as to generate high-resolution maps of material surfaces. The major and only drawback of STM is that it can only image conducting and semiconducting surfaces [13].

9.1.5 Nanobiological printing and AFM

To overcome the drawback of STM, the atomic force microscope (AFM) was invented by Binnig, Quate, and Gerber in 1985 and won the Nobel prize in physics in 1986. The AFM has the advantage of imaging almost all types of surfaces, including polymers, ceramics, composites, glass, and organic samples. Similar to STM, a sharp tip is raster-scanned over a surface using a feedback loop to regulate parameters needed to picture a surface. AFM does no longer need a conducting sample. Instead of the usage of the quantum mechanical effect of tunneling, atomic forces are used to map the tip-sample interaction. Now, there are AFM for almost any measurable force interactions, that is, van der Waals, electrical, magnetic, and thermal. For some of the extra-specialized techniques, there is a need for modified tips and software program adjustments. In addition to Angstrom-level positioning and feedback loop control, there are two factors commonly used in atomic force microscopy: deflection and force measurement. The forces between the tip and surface have an impact on AFM imaging. The force is not measured directly but calculated by measuring the deflection of the lever. Also, atomic force microscopy has a feedback loop using the laser deflection to control the force and tip position. As shown in Figure 9.3, a laser is reflected from the back of a cantilever that includes the AFM tip. As the tip interacts with the surface, the laser position on the photodetector is used in the feedback loop to track the surface for imaging and measuring [14].

9.2 2D materials fabrication and applications

As our ability to create and study nanomaterials has progressed, fascinating and surprising new properties are being discovered. This has opened up totally new avenues for future technologies that focus on the size of the material as well as its bulk properties. We are genuinely getting into the age of nanotechnology.

9.2.1 Graphene: A wonderful discovery of this century

Nanomaterials (NMs) are labeled by way of the total number of their nanoscopic dimensions: zero-dimensional (0D) material, more often acknowledged as a NP. If

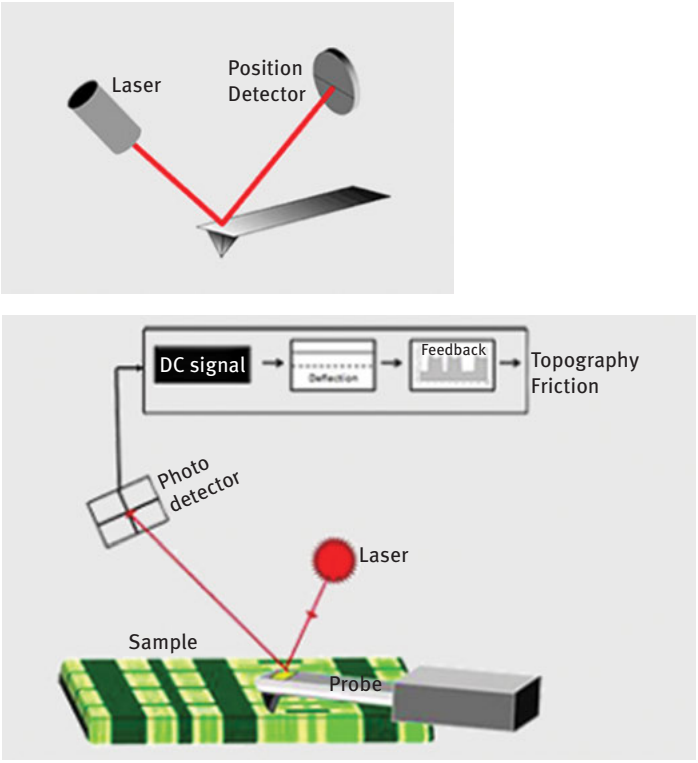

Figure 9.3: (a) Laser beam deflection for AFM and (b) schematic for contact mode AFM.

two dimensions of any materials are nanosized, with the third dimension is much larger, then this is a one dimension (1D); material or "nanotube/nanowire." If only 1D is nanosized, it would be a two-dimensional (2D) material – reminiscent of a large, however very thin sheet. The properties of 2D are widely tunable by doping, applying strain, external fields, and environmental effects, owing to the material's atomic thickness [15]. With these special properties, 2D atomic crystals have attracted scientific and technological interest.

Graphene used to be the first "modern" 2D material to be isolated in 2004. In the previous few years, the discovery of graphene has intrigued tremendous studies on novel low-dimensional materials [16]. Graphene has sp2 bonded carbon atoms which are organized in a hexagonal geometry with a zero-band gape semiconductor, because the lower strength cost carriers behave as massless Dirac Fermions of conduction π^* bond touches with the valence band at k-point in the Brillouin zone [17]. Graphene shows distinctive electronic properties with the defect [18], impurity doping [19], adsorption chemical functionalization [20], and so on. Therefore, graphene plays a vital role in electronic units [21–25].

9.2.2 Some other graphene-structured materials and their experimental development

After the experimental cognizance of monolayer graphene, it leads to a new research area of 2D materials [26, 27]. Akin to graphene, several different types of 2D materials were also invented such as phosphorene [28], silicene [29], germanene [30], single-layer transition steel dichalcogenides [31], black phosphorus (BP), boron nitride, and so on.

9.2.3 Hybrid materials

Recent technological breakthroughs and the desire for new features generate huge demand for novel materials. Many of the well-established materials, such as metals, ceramics, or plastics cannot fulfill all technological desires for the many new applications. Scientists and engineers realized early on that those composite materials can show enhanced properties than their constituents. Recently, hybrid nanocomposites have attracted the attention of the scientific community for their possible uses in devices [32–34]. This category of materials truly embodies each of the semiconducting properties of the latter species and the magnificent transport behavior of the former.

The sol–gel techniques developed in the thirties was one of the prominent driving forces that have become the wide field of inorganic–organic hybrid resources [35].

9.2.4 Heterostructured materials

Furthermore, 2D materials supply massive flexibility in the tuning of their electronic properties. Thus, bandgap engineering can be completed by altering the range of layers [36, 37]. Even more fascinating is the specific 2D physics found in such materials (e.g., Kosterlitz–Thouless behavior, characterized by the emergence of topological order, resulting from the pairing of vortices and antivortices below a threshold temperature). Crystals with transition metals in their chemical composition are typically inclined to many-body instabilities such as superconductivity, charge, and spin density waves.

Heterostructures of 2D materials provide not only a way to study these phenomena, but open wonderful probabilities of combining them for technological applications. Such stacks are very distinct from the ordinary 3D semiconductor heterostructures, as every layer acts concurrently as the bulk material and the interface, reducing the quantity of charge displacement within each layer. Still, the charge transfers between the layers can be very large, inducing massive electric fields and presenting interesting probabilities in band-structure engineering. Among the tools for band-

structure engineering in the van der Waals heterostructures are the relative alignment between the neighboring crystals, surfaces reconstruction, charge transfer, and proximity consequences (when one material can borrow the property of others in contact via quantum tunneling or Coulomb interactions). Thus, moiré structure for graphene on hexagonal boron nitride (hBN) leads to the formation of the secondary Dirac points [38, 39], commensurate in transition in the same system leads to surface reconstruction [40] and gap opening in the electron spectrum spin-orbit can be induced in graphene by the usage of neighboring transition metal dichalcogenide [39, 41].

9.2.5 MXenes

MXenes, a type of 2D material of early transition metal carbides and carbonitrides, has emerged as a unique type of layered and structured metal materials with desirable features, as specific conductivity comparable to metals, higher ionic conductivity, hydrophilic property derived from their hydroxyl or oxygen-terminated surfaces [42], and mechanical flexibility. With tunable etching methods, the morphology of MXenes can be efficiently controlled to form NPs, single layer, or multilayer nanosheets [43], which exhibit large surface areas and is favorable for bettering the sensing performance of MXenes based totally sensors [44].

MXenes or its composite show enhanced mechanical flexibility and stretchability, which enabled its wide application in the fields of wearable sensors, energy storage, and electromagnetic shielding [45].

The other big issue is the industrial production of these materials. Some do not exist in nature such as silicene and germanene, and they are extremely sensitive to the environment as BP. This will be a huge challenge to move to real applications that will be able to impact our real life.

9.3 Nanoelectronics and molecular electronics

9.3.1 Nanoelectronic devices

For the successful development of nanoelectronics, the hand-to-hand relation between engineer and science is necessary. The scientific community developed the understanding of materials; on the other hand, the engineer and physics community used this base to learn how to design circuits and systems. Science works in the nanoworld with individual atoms, molecules, nanoscale structures, and devices. But engineers work in the macroworld on complex systems with terascale device densities. They must learn to work and think about how the nanoscale world associates with the macroworld [46].

Through various research to date, researchers had proposed and demonstrated that for molecular-scale electronic devices, two primary types of current-carrying potential bases (or backbone) are used, namely, polyphenylene-based chains and carbon nanotube.

The common polyphenylene-based chains are used in molecular-scale nanoelectronic devices which are with the use of benzene ring (C6H6), by the process of oxidation removing two hydrogens from benzene, we found the structure of "phenylene," a ring which has two free binding sites. The carbon nanotube shows more extreme conductive property and the wires give astonishing results in the electrical switching. When these are implemented as micropatterned semiconductor surfaces, then the material shows the property ranging from almost the same as conductors (i.e., semimetals) to that of near insulators. Molecular transistors have been one of the greatest inventions done by researchers using carbon nanotubes. They provide a great and significant extent of improved device performance metrics, and show the elastic or retain behavior when used in the complementary metal-oxide-semiconductor (CMOS) circuits. When we go on decreasing the shape and size of any system by raising the negative power of 10 then the things get changed and this shows different behaviors in physical and chemical properties because the surface area to volume ratio increases with a decrease in size. But by making a comparison of polyphenylene-based chains with carbon nanotube, it is found that the current density of electrons transported through polyphenylene wires is having the same order of magnitude as that of copper wires (excellent conductor) because these devices are so much smaller with the much smaller cross-sectional area.

Some of the applications of the nanoelectronic devices which have been invented are conducting molecular wires, self-assembled molecular electronic circuit array, quantum dot cell (or artificial electrons), wireless electronic computing, hybrid nanoelectronic–microelectronic logic, and resonant tunneling diodes [47].

9.3.2 Molecular devices

The branch of sciences which deals with electronic processes that occur in molecular structures is known as molecular electronics. e.g. photosynthesis to signal transduction. Nanotechnology plays a vital role in both nanoelectronic devices and molecular devices; it shows when we build nanostructured devices by the study of individual molecules.

Molecular electronics aims at the fundamental understanding of charge transport through molecules and is motivated by the vision of molecular circuits to enable minuscule, powerful, and energy-efficient computers [48]. Molecular electronics focused on the fundamental understanding of charge transport through molecules and lead to the vision of molecular circuits to enable minuscule, powerful, and energy-efficient computers. The researcher produced and demonstrated that rigidly wired molecules

can emit light under voltage bias and it is astonishing results in fundamental science but it also use in the molecular electronics vision an optoelectronic component, that is, the development of optoelectronic components based on single molecules [49].

The main problem that generally arises in molecular electronics is how many molecules contribute to electron transport. The team of researchers aims to obtain molecular light-emitting devices that operate at different emissions wavelengths and a major challenge is to reduce the energy level low so that it will act as non-radiative electron transfer [50].

9.3.3 Optoelectronic nanodevices

The branch of science which deals with the interaction of light with structures of the smaller wavelength that is far below the diffraction limit which improves the quality of excitation plasmons (free electrons in metals stimulated by an energy source which produces a harmonic oscillation of the surface charges similar to waves), which leads to the intermediation of the energy exchange between photons and electrons. This is known as optoelectronics behavior in nanoelectronic devices [52]. Figure 9.4 shows some representative optoelectronic devices. In the modern era, Li-fi is the concerned topic of research that is used for sending the information through light. CMOS circuits are one method used to supply greater speed of information transmission between circuits.

The researcher aims to study the connection between atomic-scale spectroscopy with optics to resolve the physical and chemical property changes at the atomic scale level that is the electronic structure and light scattering or emission through the electron excitations from the plasmons phenomena [53].

Nowadays, researchers are focused on quantum dots infrared photodetectors to save the energy consumption with the control of parameters like low size, weight, power consumption, and cost. They implement these in a novel device structure for high sensitivity and temperature infrared photodetection [54].

9.3.4 Nanoelectronics in energy

Energy is the main source of food to live a life of all activity performing in nature whether it is any form, in a nanoelectronics researcher wants to conserve the electrical energy which is a playing a major role in generation and storage for that they create solar cells, supercapacitors lithium-ion batteries, and catalysis for fuel cells [55].

Nanoelectronics is the advancement of nanotechnology in the field of electronics and it provides essential benefits in the development of both renewable energy production through new technological solutions and optimized production technologies. The common technology used for energy conserve is to the enhancement of

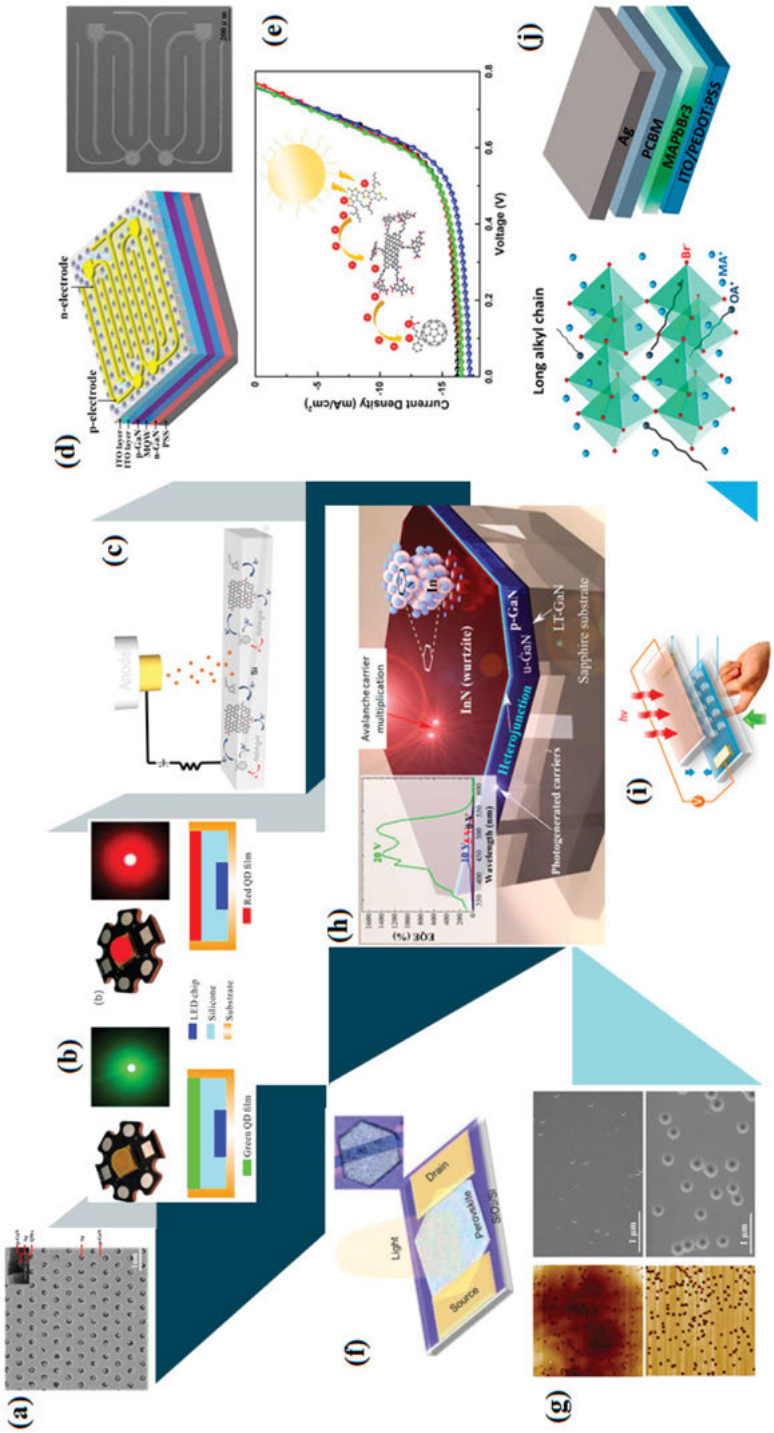

Figure 9.4: Different types of optoelectronic devices: (a) Ag-photonic crystal, (b) red quantum-dot light-emitting diode, (c) graphene oxide emitter, (d) double-layer indium tin oxide, (e) J–V curve of organic solar cells, and (f) Perovskite [51].

electrical energy stores like batteries and super-capacitors turns out to be downright promising. In nanoelectronics, till now lithium-ion technology is the most prominent variant of electrical energy storage due to high cell voltage and the outstanding power density. On the other hand, hydrogen acts as the most trustable energy store for environmentally friendly energy supply [56].

Graphene is the most superior material used in the field of nanoelectronics for energy conservation because it improves both energy capacity and charge rate in rechargeable batteries; when we use activated graphene for energy storage it makes higher-up supercapacitors; graphene electrodes may lead to a positive approach for making solar cells that are inexpensive, lightweight and flexible; and multifunctional graphene mats are promising substrates for catalytic systems [57].

9.4 DNA nanotechnology

As referred to in previous sections, nanotechnology is a subject of research and innovation concerned with constructing "things" – generally, materials and devices – on the scale of atoms and molecules. At such scales, the common rules of physics and chemistry no longer apply. For instance, materials' characteristics, such as their color, strength, conductivity, and reactivity, can differ appreciably between the nanoscale and the macro. Carbon "nanotubes" are a hundred times more advantageous than steel however six times lighter. Nanotechnology is hailed as having the plausible to increase the effectivity of energy consumption, help ease the environment, and solve foremost health problems [58]. Deoxyribonucleic acid (DNA) nanotechnology is being widely used for curing difficult areas in structural biology, biophysics alongside with the determination of structures. Nanomedicine is additionally being researched for implementation [59, 60].

The DNA molecules can be packed into the NPs and then can be inserted into the cells. In DNA, the four bases existing are adenine (A), cytosine (C), guanine (G), and thymine (T). Nucleic acids have the property that two molecules will only bind to every other to form a double helix if the two sequences are complementary with A only binding to T, and C solely to G.

9.4.1 DNA sequencing

DNA sequencing is the technique of finding out the nucleic acidic sequences of the order of nucleotides in DNA. It includes any approach or technology that is used to determine the order of the four bases: adenine, guanine, cytosine, and thymine.

The nucleotide sequence is the most indispensable level of knowledge of a gene or genome. It is the blueprint that incorporates the instructions for building an organism,

and no interpretation of genetic function or evolution could be complete without obtaining this information. The necessity of DNA sequencing, shown in Figure 9.5, was first made obvious through Francis Crick's principle that the sequence of nucleotides inside a DNA molecule without delay influenced the amino acid sequences of proteins. At the time, the trust was that a completely sequenced genome would lead to a quantum leap in understanding the biochemistry of cells and organisms [61, 62]. Modern DNA sequencing consists of high-throughput techniques that allow entire DNA sequences to be determined in a matter of hours.

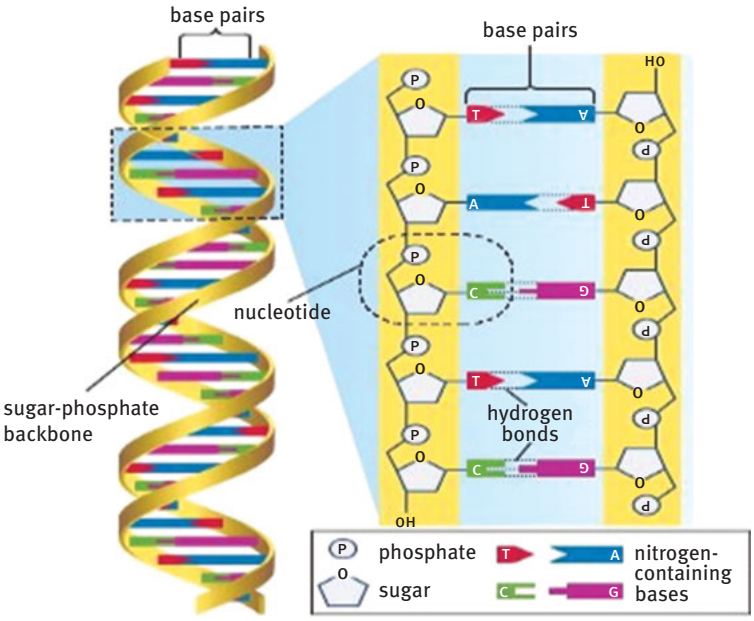

Figure 9.5: Sequence of DNA structure.

9.4.2 DNA nanoelectronics

DNA is a quite versatile biopolymer that has been a current focus in the area of nanomachines and nanoelectronics. DNA exhibits many properties, such as high stability, adjustable conductance, vast information storage, self-organizing capability, and programmability, making it the best material in the usage of nanodevices, nanoelectronics, and molecular computing [63, 64].

Even though native DNA has low conductance, it can be simply converted into an acceptable conductor by way of doping metal ions into the base pairs. DNA has already been exploited for the fabrication of nanoscaled systems. Convenient programming of

nucleotide sequences and the mechanical rigidity of short double helices of DNA molecules make DNA exceedingly favorable for the building of nanodevices with targeted 1D, 2D, or 3D structures. Moreover, DNA molecules can be effortlessly engineered by scientists with atomic precision using DNA manipulating enzymes, such as ligases, nucleases, and transferases [65].

9.4.3 Structural DNA nanotechnology

Structural DNA Nanotechnology makes use of unusual DNA motifs to construct targeted shapes and arrangements. DNA, nature's molecule of choice for storing and transmitting genetic information, is a fantastic nanoscale constructing block due to the fact of its specific 3D conformation, chemical addressability, and predictable Watson–Crick base pairing.

Structural DNA nanotechnology, derived from Seeman's revolutionary idea that DNA may want to be used as a physical material for the self-assembly of nanoscale structures, has developed with remarkable pace over the past 30 years [66]. Sticky-ended cohesion of DNA is the most predictable intermolecular interaction of any known molecular system, in the senses of affinity, diversity, and structure. A range of convenient design rules and reliable assembly techniques have been developed to engineer DNA nanostructures of growing complexity [67].

9.4.4 DNA origami and 2D nanostructures

DNA origami is one of the latest techniques of using DNA as building blocks for the synthesis of NPs. "Origami" is a Japanese word that capability the folding of an undeniable sheet into an arbitrary structure having a particular dimension [68]. DNA origami can be used to construct not only arbitrary 2D nanostructures however additionally nanosized breadboards for the arraying of NMs or even elaborate 3D nano-objects. The shorter segments connect to the primary genome and act as "staples" that preserve the DNA in a range of shapes such as squares, triangles, and stars measuring simply 100–150 nm across [69, 70]. DNA origami has proved itself to be a powerful way to construct sophisticated nanostructures for use in a mass range of devices from computing elements to drug carriers.

9.4.5 Nanorobotic arms

A new "robot arm" consisting of a square base and a protruding "gear stick," all made of DNA double helices, that can be driven through electrical fields alone, can go 100,000 cases faster in solution than other machines especially based on DNA

molecules. The nanorobot, which is made the utilization of the "DNA origami" technique, may want to locate use in robotics applications, such as cargo transfer, in biosensing, digital memory, and even to make nanoassembly systems.

DNA molecules have negative charges. The biomolecules can be moved by applying electric fields. Theoretically, this wants to allow nanobots made of DNA to be navigated by the use of electrical impulses. Applying an electric field to the arm allows one to switch its position within just milliseconds, which is at least five orders of magnitude faster than that possible using previously employed approaches. The motion can also be computer-controlled and thus produce complicated movement patterns, such as rotations with various frequencies or motion between dedicated docking sites on the platform. One can also move NPs and molecules with the arm and apply molecular forces with it [71].

The researchers fabricated their devices adopting DNA self-assembly with origami techniques. They created a platform of dimensions 55 nm × 55 nm with the integrated molecular arms of length 25 nm that can rotate around an axis at the center of the platform and be expanded to more than 400 nm. This study indicates a new future for such devices in robotic systems that may be applicable in biosensing. This is also the first example of a nanoelectromechanical devices, in which a biomolecular nanostructure is redesigned in a buffer [72]. Hopefully, these will be used to analyze biochemical samples or generate active medical agents. The required miniature machines is already been developed at a low cost using the DNA origami methods.

9.5 Computational nanomaterials and nanotechnology

9.5.1 Material modeling: Present demand and techniques

The computational NMs group uses numerical methods to turn nanoscience into nanotechnology. Design and optimization of materials are eternal and new problems; almost all matter is made up of materials. The emerging nanotechnology which changes the distribution and arrangement of atoms to get materials of different properties has brought a significant revolution for materials' design. Nowadays, nanotechnology has been extensively applied in various fields such as medical, aerospace, and energy [73–75].

Computer modeling and simulation of NMs quantitatively describe the correlation between the materials' microstructure and macro properties to a certain extent [76]. The strong computing power provided by computer overcomes the shortcomings of traditional material design and reduces the material production cycle [77–79]. In the twenty-first century, computer-aided design is playing a huge role in designing NMs [80, 81]. Out of different modeling techniques, at present, the density functional

theory-based modeling of NMs is in attracted material scientists because of its various advantages over other techniques.

9.5.2 Density functional theory: Advantages and tools

Density functional theory (DFT) is a computational quantum mechanical modeling technique used in physics, chemistry, and materials science to look into the electronic structure (or nuclear structure) (principally the ground state) of many-body systems, in specific atoms, molecules, and the condensed phases. Using this theory, the residences of a many-electron system can be determined through the use of functionals. In the case of DFT, these are functionals of the spatially dependent electron density. DFT is among the most popular and versatile techniques available in condensed-matter physics, computational physics, and chemistry [82].

The DFT is nowadays the most successful (and also the most promising) technique to compute the electronic structure of matter. Its applicability ranges from atoms, molecules, and solids to nuclei and quantum and classical fluids. In its original formulation, DFT offers the ground-state properties of a system, and the electron density plays a key role. An example: DFT predicts a tremendous range of molecular properties: molecular structures, vibrational frequencies, atomization energies, ionization energies, electric and magnetic properties, reaction paths, and so on. The original density functional concept has been generalized to deal with many distinct situations: spin-polarized systems, multicomponent systems such as nuclei and electron-hole droplets, free energy at finite temperatures, superconductors with electronic pairing mechanisms, relativistic electrons, time-dependent phenomena, and excited states, bosons, molecular dynamics, and so on [83].

All over the world, scientists are involved in developing different DFT-based tools depending on the study of various properties of materials. These tools have some advantages as well as limitations. A wide range of electronic structure codes based on the DFT used in physics and chemistry of materials are available. Some of them are free as GNU licensed [84]. Various plotting and visualization and plotting tools are also used as pre/postprocessing tools for material modeling, which are Avogadro, molden, Jmol, VESTA, GDIS, XCrysden, and so on. Nowadays, some python-based tools are being developed to the same computational time.

9.5.3 Characterization study of NMs

Manufacturing of materials at the nanoscale is termed as a nanoengineering process, which mainly involves reliable, scaled-up, low-cost manufacturing of NMs, structures, devices, and systems. Size, shape, surface structure, and chemical composition of NMs are all parameters that can be varied during NM processing [85].

These NMs can have various shapes and structures such as spherical, needle-like, tubes, platelets, etc. Chemical composition is another important parameter for the characterization of NMs, which comprise nearly all substance classes, for example, metals/metal oxides, polymers, compounds, as well as biomolecules. Under ambient conditions, NPs tend to stick together and form aggregates and agglomerates. For the characterization of materials along with the above-mentioned patterning tools like STM and AFM, experimentally SEM, TEM XRD analysis are in use. By using computer experiments, NMs in its various dimensions can easily be characterized along with the study of almost all physical and chemical properties.

9.5.4 Future scope in the improvement of novel NMs and nanotechnology

Nanofabrication techniques can be extensively divided into three categories: physical, chemical, and biological methods by which a wide range of NPs and nanostructures are produced with more advantageous physical, chemical, and biological properties. These approaches can be also labeled into three important groups: gas-phase methods, liquid-phase methods, and solid-phase methods.

A better realization of the various techniques of manufacturing of NMs in developing the quality of human lifestyles after an exciting experience in the world of nanoscience and technology has been gained. With systematic and chronic research, it can be concluded that there will be a correct scope and a higher future for NMs in the coming years [86].

9.6 Ethical and social implications of nanotechnology

As we design NM and develop the capability to redesign the structure of all materials, corresponding social and ethical questions are also created. To help sustainable, ethical, and economical development in nanotechnology, it is required to educate all stakeholders about the benefits, limitations, and dangers of nanotechnology [87]. It is vital for all to try to obtain four social objectives: (1) creating a robust perception of local and global forces and problems that affect human beings and societies, (2) guiding local/global societies to appropriate uses of technology, (3) alerting societies to technological risks and failures, and (4) growing knowledgeable and ethical personal decision-making and leadership to resolve issues in a technological world [88]. Advances in nanotechnology also present several challenges and risks in health and environmental areas. Nanotechnology risk evaluation techniques and protocols need to be developed and applied by the regulatory bodies. Eric Drexler, the author of Engines of Creation, has recognized four challenges, which are technological development,

technological foresight, credibility, and understanding, formulating public policy in dealing with the development, impact, and consequences of nanotechnology on society [89].

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Part III: **Ethical reflections in health care and environment**

Vittoria Viganò, Giovanni Bernardini and Mario Picozzi

10 Ethical principles and issues in nanomedicine: The role of clinical ethics

Abstract: Nanomedicine is the application of nanotechnology in medicine with the aim to improve disease prevention, diagnosis, and therapy, thus increasing patients' quality of life and life expectancy. As other emerging technologies, nanomedicine presents several benefits but also raises scientific, social, legal, and ethical concerns that cannot be ignored. The role of ethics in nanomedicine evaluation is twofold: to support the decision-making process policy and to support patient's care through clinical ethics consultation. In this chapter, we introduce a collection of effective tools that ethics uses for handling ethical dilemmas in nanomedicine. Some applicable approaches in the research and development field are risk-benefit analysis and the precautionary principle(s); such approaches are mainly addressed to policymakers. In clinical practice, the most common approaches are the four principles of medical ethics and the four-box approach which aim to reach a shared decision between the medical team and the patient (and/or family), regarding the patient's best care. The role of the clinical ethics consultation in nanomedicine is particularly relevant in light of the complexity and heterogeneity of nanotechnology-enabled products, and it can be categorized into four main areas: education, clinical consultation, non-clinical consultation, and policy development.

Keywords: cost-benefit analysis, precautionary principle(s), four principles of medical ethics, nano-ethics, four-box approach, clinical ethics consultation, ethics consultant, ethics committee

10.1 Nanomedicine

The term nanomedicine was introduced for the first time in 1991 in Eric Drexler's book *Unbounding the Future. The Nanotechnology Revolution* [1]. Nanomedicine is the application of nanotechnology in medicine with the aim to improve disease prevention, diagnosis, and therapy, thus increasing patients' quality of life and life expectancy. In general, nanomedicine refers to those drugs, devices, procedures, and tools that have

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one or more dimensions in the nanoscale range and display new or better features, which are not present at bigger sizes. A nanomedicine end product can fall outside the nanoscale range (0.1–100 nm, up to 1,000 nm); indeed, implantable devices can reach up to a few centimeters and, paradoxically, nanodrugs are larger than the analogous free-drug counterparts. Since several definitions of nanotechnology are currently used by stakeholders, different nanomedicine definitions exist sometimes leading to drug labeling discrepancies in different countries [2, 3]. Some authors [2, 4] have discussed the absence of a unified definition of nanotechnology and related issues; however, the Nanotechnology Task Force [5] advised not to have a "hard definition" of nanotechnology, particularly for regulatory purposes as it can be counterproductive.

Almost every field of medicine would benefit from nanomedicine applications, with oncology being the most promising candidate. Furthermore, nanotechnology is expected to become a key enabling technology for predictive, regenerative, and personalized medicine (i.e., the ability to provide the right treatment to the right patient, at the right time, in the right place, and with the right dose)

Regarding treatments, Food and Drug Administration (FDA) has already approved several devices along with more than 50 nanodrugs [6] and the global market size of nanomedicine is estimated at US$ 183.9 billion in the year 2020 [7].

10.1.1 Is technology morally neutral?

Considering the potential applications enabled by nanotechnology, we can paraphrase Stan Lee's saying: "With great technology comes great responsibility." In general, our society openly condemns the use of technology for evil purposes; however, before evaluating the purposes and related consequences of technology, we should ask ourselves the following question: Can we consider technology by itself as morally neutral or not? If the answer to this question is "yes," then an ethical analysis, far beyond the mere evaluation of consequences and purposes, is needed.

The term "technology" originates from the Greek concept of τέχνη (*téchne*)[1] and specifically refers to the knowledge of "doing" or "to make something." The word *téchne* is different from the Greek general term of knowledge (ἐπιστήμη, *epistéme*) since the former carries the notion of a specific kind of knowledge: the expertise required to produce a concrete object. In other words, technology designates the human action of creating a product, and not the technological object by itself. Accordingly, technology *per se* is not morally neutral because it consists of human decisions and actions, and therefore it is liable of moral evaluation. Consequently, we should abandon the old interpretation of use versus abuse, in which the technology is morally

1 In English, there is no difference between the words "technology" and "technique" as it exists in other languages like in Italian and German.

neutral and only the use determines its permissibility. Besides, unlike the past, modern technology is a human action that carries significant consequences on society, environment, human health, and even human identity, possibly affecting present and future generations [8].

Considering technology as a human action, it is clear that also relatively simple technology needs an ethical evaluation as well. If we consider the classification proposed by Mihail Roco [9] of the five generations of nanotechnology, even products of the first-generation require a moral evaluation, not because they are good or bad but because they entailed a human action. The White Paper on Nanotechnology Risk Governance [10] states that fundamental ethical issues arise only from second-generation applications. In response to this statement, Céline Kermisch [11] already drew attention on the fact that numerous ethical issues and principles are already at stake when considering first-generation applications. For instance, justification of (public and private) resource allocation, justice in accessing these products, public involvement, environmental protection, and workers' and patients' safety. From one generation to the next, not only technical complexity increases, but the analysis of ethical and social impacts becomes more convoluted. Each generation manifests new ethical issues that adds to those of the previous generation and they all need to be taken into consideration and be carefully evaluated.

10.2 Ethical principles and approaches in nanomedicine

The term "nano-ethics" appeared for the first time in a scientific article in 2004 [12]; however, the ethical reflection on nanomedicine has its roots in the ethical reflection on emerging technology and on medical practice. The use of the term "nano-ethics" raises some questions: Does nanomedicine present new or unique ethical dilemmas? Are the ethics principles and approaches enough to handle nanomedicine-related ethical issues? Is nano-ethics a new type of ethics? Currently no new or unique ethical issues have been identified, and it seems that existing theories and approaches are sufficient in managing nanotechnology's ethical issues [13, 14]. However, there are some reasons to support the need of a specific expertise in nano-ethics. As for other fields, a specialization could be required to comprehend and address all the information, and thus, properly analyze ethical issues involved. To identify and manage ethical questions, it is necessary to have an appropriate background in nanoscience, since the scientific complexity is high, literature is sometimes discordant, and available knowledge is often incomplete. A continuous study, a first-hand experience, and a collaboration with different stakeholders in nanotechnology and nanomedicine are essential to guarantee an effective ethical analysis that is able to give a broad view on nanotechnology's impacts on our society. Indeed, working at the nanoscale opens

the possibility to interfere with every biological process of the human body, leading to several advantages and challenges. Furthermore, the extraordinary heterogenicity of nanomedicine hinders the use of general statements and an approach that refers to every case should be favored over a generalization. Nanomedicine can range from patches containing silver nanoparticles to computer–brain interface; leading to entirely different level of complexity. Therefore, the presence of experts in nano-ethics is required today mainly for pragmatic reasons rather than philosophical interpretations.

Bioethics and medical ethics offer an extremely large toolbox that we can (or have to) use, in order to deal with moral dilemmas. An ethical analysis of nanomedicine should start from principles and approaches that are commonly used and accepted in ethics. As for every other field, a single principle or theory alone is not sufficient to comprise the complexity of reality and all interests at stake. Besides, exclusively inductive or deductive approaches should be avoided as they would fail to include both general and particular aspects of reality. A circular approach should be preferred instead, because the combination of inductive and deductive reasoning would enable making general assumptions starting from single cases and vice versa.

10.2.1 Ethical approaches for policymakers

In the analysis of emerging technologies, two approaches are worth mentioning: the cost-benefit analysis and the precautionary principle(s), both primarily addressed to policymakers.

10.2.1.1 The cost-benefit analysis

The cost-benefit analysis evaluates if benefits outweigh the costs and thus, whether or not to implement a new application. As for other theories and approaches, the cost-benefit analysis presents different nuances depending on the authors [4]. The result of a cost-benefit analysis is reliable in two cases: when there is an uncertainty regarding outcomes and known probabilities of these outcomes; and when there is uncertainty regarding outcomes but known possibilities. However, the cost-benefit analysis may fail in the presence of uncertain outcomes and uncertain probabilities, posing the risk of making the wrong decision [4]. Obviously, emerging technologies are an example of uncertain outcomes and uncertain probabilities, and consequently the cost-benefit analysis may turn out to be precarious. To decrease the risk of making a wrong decision in presence of unknown possibilities, two ways are viable: the first solution is to delay the decision until new knowledge about outcomes possibilities is available, and the second solution is to integrate the cost-benefit analysis with the precautionary principle(s) in order to deal with the uncertainties [4].

10.2.1.2 The precautionary principle(s)

The precautionary principle(s) was initially developed to boost decision-making process for the environmental protection. The Declaration on Environment and Development 1992 states that "in order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as reason for postponing cost-effective measures to prevent environmental degradation" [15]. Since then, the precautionary principle(s) was used in several contexts and took different shapes and meanings [4]. Even if the precautionary principle(s) is improperly exploited in attempt of halting technologies, its aim is far from hindering technological development. First of all, to appeal to a precautionary principle, some preliminary scientific data, regarding the correlation between an application and serious or irreversible consequences for the environment or human health, should exist. In addition, the range of preventive measures is broad, and the ban of the technology or its application is the last option and an extreme one. Furthermore, precaution, rather than abolishing research, asks for an implementation of basic knowledge (such as toxicology and characterization studies), leading to a better understanding of underlying mechanisms and an increased public trust. The precautionary principle(s) does not look for the risk zero, which is not only impossible to achieve, but it is alone not a good by itself since a "good" which is not practically feasible is not a "good" for that person or that society [16]. Indeed, if something with the potential of being beneficial is not achievable, it cannot be considered beneficial for a person or society, because it is not practically feasible.

In this process, the risk assessment is fundaments. The term "risk" refers to "a possible future harm, where harm is defined as a setback to interests, particularly in life, health and welfare" [17]. For every risk, it is possible to estimate the probability of occurrence of a harm or the magnitude (severity) of a harm [17]. The first step is to identify all risks and their magnitude, though a consensus notion of risk does not yet exist. On the one hand, technical experts tend to refer to a "narrow" meaning of risk, which takes into consideration the technological risk as a probability of physical harm. Consequently, the information needed is the probability and the magnitude of all expected harms. On the other hand, ethical experts tend to prefer a "broad" meaning of risk which considers both physical harm and threats of other goods (e.g., human identity) [4]. This broad approach, even though it requires more information, it is open to patients and general public involvement, because it allows everyone to convey his/her perception of new technologies, from a personal point of view. The second step is the evaluation of risk distribution to understand the distribution of the risks and benefits, both during the clinical, phase I trials in particular, and the clinical practice.

10.2.2 Ethical approaches in clinic

10.2.2.1 The four principles of medicinal ethics

The four principles of biomedical ethics is a pragmatic approach developed by Tom Beauchamp and James Childress [17], and it is based on four commonly shared moral principles: respect for autonomy, non-maleficence, beneficence, and justice. This approach rapidly became the main approach in clinical practices and in clinical trials, since it considers clinical and non-clinical parameters such as patients' preferences and wishes, risks and benefits, and resources allocation. Despite its importance in medical ethics, it has two main limits: the reductionism, since only four principles cannot capture all aspects of morality [18]; and difficulties in balancing these principles, due to the absence of a hierarchy.

The principle of autonomy implies the respect for people decisions, preferences, and privacy. To "respect autonomous agents is to acknowledge their right to hold views, to make choices, and to take actions based on their personal values and beliefs [. . .] Respect, in this account, involves acknowledging the value and decision-making rights of persons and enabling them to act autonomously, whereas disrespect for autonomy involves attitudes and actions that ignore, insult, demean, or are inattentive to others' rights of autonomous action" [17]. Over the past few years, the respect for autonomy of patients has gained a central role in medicine, and the informed consent, that leads the patient to express his/her assent or dissent, has become essential in medical practice.

The principle of non-maleficence "imposes an obligation not to inflict harm on others" and "not to impose risks of harm" [17]. To respect the principle of non-maleficence, people must not to kill, cause pain or suffering, or incapacitate others intentionally; consequently, non-maleficence is strongly linked to laws, and the non-maleficence principle is used to state when an action is illegal [17]. This principle is also intended in a less strict way, as that of the moral obligation, to minimize risks and side effects in order to have the benefits risks ratio, always in favor of the benefits.

The principle of beneficence "refers to a statement of moral obligation to act for the benefit of others" [17]. The principle of beneficence includes all those actions that benefit others, promoting good, preventing harm, and eliminating harm.

Finally, the principle of justice requires a "fair, equitable, and appropriate treatment in light of what is due or owed to persons. Justice involves both benefits and burdens depending on particular properties or circumstances; therefore, justice is linked to rights-duties perspectives" [17].

10.2.2.2 The four-box approach

The four-box approach [19] is one of the main approaches to clinical ethical decision-making. It is a pragmatical method meant to help physician organize and

document the ethical reasoning in "four boxes" or "four quadrants": medical indications, patient preferences, quality of life, and the contextual features. In the medical indications box, the ethics consultant or the physician should include all the relevant information regarding patient's medical problem, history, diagnosis, and prognosis. The medical team has to indicate whether the disease is chronic or acute, the damage is reversible or irreversible, and whether there are other diseases. Then they should write all possible strategies of care, their aims, and their likelihood of success (considering also a scenario where no interventions have success). The physician, or the medical team, has to fill this first quadrant, considering differences of opinion that may arise among experts regarding the strategies and possible outcomes. All the proposed interventions should respect both beneficence and non-maleficence principles, thus taking into account a risks-benefits calculation. The closer the proximity between risks and benefits becomes, the more complex and challenging it is to make a decision. For this reason, it is important to remember that, in some cases, palliative care is also a potential strategy [19].

In the patient preferences quadrant, we should document the patient's preference regarding medical treatments (or more in general regarding the care). It is also demanded to report whether the patient is mentally capable and legally competent, and if the patient has a legal guardian or a surrogate decision maker. This box is overlapping with the principle of respect for autonomy and aims to document an informed consent or to report presumed wishes of the patient. Therefore, in this quadrant, we have to report all the expressed and presumed preferences, wishes, beliefs, and values of the patient. Besides, it is important to assure that the physician has provided sufficient information, and to assess the patient's understanding of the possible treatments, probabilities, and outcomes. In this step, we have to take into consideration possible influences (or even coercions) on the patient's decision [19].

In the quality of life quadrant, we have to report how the quality of life of the patient will be affected by the different decisions, bearing in mind that a good quality of life can have a different meaning for different individuals; therefore, it is important to understand the patient's perspective of what a "good life" means. In this box, there is a balance between beneficence, non-maleficence, and respect for autonomy. In this quadrant we have to report whether there are changes to return to a normal life and what physical and mental deficits the patient is going to experience with or without the treatment [19].

Finally, there is the contextual features quadrant that represents the context in which the specific case is inserted. The main examples of these features are family dynamics, financial and economic factors, living situation, and religious and cultural beliefs of the patient and his family [20]. In this last box, we have to identify the principal caregiver(s), and how the possible decisions taken may affect the caregiver's life. For these reasons, the contextual features quadrant reflects the justice principle and the law [19].

10.3 Ethical issues in nanomedicine

Ethical issues in nanomedicine may be divided into four overlapping categories depending on their impacts on: human health, human identity, society, and environment. This chapter focuses on human health topic, since it is a central topic in a clinical ethics consultation.

10.3.1 Nanomedicine and human health

Nanomedicine generally follows the principle of beneficence, since the goal is healing or improving patients' quality of life or life expectancy. Nanomedicine is bringing enhanced therapies into the clinical practice, for instance, superparamagnetic iron oxide nanoparticles for cancer treatment; indeed, the largest market revenue from nanomedicine applications presently comes from the therapeutic field, encompassing drugs, devices, drug delivery systems [21], and nanomaterials. Exciting novel nanotechnology-enabled products are implantable devices which gradually release active agents over long time periods (months or even years). Nanodevices present numerous advantages compared to the traditional systemic delivery approaches, since they can overcome the low compliance generally associated with chronic treatments and can reduce the fluctuation of plasmatic drug concentrations maintaining it within the therapeutic window (and thus reducing underdosing along with peak doses and the related toxic effects) [22]. Consequently, they can reduce burdens and disability, increasing quality of life.

Nanomedicine is also improving diagnosis, including early disease detection, and disease monitoring, through the enhancement of laboratory tests, imaging procedures, and implantable sensors [23]. Early and accurate diagnosis is fundamental to receive treatment on time, and it correlates with better prognosis and lower medical, economic, social, and psychological burdens. Despite the advantages, these new possibilities raise two crucial moral issues. First, the early diagnosis procedures may become so sensitive to predict the occurrence of an incurable disease years before the onset of symptoms (note that the same issue was raised when genetic testing were introduced). On the one hand, this possibility may liberate individuals from the burden of uncertainty and provide the knowledge that allows them to make informed decisions (such as reproductive choices); on the other hand, however, this can also lead to a situation in which these individuals live the rest of their lives with the psychological burden of the prospect to develop a severe disease, possibly decreasing the overall quality of life. The second moral issue regarding early detection is the possibility to reveal microscopic pathological features leading to uncertainty regarding diagnosis. The main example is cancer: even if there is a technology able to detect a single malignant cell, would that be sufficient to diagnose a tumor? What is the threshold number of muted cells necessary to confirm a cancer diagnosis? [23]. Besides, should a person undergo a

treatment if there is no certainty of disease? [24]. Moreover, should a physician prescribe a treatment without the certainty of a disease? This last issue shares some similarities with genetic testing for risk factors where having one or more allelic variants does not mean the certainty to develop the disease. Nanomedicine can thus lead to the need to reconceptualize how we perceive disease [23] and it will also become more and more challenging for physicians to extract clinically relevant information from the excessive amount of data that nanomedicine can produce. This fact is particularly relevant in light of the clinical appropriateness.

The beneficence principle is tightly linked to the non-maleficence principle since it is also intended to evaluate the benefits in relation to risks and costs; therefore, a risk-benefit-cost analysis is always required. Benefit generally "refers to something of positive value, such as life or health"; therefore, benefit is not a probabilistic term as risk is [17]. "Costs include the resources required to bring about a benefit, as well as the negative effects of pursuing and realizing that benefit" [17]. FDA, European Medicines Agency, and other agencies approve a new medical application only after the demonstration that the benefits outweigh the risks, with acceptable costs. Safety is thus a focal point of nanomedicine assessment and, since every nanoproduct possesses a specific toxicological profile, general statements on this topic must be avoided. The characterization of nanoproducts is fundamental [25–28], since tiny variations of composition, size, shape, surface charge, and aggregation/disaggregation status change their behavior and thus their toxicology, and interaction with human body and environment [29, 30]. An interesting issue linked to safety is the manufacturing processes, which should present a unified final product since nanoparticles' activity depends on the particles size and shapes. Current manufacturing methods cannot completely guarantee a unified final product, therefore several initiatives have been trying to overcome this issue [28].

Non-maleficence plays a relevant role in clinical trials, where the Belmont report is the principal reference point, and in clinical practice. Clinical trials, in particular phase I trials, represent the delicate balance between benefits for the society and benefits for the individual; indeed, the Universal Declaration on Bioethics and Human Rights [31] states that "the interests and welfare of the individual should have priority over the sole interest of science or society." To translate basic research into clinical applications, patients must be enrolled into a phase I study designed not to offer a benefit, but to obtain knowledge about safety. This leads to unresolvable ethical issue regarding a fair distribution of risks and benefits, which may be exceptionally acute in the case of emerging technology, given the lack of scientific knowledge.

The fears of possible harms coming from nanoapplications is frequent in literature; however, no deaths nor serious injuries linked to nanomedicine products have been reported yet, and only a selected few FDA-approved nanodrugs have been withdrawn from the market for safety reasons (such as Resovist) [32]. Moreover, the majority of currently approved nanodrugs are reformulations of already approved drugs that display a safer toxicity profile rather than higher efficacy [33]. Indeed,

nanomedicine applications present safety and efficacy [29, 32], increasing patients' compliance, quality of life, and life expectancy. Interestingly, among the approved nanodrugs, most are reformulations, and only few are new molecules [34].

Nowadays, there are no specific regulations meant for nanoproducts, and nanomedicine products' approval procedure is essentially the same as traditional drugs, biologicals, and devices [35]. The development of such regulations may be encouraged, but these do not mean that they should be stricter. Potential new regulations would have to acknowledge the peculiarities of nanomedicine, but in order to do so, countries should increase funds for research, directed to the development of new methods, addressing characterization, testing, and manufacture of nanomedical products. In conclusion, regulations should find the balance between overprotection and underprotection, since delaying research and marketing of new therapies may lead to the unjustified death of people waiting for a cure; rushing this process, however, means exposing people to excessive risks in the name of scientific progress.

The impact of nanomedicine regarding the respect for autonomy is twofold. Nanomedicine increases diagnostic and treatment possibilities giving more choices to the patient. However, it also presents some issues regarding informed consent, since it is not easy to explain and to understand what nanomedicine is. It may also raise privacy concern, because nanotechnology allows to perform cheaper and faster laboratory analysis such as DNA and RNA sequencing and biochemical tests. Therefore, a significant amount of individuals' personal information can be acquired. For instance, implantable devices could constantly monitor biochemical parameters of a person, or, tracking pills could notify a patient compliance via app. This evokes some questions, mainly if these chips are linked to patients' medical records since there is the possibility of hostile or unrelated entities to access patients' personal data [34]. Besides, major concerns regarding the respect for autonomy are raised by possible surveillance by employers and insurance companies about the health status of employees or clients [34].

Finally, the justice principle is the more controversial one, since research, development, and manufacturing are significantly more expensive than conventional medicine, leading to a higher selling price of the final product. Nanomedicine poses serious challenges in product manufacturing and scale-up; indeed, several clinical trials were terminated or delayed due to excessive costs [36]. On the face of it, nanomedicine seems not to take into consideration the justice principle, and many authors try to justify this fact by addressing the possibility, that the cost of single products will decrease over time, and early diagnosis and better therapies will decrease costs related to disease management. A more engaging way to justify investments is refers to cost-effectiveness, but only few data is available. The analysis of costs is generally limited to the direct costs of treatments (or applications) excluding all indirect costs [21]. The only analysis which considers both direct and indirect costs in a nanomedical product is the comparison between the first generation PEGylated liposomal doxorubicin with gemcitabine in the treatment of recurrent or progressive ovarian cancer [37]. This work showed that nanomedicine was not only cost-effective but also cost-saving,

after two years of treatment. Despite the high initial costs, nanomedicine can be less expensive considering the overall process and all indirect costs such as: increased survival, fewer days of hospitalization, more days at work, and fewer side effects.

10.3.2 Nanomedicine and human identity

Nanomedicine future applications may alter self-consciousness and human identity through medicalization of life and human enhancement. Nowadays, the applications of nanomedicine do not seem to have major impacts on human identity; but this can rapidly change. Nanomedicine, along with other emerging technologies, is leading to an increased importance of health status in the society, which is obviously a positive consequence; however, these technologies are also modifying our perception of what we intend as disease and health. Indeed, the threshold between disease and health is constantly moving upward, more and more features and parameters that were considered in the physiological range of normal or healthy in the past may be considered pathological or borderline in the future. Besides, nanomedicine applications may allow human enhancement, which can be defined as a non-disease-related improvement of physical, mental, and moral features by pharmacological or surgical procedures, in order to meet a standard or to reach a specific goal (athletic, aesthetic, cognitive, work-related, cultural, sexual, and so on) [24, 38]. Human enhancement presents several issues regarding beneficence, nonmaleficence, and justice.

10.3.3 Nanomedicine and society

From the perspective of society, the ethical concerns of primary importance are the justification of resources allocation [14], respect of privacy, surveillance, military and terrorist use, and public involvement in nanomedicine debate. Regarding resources allocation, nanomedicine could aggravate the inequalities between countries and within a country. The poverty derived from an unfair distribution of nanotechnology-enabled products has been called nanopoverty or nanodivide [14, 39]. The main concern is that, due to the high cost, nanoproducts will be a prerogative only for wealthy people, even though public funding was engaged in research or development. The considerable extent of investments in nanomedicine, both from public and private funding, require a reflection on the supply sustainability of these products, by different health-care systems. However, nanomedicine can also allow the development of cost-effective technologies for the most urgent social and health issues in emerging countries, such as water and infectious diseases [3, 26].

10.3.4 Nanomedicine and environment

Nowadays, the environmental impact of nanomedicine seems to be very modest, in particular compared to the impact of nanocompounds daily dispersion into the biosphere from industries [40]. However, even if this impact is relative, it should be analyzed carefully, and two main aspects should be considered: the environmental impact of drug companies and the ecotoxicological effects of medical products' residues [41, 42]. At the present, there are no studies that explore the connection between nanomedical products and environmental effects [42] and thus no possible conclusion can be drawn. However, since studies regarding ecotoxicological effects of conventional drugs are increasing, the same trend is expected for nanodrugs.

10.4 The role of the ethics consultant and the role of ethics committee

The increased number and frequency of ethical problems in health-care settings allowed the development of clinical ethics in the late 1970s and early 1980s in North America [43]. Since then, the role of the ethics consultant has been well-defined and accepted into the medical practices in North America and in few other countries; however, in several countries (e.g., in Italy), this profession is still partially (or even completely) unknown. The clinical ethics consultations can be performed by a single ethics consultant, a small group, or a committee.

The clinical ethics tries to address the issues raised by the increasing technological development and the shift from a patriarchal model, in which all therapeutic decisions were taken by the physician, to a shared decision-making model, in which both patient (and sometimes family) and physician are involved [44]. The core of ethics consultation is the patient-centered care with the objective of reaching a shared decision between the medical team and the patient (and the family/caregivers). The setting of clinical ethics is not the university but the hospital, or rather, the patient's bedside, for this reason, it is also called "bedside ethics." The ethics consultation is defined as "a set of services provided by an individual or group in response to questions from patients, families, surrogates, health care providers, or other involved parties who seek to resolve uncertainty or conflict regarding value-laden concerns that emerge in health care" [45, 46].

The clinical ethics offer a wide spectrum of ethics services that can be divided into four main categories: educations, case consultations, non-case consultations (e.g., clarification of ethical aspects related to specific topics), and policy development [43–45].

Regarding nanomedicine, the education is relevant in light of the fact that nanotechnology is not present in the medical training curriculum [47], and also ethics is

generally a single small exam. Therefore, in addition to education focused on the classic ethics topics (i.e., the end of life issues, withdrawing and withholding treatments or life-sustaining measures, the informed consent, and surrogate decision-making), a specific training regarding nanomedicine should be promoted whether nanotechnology-enabled products are used in patients' care. The education should be based on the actual need of the hospital unit and should be oriented to the practice in order to handle or difficult situations or conflicts that may arise in clinical practice.

The case consultation is the most known area of clinical ethics consultations and, depending on the country, it can be requested by the care attendant, the patient, the family, or even the clinical ethics consultant. The goal is to reach a shared decision for the patient's care, and this is achieved through different ways: identifying a surrogate decision-maker, mediating a conflict between the medical team and the patient or within the family members, facilitating the understanding and agreement of the patient (and family), identifying allowed options, and clarifying some ethical concepts.

A central point is the informed consent which is the basis of the patient's understanding and involvement. A central point is whether an information including the term "nano" can or cannot boost autonomous decisions. The term "nano" can generate excessive promise and enthusiasm both in patients [48] and in physicians; however, with that, it also raises unjustified fears. Note that only informing a patient of the presence of nanotechnology could lead him to believe that it is more dangerous or better than traditional treatments. A simple indication to the patient that a treatment is composed of nanotechnology is insufficient and should also be discouraged. An approach that supports the involvement of the patient through information sharing (according to his comprehension skills and to his level of education) not only promotes the patient's competence to take a decision within a doctor–patient relationship based on trust, but also promotes a more general trust of society regarding science, medicine and their methods.[2]

The case consultation may be particularly hard when the patient is not competent to make a decision, or if the patient has a mental disorder, which are generally associated with a low compliance. An interesting example regards tracking pills

2 This aspect is correlated to a more general consideration which is the public involvement [52–54], not as a way to convince society of the decency or the benefits of decisions of scientists and policy-makers [52], but to allow sharing and distinguishing different perspectives, and to create a culture of a fruitful discussion with regard to specific issues. Therefore, public involvement is not merely the idea of avoiding the "GMOs effect" or "fake news" proliferation, but it is the possibility to be transparent and to gain new perspectives, that scientists and policy-makers may fail to see while focusing on the narrow analysis of risk and harm. Consequently, public engagement does not merely aim for the public's understanding of science, but for the comprehension of how science is meaningful for people's lives. In this way, science become a "project that is co-produced, collectively owned, and crucial meaningful to the people's lives" [52]. However, it is unrealistic to make an entire population comprehend every aspect of every issue affecting society.

and implantable devices for mental disorders treatment. Tracking pills remind patients to consume their drug and monitor the patient's compliance notifying the physician or caregiver if the medicine is taken as needed [49, 50]. Implantable devices, instead, partially overcome the compliance issue, since they only require the refilling of the medicine few times per year. A case consultation may be required, for instance, if a patient with a mental disorder, which relies on an implantable drug delivery device, requests to remove the device. In this case, a clinical ethics consultation has to identify the benefits and the burdens (physical, moral, social, and economical) for the patient and the family, and try to mediate the conflict in order reach the best possible outcome for the patient.

The non-clinical consultation consists of meetings designated to the clarification of ethical aspects of health-care issues and topic. The consultation is generally specific (e.g., a hospital policy regarding the Do Not Resuscitate (DNR) code), with information regarding ethics perspectives and approaches, procedures, institutional policies, and laws. For example, a non-case consultation in nanomedicine may be required for resource allocation concerns and a better comprehension of cost-effectiveness.

Finally, the policy development area entails the development of written documents for a unit or a hospital, regarding specific recurring ethical issues (e.g., informed consent and withholding and withdrawing artificial nutrition and hydration). These documents are produced in collaboration with the hospital ethics committee, and they are a useful compass for daily clinical practice; however, since every case is unique, these documents cannot be applied aprioristically without performing a careful evaluation.

10.5 Conclusions

Nanotechnology is a rapidly evolving field of technology, which emerges from the convergence of several other areas, such as mathematics, physics, chemistry, biology, and computer science. Nanotechnology allows to control and work with the matter at the nanorange scale, enabling new and better applications due to the manifestation of new properties. Considering how heterogeneous the nanomedicine field can be, generalizations should be avoided, and an ethical analysis following a case-by-case approach should be preferred. In this chapter, we discussed some approaches to handle ethical issues raised by nanomedicine, with a special focus on clinical ethics consultation.

The ethical concerns raised by nanotechnology are, essentially, the same ethical issues related to other emerging technologies, biotechnology in particular. Nowadays, no unique ethical issues have been identified, and no new ethical theories and approaches have been proposed, since existent ethics tools are already sufficient to manage ethical issues in nanotechnology and nanomedicine [13]. However, it is possible to justify the need of experts in nano-ethics for pragmatic reasons: first, to deal with the

complexity of nanotechnology and nanotechnology implications; and second, to be up to date with rapid development and high specialization of nanotechnology.

Each time new discoveries are made or new applications become possible, an ethical evaluation is mandatory. An approach based on the ethics-first model demands an ethical reflection before a new technology is developed, however the main risk of such a conservative approach might be an excess of caution: too much focus on specific issues may exaggerate the fear of harmful consequences and divert the attention from the bigger picture. On the other side of the spectrum, an ethics-last model suggests delaying an ethical reflection until a new technology is effectively employed, so that our reasoning can be based on outcomes and experience. The obvious risk of this approach is to cause a damage that would have been predictable, and hopefully avoided [12]. Therefore, an ethical reflection should begin as soon as possible, even if a technology is not yet developed, and it should be adjusted and updated as scientific data and impacts on society, humans and environment are collected. Despite all the best intentions, it is challenging not to fall into the Collingridge dilemma [51]: when we can still influence the course of a new technology, we lack the sufficient knowledge about its effects; however, when we have enough information, the technology is then so rooted in society, that we are no longer able to significantly shape its development. It is possible to assess the impact of a technology retrospectively when all facts are available, but it is more difficult to do this prospectively, since there is a big component of speculation.

Ethics work on different levels and can help both policymakers and clinicians. In this perspective, the cost-benefit analysis, the precaution principles, and the risk assessment analysis play an important role in guiding policymakers through uncertainties, in order to make decisions that enhance research and all those preventive measures that avoid serious and irreversible damages. The ethics evaluation should always include the impacts of a technology on human health, human identity, society and environment.

In the clinical practice, ethics should guide toward a patient–physician shared decision. Both the four principles of medical ethics and the four-box approach are valuable tools for physicians and clinical ethics consultants. The role of clinical ethics consultation in nanomedicine has not been explored yet, but we may assume that it has to be the same as in other medical fields. The clinical ethics consultation presents four overlapping areas: education, case consultations, non-case consultations, and policy development [43–45]. All these areas are crucial for a patient-centered approach in medicine, and in order to decrease health-care professionals' moral distress in handling difficult situations and decisions.

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Kathleen Spring and Klaus-Michael Weltring

11 Ethical and social aspects arising from nanomedicine in health care

Abstract: Introducing nanotechnology in medical applications, abbreviated as nanomedicine, has caused significant changes in the way diseases are diagnosed and treated. After two decades with 50 products on the market and more than 400 candidates currently in clinical trials, this new field has matured. It helps to predict genetic disorders early and to personalize treatment based on better understanding of disease at the molecular level. Nano designed and functionalized materials enable more targeted delivery of drugs, increase miniaturization and biocompatibility of in- or on-body sensors, and provide scaffolds for regeneration of body parts. The resulting paradigm shift from acute to predictive, personalized and participatory precision medicine raises ethical, legal and social questions for individuals, society, and the health care system. Aspects such as self-determination, the right not to know, human enhancement, or social divide plus issues such as data protection and data privacy or body integrity need to be discussed involving all stakeholders in the health care system. Especially, patients and doctors have to redefine their roles in the future Continuum of Integrated Health care where patients are more responsible for their health and doctors have to learn how to include information technology (IT)-based assistance tools in their decisions for more personalized treatment of patients.

Keywords: nanomedicine, personalization, continuum of care, regenerative medicine, health care ethics

11.1 Introduction

The emergence of nanotechnology as a new field mainly started with the development of the atomic force microscopy which allowed to analyze and manipulate material at the molecular, more precisely, the nanoscale. Especially, the ability to precisely design and assemble molecules at the nanoscale to build particles with large active surfaces, which also can be loaded with drugs and functionalized with targeting molecules, created a new option to precisely deliver medication to diseased parts of the body. Accordingly, the early nanomedicines on the market were mostly drug delivery systems containing an active component drug as medication. As recently published by Germain and co-authors, the number of approved nanomedicine products targeting different diseases increased tremendously in the last decades (see Figure 11.1) [1]. Together with

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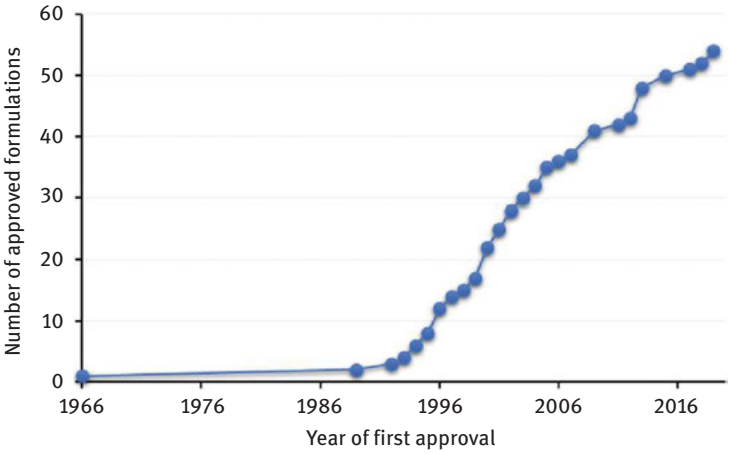

Figure 11.1: The graph shows the evolution of the approved nanomedicine formulations (cumulative number/year). The first year of approval is reported for formulations which are approved by multiple agencies (e.g., EMA and FDA). The graph is published by Germain et al. in the Journal of Controlled Release [1].

the increasing number of approved new nanomedicines, therapeutic efficiency, clinical outcome, as well as patient benefit improved over the years [1, 2].

Most nanomedicine systems still focus on cancer, but the percentage of other indications targeted by nanomedicines increases continuously (see Figure 11.2). Among these other indications, vaccines and treatment of (rare) genetic diseases are especially interesting because in both cases nanoparticles are used to deliver nucleic acids as active component [2, 3]. Nanomedicine is the first technology to deliver these nucleic acid-based drugs and therefore offers multiple options to treat patients. Currently, this technology provides a new promising approach, for example, to develop a vaccine against SARS-CoV-2 or to cure genetic diseases [4]. Since May 2020, clinical trials for nanoparticle-based approaches for SARS-CoV-2 vaccines are ongoing [1].

In addition to the carrier function, a new nanomedicine generation can behave as active component due to its unique characteristics. For instance, the new class of radiation-enhancing nanoparticles applicable for the treatment of solid tumors enhances the local dose of radiation in the tumor leading to higher tumor cell death. In consequence, side effects on healthy tissue surrounding the tumor are reduced and quality of life for patients is improved [5]. These new nanotechnology approaches can be seen as the breakthrough approach using the specific characteristics of nanomedicine to improve therapeutic applications which foster the perception of nanomedicine as new approach for innovative therapeutic applications [1].

Beside the ability to manipulate materials at the nanoscale, new high-resolution analytical techniques such as STED microscopy or mass spectrometry in biological systems enabled a much more precise analysis and deeper understanding of physiological

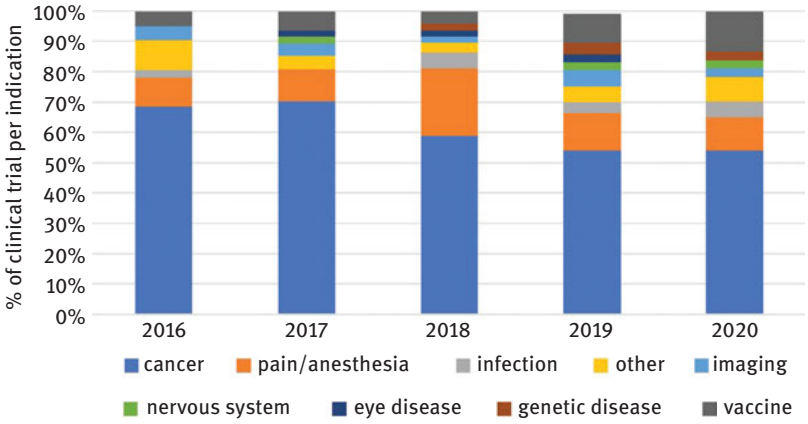

Figure 11.2: Categorization of clinical trials based on nanomedicine formulation per indication. The repartition of indications per year in the period from 2016 until May 2020 is shown. The graph includes 333 trials. The graph is published by Germain et al. in the Journal of Controlled Release [1].

processes at the molecular scale [6, 7]. Nanotechnology supported this not only at device level but also in delivering solutions for tracing and imaging in tissue [8–10]. This knowledge was supplemented with information about the genomic background of an individual facilitated by nanopore-based next generation sequencing methods [11, 12–14]. All together, these nanotechnology-related innovations gave rise to a much better understanding of the cause, the development, and the evolution of diseases by matching the genetic background with physiological processes and disease symptoms. As a result, new possible targets for not only pharmaceutical therapies but also new possible biomarkers for earlier and more precise diagnostic and progression control of diseases became available [1]. The new technological possibilities allow to follow a patient during their clinical pathway very closely and to improve personalized treatment and therapy.

11.2 Gene therapy based on nanoparticles

The availability of early predictive and more precise therapeutic interventions not only promises benefit for patients, but also raises some important ethical questions. A fundamental one is: How to define disease? Can a genetic predisposition, for example, of a metabolic syndrome such as obesity, be considered as disease even if no symptoms occur? The answer to this question is of increasing importance since gene-based therapies such as delivery of micro-RNA via nanoparticles to target specific genes become available to cure diseases before their onset. As an example, Duchenne muscular atrophy, a congenital disease, which was incurable for decades, can now be successfully

treated by using nanocarriers to deliver tools to edit the defect gene ("gene repair") even before symptoms occur [15–17]. The potential and the power in terms of social, economic, and ethical impact of this treatment is enormous. Its extraordinary high prize raises the question of who will get access to the treatment and how the decision process is designed. In curable diseases, gene therapy causes the ethical dilemma to decide whether a person gets the expensive cure by gene-based therapy or the "classical" therapy once the symptoms occur. In other words, the new generation of nanomedicines is provoking some known questions such as: Should an application of most innovative nanomedicine always be the first choice when treating patients despite potentially higher costs? The debate for a balanced risk-benefit ratio for patient treated with innovative nanomedicine is not new and reflects past discussions which took place for other medical products. To intensify the mentioned dilemma: What would be the answer in case of diseases with higher incidence in most societies, for instance metabolic syndrome-related health concerns? Is a treatment modifying genes with the help of nanocarriers for patients with increased risk for obesity appropriate? The dilemma is also partly connected to the fundamental concern that we might start to play God by altering the "native" genome toward what we or the society consider as "good" or "normal". The step toward eugenic and human enhancement is certainly not far away.

11.3 Patient monitoring built on nanotechnology-based devices

Nanotechnology not only contributes significantly to the molecular understanding of disease but also adds special features to devices needed to detect the new biomarkers. Nanostructured surfaces in microfluidic lab-on-chips and fluorescent or electrochemical nanoparticles in multiplexing point-of-care devices provide the tools necessary to not only predict but also monitor disease development and progression [18–20]. These devices facilitate a better stratification of patients which leads to a more precise and personalized therapy [21]. This option becomes an ethical issue if the stratification reveals that a person is a non-responder to the only available therapy or that there is no therapy at all. This scenario is the reason why the possibility to predict and monitor the onset of a disease needs to acknowledge the "right not to know" and the "right of self-determination." These two rights should also apply if a therapy is available even if health insurances or the society urge patients to receive and follow a therapy. This is not a new dilemma only applying to nanomedicine. Society faced similar questions in other topics. When the technological capacities allowed screening of breast cancer with higher precision and at lower costs, these methods were included into the standard prevention plan of patients in most countries. Here, in case of a positive result, the same

questions occur: Is there a "right not to know" about one's diagnostic results which could be life threatening or at least life changing? Or are we obliged to react and to receive a treatment when a diagnostic result is positive for a disease?

The ability to monitor a person becomes even more sophisticated due to devices which can monitor biomarkers reflecting body functions. The nano-based miniaturization and design of biocompatible nanostructured surfaces of these devices allow to implant them into patients which is supposed to increase the comfort and user-friendliness of such devices. However, as mentioned previously, questions light up concerning the discussion around body enhancement versus necessary body supplements. Are implantable monitoring devices at the edge of body enhancement or is the only purpose of such an implantable device pivotal to take a decision about necessary supplements?

An additional aspect of these new monitoring devices is their connectivity. These devices are usually designed so that they can transmit the collected data to external recipients including smart watches and smartphones, and also medical care units and doctors' offices. Depending by whom the devices are controlled and managed, for example, by the patient or by health care providers, questions of data access and security arise. In case the patient controls and owns the data as in the case of diabetes and continuous glucose monitoring, the decision to share these data with health care providers to optimize the therapy is on the patient side. In the case of automatic data transmission to external users, the written consent based on the ability to take a self-determined decision is crucial. In case the person is not able to take a self-determined decision, it becomes a demanding ethical challenge for family members or medical professionals to decide on the degree and technology used for the surveillance of a patient. This applies also to the data management of such a patient. However, there might be other aspects including social or economic pressure to share the data with additional stakeholders such as research organizations or health insurances and even public authorities. There might be a potential risk, for example, a diabetic patient is seen as a risk factor in his professional work environment due to unbalanced blood glucose level getting out of control. It is conceivable that the access to the glucose-monitoring data of a diabetic patient is requested by authorities to certify the patient's suitability for a high-risk job. The consequences for each concerned individual could be crucial and should be included in the decision-finding process. This scenario also reveals the far-reaching impact that an enabling technology such as nanotechnology can have on ethical and social consequences.

11.4 Nano-enabled regenerative medicine

As mentioned previously, at the beginning, nanotechnology not only provided high-resolution analytical methods and particles for delivery and imaging, but also the

ability to assemble nanostructured surfaces, scaffolds, and composite materials. It became possible to coat implants such as stents, artificial joints, or bone and dental implants. These coatings were designed either to prevent microbial infections on surfaces due to colonization with microbiota or to attract cells of different origin, for example, to promote wound healing [22–24]. A more recent development is the design of specific tissue or organs with the help of three-dimensional printed scaffolds made of (nano)biomaterials with the possibility to nano-based surface tailoring methods [25, 26]. These scaffolds provide a basis for the colonization by pluripotent cells with the goal to build a complex tissue format. In the future, almost all parts of the body might be replaced by artificial tissue parts if needed. As much as the replacement or regeneration of defect body parts are an attractive perspective, especially for chronic patients, it raises the question of body integrity and body enhancement in the light of necessary medical treatment and questionable body supplement. In the case of brain implants, the level is even higher than only the question of body integrity. The so-called mental integrity adds a layer of complexity to this question since an altered mental integrity might change the behavior and perception of an individual. How many parts can be replaced to still be the same person? Who decides according to which criteria who gets an implant and what kind of implant? Will an alcoholic patient with a strongly affected liver receive a new expensive organ grown with the help of most advanced technologies and developed with high cost research? Who pays in this case?

11.5 Impact of nanomedicineon the delivery of health care

The nano-enhanced diagnostic and therapeutic products described previously will allow to monitor patients from healthy status in the wellness phase up to a chronic status in the homecare phase often occurring in elderly patients. As a consequence, arising patient-related health data during the medical pathway will create a “Continuum of Integrated Care” with new precise personalized diagnostic and therapeutic options enabled by nanotechnology for all phases of health care (in preparation for publication). The five phases of the “Continuum of Integrated Care” are described briefly in the following section:

Wellness phase generates genetic, physiological, social, and environmental data. Nano-enabled devices and sensors are required to generate and collect these data providing the “baseline” for a personal health status. Together with IT-based tools, nano-enabled devices will promote healthy living and wellbeing. Individualized guidelines for healthy living advice each person how to maintain health and healthy living.

Pre-acute phase uses these data to monitor health status deviation from the individual "health baseline"oriented on previous collected health data. Used technologies in this phase are lab-on chip systems with nanostructured surfaces, nano-enabled sensors and devices and nano-enhanced screening tools for patient checkups. This phase is of enormous relevance to attenuate or delay an acute medical event due to earlier and precise nano-enhanced diagnostic and monitoring.

Acute phase uses the accumulated previous health data to personalize the therapeutic treatment, for example, through medication considering the genetic and physiological data. Nano-based surface tailored, cell- and biomaterial-generated artificial tissue parts support the replacement or repair of damaged body parts. Additionally, nanomedicine offers new possibility for therapy, for example, via innovative delivery systems or by taking advantage of the unique characteristics of nanomedicine for therapeutic purpose. Disease progression could be monitored by advanced imaging techniques using nanoparticle as tracers.

Post-acute phase also uses personal health data as well as social and psychological environment data to define appropriate support measures for patient rehabilitation. Patient adherence to therapeutic and rehabilitation programs or to chronic therapy is monitored by nano-enhanced devices and sensors to maintain or improve the status of the patient and to avoid relapse.

Home care is characterized by remote monitoring through nano-enhanced devices and sensors. These devices can be implantable devices designed to be most biocompatible by nano-tailoring the device surfaces. The goal is that the quality of life of patients is increased and patient can live as long as possible self-determined in their homes.

The difference to the current "reactive medicine" system is the interrelation between all phases facilitated by continuous collection, interpretation, and availability of personal health, social, and environmental data throughout the lifetime of an individual. These data support medical professionals to make better-informed decisions about a precise and successful personalized treatment for each patient. As mentioned previously, the advances in analytical power and understanding of molecular processes at the nanoscale paved the way to new diagnostic and therapeutic approaches. However, to continue to realize these approaches, nanotechnology has to team up with other technologies such as electronics, photonics, big data, artificial intelligence, (bio)material science, and even textiles, to develop and produce diagnostic tests, monitoring devices, pharmaceutical delivery systems, and surgical methods necessary for the maintenance of a Continuum of fully Integrated Care.

11.6 The impact of the Continuum of Integrated Care on patients and the society at whole

For patients, the development toward a Continuum of Integrated Care includes several changes compared to the current situation. They will be more involved in their own health management and well-being enabled through the above-mentioned health technology innovations. All kinds of nano-enhanced wearables and sensors to track health parameters empower patients to actively engage in their health maintenance and promotion or in the self-management of chronic diseases. They will participate more actively in the definition and process of therapy instead of only passively receiving treatment when a health concern occurs. More precisely, the decision-making process might be shared more equally between patients and professional health care providers. That means that the patient's self-determination is better reflected and respected. However, the challenge of these new opportunities for patients is to have the freedom to act or not in response to a health concern. During their medical pathway, they will face crucial decisions, for example, to start a therapy for some diseases even if symptoms have not appeared yet and they feel "healthy." To cope with this increased responsibility, new educational concepts for patients are required to build a minimum health literacy. Topics of interest might be on the on hand healthy lifestyle, nutrition, motility and mobility, as well as how to deal with prediction of potential diseases based on genetic markers, whereas the interaction with (health-related) technologies such as communication with medical chatbots for instance instead of having a physical appointment is the other main topic to cover. An important related question is: How much privacy and information about personal behavior will a patient be willing to share with a medical device, a physician, a hospital, or even the health insurance? It is obvious that the issue of "giving consent" will have to be broadened quite a bit.

Many people surely want to engage and participate in their own health process. They will probably accept the new technologies and the resulting differences in health care delivery. The challenge is indeed to integrate all patient groups, even when they are less prone to technology. The risk is that new technologies and their potential generate an even more divided multilevel society with those being able to cope with the change and those reluctant or unable to change. What happens with the latter ones? In view of this scenario, it is essential to promote digital literacy in all groups since digitalization will have major impact on the health care system and its transition towards a Continuum of Integrated Care [27]. To reach this goal, coaching and accompanied support to access all services of the health care systems – digitalized or not – will be a key feature to integrate all groups.

Regarding the difference in social tiers of a society, can the Continuum of Integrated Care offer a barrier-free access for everyone? Or will different financial capacities of people lead to well-being differences because financial power can pay for

longer and exclusive life support as well as optimal technical support? This challenge will become even more important in view of the future population dynamics. The demographic development predicts in average older population which live mainly in developed countries in the coming 30 years [28]. However, also in developing countries, the percentage of an older population will be higher due to favorable environmental conditions promoting longer lifetime. In addition, the United Nation report of the "World population prospects" forecasts an increase in world population, but with an unequal distribution [28]. Multiple diseases will occur in the older population paired with complex care needs also beyond health care. In addition, social problems such as loneliness of older people will become more frequent [29]. In consequence, the focus for the health care sector will also be broadened to cover (home) care and end-of-life services in order to respond to these new demands. Will society agree and support to raise the resources to pay for equal access to meet these demands?

11.7 Conclusion

At the begining nanomedicine created a big hype. It was expected to solve all medical problems, that is, to erase cancer or infectious diseases. Tiny robots were envisioned to float around in the blood attacking cancer cells and pathogens or crossing the blood brain barrier to cure mental illnesses. About two decades later the hype is gone, and it became clear that nanotechnology is not a "wonder" technology solving all problems. However, as with other technologies, the end of the hype marks the edge of a new more mature era. Accordingly, 50 products on the market and more than 400 candidates currently in clinical trials demonstrate that nanomedicine can provide new options for diagnosis and therapy including nano-based approaches such as nanoparticles enhancing radiation efficiency or delivering nucleic acids to cure, for example, genetic diseases. These examples and the nanostructured and functionalized scaffolds for regeneration of tissues and organs reveal that nanotechnology has a big and specific impact on medicine enabling treatments not possible or less effective without it. So, the "proof of concept" has been made.

The last decades also proved that the introduction of nanomedicine products is not counteracted by the fear of toxic effects of nanomaterials. This is mainly due to the fact that all nanomedicines must go through the same thorough pre-clinical and clinical testing all medical products have to overcome to proof their safety and efficacy. This strict regulatory process and the routine in medicine to counterbalance the benefit for patients with possible toxic side effects avoided the severe discussions we have seen about the safety of nanomaterials in consumer products. This is true even though pre-clinical characterization of nanomaterials, especially nanoparticles, is quite a challenge due to their special characteristics. Many required assays

had to be adapted and there are still several gaps to be filled [30]. Projects such as the European Nanomedicine Characterisation Lab and its US counterpart United States Nanomedicine Characterization Lab or the EU-project REFINE have done pioneering work to close these gaps [31–33]. More funding is needed to continue this work to further increase the translation of innovative nanomedicine solution into real life for the benefit of patients.

As with other technologies the ambiguity between "boon and bane" of nanomedicine demands to critically challenge them. However, this debate must include other technologies because nanotechnology interacts with other technologies in the new cross-technology products. Society will have to discuss and critically evaluate the new developments and what they mean for each individual and the society. Socially accepted standards for data access and processing, for example, in the pre-acute and homecare phase are such an ambiguous example open for reflections: Will connected "smart homes" and nano-enabled wearables be regarded as help for convalescence of patients and elderly citizens or seen as surveillance by the health care system and health insurances? Are new technologies and their potentials accepted entirely by the society? Moreover, another aspect to consider is the influence or pressure on people to follow healthy guidelines according to their genetic and environmental conditions imposed by the society, health insurances and companies for instance. To promote the engagement in the health guidelines, a reward system agreed by the society might be introduced as it is known in China for intended social behaviour. However, as this example shows, a careful and critical discourse is needed, and the debate of such questions should be addressed in future research projects.

In summary, new technologies such as nanotechnology and their deployment into health care should be fully transparently discussed with all stakeholder groups including ethical and social sciences as it had been done in a previous EU projects such as Nano Med Round Table [34]. A critical discourse of these stakeholders which has to start ideally already during the development of new nanomedical products will balance the reasons whether one or another technology should be introduced in health care. Accordingly, a multidisciplinary dialogue with all stakeholder groups should be part of future research programs.

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12 Ethics reflection and responsibility of nano drugs

Abstract: In the last decades, nanomedicines moved from research and development to clinical trials and entered medical practices for the treatment of many acute and chronic disease. These nanomedicines are more complex and sophisticated than traditional medicines and require specific attention and regulation. The scientific community, the pharmaceutical industry, and the regulatory bodies report a lack of clear regulatory guidelines for nanomedicines and asks of the urgent need of tools to manage the risks associated to these complex nanomedicines in order to guide their development and to approve safe nanomedicines in the pharmaceutical market. A new tool, the multicriteria decision approach, is required to ensure nanomedicine risk management taking all the complexity and challenges of nanomedicines into consideration. This will be accompanied with a transparent communication to public and improvement of education. This review aims to make an overview of what is ongoing and what is missing, and put in evidence for future development and requirement to proactively address the ethical, social, and regulatory aspects of nanomedicine by multicriteria approach to minimize adverse impacts on public health and to facilitate innovation.

Keywords: nanomedicines, immunotherapy, nanotoxicology, in silico

Index: nanomedicines, EMA, nanomedicine, ethic, multicriteria decision analysis, characterization, preclinical, regulation, risk, nanomaterial, nanosimilar, drug delivery, communication

12.1 Introduction

Since the 2000s, medicine has been revolutionized by nanotechnology. These new medicines, also called nanomedicines, have been developed with positive impact on human health. In fact, nanotechnology not only improved the development of new drugs or efficacy or bioavailability of existing therapeutics, but also modified laboratory analysis tests [1–3]. Due to the complexity of nanomedicine research field with

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many different types of nanomedicine, they are classified based on their size: (i) dendrimers, nanotubes, quantum dots, (0.1–1 nm); (ii) polymer nanoparticles, micelles, liposomes (10–1,000 nm); and (iii) microparticles (1–100 μm) [4, 5]. In the European Union, nanomedicines on the market are mostly inorganic nanoparticles, liposomes, nanocrystals, nanoemulsions, polymeric nanocarriers, and nanocomplexes, representing three-quarters of nanomedicines in clinical use [3, 6, 7]. These nanomedicines are used in several applications, including drug delivery, therapy, in vitro diagnostics, in vivo imaging, biomaterials and active implants, biosensors, microfluidics, drug delivery, and microarray tests to tissue engineering [5, 8]. The most used nanomedicines against cancer are Abraxane, Caelyx, Depocyt, Oncospar, Doxil, Neulasta, Mepact, and Myocet [9]. Remicade and Humira contributed to the treatment of autoimmune-related inflammatory diseases [9]. In addition, nanomedicine also contributed to a wide variety of anti-infective products, such as PEGylated interferons in viral diseases or nanocrystalline silver in wound infections [9].

But before entering on the market, these nanomedicines followed the same development and approval steps as other drugs to obtain medical agency authorization [10, 11]. Food and Drug Administration (FDA) or European Medicines Agency (EMA) have approved at least 28 nanomedicine products and more than 75 are not yet FDA- or EMA approved but are currently being evaluated in ongoing clinical trials [9, 12]. At the time to writing this book, 326 clinical trials including nanomedicine have been listed, all beginning, ongoing, or finished on ClinicalTrials.gov. Most of these clinical trials are for the treatment of various cancers, radiation exposure, arthritis, and pneumonia. In addition, other pathologies are also assessed, including central nervous system, cardiovascular, or inflammatory disease [3, 9, 13]. Some of the companies having clinical-stage developments of nanomedicine against cancers are Celgene, Access, Camurus, and Cytimmune [9].

The future perspectives of nanomedicine development in the research field of cancer are in immunotherapy, photothermal therapy, or improvement of anticancer drug selectivity [13, 14]. Other promising research development are: improvement of drug delivery across the blood–brain barrier to treat neurodegenerative diseases [15]; cytotoxic agents for photodynamic therapy, photothermic therapy, or magnetic hyperthermia; or tissue engineering, neuroprosthetic implants, artificial organs, and antibacterial coatings [14].

All these applications required extensive financial support from public and private resources. For years, nanotechnology, and in particular nanomedicine, has received many funding from authorities and private companies for research and development (R&D). More than 200 companies (SME or big companies) are involved in nanomedicine for about $30 billion per year of investment with a financial grow projection of 14% (annual rate). For nanotechnology, the global funding reached $138.8 billion in 2016 [5]. In parallel to R&D support, governments also finance educational programs on ethical, social, and legal issues related to nanotechnology [16]. In fact, as nanomedicines moved from laboratory testing to clinical trials and to medical applications in few years, it is important to support ethic and regulatory research on nanomedicines in order to minimize their adverse impacts on public health and environment. To do that,

researchers, politicians, and consumer advocates need to work with government agencies and private companies to address ethical, social, and regulatory aspects of nanotechnology, and nanomedicines in particular [16, 17].

12.2 Definitions

It is not possible to consider the regulatory question of nanomaterials and nanomedicines or establishment of classification system without adoption of clear definitions of each term. In 2011, European Union adopted a definition for "Nanomaterial" as *A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm – 100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%. By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.* (2011/696/EU) (Last updated: 31/12/2019 – https://ec.europa.eu/environment/chemicals/nanotech/faq/definition_en.htm).

For nanomedicine, the regulatory agency competent in Europe is EMA which defines nanotechnology as *the production and application of structures, devices and systems by controlling the shape and size of materials at nanometer scale* [7, 18]. Based on this definition, EMA has defined nanomedicine as *the application of nanotechnology in view of making of a medical diagnosis or treating or preventing disease. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometer scale* [18].

The criterion of choice of these definitions is the size for nanomaterial. This is so restrictive as nanomaterials, and in particular nanomedicines, have other parameters that could be criteria as important as size. In fact, most of the available nanomedicines are larger than 100 nm and parameters linked to their fabrication processes during pharmaceutical development can alter they size as solubility, melting point, color, etc. These properties need to be considered when defining a nanomedicine [19]. The proposed definitions are thus a starting point for regulation of nanomedicines but it is important that these definitions could be modified based on scientific knowledge improvement and by consideration of ethical issues [20].

12.3 Pharmaceutical development

Many parameters need to be considered during development of nanomedicines. These parameters are the same as for drugs including physicochemical characterization,

biocompatibility and nanotoxicology evaluation, pharmacokinetics (PK) and pharmacodynamics (PD) assessment, clinical assessment, and scale-reproducibility [8]. But nanomedicine required some specific attention as described below.

12.3.1 Physicochemical characterization

In term of regulation, size remains the most important physicochemical parameter included in the definitions. But, due to nanomedicine specificity and complexity, other parameters are also important, such as structure–function relationship, surface properties (e.g., surface area, surface charge, chemical reactivity, hydrophobicity, and roughness), coating properties, porosity (if it relates to a function, e.g., capacity to load a drug), particle concentration, crystal or amorphous form, impurities, sterility and endotoxin levels, permeability, solubility, and in vitro release [21–23].

In fact, nanomaterials, including nanomedicines, can be of many forms, chemical compositions, and have no common properties other than size (1–100 nm). It is not an unified class of compounds, each type of material must be assessed by its own and inside the same class, different comportment may be observed based on their physico-chemical properties [24]. For example, variations in size and shape can have dramatic and unpredictable effects on particle comportment and toxicity: a substance that is nontoxic at 50 nm may be toxic at 1 nm or vice versa. This suggests that even small changes to the physicochemical properties can have a significant impact on their bioreactivity, making predictive toxicology impossible [25]. As each physico-chemical parameter can influence the toxicity, it is evident that particles will need to be assessed case by case. Furthermore, nanomedicine characterization required specific, validated but also affordable characterization techniques compared to other drugs [22, 23]. These characterization techniques need to be developed and validated and guidelines are required for a regulatory purpose.

But for nanomedicines, other parameters can influence their physicochemical properties. In fact, as they are heavily dependent of their microenvironment, they may change in size or shape inside an organism. A 100 nm particle could disintegrate into 1 nm particles, or 1 nm particles could aggregate into a 100 nm particle, inducing changes in behavior in an organism than in cell culture [24]. Many publications explore structure–activity relations of the physicochemical characteristics of nanomedicines. But today, it remains unclear if they are clinically meaningful to the patient, or in fact whether all relevant characteristics have been identified yet [7, 26]. Determination and characterization of relevant properties is still complicated by the fact that nanomedicines are designed in order to modify PK and/or PD properties of a drug, including its toxicity [21].

Another important point is the importance of stability and reproducibility studies. For nanomedicines, significant differences on the performance, manufacturability, and quality of them can be observed between the development steps and the

production of batches for clinical trials (safety, efficacy, bioavailability, bioequivalence). The fabrication process is of major importance and can have a high impact on potential toxicity. For example, the fabrication at large scale with passage from laboratory to industrial fabrication process may modify the product process due to the scale change and required specific complete characterization criteria, to assure batch-to-batch stability. The collection of process monitoring data during the development of the manufacturing process is thus essential and can provide useful information to enhance process understanding. An understanding of process robustness can be useful in risk assessment and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (ICH Q8 R2) [27].

Based on all the specific parameters that need to be assessed, it is clear that the evaluation of nanomedicines only based on their size is too simple and does not reflect the nanomedicine complexity.

12.3.2 Preclinical evaluation

The translation of nanotechnology from the bench to the market for diagnosis, prevention, or treatment of diseases imposed complete characterization but also extensive pre-clinical and clinical testing.

As a first approach, in vitro assays can predict interaction of drugs with specific proteins, cells, or part of the body. The main advantage of in vitro tests is to determine the effect of nanomedicines on a specific target. Furthermore, in vitro tests are less time consuming, simpler, more cost-effective, and permit a better control of experimental parameters/conditions [28, 29]. But the main difficulty is the reproduction of all the complex interactions in the human body between subcellular levels, cells, organs, tissues, and membranes. In vitro tests cannot predict physiological response of the human body when exposed to nanomedicines [28, 29]. Furthermore, nanomedicines can interact with the reagents of the assay. Nanomedicine properties that make them so interesting for their final application can lead to interaction/interference with test reagents. For example, high adsorption capacity, optical and magnetic properties, catalytic activity, dissolution, acidity, or alkalinity of the nanomedicine are some of the properties that may promote these interactions [30].

The second step is in vivo experiments performed following the ICH M3 guideline of EMA on the non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals [31]. In vivo studies are time-consuming, expensive and sometimes the end points achieved cannot predict what happens in the biological systems of animals and the translation to the human body still complicated with nanomedicines [32]. As nanomaterials, including nanomedicines, can cross cell membranes and the blood–brain barrier or translocate from exposure site to other parts of the body, their in vivo comportments till more unpredictable and may vary from species [33, 34]. For example, inhaled nanomaterials can enter the capillaries, and

once in the circulation system, they may enter the liver, lymph nodes, spleen, and bone marrow [24, 34]. But nanomaterials may also accumulate in parts of the body and produce adverse effects. Furthermore, the risks associated with exposure to nanomaterials often vary according to the route of exposure: a particle that is safe after ingestion can be toxic when inhaled [13, 16, 24, 33]. All the properties that make nanomaterials so interesting for applications in medicine can lead to unpredictable and potentially toxic effects on human [16].

The lack of consistence of in vitro data produced for nanomedicines have raised many questions by regulators. New assays for a correct evaluation of the nanomedicine toxicity are needed. In this context, new approaches have arisen, such as the in silico safe-by-design approach or toxicogenomic. In European Union, under the H2020 research program on nanomaterials, many programs aimed at studying the risks of nanomaterials, including nanomedicine, in vitro but also in vivo. Based on these research programs, many data on toxicological and PD/PK have been published [35, 36]. These data are useful for the development of in silico methods, the safe-by-design, combining toxicology data with computational tools and biostatistical methods for the evaluation and prediction of toxicity. By using computational tools, it is possible to analyze more nanomedicines, combine different endpoints and pathways of nanotoxicity, being less time consuming and avoiding all the ethical questions [37, 38]. The safe-by-design methods are very interesting in nanomedicine research and development to adapt the physicochemical parameters of developed nanomedicine products based on predictive toxicology profile [24, 39].

The recent new area of nanotoxicology is the toxicogenomic. Toxicogenomic is a combination between genomics and nanotoxicology in order to determine toxicological profile of nanomedicine based on gene or protein expression modifications in vitro or in vivo [28, 40]. This promising research area is still at the beginning but of major interest to reduce case-by-case analysis.

Although physico-chemical characterization, in vitro assays, in vivo animal experiments, and ex vivo laboratory analyses can improve our understanding of nanomedicine interactions with biological systems, they cannot eliminate all of the uncertainty surrounding the exposure of a human subject to nanomedicine products in clinical trials [16].

12.3.3 Clinical research

Preclinical experiments are essential in nanomedicine development but they cannot totally replace human assessment in clinical trials [16]. Uncertainties are particularly present in the first exposure of a human subject to a particular type of nanomedicine product in a phase I clinical trial. Ethical guidelines and regulations required that risks to human subjects be reasonable in relation to the potential benefits to the subjects and society and that risks be minimized, wherever possible [17].

Significant risks can still develop after a product has cleared the phase I hurdle and is in phase II or III clinical trial. As undesirable effects are less predictive with nanomedicine, specific guidance documents and a specific attention is required. In fact, to minimize research risks in nanomedicine clinical trials, a careful review of the relevant literature, solid research design, appropriate inclusion and exclusion criteria, clinical monitoring, well-trained personnel, timely adverse event reporting, protection of confidentiality, standard operating procedures, and follow-up with subjects after they complete the study are required [41]. Communicating the risks of nanotechnology to research subjects also poses a difficult challenge. Ethical and legal rules require that an investigator inform a potential research subject (or his or her representative) about the purpose of the study, procedures, benefits, risks, alternatives, confidentiality protections, and other information the subject would need to decide whether to participate [6]. Studies have shown that subjects often underestimate the risks of research participation and overestimate the benefits. Subjects also often fail to understand that the main goal of a clinical study is generate new knowledge that may help other patients, not to provide optimal medical care for the people who are participating in the study [25]. This is mostly true that research subjects are not well educated about nanomedicine. It is important for investigators to clearly explain the benefits and risks of participating in research involving nanomedicine during the consent process. In fact, as nanomedicines are novel materials that have not been thoroughly studied, investigators should inform subjects that there may be some risks that cannot be anticipated [6].

12.3.4 Post-marketing

Adverse reactions and unexpected side effects can also occur after a product has been approved and is on the market. For drugs, and also for nanomedicines, these negative effects could appear several years after being on the market because clinical trials usually do not include enough subjects to detect rare side effects and some health problems require years of exposure to develop [24]. It is thus of major importance for physicians to report these problems to the relevant safety agency (such as FDA, EMA), and for companies to conduct phase IV (post-marketing) studies. But these studies are not legally required, with no obligation for private companies to conduct post-marketing studies. To monitor the safety of nanomedicine products, government agencies should sponsor research on the long-term effects, with 5–10 years of exposure [16, 41, 42]. This highlighted the importance of pharmacovigilance with nanomedicine, the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem [43].

12.4 Risk management

With continuous development and commercialization of nanomedicines, governments and regulatory agencies need to consider their risks, not only by safety and efficacy evaluation but also by including comparison with existing medicine [8]. Scientific community, pharmaceutical industry, and regulatory bodies agree that nanomedicines are complex nanomaterials. The specific physicochemical characteristics that make nanomaterials so interesting for medical application, give them requirement of specific legislation linked to their size. In fact, classical tests used to determine safety of chemical products and drugs are not adapted to specificity of nanomedicine. Some problems can occur with nanomedicines: distribution to other sites than the expected one, passage across biological barrier, need of adapted laboratory tests (characterization and in vitro) due to interference with classic tests, risk for human, and interaction with other drugs [10, 24]. This is some of the risks that need to be apprehended for nanomedicine.

Furthermore, in the process of approval, nanomedicines are introduced under the traditional framework of the benefit/risk analysis. Many national and international agencies take into consideration the urgent need of specific legislation. The US Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Science Foundation, and the National Institute of Occupational Safety and Health have supported a variety of programs aimed at studying the risks of nanomaterials [6]. In Europe, for regulatory purposes, nanomedicines are under the framework set by EMA. This includes recommendations for comparative quality, non-clinical, and clinical studies. Until now, no general recommendations are available for nanomedicine and they are evaluated in case-by-case basis [44].

To solve this problem, some reflection papers of EMA working groups examine the possibility to create nanomedicine groups like liposomes, surface coating, or iron-based nanomedicines with a different regulatory approach for each group [25, 26, 45]. These papers address general issues regarding the complexity of the nanomedicine and provide basic information for the pharmaceutical development, nonclinical and early clinical studies of nanomedicines to determine pharmacokinetic stability, and distribution of incorporated or conjugated active substances in vivo. Important factors are described related to the exact nature of the particle characteristics, influencing the kinetic parameters and consequently the toxicity such as the physicochemical nature of the coating, the respective uniformity and stability (susceptibility to degradation), the bio-distribution of the product, and its intracellular fate are specifically detailed [26].

12.4.1 Multicriteria decision analysis

Scientific community and regulators agree that safety and risk issues of nanomedicine must be understood with new regulatory tools [9, 11, 12]. These tools are required

for development of safe nanomedicine (drug delivery systems and nanomedical devices) for human health, environment but also transport. European Commission noted that comparative and adaptive approach is fundamental to develop robust nanomedicine risk assessment in the future [46]. This is not feasible without a method integrating the abundance of nanospecific information to manage industrial production and safety assessment of nanomedicine [46]. A promising and integrating strategy, the multicriteria decision analysis (MCDA), has been proposed by Linkov et al. [47]. This approach combines information from all aspect of nanomedicine development like data from physicochemical characterization, toxicology, risk assessment, modeling tools to address risks, and costs/benefits of nanomedicine under development or on use [48, 49]. It requires a transparent information exchange between industries, academia, public, and government recommendation to have a robust tool [46]. The MCDA aims to efficiently assess risks posed by all aspect of nanomedicine from development to final use and help for risk decisions [48, 49].

The advantages of MCDA approach in nanomedicine development and risk assessment are:

- promotes safe-by-design principles by highlighting characteristics of a nanomedicine that contribute to an elevated safety risk, and favorize the modifications to improved nanomedicine
- integrate heterogeneous information – like cost, environmental, social, toxicology, and safety data from many sources, to make a more informed decision and what information could be considered as important.
- allows transparency in decision-making and help in communication between regulators, scientists, and patients who will benefit from safe, effective, and sustainable nanomedicines [46, 47].

All of these advantages are of major importance in the future nanomedicine development and for governments to make decisions about risk over time. The MCDA would inevitably be comparative and adaptive by using a mixture of available data to address risk, cost, and benefit for nanomedicine for a given therapeutic or diagnostic application [46]. But this risk evaluation needs to be compared not only between new nanomedicine but also with existing medicines.

12.4.2 What about generic drugs/nanosimilar?

Another related challenge is the development of a specific regulation for the evaluation of the generic nanomedicines at the time of reference nanomedicine patent expiration [50, 51]. In fact, when patent come to expiration, generic drugs could be introduced on the pharmaceutical market. For nanomedicine generics, a more complete analysis than just the same efficacy needs to be demonstrated to ensure safety of these generics. Several parameters like a comparison of bioequivalence, safety,

quality, and efficacy, in relation to the reference medicine, which leads to therapeutic equivalence and consequently interchangeability, are required [52]. The scientific community, the pharmaceutical industry, and the EMA have acknowledged that it is scientifically challenging to demonstrate sameness of a generic to a reference nanomedicine [21, 45, 53]. Due to their complexity, the generic "sameness" approach was deemed invalid for nanomedicines and the term "nanosimilar" was suggested instead [44, 50].

As previously described, minor changes in physicochemical properties or in manufacturing process may change the product composition, affecting biological but also toxicological properties. During the development process of nanosimilar, all the parameters need to be considered and evaluated [44, 50]. But other studies like in vivo studies may be required for nanosimilar products to demonstrate bioequivalence or comparable distribution and targeting pattern of them to their reference products during the different stages of development [53].

12.4.3 Communication

With increasing access to the knowledge and information available on nanomaterials and nanomedicines, it is important to communicate and proactively address the ethical, social, and regulatory aspects to minimize its side impacts on the environment and public health and to avoid a public reaction due to misunderstanding [16, 34, 39]. In fact, most people do not know the exact signification of nanomaterial. They only know that it is very small. So, the public may have difficulty understanding the complexity of nanotechnology, with complexity as the size dependence of physical or chemical properties related to nanomaterials [19]. Most people are not informed that some nanomedicines are on the market. It is thus very interesting to propose a clear classification, indicating either limited/no, medium, or higher risk of nanoparticles [19].

Risk communication with member society is important so that nanomedicine may gain and maintain public support. Researchers should educate the public about how nanotechnology can be used in medicine, the benefits of nanomedicine, and the risks of nanomedicine. When people are not well informed about a new technology, they are likely to view it as dangerous or disruptive. Europe's reaction to genetically modified (GM) foods illustrate the importance of engaging the public in a dialogue concerning a new technology, with exchanges between experts, industry, and public. To avoid a disconnection between scientists and public similar to what happened with GM foods, it is of major importance to have a transparent communication with public.

As example, a nanomaterial has been in controversy recently: the titanium dioxide nanoparticles are used for many applications, among which are consumer products as food additive nanoparticles. Many consumer organizations have informed public on titanium dioxide nanomaterial risk classification, without a clear

position of legal authorities leading to misunderstanding of population [54]. To avoid repeating the mistakes of the past, nanomedicine manufacturers, researchers, and government agencies should educate and inform the public about nanomedicines and develop an integrated program to an open discussion about the ethical, social and legal issues of them [16].

12.5 Conclusion

Nanomedicines present interesting properties offering many possibilities in drug development as for example modification in solubility/bioavailability, better safety and efficacy profile, targeting specific tissues, crossing biological barriers, and extended drug exposure with a larger therapeutic window. In the last decades, nanomedicines entered clinical practices, not only as medical devices but also as new drugs for the treatment of many acute and chronic diseases. The ongoing research leads to the emergence of more complex and sophisticated nanomedicines requiring good understanding of pharmacokinetic and pharmacodynamic properties associated to chemical composition and physicochemical properties characterization, which thus pose additional challenges in terms of regulation. The scientific community, the pharmaceutical industry, and the regulatory bodies agree that it is an urgent need of tools to manage the risks associated to this expansion of nanomedicines. In fact, there is still a long way toward the complete regulation of nanomedicines, from the creation of harmonized definitions in Europe and worldwide to the development of protocols for the characterization, evaluation, and risk management of nanomedicines.

The development of specific guidelines for all the aspects of nanomedicines is mandatory, in order to guide their development and to approve new and innovative nanomedicines in the pharmaceutical market. This process must be also carried out along with interagency harmonization efforts, to support rational decisions pertaining to scientific and regulatory aspects, financing and market access. This will begin by a worldwide universally accepted definition for nanomedicine still does not exist, and may require integration of more characteristics than only size to cover all the complexity of nanomedicines. In fact, the physicochemical characterization is a critical point to be considered in nanomedicine risk management to ensure safe nanomedicine development as small changes of nanomedicine physicochemical properties at each development step, from synthesis to in vivo interactions, can modify their biological and toxicological profiles. A complete characterization at each development step is thus necessary and needs to be evaluated and regulated by European agencies like EMA to help researcher and industry to have complete registration document. This is more true for nanosimilar which can have different properties than the original nanomedicine. An evaluation and regulation of determining characteristics and having a clear and specific legislation for nanosimilar is very important

as some minor changes in synthesis process can induce biological or toxicological effects.

Nanomedicines are in constant evolution and the next generations will have more sophisticated drug products. This will make the future development, evaluation, and use of nanomedicines and nanosimilars even more complex. The EMA needs to act now, to be one step ahead and lead the nanomedicine field to the next level, where safe and efficacious nanomedicine products, and nanosimilar, are available for the patient. A new solid system is thus required to ensure nanomedicine risk assessment taken into consideration all the complexity and challenges of nanomedicines. To do that, a multicriteria decision approach is needed to help regulator. The MCDA take into consideration many aspects like characterization, toxicology, safety, and efficacy of nanomedicines to facilitate risk assessment. The MCDA ensures the development of nanomedicine in a governance environment with clearly defines rules for regulators but also for scientific and industrial developers. This strength of this approach is the multifactor comparison to evaluate potential risks, benefits, and cost of nanomedicine.

Furthermore, a transparent communication of regulators and governments as education of people about nanomedicine is urgent. In fact, it is important to educate society members about the benefits and risks of nanomedicine not only to gain and maintain public support but also to help people of having an informed opinion as clinical volunteers for clinical trials.

Finally, governments and regulators need to make attention that innovation with nanomedicine does not induce a medicine with two speed, assuring social justice with access to health care for each individual.

It is now urgent to proactively address the ethical, social, and regulatory aspects of nanomedicine by multicriteria decision approach for risk management to avoid actual case-by-case analysis, minimize its adverse impacts on public health, and facilitate innovation.

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13 Nanocosmetics: Technological advances and ethics

Abstract: Nanocosmetics, a new category of cosmetics, is a blend of two words: nano and cosmetics. It means that nanosized materials are loaded in cosmetic products. The transformation of macromaterial into nanomaterial renders extraordinary beneficial properties and potential hazards concerning health and the environment. To achieve quality, safety, and transparency, the prominent regulatory agencies like the Federal Drug Administration and European Union established some rules and regulations for the cosmetic products placed on the market. In light of uncertainties and lack of specific rules and regulations, several debates and ambiguities exist, which questioned the ethical line of humanity. The development of nanocosmetics is concomitant with ethical issues. Some see it as a great potential while others express fear. Is nano cosmetics our friend or foe? There is a requirement of adequate protocols and methodologies for risk analysis and quantification. This chapter highlights the benefits, toxicities, regulations, and critical discussion of ethical issues surrounding nanocosmetics while supporting the continuous advancements and evolution in this area.

Keywords: nanocosmetics, benefits, toxicities, regulations, ethics

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13.1 Nanocosmetics: An updated version

Since the last decade, nanotechnology tends to be at the leading edge of technological development. It is the escalating and captivating element of science which involves the arrangement of atoms and molecules at the nano level. This rapidly expanding sector finds numerous applications in electronics, medical devices, medicinal products, and majorly in cosmetics [1–3].

Cosmetics are the products used for embellishing, amplifying, and magnifying the beauty or to amend the appearance of human [4]. The rising interest of personal care products and to leverage the advanced features of nanoscale materials led to the development of nanocosmetics. This updated version of cosmetics covers various cosmetic products and nanoscale materials with novel features and functionalities [5].

The distinctive behavior and properties acquired by them are due to the extremely small size of the substance. The particle size is indirectly proportional to the ratio of surface area to volume. A decrease in the particle size means an increase in the surface area. The maximum surface area exposed means maximum reactivity. Also, the gravitational forces are not dominant on the small-mass particles than macroscale counterparts and the random kinetic motion causes nanoscale particles to not settle down and provide a longer shelf life [6].

A plethora of nanotechnology-based cosmetics products are available in the market and are used such as skincare products, hair care products, dental care, and decorative cosmetics [7]. In contrast to the conventional products, these innovative products (Table 13.1) which are infused with nanomaterials offer advantages in terms of

Table 13.1: Some marketed nanocosmetic products [4, 13–15].

Product	Company	Nanoformulation	Use
Revital Lift Antiwrinkle & firming Face & Neck Contour Cream	L'Oreal	Nanosome	Anti-wrinkle
Hydra flash Bronzer Daily face moisturizer	Lancome	Nanocapsules	Moisturizer
Eye Tender	Kara Vita	Nanosphere	Anti-wrinkle eye treatment
Nanocyclin Cleanser Silver	Nanocyclic	Nanosilver	Cleanser
Lip Tender	Kara Vita	Nanosphere	Lip moisturizer
Nano Care Gold	Dental Nanotech	Nanoparticle	Dental care
Primordiale Optimum Lip	Lancome	Nanocapsule	Lip treatment
Dior Snow Pure UV base SPF 50	Dior	Nanoparticle	Sunscreen

enhanced physicochemical properties, improved solubility, better texture and quality, desired stability and efficacy, extraordinary performance, and prolonged effect by controlling the release of the active element, securing the active element, and modulating its transport to the skin [8, 9].

Modification of bulk materials into nanoscale collocate new optical, mechanical, and biological properties [10]. These exciting properties that make nanoparticles desirable also contribute to the hazards and danger to human health and the surroundings [11, 12]. Almost all useful substances have the potential to cause toxicity. When added before a material or substance name, the word "nano" can act in a fundamentally different way. Their safety profile cannot be presumed from the specifics available for bulk parts.

13.2 Nanocosmetics: Friend or foe?

Size is a key factor that predicts whether nanocosmetics have powerful or harmful effects. The use of an updated version of cosmetics has raised questions like: Do the advantages outweigh the disadvantages? Can small size do wondrous or deleterious things? Is it ethically right to use it?

13.2.1 Small size can do wondrous things

The evolution of cosmetics through nanotechnology is like a breath of fresh air in the cosmetic market. The small size of the particle delivers more immense benefits that cannot be offered by larger counterparts. It is like a big bang in a small packet. The benefits like improved physicochemical properties, enhanced solubility, better texture and quality, desired stability and efficacy, extraordinary performance, and extended effect by retarding the release of the active component, protecting the biologically active substance, and modulating its transport to the skin reflect the strength of this sector [3, 16–19]. The following section includes a range of advantages that nano-based systems, materials, and products hold for expanding the performance of cosmetics. This can be categorized as:

a) Nanosystems

Systems engineered at the nanoscale that design and develop materials in it. Table 13.2 represents the advantages associated with some of the nanosystems.

Table 13.2: Advantages of nanosystems.

Carrier	Advantages	References
Liposomes	Deliver cosmetic AI vitamins, minerals, and antiaging and antioxidant materials; increase the absorption of active ingredient	[20, 21]
Solid lipid nanoparticles	Protect the encapsulated AI from degradation, improve skin hydration, control the release of drug	[22, 23]
Nanostructured lipid carriers	High loading capacity for both lipophilic and hydrophilic drug, high physical stability, avoids chemical decomposition of AI, improved skin hydration and elasticity	[24, 25]
Nanoemulsion	Smaller droplet size, higher efficiency, stability, and greater transparency, increased shelf life, rapid penetration power, safe and good carriers for the formulation of cosmetic products, pleasant sensory aspect	[26, 27]
Nanocapsules	Capability to functionalize polymers, release payload depending on composition or environment characteristics, protect AI from degradation	[28]

b) Nanomaterial

Materials converted to nanosize exhibit unique properties

(i) Silica

Silica, in its nanoscale, encounters various applications in cosmetics. Employing nano-silica in the products enhances the shelf life, effectiveness, and texture of the finished product. It can protect, encapsulate, transport and sustain the release of the drug or cosmetic ingredient to the site of action, therefore it is a good candidate used in pharmaceuticals [29]. They possess unique properties and have biocompatibility. In addition to this, they also contribute to the uniform distribution of pigment in lipsticks and cease the bleeding of oil into the lips. L'Oreal uses nano-silica in its product as it delivers the best texture and imparts a matte finish on the skin [30]. At 206 nm, colored silica nanoparticles dye the human hair fibers [31].

(ii) Silver

Silver in its nano form is a powerful weapon used in the cosmetic industry. It is a noble metal and possesses enormous therapeutic and other benefits like antibacterial, antifungal, anti-inflammatory, skin disinfectant, and has healing properties [32]. Mainly, it controls the antibacterial growth. They play the most crucial role in cosmetic preparation as a safe and stable preservative [33]. Nanoscopic silver particles occupy a greater ratio of surface area to volume and exhibit significant

antibacterial effects [34]. In denitrifies, silver nanoparticles are used as they kill the yeast that causes diseases in the mouth. They have been included in skincare products, different soaps, day and night creams, deodorants, and toothpaste [35, 36]. One such product is Nano Cyclic Pink Cleanser bar, a combination of nanosilver and natural components produced by Nano Cyclic INC eliminates fungi and bacteria, diminishes age spots, and confronts acne [37]. Deodorants with silver nanoparticles help prevent and mask body odor. Additionally, shampoo containing nanosilver deals with dandruff, itchy scalp, and so on. Also, lipsticks of different shades are prepared.

(iii) Gold

Gold nanoparticles have found applications in soaps, shower gels, creams, masks, and other cosmetics with bactericidal activities. There are creams with nanogold particles that reach the cellular level and have healing power. Gold nanoparticles are also incorporated in oral care formulations; the presence of gold provides an antibacterial effect [17].

The nanometric particles of gold are wine red compounds with antioxidant properties, while the larger size gold particles are yellow inert solid. Gold nano particles also interact with the skin barrier, enhance skin penetration, and improve the delivery of ingredient. They exhibit a size range of 5–400 nm [38, 39]. High payload capacity, stability, and targeted delivery are features of nanogold [40]. They have been employed in several beauty care products like creams, antiaging creams, and face packs. These nanoparticles have antibacterial and antifungal properties. Importantly, nanoparticles of gold have therapeutic actions like antiseptic, anti-aging, and anti-inflammatory effects, reviving skin metabolism, maintenance and improvisation of skin elasticity. Many cosmetic brands like L'Core and L'Oreal use nanometric gold in lotions and creams [3].

(iv) Carbon black

An inorganic nanomaterial widely used in cosmetics intended to be applied to the area of the eye for decorative purposes [41]. It is an insoluble colorant for makeup products, primarily used in eye pencils, eyeliner, mascara, and kajal. L'Oreal uses nanocarbon as it increases the black intensity in mascara [30]. Also, nano kajals are synthesized using carbon nanoparticles that give protection to the eye due to their antibacterial property [42]. The percentage of nano carbon used in skin products is about 0.001%, for nail enamel and mascara is 5% and the maximum concentration used is 10% for eye products such as eye pencils, eyeliners, eye shadow.

Fullerene C60 (pristine fullerene), a stable nanomaterial is emerging in the field of cosmetics. This novel material acts as an acceptor of electron and can bind to free radicals, also possess unique antioxidant properties, and is employed in anti-wrinkle, antiaging, and sunscreen products, especially in acne therapy. They are introduced in skin-rejuvenating formulations due to their scavenging activity

against radical oxygen species [43]. It also suppresses sebum production. It causes de novo hair follicle generation and accelerates the growth of hair [44].

(v) TiO_2 and ZnO

TiO_2 and ZnO in their nano dimension are the most widely used inorganic nanoparticles. TiO_2 possess a high value of sun protection factor that leaves an alluring cosmetic appeal and is highly efficient. ZnO is known for its protective properties. Significantly, they are used in sunscreens or as sun-blocking agents. These ingredients in the product absorb the ultraviolet A (UVA) and UVB radiations. It improves product performance, quality, comfort, and texture.

The optimum size for diminishing the strength of radiations is 40–60 nm [45]. Especially, they eliminate chalky appearance and make it photostable and transparent to the eyes. Also, they improve spreadability [46, 47].

c) Nano-based products

Nanosystems incorporating nanomaterials and actives result in a finished product

(i) Decorative cosmetics

Decorative cosmetics are colorful objects in the form of lipsticks, nail paints, eye makeup, and so on. These boxes of colors, when coupled with nanotechnology, enhance a woman's beauty and allure. This class of nanocosmetics is like a windfall for women. The following section deals with the benefits of decorative cosmetic products containing nanomaterials in it.

Lipstick [48, 49]

- Makes the product more pleasing by affecting its sensorial properties.
- Imparts gloss and is long-wearing.
- Improves transfer resistance and film brightness.
- Prevents bleeding of oil into lips.
- Softens the lips by preventing transepidermal water loss and provides better coverage.
- Diminishes the wrinkles of lips.

Nail lacquer [50–52]

- Excellent hardness and firmness.
- It offers twice the durability as compared to the conventional one.
- Fast drying and dries to a very hard state.
- Its flexibility allows for effective and easy application.
- It offers a great range of colors.
- Strong against chipping and cracking and scratching.

- Better color, coat, and longer-lasting finish.
- It can create unique therapeutic products such as antifungal nail polish to cure fungal toenail diseases.

Eye makeup
- Mascara adds thickness and length to lashes, builds up the volume, resists clumping, and provides greater intensity of the black shade [30].
- Kajal increases the black intensity, protects the eye against any infection or irritation, and has antibacterial action [42].

(ii) Haircare products

Not only women but also men across the globe have an obsession with luxuriant hair. People are in the hunt for products that provide several benefits to their tresses. Haircare products infused with nanomaterials in it include shampoo, hair growth stimulants, conditioning agents, styling, and coloring products.
- Shampoo (nano) forms a barrier by maintaining resident contact time with scalp and hair follicles. In the cuticles, it seals the moisture. The intrinsic property of nanoparticles allows for an increased quantity of active ingredient and shaft targeting [53].
- Conditioning agents impart softness, shine, gloss, and reduce the tangling of hairs.
- Hair dyes provide long-lasting color, precipitate the penetration of coloring agent through hair cuticle, cause less damage to hair fibers [54, 55].

(iii) Skincare products

Skin problems are common and are alarming. For a blooming skin, various skincare products are available in the market depending on the application.
- Moisturizer forms a thin film of humectant, helps re-establish the functions of stratum corneum, prevent transepidermal water loss [4].
- Sunscreen creates a defensive film on the skin, restrict deeper penetration of rays, and absorb UVA and UVB rays [46].
- Cleanser removes makeup effectively, kills bacteria, fights against acne, and prevents age spots.
- Antiaging blocks the mechanism of reactive oxygen species (ROS), helps treat DNA damage, and prevents collagen and elastin breakage [3, 4].

(iv) Dental care products

It includes toothpaste and mouthwashes. Nanocosmetic in dental care products enhances the antibacterial activity, builds up enamel, and helps better hygiene [38].

13.2.2 Small size can do deleterious things

Nanotechnology in cosmetics is a double-edged sword that cuts both ways. The attractive benefits and extraordinary attributes of nanocosmetics is not a reliable indication of its true nature. While reaping the benefits of small size particles, the user and environment have to endure the unpredictable harmful effects and toxicities of nano-based cosmetic products [8].

Very little research has been done concerning the impact of nano sized materials on environment. Normally, they are swept away. These particles can easily pass through any filtering device to find space in the rivers, given their minute, and eventually, affect the entire food chain. Some possible examples like exposure to nanoscale aluminum, which is used in sunscreen, have already been found to delay root development. Carbon fullerenes, used in some facial creams and moisturizers, have also been found to kill water fleas and beneficial bacteria [44].

The toxicity of nanomaterials rather than its benefits has been analyzed in the last ten years. Nanotoxicity deals with the study of interactions between nanomaterials and biological systems to determine the harmful effects in living organisms [56].

The nano-ness of particle generates an enormous increase in surface area that trigger chemical reactions, and it means greater chemical reactivity takes place at the surface. This mass of nanoparticles have the possibility for biological interactions that leads to the production of a group of free radicals and reactive molecules, ROS. Consequently, an unavoidable consequence is the generation of free radical and the destruction of antioxidant defense; this state is said to be oxidative stress. It attacks important macromolecules and damages the cell, DNA, protein, and lipids. Oxidative stress results in inflammatory diseases, ischemic diseases, and neurological diseases and contributes to the process of aging [57, 58] (Figure 13.1).

By this, it can be comprehended that there are risks and uncertainties associated with nanoparticles throughout their lifecycle from production to disposition. Toxicities are attributable to the shape, charge, surface area of nanoparticle but predominantly to its size. Because of nanosize, the particle can easily approach the systemic circulation via inhalation or penetration and then travel to various organs and tissues. The primary and major routes of exposure to nanomaterials are inhalation, ingestion, and penetration [58–60]. (Figure 13.2)

13.2.2.1 Toxicities associated with silica

Inhalation toxicity study of silicon dioxide indicates that particle size of 1–5 nm gives rise to more toxicological response than 10 nm at an equivalent dose [61]. Results are debatable concerning the safety of silica-based nanoparticles. While assessing the toxicity of silica nanoparticles, parameters such as size, shape, and surface modifications

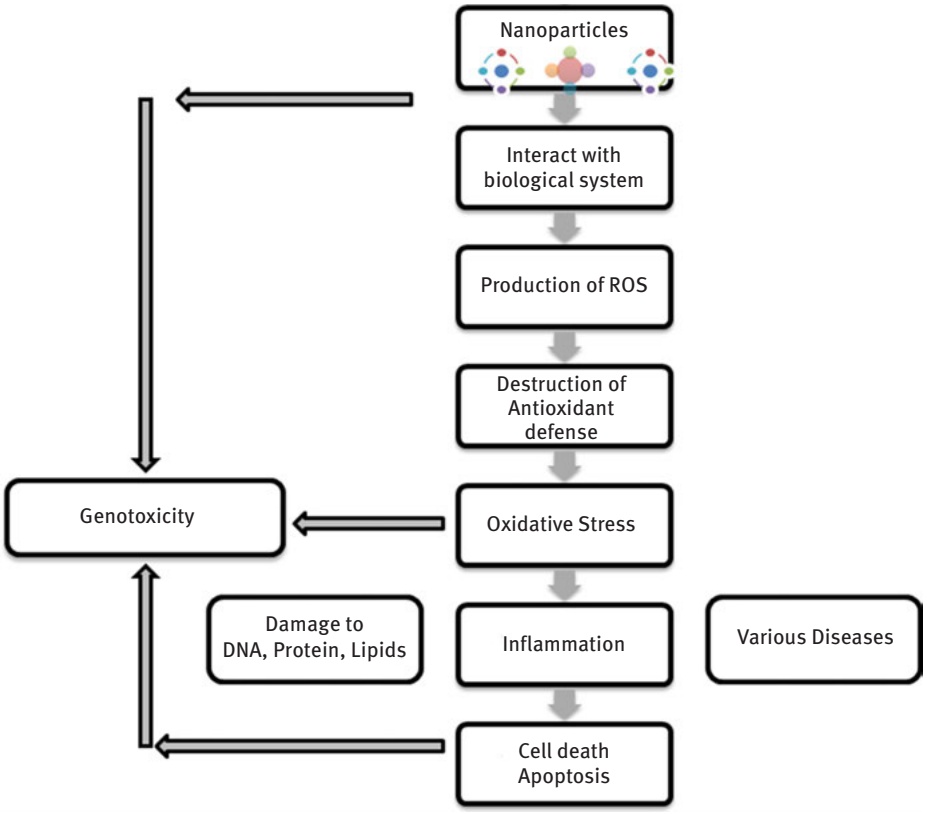

Figure 13.1: General mechanism of ROS production and its consequences.

should be taken into account. The application and use of silica in nanocosmetics are still indecisive, and long duration tests are required [62, 63].

13.2.2.2 Toxicities associated with carbon

A patent was filed on hair coloring and cosmetic compositions comprising carbon nanotubes (CNT); it suggests that CNTs are promising candidates that can be incorporated in cosmetic products [3]. The lipophilic character, higher reactivity, and long life of CNTs contribute to the negative effect on the environment and human health. They can easily pass the biological membranes and get distributed into the cellular and subcellular organs, but their toxicity is concentration dependent. Inhalation exposure in mice can cause pleural fibrosis in some cases. In vitro toxicity studies in cell lines demonstrated ROS production, inflammation, damage of DNA, and proteins [64]. Studies have proven that nanotubes of carbon may cause cell

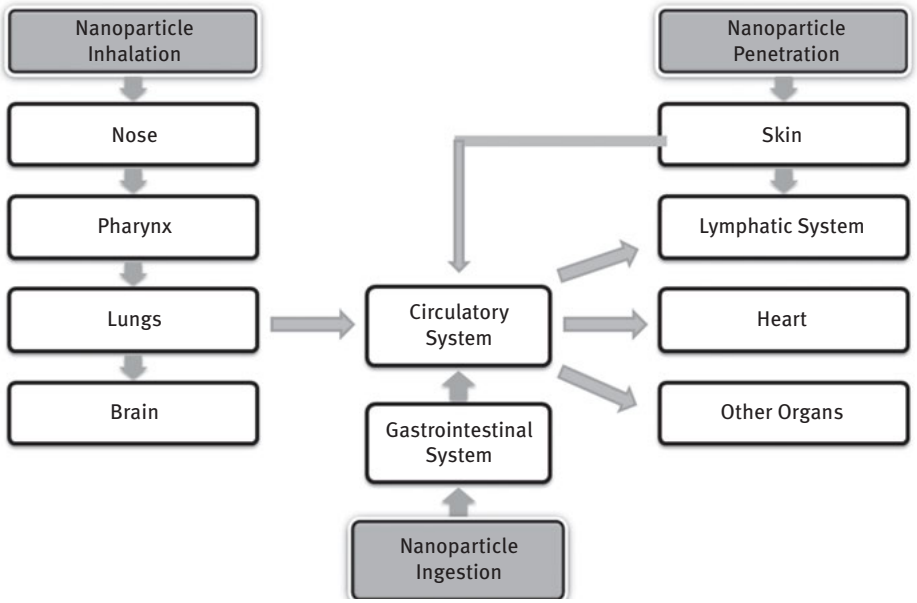

Figure 13.2: Routes of exposure to nanoparticles.

death in kidney and restrict cell growth. It also produces inflammation in the abdominal cavity of mice.

Various experiments conducted on CNTs demonstrated that interstitial inflammation and epithelioid granulomatous lesions are caused in the lungs on chronic exposure [3]. The respiratory toxicity of single-walled CNTs was carried out by pharyngeal aspiration in C57BL/6 mice revealed an acute pulmonary inflammation that further developed to granulomas and fibrosis [65, 66].

Fullerenes in face creams and moisturizers are used, but the toxicity associated with them is unclear. A report suggests that face creams containing fullerenes are found to cause brain damage to fishes and harmful effects in human liver cells [67]. Some research illustrates that fullerene-based peptides had the capability of penetrating intact skin and their traversal into the dermis could be easy due to mechanical stressor. Furthermore, it was found that water-soluble fullerenes at a lower level are hazardous to carcinoma cells, dermal fibroblasts in vitro, and human liver cells [68].

13.2.2.3 Toxicities associated with silver

The concentration of silver, which is fatal for bacteria, is equivalent to the amount that is fatal for keratinocytes and fibroblasts [69]. It was observed that silver nanoparticles at a low level when exposed to mouse stem cell and rat's neuronal cells result in

irregularities in shape and decrease in size. Also, it diminished the cell viability and function of mitochondria [61, 70].

The continuous exposure of Ag nanoparticle coated with polyvinyl pyrrolidone (PVP) with a particle size of 15 nm of different concentrations on epidermal keratinocytes could lead to DNA damage. At 35 nm silver, NP exposed to neonatal Daphnia Magna for 96 h demonstrated that they were twice as toxic as microparticles.

The size-dependent cellular toxicity of silver nanoparticles was evaluated at 10, 50, and 100 nm on MC3T3-E1 and PC12 cell lines [71]. Their results showed that the smaller the size, the greater the risk. The smallest size of silver 10 nm had a greater ability to induce apoptosis cells than the other sizes.

13.2.2.4 Toxicities associated with gold

The use of gold nanoparticles of different size (40 and 80 nm) with different surface coatings like polyethylene glycol, lipoic acid, and polyethyleneimine revealed that surface chemistry can activate the modulating expression of genes involved in DNA damage, and affect the cellular uptake of gold nanoparticles, mitochondrial energy metabolism, oxidative stress, and endoplasmic reticulum stress.

Exposure of nanometric gold of 2, 40, and 100 nm size via intratracheal route affected the liver and macrophages. Oral ingestion of 13.5 nm gold nanoparticle to mice caused a marked decrease in the body weight, spleen index, and RBCs [3, 72].

13.2.2.5 Toxicities associated with TiO_2 and ZnO

Nano titanium dioxide and nano zinc oxide contribute to the production of free radical and ROS, which can destroy the defense action and lead to oxidative stress and inflammatory responses. This can significantly attack the RNA, DNA, membranes, lipids, and protein and damage them. The anatase form of TiO_2 in nanosize has induced higher photocytotoxicity than its rutile form. Moreover, toxicity increases with a decrease in particle size. TiO_2 of 25 nm can destroy DNA, whereas 500 nm has very little ability to cause DNA strand breakage [73].

The research demonstrated that administration of TiO_2 nanoparticle subcutaneously to pregnant mice was transferred to their offspring and results in decreased sperm production in male and brain damage [74]. An in vitro study was conducted that examined TiO_2 nanoparticles using Caco-2 cell for 4, 24, and 48 h, and it demonstrated that after 24 h exposure the intestinal epithelium layer was affected and cell viability was reduced to about 13% [75]. Examination of TiO_2 nanoparticles in BEAS-2B cell forms such as rods, platelets, and bipyramids. The rod form showed higher cytotoxicity as compared to platelets or bipyramids. Accumulation of platelets was higher and could cause oxidative DNA damage and direct genotoxicity [76].

Exposure of ZnO NP (40–48 nm) to *Chlorella vulgaris* for 24 and 72 h resulted reduced viability and superoxide dismutase and an increase in lactate dehydrogenase [77]. Also, positively charged ZnO induced higher cytotoxicity than that of negative [78]. According to an in vivo toxicity study, when 30 nm ZnO was exposed, it resulted in major accumulation in liver and necrosis [79]. *Drosophila melanogaster* exposed to ZnO led to a decrease in inhibitory protein in the cell (nuclear factor κB (NF-κB)) and consequently increased level of NF-κB dimers in the nucleus; this provoked the breakage of double-stranded DNA [80].

13.3 Ethical issues in nanocosmetics [81–83]

Technology sums up the innovation and invention of methods, processes, and products. Applying technology at the nano level in cosmetics has enabled new characteristics and desired benefits to adorn and alter the appearance of a human. For example, TiO_2 and ZnO have many applications in cosmetics, widely used in sunscreens. The nanometric form of TiO_2 especially has white coloring and UV filtration properties. It improves product performance, quality, comfort, and texture. Likewise, ZnO is known for its protective properties. The nano form of ZnO in the formula reflects UVA and UVB rays, used as a sun filter. At the same time, metal oxides nanoparticle (TiO_2 and ZnO) are accused of causing the production of ROS, extremely reactive chemical species result in oxidative damage, and it develops when the balance between free radical and defense mechanism is unfavorable. This all leads to mitochondrial dysfunction, DNA damage, and genotoxicity [58].

Despite the potential benefits associated with the use of nanocosmetics, it is difficult to deny the uncertainties with the use of nanotechnology in cosmetics. Some may see it as a fantasy world; others speculate that it is an inevitability that will be the beginning of the destructing end. Imagine a world in which human bodies are furnished with paints, glitter, and gloss but are hollow inside. Sounds like fiction? Well, if the trend of nanotechnology in cosmetics continues into the future, we will reach a critical point where the blurry line between fantasy and reality will be more transparent. It indicates that as nanocosmetics add aesthetic value, it subtracts the idea of longer life too. Just for the sake of beautification and adornment, the following queries are proposed regarding humanity. Are we not crossing the ethical line of humankind? Is suffering and despair humanity's fate? Should we proceed? Do we wish to inhabit and leave this kind of world for the following generations? From the ethical point of view, it would be unethical to proceed with any technology that exposes the population to risk. There is a limit to human endurance; once we cross it, the body begins eating itself.

Available current approaches do not adequately address the parameters necessary to determine whether it is ethically right or wrong and to assess the toxicity and characterization of nanomaterials in the absence of precise methodologies.

Nonetheless, it would be ethically right if we keep in mind that no progress is possible with zero risks. There is a need to quantify the risk, how much risk is acceptable. And this is feasible only when the goal is the availability of validated and standardized methods for toxicity assessment and responsible development of nanoproducts considering the legal, social, and ethical implications. This can bring significant progress in elevating humanity. Researchers and regulators should emphasize on developing standard rules and regulations especially on a strong set of ethical guidelines and policies to eliminate or minimize its damaging effects on society, the environment, and humans for a healthier destiny. They should also address the accurate characterization of nanomaterials and positive and negative impacts need to be identified.

Regardless of anticipated catastrophic effects and complications posed by cosmetic products containing nanomaterials, continuous advancements and modifications should be carried out in this field concurrently with a watch on the degree of risks and its limit.

13.4 Regulations

The progression of nanotechnology in cosmetics had provoked the prominent regulatory bodies and consumers across the world. The regulatory bodies of the United States, Europe, Japan, and Australia established some norms and regulations to ensure nanocosmetics product's safety and efficacy. Regulations are the minimum mandated standards that aim to streamline the process of achieving quality and safety. These technical guidelines maintain the highest level of consumer protection and confidence. In other words, it is a safeguard for the users. Also, regulation compels the manufacturer to comply with the rules related to the quality and safety of products [84].

13.4.1 US FDA regulatory aspects

In 2006, an initiative was taken to establish FDA Nanotechnology "Task Force" to determine regulatory aspects that endorse the development of safe and effective FDA-regulated products. In 2007, Task Force submitted a report enclosing the data related to the safety and effectiveness of US Federal Drug Administration (FDA)-controlled products containing nanomaterials. Highlighting the cosmetic products, Task Force

made recommendations and issued a guidance report that described cosmetic products loaded with nanomaterials that are safe and free from adulteration.

In light of these considerations, US FDA in June 2014 unfolded a guidance document with docket number FDA-2011-D-0489 under the title "Guidance for Industry: Safety of Nanomaterials in Cosmetic Products" [85]. The guidance was developed based on information obtained from the following:

a) Data submitted by the cosmetic industry to International Cooperation Regulations (ICCR)
b) Reports and publications on recent advances in nanotechnology and its safety.
c) Relevant reports such as "Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials," the Scientific Committee on Consumer Safety (SCCS) "Guidance on the Safety Assessment of Nanomaterials in Cosmetics," "Currently Available Methods for Characterization of Nanomaterials," and "Principles of Cosmetic Product Safety Assessment."

Cosmetic FDA has not established any pinpoint definition of nanotechnology, nanomaterial, or any nano-related terms. According to guidance described by FDA, any product involving the use of nanotechnology should consider the following two points [86]:

- Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 to 100 nm); and
- Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)

Another key element of the guidance document discusses the safety assessment of nanomaterials in cosmetic products. According to section 301 (a) of Food, Drug and Cosmetic Act, the marketing of adulterated or misbranded cosmetics is forbidden. This Act also declared that cosmetics or cosmetic ingredients are exempted from premarket approval except for color additives and the products prohibited from use in cosmetics. All the data and information needed to substantiate the safety of products before their commercialization is the sole responsibility of the manufacturer. For assessing the safety of cosmetic products containing nanoscale materials or macrosize materials with the same chemical composition, some general considerations are applicable. However, traditional testing methods are not appropriate to use due to the novel, distinctive physicochemical characteristics, and behavior of nanomaterials.

This section of the document spotlights the relevant scientific considerations regarding the assessment of the safety of nanomaterials used in cosmetics. Evaluation of the safety of nanomaterials in cosmetic products can be addressed by its toxicology and absorption, distribution, metabolism, and excretion. Further, this can be

comprehended by routes of exposure, absorption, uptake, and toxicity testing. Modified traditional toxicity methods or new methods should be developed for consideration of both ingredients and impurities.

The considerations are profoundly elaborated below:

1) Nanomaterial characterization

The characterization and evaluation of nanomaterials is an essential and fundamental part of the safety assessment. This includes attributes such as structure, configuration, physical, chemical, and biological properties. This would also have the evaluation of nanomaterial in its raw form and finished product. Furthermore, stability studies of nanoscale materials should be determined in a formulation under different test conditions.

2) Toxicological considerations

While developing suitable toxicological test methods, the manufacturer should examine the parameters and interactions. (Figure 13.3)

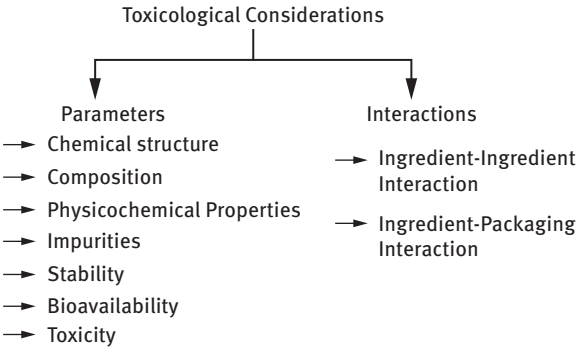

Figure 13.3: Toxicological considerations proposed by FDA.

13.4.2 European regulatory aspects

Europe has been leading the global cosmetic market for decades. The EU recasts various directives and regulations to strengthen the safety of cosmetic products and to ensure the highest level of human health. Finished cosmetic products placed on the EU market are validated by safety requirements described in Regulation (EC) No 1223/2009, the principal regulatory framework.

The key points introduced by Cosmetic Regulation include [87]:

- Reinforce safety specifications for cosmetic products.
- Introduction of “Responsible person” and its responsibilities.

- Information on safety assessment.
- Notification to the Commission for all cosmetic products regulated by the EU market.
- Instruction for the use of nanomaterial in cosmetic products.
- Directions for labeling.

Cosmetic Regulation (EC) No 1223/2009 issued an edict of nanomaterials and its particulars. According to the legislation provided in Table 13.3.

According to Article 16(3), the following information shall be notified to the Commission:

Table 13.3: Directives issued by Cosmetic Regulation (EC) No 1223/2009 [88].

Reference	Title	Description
Article2 (k)	Definition of Nanomaterial	"An insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm."
Article 4 & 5	Notion and Obligations of Responsible person	For each cosmetic product, including nanocosmetic placed on the market, the Responsible person is accountable and must comply with the relevant obligation.
Article 13(1)(f)	Centralized Notification	The electronic dossier must contain information regarding the "presence of substances in the form of nanomaterial's".
Article 16	Addresses Nanomaterials Specifically	Deals with issues associated with nanomaterials except for colorants, UV-filters, or preservatives in nano size.
Article 16(3)	Nanonotification	The responsible person should notify the commission at least six months prior to being placed on the market, and the information is submitted through electronic means CPNP.
Article 16(4)	Safety of Nanomaterials	In case of concern regarding the safety of NM, the European Commission refers it to the SCCS for a scientific opinion. The SCCS shall deliver its advice within six months of its request.
Article 16(10)(a)	Public Information on Nanomaterials	EC shall create a publically available catalogue of NM used in cosmetic products placed on the EU market, and this shall be regularly updated.
Article 19	Labelling of Nanomaterials	Materials in the nano form shall be clearly indicated in the list and names of nano ingredients shall be followed by the word "nano" in brackets.

- The identification of the nanomaterial including its chemical name (IUPAC) and other descriptors as specified in point 2 of the Preamble to Annexes II to VI;
- The specification of the nanomaterial including size of particles and physical and chemical properties;
- An estimate of the quantity of nanomaterial contained in cosmetic products intended to be placed on the market per year;
- The toxicological profile of the nanomaterial;
- The safety data of the nanomaterial relating to the category of the cosmetic product, as used in such products;
- The reasonably foreseeable exposure conditions.

The European Commission in collaboration with the SCCS provides opinions linked to cosmetic products. The Committee shall provide Opinions on consumer health, public safety, and the environment and prepare policy concerning all types of health and safety risks [89].

In 2012, the SCCS published Guidance on the safety assessment of nanomaterials in cosmetics (SCCS/1484/12) stating the conditions to regulate the physicochemical characterization and to evaluate the toxicological profile and the reasonably foreseeable exposure conditions of a nanomaterial. Moreover, to assure the consumers regarding the safety of cosmetic products incorporating nanomaterials, the manufacturers should add the word "nano" after the name of the material [Article 19, Regulation (CE) No 1223/2009] [90].

The cosmetic directive replaced by cosmetic regulations as of July 11, 2013, both has provisions to explicitly discontinue animal testing for cosmetic purposes, irrespective of the substitute to animal tests. It specifically includes a testing ban – prohibits the testing of cosmetic products on animals (applied since September 11, 2004) and a marketing ban – prohibit marketing of animal-tested cosmetic products or any type of ingredient (applied since March 11, 2009) and excludes the tests for reproductive toxicity, toxicokinetics, and repeated dose toxicity

In 2018, the SCCS published the tenth revised version of "The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation." It dictates testing and safety evaluation of cosmetic ingredients to improve harmonized compliance with the current cosmetic EU legislation. The SCCS considers any toxicological data derived from alternative means, such as in vitro and ex vivo methods, in silico models, grouping, and read-across, physiologically based pharmacokinetic or toxicokinetics modeling (SCCS Notes of Guidance SCCS/1602/18, or most recent version). These approaches are currently at the primary stage for NMs, and the use of such methods needs justification on scientific grounds [91].

The SCCS (SCCS/1611/19) Guidance on the Safety Assessment of Nanomaterials in Cosmetics includes the requirements for the safety assessment of nanomaterials used as cosmetic component taking into account the nano-specific properties and

the animal testing bans. Elaborated identification and characterization of nanomaterials is the need for safety assessment [92].

REACH is the EU regulation (EC) No 1907/2006 stands for Registration, Evaluation, and Authorization of Chemicals. The objective of the program is to assure high-grade protection to human and the environment. To provide adequate information to end-users for the safety of the products, the European Union Observatory for Nanomaterials declared that all cosmetic industries that use and manufacture nano form materials must oblige with the REACH registration [93].

13.5 Requirement of regulations: Need of the hour

The previous section of the chapter outlined the regulatory aspects of nanotechnology in cosmetics by US FDA and Europe. Regulations are standards that help achieve quality and safety to the consumer and the environment. Cosmetic regulations are specifically created to assure product safety. Regardless of continuous amendments and upgradation to the directives, scientific uncertainties and numerous ambiguities may exist. The proposed regulation in its current form is still grappling with the ethics of nanocosmetics, and continuously questions are raised concerning the characterization of nanoparticles, determination of potential exposure pathways and, and toxicity caused by commercially available nanocosmetic products.

13.6 Conclusion

Nanotechnology has fixed its position in the cosmetic industry. The nanometric particles in cosmetic are quite widespread, influential and prolific, although not high profile yet. Nanoness creates uniqueness. Thousands of products like skincare, haircare, and decorative cosmetics are lined up on shelves in combination with materials of nano size. Compared to conventional cosmetics, the new nanocosmetic products blazed a trail with its several benefits. But all that glitters is not gold; due to the scarcity of explicit scientific data published on the evaluation of marketed nanocosmetic products on humans application is riddled with toxicities and uncertainties that have questioned humanity. The use and commercialization of such products are debatable. On the one hand, it is problematic from a public health perspective to use such products as this can negatively impact public health as nanomaterials interact with the cellular process and compromise cell function. Also, spending hundreds of dollars on these products does not assure health safety.

On the other hand, if proper well-established toxicity testing methods and characterization procedures of nanomaterials are established and developed, there will be ease to quantify the risks and decide on a limit. Nevertheless, adequate data and

transparent specifics help the evolution of nanocosmetics. Researchers need to fulfil the scarcity of methods available and more international collaborative efforts between the regulatory experts to upgrade the regulations and harmonize the guidelines. Manufacturers must comply with all the requirements and recommendations to ensure and strengthen the safety before placing it on the market. This should and could be done to alleviate real human pain and for a beautiful, healthier, and safer future.

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14 Safety of biomedical nanomaterials

Abstract: In this chapter, we will discuss the safety concerns of nanomaterials in biomedical applications. Nanotechnology is nowadays widely studied for therapeutic and diagnostic purposes, and an increasing number of nanomedicines have been approved for clinical use. The rate of expansion of biomedical nanomaterials calls for a better understanding of their safety profile. Herein, the toxicity of nanomaterials is reviewed from the property, mechanism, and regulatory perspective. In terms of unique physicochemical characteristics of nanomaterials, factors such as chemical composition, size, shape, and surface properties are closely related to nanomaterial toxicity. While interacting within biological systems, nanomaterials are found to cause toxic effects during their pharmacokinetic process including blood circulation, organ accumulation, and cellular uptake. What is more, the current progress in making regulatory guidance in different countries for biomedical nanotechnology is also presented. We intend to provide a general introduction to emphasize the importance of safety study in nano-biomedical applications.

Keywords: nanomaterials, nanotoxicological, biomedical, biostatistical, toxicology

14.1 Introduction

Since 1980, a remarkable increase in commercially available nanobased pharmaceutical products has been witnessed [1]. Nanomaterials possess unique characteristics that make them ideal candidates for a variety of biomedical applications. One of the major advantages of nanomaterials is their small size (typically less than

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100 nm), enabling them to circulate the body without interfering blood flow [2]. Smaller size is accompanied by a large surface area, which makes nanomaterials suitable for various kinds of drug delivery [3]. In addition, based on their intrinsic physical and chemical properties (such as electronic and optical properties, magnetic permeability, chemical reactivity), nanomaterials are also widely studied for a variety of biomedical applications, including but not limited to medical imaging (e.g., magnetic resonance imaging (MRI), computerized tomography (CT), fluorescence imaging), biosensors, drug/gene delivery, cancer treatment (e.g., photothermal therapy, photodynamic therapy, radiotherapy, or immunotherapy), antibacterial, tissue engineering (e.g., implants or prostheses), and chronic diseases [4–8]. Different types of nanoparticles, such as liposome, polymers, nanocrystal, inorganic nanomaterials, micelles, and so on, have been approved for clinical use [9, 10]. The exploration and application of nanotechnology in the field of biomedicine are currently thriving more than ever before.

However, the outcome of the rapid development of biomedical nanotechnology is not all encouraging. As the saying goes, technology is a double-edged sword. The number of toxicity assessment reports on nanomaterials has been growing with the number of biomedical research related to them [11]. The exposure of nanomedicine via different routes, including but not exclusive to, parenteral (intravenous, intraperitoneal, intramuscular, subcutaneous routes), pulmonary, nasal, oral, transdermal, and ocular pathway, may pose unknown risks to biological systems [12]. Upon entering the biological body, nanoparticles usually go through adsorption, biodistribution, metabolism, and excretion before or after finishing its function. Identifying and understanding the behaviors of nanoparticles during these processes are essential for studying their toxicity [13, 14]. It has been reported that possible toxicity, such as hematological abnormality, organ/immune/neuro/reproductive toxicity, hepatic damage, or nephrotoxicity, is anticipated to lie in the pharmacokinetics of extraneous nanomedicine in vivo (Figure 14.1) [15]. As such, the safety study of biomedical nanomaterials is of the same importance as the exploration of novel functional nanomedicines.

Following, in this chapter, we put our focus on the safety profile of biomedical nanomaterials. Since the toxicology of nanomaterials is closely related to their unique properties, this chapter primarily gives an overall introduction of the most widely recognized characteristics that may influence the toxic profile of nanomaterials. Properties such as chemical composition, size and surface area, shape and morphology, and surface properties are presented in detail. Next, in vivo nanoparticle toxicity mechanisms including nanoparticle–blood interaction, nanoparticle–organ interaction, and nanoparticle–cell interaction are discussed. In the fourth section of this chapter, we also provide a glance at the current regulatory guidance that is associated with biomedical nanoproducts. In the end, concerns regarding this important field of study are also proposed.

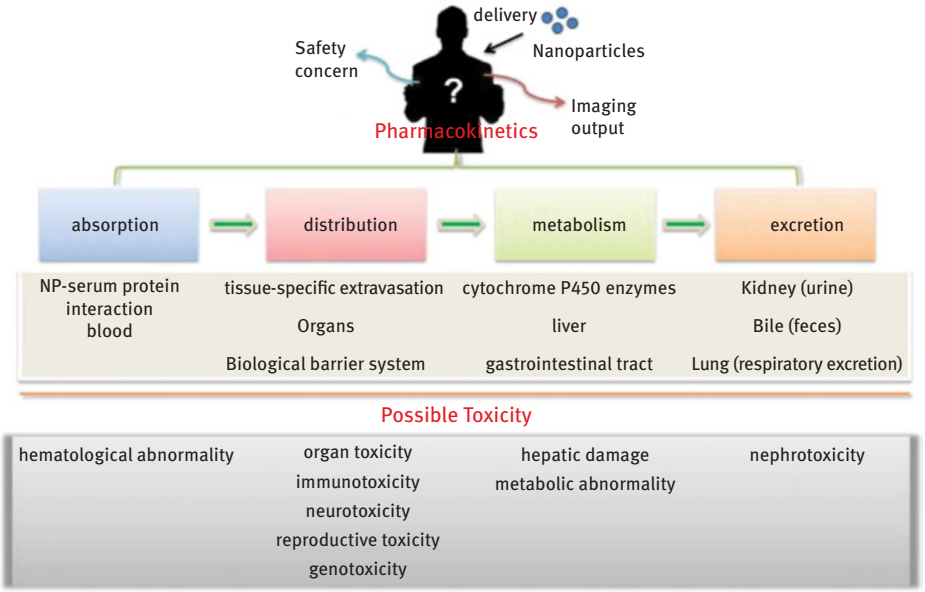

Figure 14.1: An illustrative scheme for the pharmacokinetics of extraneous nanoparticles in vivo and possible toxicities that may arise. Adapted with permission [15].

14.2 Properties that influence nanoparticle toxicity in biomedical application

The physical and chemical properties of nanoparticles are closely related to their toxicology. Nanomaterials can become highly active at nanosized dimensions even when made of the inert element (e.g., gold) [16]. The properties also pose a great influence on how nanoparticles interact with biological systems and cells. The following content introduces several nanoparticle properties that are generally acknowledged to play an important role in determining nanotoxicity. In addition to the following mentioned properties, features such as crystallinity, dosage, coating, longevity, and stability in biological fluids, catalytic activity, and so on are also considered as influencing parameters [16, 17].

14.2.1 Chemical composition

Chemical composition of nanomaterials can cause toxicity in both direct and indirect ways. As for the direct way, different chemical component exerts different toxic effects. For instance, SiO_2 nanoparticles alter the DNA structure while ZnO nanoparticles

of the same size cause oxidative stress [18]. On the other hand, the toxicity induced by indirect way is mostly dependent on nanoparticle degradation. Biomedical nanomaterials can be degraded in different conditions inside the body (e.g., the change of pH), which can cause the leakage of metal ions. Some metal ions such as silver are intrinsically toxic, resulting in damage to the cell; other metal ions such as Fe, although biologically non-toxic, demonstrate adverse effects at high concentrations [17]. In addition to chemical composition, crystal structure can also affect the toxic mechanism of certain nanoparticles. For instance, anatase TiO_2 nanoparticles are found to induce cell necrosis, whereas rutile TiO_2 nanoparticles initiated apoptosis via reactive oxygen species (ROS) production [19].

14.2.2 Size and surface area

Particle size and surface area play a vital role in determining the toxic profile of nanomaterials. In general, a reduction in size leads to an increase in particle surface area. Therefore, smaller particles typically exhibit a larger surface area-to-volume ratio, which may cause more chemical or biomolecules to be attached to the nanoparticle surface and consequently increase its reactivity and toxic effect [20]. This further changes its surface property and thus influences its fate inside the body. Small size also increases mobility and transportation, making nanoparticles more accessible to a broad range of organs, cellular, and intracellular targets than larger particles [21]. Such property may enable nanoparticles to cause severe damage at an unexpected site. For instance, gold nanoparticles of no larger than 6 nm in size are reported to be able to enter cell nucleus [22]. In addition, a specific surface area has an impact on the adsorption of nanoparticles to cell surface [17]. For example, 100-nm-sized nanoparticles could be effectively absorbed on enthrocyte surface without causing cell damage, while 600 nm nanoparticles lead to membrane deformation and erythrocyte destruction [23].

14.2.3 Shape and morphology

Along with nanoparticle size, morphology and shape profile also influences the toxicity of nanoparticles, especially in cellular internationalization mechanism. Extensive studies have reported tons of shapes of nanoparticles such as planar, spheres, tubes, fibers, cubes, triangular, hexagon, and so on [24]. Typically, size and concentration may play a major role in the induction of nanoparticle endocytosis, whereas shape-dependent endocytosis is considered to be more important for successful engulfment [25, 26]. For instance, needle-like nanoparticles can be uptaken by cells via both endocytosis and diffusion [27], and needle-shaped polymeric particles are more likely to induce disruption of cell membrane [28]; Graphene oxide (GO) with sharp edges can directly destroy bacteria membrane [29]. In addition, shape also

influences the level of nanoparticle toxicity. It is reported that compared to anatase or rutile, amorphous TiO_2 of similar size can produce more ROS [30], and rod-shaped Fe_3O_4 are more toxic than sphere-shaped ones to murine macrophage cells [31].

14.2.4 Surface property

As far as surface property is concerned, surface charge is the foremost concern, as it largely determines the interaction between nanoparticle and biological systems. Generally speaking, positively charged nanoparticles are more cytotoxic than negatively charged or neutral nanoparticles. This is possibly because the positively charged nanoparticles not only penetrate more easily through cell membrane via electrostatic attraction with negatively charged cell membrane glycoproteins, but also bind more strongly with negatively charged DNA to cause cellular damage [17, 32]. Thus, nanoparticles with positively charged surface are expected to have a higher non-specific cellular-uptake rate and short blood circulation time [33]. Apart from surface charge, surface hydrophobicity/hydrophilicity also influences nanoparticle toxicity. Hydrophobic particles tend to be coated by plasma and complement proteins, which further influence surface chemistry, blood circulation period, and cellular interaction [21]. What is more, although the toxicity of nanoparticle is largely dependent on their intrinsic characteristics, the influence of surface modification should not be disregarded. With proper coating, hydrophobic nanoparticles can turn into hydrophilic nanoparticles. In addition, roughness, defects, porosity, ligands presence, or valence and conductance states all affect surface properties and thus influence nanoparticle toxicity [34].

14.3 Mechanisms of nanoparticle toxicity in vivo

There have been extensive nanotoxicological studies that aim to identify the exact mechanism of in vivo nanotoxicity. The toxicological mechanism of certain nanomaterials can be revealed at tissue, cell, and molecular level. As nanoparticles circulate through the body, they can be easily exposed to different biological environments such as blood, various organs, extracellular matrix, and cellular organelles [35]. The interaction between nanoparticle with different biological systems may induce unexpected adverse responses.

14.3.1 Nanoparticle–blood interaction

In most of in vivo biomedical applications, especially when intravenously injected, nanomaterials inevitably interact with cellular and acellular components in blood.

Cellular portion of the blood mainly contains erythrocyte (red blood cells), leukocyte (white blood cells), and thrombocytes (platelets); while acellular plasma is composed of water, a small number of biomolecules and a collection of over 1,100 multifunctional proteins [36]. The interaction of nanomaterials with blood cellular components may lead to erythrocyte breakage or lysis, blood clotting, thrombosis, and produce an inflammatory response [37]. Once nanomaterials enter the body, they are generally considered as foreign particles and different immune cells and proteins can be stimulated to bring about opsonization [37]. However, so far, there is no evidence that nanomaterials can interact with associated cells/molecules and generate a series of potential toxic effects just by entering the bloodstream [38]. As nanomaterials go through the systematic circulation, a "protein corona" is formed through the protein adsorption on the surface of nanomaterials. This process is an important issue as it contributes the most to change the "synthetic identity" and the biological fate of a nanoparticle. The synthetic identity typically refers to the physicochemical properties of nanomaterials that define the size, shape, surface chemistry/functionalization, aggregation state, and so on of a nanoparticle [39, 40]. The alteration in the synthetic identity of a nanoparticle can greatly influence its fate inside the organism, such as retention time in the bloodstream, biodistribution, cellular uptake/interaction, accumulation, inflammation, immunogenicity, and degradation [39, 41–43]. Both cellular and acellular components interact with each other on nanomaterials surface, further changing protein conformation, binding affinity, and blood physiology [36, 44].

14.3.2 Nanoparticle–organ interaction

Through the translocation across the biological barriers, nanomaterials can reach and accumulate at secondary target organs where adverse effects may be induced. Generally speaking, organs with higher nanoparticle accumulation potential are at greater risk of nanoparticle damage [35]. As mentioned above, nanomaterials as foreign particles can be readily removed by mononuclear phagocyte system (MPS) cells and organs from bloodstream. Nanomaterials first undergo intracellular degradation by MPS cells when phagocytosed. If they fail to be decomposed, they would remain within the cell and be retained in MPS organs, which include liver, spleen, lymph nodes, and other organs that consist of phagocytic cells [45, 46]. Evidence has shown that nanoparticles can stay in MPS organ for more than six months and induce chronic toxicity [47]. Herein, one organ should be given special attention – liver. In addition to being one of the important MPS organs, the liver also offers hepatobiliary clearance to eliminate foreign substances with the help of the biliary system, where nanoparticles can enter liver via portal triads [47]. Hepatocytes play a dominant role in the metabolism of nanomaterials. This further increases the potential of toxicity to the liver. Moreover, kidney is another organ that may suffer from nanoparticle toxicity, as it is particularly susceptible to xenobiotics and offers a major

route to eliminate nanoparticles from a living organism [48]. Studies have shown that nanoparticles exhibit nephrotoxic potential both at tubular and glomerular level [49]. In these cases, the capture of nanoparticles by liver, MPS organs, and kidney not only poses risk of toxicity to these organs but also is a big challenge for the development of nanomedicine due to the off-target effect [50]. Additionally, size plays an important role in this scenario as nanoparticles with sizes larger than renal filtration limit (6 nm) are more likely to be sequestered by liver and spleen [51–53]. Apart from metabolic and excretal organs, nanomaterials may also exert adverse effects on other organs based on different exposure routes, such as lungs or brain (inhalation) [54], skin or eyes (airborne or drop) [55], and gastrointestinal system (oral) [56, 57]. The mechanism for nanoparticle–organ damage can be originated from cellular and molecular level, which will be discussed in detailed in next sections.

14.3.3 Nanoparticle–cell interaction

The most widely recognized mechanism for nanoparticle cellular uptake is endocytosis. It starts with the engulfment of nanoparticles via membrane invagination, followed by the formation of endocytic vesicles and then transported to intracellular sorting compartments [58]. In addition to endocytosis, other cell entry mechanisms such as passive diffusion, hole formation, and electroporation have also been reported [59, 60]. Nanoparticles with rigid surface and sharp edges are reported to cause disruption on cellular membrane structure [61]. Such damage to membrane integrity may cause leakage of cellular content, cell stress induction, and cell/organelle dysfunction (such as endoplasmic reticulum stress and mitochondrial dysfunction) [35, 62]. Next, another major mechanism of nano-cytotoxicity is the elevation of the level of oxidative stress via ROS production induced by nanoparticle internalization [63]. These high reactive species can destroy lipids, nucleic acid, enzymes, and other essential cellular biomolecules [32]. Consequently, the damage induced by elevated ROS level is extensive, which includes but is not limited to mitochondrial/endoplasmic reticulum damage, perturbation of calcium homeostasis, electron transport chain impairment, ATP production interference, and so on [64, 65]. Additionally, nanoparticle-triggered oxidative stress responses have also been reported to induce other pathophysiological effects such as inflammation, genotoxicity, and fibrosis [64, 66]. What is more, apart from membrane disruption and oxidative stress, nanomaterials dissolution, which involves the release of toxic ions that affect the organism, can also impair essential protein functions or cause DNA damage [67]. As a result of cellular damage, programmed cell death can be induced by nanoparticles. In terms of the morphologies of mammalian cells, the mechanisms of cell death can be classified into apoptosis, autophagy, and necrosis [68].

14.4 Regulations/guidelines regarding biomedical nanomaterials

As demonstrated previously, nanomaterials possess unique properties and toxicities. Until now, the precise interaction between many nanomaterials with biological systems are not yet fully comprehensively understood [69]. This makes it difficult to understand or identify the toxic profile of biomedical nanomaterials. In addition, the nanotechnology industry is growing so fast that tons of advanced nanoparticles with different novel functions have been synthesized. However, the number of approved nanomedicines is greatly limited. Thus, it is difficult to obtain robust data sets for general information associated with nanomedicine's quality and safety [70]. Some regulatory bodies currently use safety data that is based on bulk materials, which do not share the same pharmacodynamic/kinetic activity with nanomedicine [71]. Therefore, due to the complexity associated with nanomaterial properties, the deficiency of robust toxicological data sets, the selection regulatory path for biomedical nanomaterials may be difficult to determine and only limited regulatory guidance is available at the moment.

Efforts have been devoted to nanosafety assessment and standardization all over the world. The International Organization for Standardization Technical Committee (ISO/TC 229) of Nanotechnologies was established for developing standards for terminology and nomenclature, metrology and instrumentation, test methodologies modeling and simulations, as well as science-based health, safety, and environmental practice [72]. Organisation for Economic Co-operation and Development (OCED) initiated the Working Party on Manufactured Nanomaterials and works on the safety evaluation and risk assessment of manufactured nanomaterials [73]. But the focus of this program is chemical products instead of biomedicines. While another regulatory body of the European Union (EU), the European Medicines Agency, has published a few guidelines for the preparation of a range of medical products [74, 75]. In 2017, the Food and Drug Administration (USA) drafted guidance on drug products, including biological products, that contain nanomaterials [76]. In Japan, the regulatory bodies such as Ministry of Health, Labour and Welfare had issued a guideline for liposome drug product development in 2016 [77]. What is more, general guidance on nanotechnology-based health products and food was reported by Health Canada [78]. For many countries and regions such as EU, Japan, and Korea, the general medicinal/therapeutic product legislation was used for nanomedicine [70]. Moreover, countries like the United States and the United Kingdom also suggest that nanoproducts are not categorized as safe or harmful but the evaluation of which should be considered on a case-by-case basis [79]. Figure 14.2 is adapted from a recently published white paper entitled "Anticipation of regulatory needs for nanotechnology-enabled health products" by European Commission. It summarizes a few initial guidance

Category of product addressed by the document	Initial guidance documents addressing nanotechnology-based medical products
All products including health care products	
Consumer products including medical products	• SCENIHR. Risk assessment of products of nanotechnologies; 2009
Products containing nano-silver	• SCENIHR. Nanosilver: safety, health and environmental effects and role in antimicrobial resistance; 2014
Medicinal products	
Medicinal products containing nanomaterials	• EMA Reflection paper on nanotechnology-based medicinal products for Human Use. EMEA/CHMP/79769/2006 • FDA/CDER. Guidance for Industry: Drug Products, including Biological Products, that Contain Nanomaterials: (2017) (draft guidance)
Liposomal products	• EMA/CHMP. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. London; 2013; EMA/CHMP/806058/2009/Rev.02. • FDA/CDER. Guidance for Industry. Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2018) • MHLW. Guideline for the development of liposome drug products (2016)
Block copolymer micelle products	• EMA/CHMP/ MHLW. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products. London; 2013; EMA/CHMP/13099/2013.
Iron based nano-colloidal products	• EMA/CHMP. Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product. London; 2015; EMA/CHMP/SWP/620008/2012.
Nucleic acid-loaded nanotechnology based drug products	• MHLW. Reflection paper on nucleic acids (siRNA)-loaded nanotechnology based drug products (2016)
Coated nanomedicine products	• EMA/CHMP. Reflection paper on surface coatings : general issues for consideration regarding parenteral administration of coated nanomedicine products. London; 2013; EMA/325027/2013.
Medical devices	
Medical devices containing nanomaterial	• SCENIHR. Opinion on the guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices; 2015 • ISO TR 10993-22: Biological Evaluation of medical devices – Part 22: Guidance on nanomaterials.

Figure 14.2: Regulatory documents specifically addressing nanotechnology-enabled health products. EMA: European Medicines Agency, FDA: Food and Drug Administration (USA), MHLW: Ministry of Health, Labour and Welfare (Japan), SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks (EU). Adapted with permission [80].

documents addressing nanotechnology-based medical products, in terms of products that include health-care products, medicinal products, and medical devices [80].

Regardless of the regulation-drafting progress, debates over whether new biomedical nanomaterial-specific regulations are warranted have lasted for years. From the proponent view, nanomaterials are so different from conventional materials, and its risk to human health is poorly understood [81]. The existing legal frameworks cannot cover the novel properties of all kinds of nanomaterials. Therefore, without standard regulatory guidance, it is difficult to draw conclusions on the toxicological properties of nanomedicine. Furthermore, researchers, manufacturers, policymakers, and the public will not be able to use nanoproducts with clarity and legal certainty without solid guidance [79]. However, on the other hand, the opponents of new regulations hold an opinion that if the other emerging technologies (such as gene therapy) works well with the existing legal frameworks, nanotechnology should not be an exception [81]. In addition, the current assessment of small molecule drugs or biologics might be sufficient for nanomedicine considering that different therapeutics have a large number of different biological effects, and the nano-dimension itself does not pose a safety risk [35]. Nevertheless, despite the controversies, the need for the identification of proper assays for nanosafety assessment is acknowledged by both sides.

14.5 Conclusion

In this chapter, we give a brief discussion on the unique properties, mechanisms, and regulation development that are related to the safety profile of biomedical nanomaterials. In terms of nanosafety, the first and foremost factor that needs to be taken into consideration is the special characteristics of nanomaterials. A thorough investigation into the distinguishable physiochemical properties of nanoparticles is necessary, as they play an essential part in determining their toxicological results. Next, understanding the in vivo fate of nanomaterials, which involves the uptake, trafficking, pharmacokinetics, and clearance, can help us design safety nanomedicine to avoid undesired toxic effects. Lastly, reliable regulatory guidance can also support the proper production and use of biomedical nanomaterials without sacrificing potential social, financial and clinical benefits.

However, when it comes to regulatory guidance for nanomedicine, one simple but fundamental challenge faced at this point is the lack of consistent terminology and categorization [70]. For instance, nanomedicine can be regarded as a medicine or a medical device in different countries [79]. Consequently, specific safety standards will differ accordingly and a certain nanomedicine may be able to be used in some countries while being regulatory prohibited in another country. In addition, as pointed out previously, a systematic characterization, quality and safety testing of nanomaterials that helps to understand the physiochemical features and how

they can influence the therapeutic efficacy and product safety is important for nanomaterials in biomedical application. However, due to the lack of standards, the tests also vary significantly. Take the testing model as an example. Currently, the commonly used toxicity tests are performed on in vitro and in vivo models. In vitro experiment typically refers to cell cultures, including 2d models such as inverted cell culture and 3d models such as spheroid microtissues, organoid, or organ-on-a-chip, while in vivo models mostly indicate aquatic (e.g., zebrafish) or mammal (e.g., rabbit or rodent) animals [82]. In nanosafety research, different lab employs different models, of which the results will not be comparable. Even using the same cell line, different culture or experiment protocols can result in changes in cytotoxicity [11]. Therefore, sometimes even within one research, different protocols may lead to different outcomes. For instance, nanoparticle uptake and cytotoxicity results may not be comparable in the same cell line if cells are prepared via different protocols. This further causes concerns on the validity of toxicity testing results of nanomaterials based on different protocols and labs. Until now, there are no specific standards for the analytical methods used in nanoparticle toxicity testing. What is more, when contemplating the impact of nanomedicine, another factor that should be taken into consideration is their potential environmental effects [83, 84]. It may occur during production, after use, or upon disposal. Although environmental pollution risk derived from nanomedicine may not be a concern as big as human health risk (as nanomedicine might go through transformation in the environment to lessen its hazardousness) [85], the lack of investigation on this point leaves a significant gap with regard to ecosystem safety data and environmental regulations [83]. The accumulation of nanomaterials in the environment could result from nanowaste [86]. After all, the central ethical issue in terms of nanotechnology research relates to the protection of human health as well as the environment [87].

Nowadays, an ethical issue regarding the toxicity assessment of nanomedicine is raising more and more attention. In traditional toxicology studies, animal testing of nanomaterials is usually needed. However, it does not seem justifiable to test every nanomaterial in animals, from a practical, economical, or ethical perspective [88]. On the other hand, in vitro screening, such as in silico assay, that utilizes computational tools and biostatistical methods for the evaluation and prediction of toxicity seems to be a promisingly alternative approach [89]. The application of such methods can not only avoid ethical conflicts but also realize fast and cost-effective toxicity screening. It is anticipated that such reliable and powerful methods may be extensively used in future nanomedicine toxicology testing studies [34].

In short, the field of nanosafety study is equally important to the development of novel biomedical nanomaterials for health care. At this point, the collaboration of scientific researchers, doctors, pharmacists, manufacturers, and policymakers is called for safer use and regulation of biomedical nanomaterials. Given the prospect of nanomedicine in clinical use seemed remote only a couple of years ago [90], the safe use of biomedical nanomaterials may become reality sooner than expected.

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Marcel Van de Voorde and Gunjan Jeswani

Conclusion

> The use of scientific knowledge needs the guiding light of ethical wisdom. Such is the wisdom that inspired the Hippocratic Oath, the 1948 Universal Declaration of Human Rights, the Geneva Convention, and other laudable international codes of conduct. Hence religious and ethical wisdom, by answering questions of meaning and value, play a central role in professional formation. And consequently, those universities where the quest for truth goes hand in hand with the search for what is good and noble, offer an indispensable service to society.[1]
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> *Pope Benedict XVI, Blessing of the cornerstone of Madaba University of the Latin Patriarchate, in Jordan, May 9, 2009*

Nanotechnology is clearly a breakthrough technology because it unleashes power to manipulate matter on nanoscale, tailoring it to individual and societal needs. Indeed, current nanotechnology research is aimed at the development, analysis, and application of a wide variety of incredible nanostructures such as buckminsterfullerene, nanotubes, nanoparticles, molecular motors, a range of biomolecules, quantum dots and quantum wires, nanocapsules, nanopores, and self-assembling nanorobots. Such applications promise to improve the standard of living, health care, and nutrition for people worldwide. Nanotechnology also promises to minimize or perhaps eliminate pollution, mitigate existing ecological imbalance, and eradicate various diseases by offering protection against harmful bacteria and viruses, including the dreadful plague of Covid-19. In the future, nanotechnology is expected to bring effective innovations to enhance health care and in critical resources: water and energy supply, agriculture, and industrial engineering.

At present, both excitement and apprehension surround nanoscale technologies. Uncertainty about nanotechnology's possible adverse effects on human health and the environment cannot be overlooked at present. Many experts fear that the power of knowledge provided by nanotechnologies, most often combined with artificial intelligence and localization techniques, might disproportionately benefit private companies rather than the general public of individuals in society at the cost of important privacy concerns. Optimists believe that to solve the problem of war and terrorism and foster peace, nanotechnology is urgently needed. Pessimists fear that nanotechnology will be used for unethical purposes, such as creating weapons of mass destruction

1 On the Vatican official website : http://www.vatican.va/content/benedict-xvi/en/speeches/2009/may/documents/hf_ben-xvi_spe_20090509_pietra-madaba.html

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that are used to start wars in times of peace. Uncertainty surrounds many threats and risks posed by nanotechnology. There is a great debate regarding the methodological challenge to risk management. Without input from informed stakeholders, it is impossible to determine the appropriate benchmarks that will detect, predict, control risks, or choose which trade-offs are made for the good of civil society and human civilization.

Balanced and inclusive development of nanotechnology requires international interdisciplinarity and international cooperation to coordinate training, research, and technology transfer between different regions and countries and also fill the gap between developed and developing countries. Given the extraordinary economic and social potential of nanotechnology, attempting to stifle scientific and technological developments in nanotechnology would be immoral, but developing this enormous potential without integrated ethical conduct would be equally immoral. Therefore, the development of this disruptive technology requires forethought. Facing numerous promises and fear, it is important to decide the direction of development, its extent, and methodology, in tune with ethical reflection. Nanoethics cannot lag behind nanotechnology.

Therefore, this book on "Nanoethics" provides a vital forum for informed discussion on ethical, legal, psychological, economic, cultural, and social concerns related to nanotechnology. Some major points to ponder include: Should not the orientation of research and development projects be geared towards the public good since the massive amounts of funds are contributed by the public? Is it not the aim of nanotechnology to improve the well-being of the society? In different chapters, solutions are given to the queries, and at the same time, important questions are asked; for example: What are the numerous stakeholders searching for? Immediate financial profit? Personal development and a contribution to science through nanoscale discovery and new engineered applications? Do they have the common good as their primary goal? And if so, what are their working assumptions about the common good? Are these assumptions focused on the benefits for all or a few? Do they minimize dangers for the present generation and consider future generations? And, notably, have they considered these questions?

In this book, attempts have been made to find solutions to some of the most pressing queries while raising questions that require further examination:

1. Who will be benefited from advances in nanotechnology, and at what cost?
2. Who will take the responsibility for the potential adverse effects of these devices and systems that are invisible to the human eye?
3. How does international competition affect the development of nanotechnology? How will world powers introduce and regulate nanotechnology applications?
4. Is the public aware of the potential and associated risks of nanotechnology? How can the developments of nanotechnology be made more transparent to the public?

The present situation calls for shared and widespread recognition of nanotechnological innovations that may come with possible risks. Therefore, it is utmost important to identify and assess the risks regarding their acceptability in light of gains.

The following key conclusions are drawn from the topics discussed in the various chapters in the book. Nanoethics offers a rigorous study of philosophical, scientific, ethical, social issues, and political problems. It allocates responsibility and enables funding conditions that impact the ability of decision-makers to pause and include ethics in their plans for nanotechnology research, in light of the social problems. It also gives ethics its rightful place in nanotechnology.

Nanotechnology obviously, enhances other technologies; for example, computer and material sciences. Therefore, in rigorous discussion of social and ethical issues, scientists and researchers from those disciplines as well as from nanotechnology must be involved. This critical issue requires an interdisciplinary perspective. Hence, nanoscientists, engineers, ethicists, and, more generally, philosophers, social scientists, psychologists, economists, science communicators, ecologists, agriculturalists, and health workers must be brought together, depending on the particular problem being explored. Therefore, public and private funding organizations must take serious account of the ethical reflections put forward in various aspects of this book. Academic and corporate training must contribute to this as an integral part of a humanistic education that cultivates all human dimensions, arouses curiosity, and awakens a sense of individual and communal responsibility.

Solving current ethical problems will hopefully incentivize ongoing interdisciplinary discussions that will include stakeholders reflecting a multidirectional nanoscene Ethical debate must continue until questions regarding the potential, capacity, and controllability of nanotechnology coexist.

The development of nanotechnology is in a phase where it is still possible to choose the road to more inclusive applications and balance the power of different social groups. Nanotechnology is a vehicle for applying or discarding the traditional paradigm. It is expected that this comprehensive resource can function as the first step toward inclusive debate that will equitably benefit all stakeholders. The readers are provided with solutions and recommendations suggested by eminent scientists and philosophers working on nanotechnology and its implications. Let us give the last word to one of the most courageous minds of our time Andrei Sakharov, as Mrs. von der Leyen said at the beginning of her European Union speech:

He always spoke of his unshakeable faith in the hidden power of the human spirit.

May this strength, found within the hidden power of material at the nanoscale, make nanotechnology the lever for a future commensurate with the highest of human aspirations, and may ongoing ethical reflection be our moral compass as we traverse uncharted nanoethics using this book as our roadmap.

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