A Handbook of Environmental Toxicology

Human Disorders and Ecotoxicology

Edited by **J. P. F. D'Mello**

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Edited by

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Preface

History

It will surprise many to learn that global environmental pollution can be traced back to Roman times, with respect to lead emissions following gold extraction processes (Hillman *et al.*, 2017). However, the emergence of environmental toxicology as a formal discipline in its own right occurred much later as a direct result of major pollution and contamination episodes around the world, including, for example, deployment of two atomic weapons, accidents at nuclear power stations, oil spills and vehicular emissions (see Table 1). Consistent with this development, the traditional approach based on lethality and chronic tests has been replaced in this volume, in favour of a more practical, relevant and contemporary presentation of toxicology.

Major Contamination Incidents

A significant number of contamination events has occurred since 1945 and these are recorded for the benefit of readers who are new to the field of environmental toxicology. Details of some of these cases are included in the text of this volume to illustrate specific issues. Table 1 is not designed to be comprehensive but, rather, illustrative of the diverse nature of pollutants deliberately or accidentally released into the environment and the regular incidence of crude oil and radiological contamination. This list is arranged in chronological order to highlight the regular frequency of such events.

Two sets of events deserve special mention, due to profound long-term human health and ecological implications. The devastation caused by the detonation of two atomic devices at Hiroshima and Nagasaki (Fig. 1) will always represent an ignominious phase in human history. However, whereas the infrastructure has now been restored in both cities, the toxic legacy for survivors remains to this day, arguably the most cogent expression of 'Man's inhumanity to man'. For example, the incidence and analysis of myelodysplastic syndromes afflicting these subjects have been investigated in recent toxicological research (Horai *et al.*, 2018). In addition, accidents and regular radiation leaks from nuclear power stations present continuing worldwide risks (Table 1).

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Table 1. Major environmental contamination incidents in recent history.

Year/frequency	Incident	Principal contaminants
1945	Detonation of two nuclear weapons over Hiroshima and Nagasaki (Japan)	Radionuclides
1952	The Great Smog (London)	Particulates and gaseous mixture (Chapters 5–8, 40)
1956	Minamata disease outbreak (Japan)	Methylmercury (Chapter 24)
1961–1971	Vietnam War	Agent Orange containing a mixture of two herbicides and traces of dioxin (Chapter 13)
1965	San Jacinto river contamination (USA)	PCDD and PCDFs
1967	*Torrey Canyon* oil spill (UK)	Crude oil (Chapter 40)
1976	Seveso chemical plant explosion (Italy)	TCDD release (Chapters 12 and 13)
1978	*Amoco Cadiz* oil spill (France)	Crude oil
1979	Three Mile Island accident (USA)	Radionuclides
1979	Ixtoc oil well explosion (Mexico)	Crude oil
1979–1985	Gold-mining pollution (Brazil)	Mercury
1983	*Castillo de Bellver* oil spill (South Africa)	Crude oil
1984	Bhopal disaster (India)	Methyl isocyanate
1986	Chernobyl explosion (Ukraine)	Radionuclides
1988	*Piper Alpha* offshore oil and gas explosion (UK)	Crude oil
1988	*Odyssey* oil spill (Canada)	Crude oil
1989	*Exxon Valdez* oil spill (Alaska)	Crude oil (Chapter 22)
1997–2004	Endemic neurolathyrism (Ethiopia)	Dietary exposure to lathyrogenic amino acids (Chapter 2)
2002	*Prestige* oil spill (Spain)	Crude oil
2004	Acute aflatoxicosis (Kenya)	Dietary intake of aflatoxins (Chapter 2)
2010	*Deepwater Horizon* accident (Gulf of Mexico)	Crude oil (Chapters 20 and 21)
2011	Fukushima nuclear accident (Japan)	Radionuclides (Chapter 34)
2014	Flint water contamination (USA)	Lead (Chapter 25)
2015	'Defeat software' fitted to certain vehicles to falsify results in emissions tests (USA)	Carbon dioxide and nitrogen dioxide (Chapters 7 and 40)
2017	Wastewater release from shale oil and gas exploration (fracking) (USA)	Diverse 'toxic chemical substances' (Chapter 23)
Regular	Vehicular emissions	Nitrogen dioxide and particulates (Chapters 7, 28 and 29)
Regular	Lake Erie hypoxia (North America)	Fertilizer pollution
Regular	Arable farming, worldwide	Pesticides (Chapters 16–19)
Regular	Radiation leaks from nuclear plants and storage: based on local reports on both sides of the Atlantic	Radionuclides (Chapter 34)

In the case of crude oil pollution, the *Deepwater Horizon* debacle (Fig. 2) is destined to symbolize an iconic image of ecological catastrophe for future generations of environmentalists. The risks remain, driven by the unremitting demand for fuel on an industrial scale. Thus, emissions of noxious gases and particulates from vehicles are regularly linked with a diverse range of human health disorders. The recent headline that London breached annual air pollution limits for 2017 in just 5 days gives immense cause for concern, but does anybody care?

It is within the context of these events that I present a new volume on environmental toxicology, based on fundamentals and relevance to specific case-studies, both historical and contemporary.

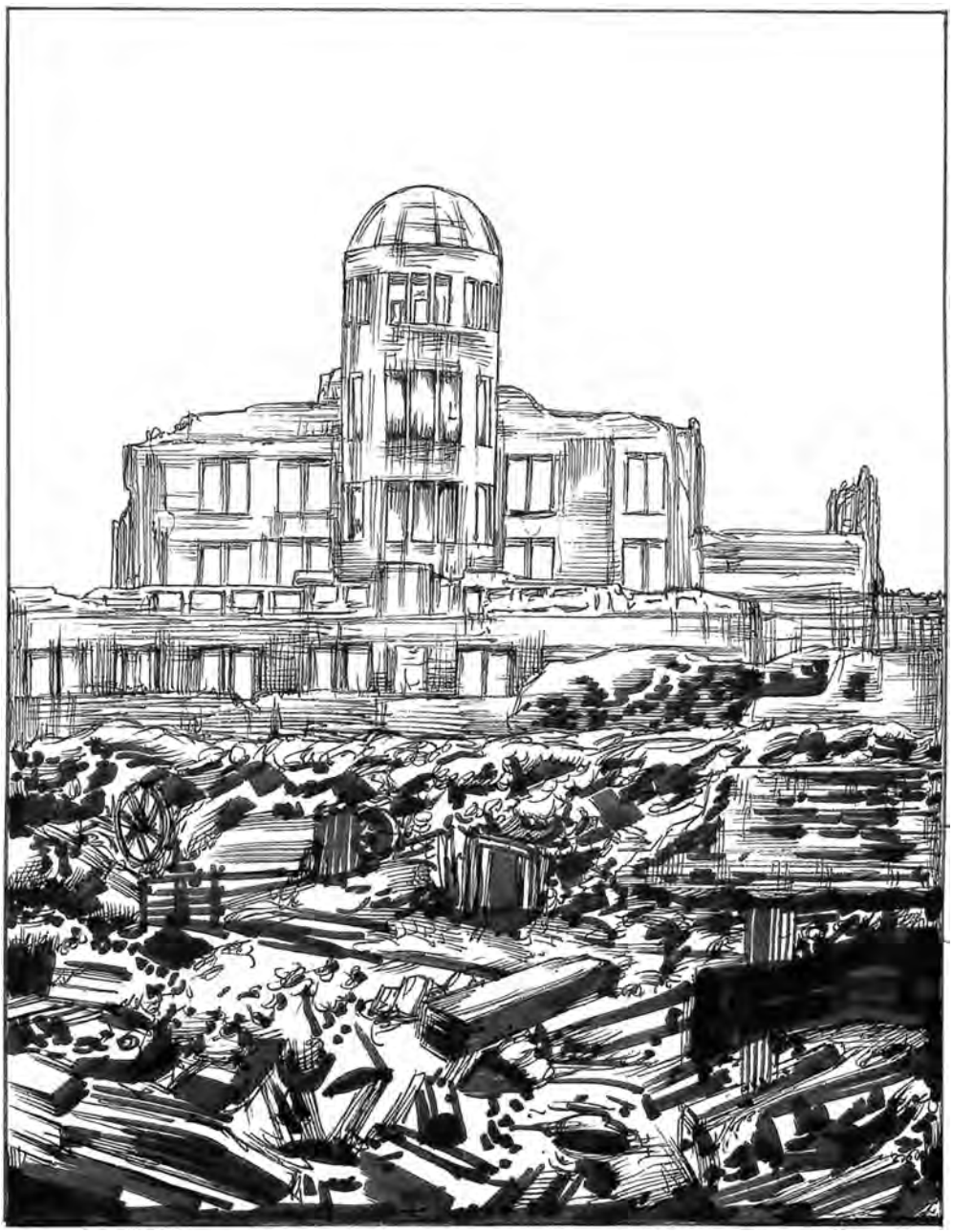

Fig. 1. Toxic legacy I. Radionuclide contamination following the disproportionate and reckless detonation of two atomic weapons at Hiroshima and Nagasaki (an artist's composite interpretation; courtesy of Mr T.F. D'Mello). Although the infrastructure has now been restored, the toxic effects for survivors remains to this day (Horai *et al*., 2018). Furthermore, accidents and regular radiation leaks from nuclear power stations and storage facilities present continuing risks worldwide (Table 1).

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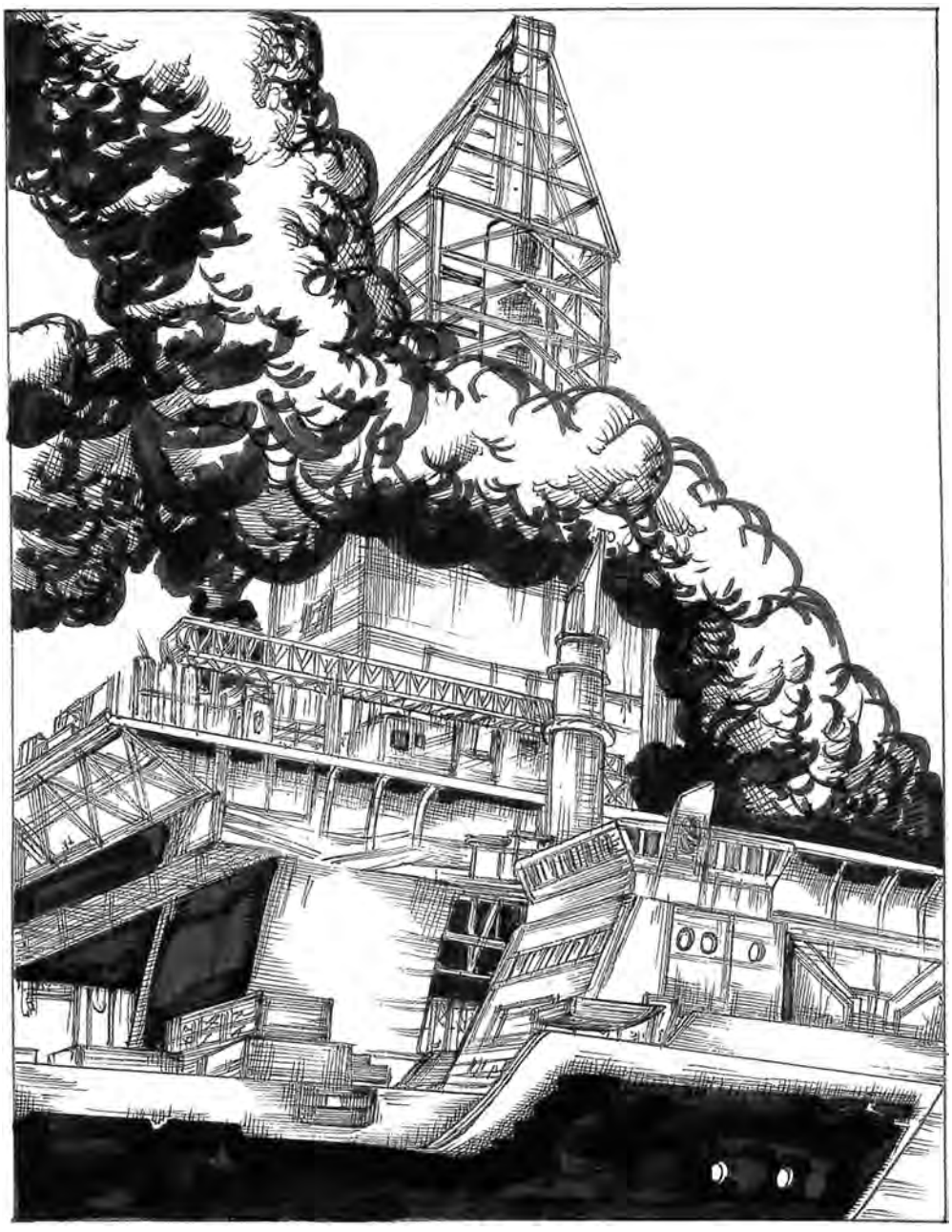

Fig. 2. Toxic legacy II. The *Deepwater Horizon* oil spill in the Gulf of Mexico (an artist's portrayal designed to reflect also the preceding *Piper Alpha* accident in North Sea; courtesy of Mr T.F. D'Mello). These events are destined to serve as an iconic beacon of ecotoxicity, resonating long into the future. Crude oil pollution is likely to continue, driven by regular accidents and consumer demand for fuel in transport, power generation and other activities. Nevertheless, it should be recognized that offshore oil and gas platforms in waters of between 25 and 30 m may provide niches for colonization by corals (Kolian *et al*., 2017).

A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology

Background

The concept for a new edition of this volume emerged during my tenure as Academic Director of a first-degree course in 'Environmental Protection and Management' (EP&M) validated by the University of Edinburgh and delivered to undergraduates at the Scottish Agricultural College. In particular, my role as coordinator of a third-year EP&M module in Environmental Chemistry, including a series of lectures on 'Environmental Toxicology', crystallized in my mind the need for an up-to-date advanced text on this subject. Further impetus was provided through my research interests in the toxicology of natural compounds associated with the secondary metabolism of plants and fungi. In addition, my experience in the provision of consultancy services in mycotoxin contamination of primary foods and animal feeding-stuffs allowed me to develop practical credentials in a relevant branch of environmental toxicology. Subsequent to my retirement, the EP&M course was replaced by a postgraduate degree within the Masters programme.

Context

Following recent declarations in Europe and North America, it has become patently clear that our elected leaders are unreliable custodians of the environment. The assertion in the USA that global climate change is an irrelevance compared with the regeneration of the 'rust belt' is evidence of a short-sighted attitude. Somewhere in the arguments currently being promulgated is the notion that the global warming issue is a myth invented by third-world agencies to present manufacturing in advanced economies as less competitive. Furthermore, the edict of protectionism in economic matters is gathering momentum on both sides of the Atlantic, with the likely effect that international cooperation on pollution research and adherence to the Paris Climate Agreement will be severely compromised. Insular policies will not only serve to exacerbate environmental disparities for communities in vulnerable regions but also jeopardize human health and biodiversity in affluent countries.

Against this backdrop of confused thinking, there is now an opportunity for environmental toxicologists to demonstrate leadership and it is envisaged that publication of this volume will contribute to an active debate on all aspects of human health and ecological conservation. The initial signs are encouraging. For example, the work of Landrigan (2017) linking air pollution with human morbidity has attracted wide attention in the media, due to the bold expression of current and projected data. *The Lancet* has also been at the forefront of this activity by highlighting key public health disorders associated with environmental pollution (see, for example, Samet *et al.*, 2013; Shah *et al.*, 2013; Beelen *et al.*, 2014; Guarnieri and Balmes, 2014; and Landrigan, 2017).

Faltering Progress

The history of environmental protection and management is marked by significant developments in risk assessment across a wide spectrum of pollutants, but the translation of results into policies of statutory regulation, interventions and compliance has been ponderous at best. Many observers would argue that intransigence and inaction have been the hallmarks of recent efforts to address global issues in the pollution–human-welfare–ecology axis. Thus, despite the occurrence of the Great Smog of 1952, limited steps have only recently been implemented to control traffic pollution in London. The legacy of persistent organic pollutants (POPs) is still with us notwithstanding all the advances in toxicological research and definitive evidence of human morbidity associated with dioxins, polychlorinated biphenyls (PCBs) and certain pesticides. For example, there are concerns over the pesticides Fipronil and pyrethroids in eggs while other surveillance has revealed the occurrence of neonicotinoids in global honey supplies. It is also disturbing that 60 years after identification of Minamata disease in Japan, steps are only now being undertaken to curb mercury contamination on

a worldwide basis. For example, a report by Taylor and Williamson (2017) demonstrated an ongoing issue of mercury contamination in US coastal fisheries.

Approach

In designing this *Handbook*, I have commissioned a team of experts from around the world to submit critical reviews highlighting the effects of diverse pollutants on human morbidity and on ecotoxicology. However, in addition to chapters presented in conventional format, I invited a few authors to submit short 'research communication'-style papers to demonstrate to advanced students the specialist aspects of current work. Environmental toxicology is increasingly perceived as a scientific evidence-based discipline. It is all too easy to dismiss evidence linking environmental contaminants to ill-health in humans and habitat degradation as merely statistical inference lacking biochemical basis. However, several authors contributing to this *Handbook* are at pains to point to biologically plausible mechanisms underlying the said adverse effects. Furthermore, these authors have published detailed evidence in refereed papers in respected journals such as *The Lancet*, *European Respiratory Journal*, *Environmental Health Perspectives*, *Toxicological Research*, *Marine and Freshwater Research*, *Marine Pollution Bulletin* and many others.

Overview and Design

A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology is published specifically to promote debate and research in academic and corporate institutions in Europe, the USA, Canada, Japan, Australia and New Zealand but generally in all countries where the English language is a primary medium of communication. This *Handbook* should appeal to a wide readership, including advanced undergraduate and graduate students in addition to teaching and research staff in colleges, universities and state-funded institutes. *A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology* is recommended for courses in environmental protection and management, ecology, toxicology and the biological and medical sciences. A major objective is to encourage the incorporation of environmental toxicology into existing Masters programmes provided at UK and US universities to enhance the scientific base of advanced degrees. This volume should also be of interest to scientists and managers in the commercial sector, for example oil and energy companies. Furthermore, it is important, through this *Handbook*, to engage with local authorities, particularly with respect to rural and urban pollution, recycling measures and remediation technologies.

The chapters in this volume are arranged in nine sections, each representing a particular theme and representing diversity of biogenic compounds and pollutants impinging on human health and ecotoxicity. The nature of the subjects under review and the need for continuity necessarily involves a certain degree of overlap. This is not envisaged as a detraction, as individual chapters are self-contained as a consequence, thereby reducing the need for cross-referencing to other parts of the book. More importantly, this approach has also allowed authors increased flexibility in terms of emphasis and interpretation.

PART I BIOGENIC COMPOUNDS. Three chapters herein highlight important secondary metabolites, including phytotoxins, mycotoxins and cyanobacterial toxins synthesized by plants and microbes. Consideration of these compounds is justified, because their occurrence may be affected by environmental factors, for example global climate change, or the potential for the production of biopesticides to replace existing harmful synthetic insecticides, fungicides and herbicides. The toxicology of biogenic compounds is characterized by diverse and profound effects in humans and other vertebrates following intake via contaminated food and water or exposure in damp dwellings characterized by the 'sick building syndrome'. Both acute and chronic effects are exemplified in epidemiological reports of poisonings caused by biogenic metabolites. Plants and microbes may also exert physical effects affecting, for example, habitat selection by vectors (Binckley, 2017) or efficacy of oceans to extract carbon from the atmosphere (Kondrik *et al.*, 2018). Such issues are

outside the scope of this volume but should contribute to the general model of biological–environmental interactions.

PART II AMBIENT GASES AFFECTING HUMAN HEALTH AND ADAPTATION IN HIGHER PLANTS. Recent research has confirmed the detrimental health hazards associated with ambient air pollution. The effects of ozone, nitrogen dioxide, sulfur dioxide, polyaromatic hydrocarbons and particulates are under regular scrutiny not only for individual contributions to human morbidity but also with respect to interactions within this group. Specific conditions currently under investigation include exacerbation of idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease (CVD), metabolic syndromes (particularly childhood obesity), type 2 diabetes and diverse forms of cancer. The cognitive and neurological effects of air pollutants are an additional source of concern and *in utero* exposure may be a contributory feature in certain cases, such as the incidence of autism. Interactions between certain gaseous pollutants and other ambient air contaminants, for example particulates, inevitably add to the difficulties in interpretation of emerging data for these conditions. Although much of the evidence is based on epidemiological approaches, several research scientists consistently point to biologically plausible mechanisms underlying morbidity caused by gaseous pollutants. The diverse effects of acid rain on adaptation mechanisms in higher plants are relevant here, since the main contributors to this type of precipitation include sulfur dioxide and nitrogen oxides. The toxic effects in plants include adaptations in morphology, photosynthesis, nutrient uptake and oxidative status.

PART III PERSISTENT ORGANIC POLLUTANTS (POPS). This diverse group is of immense significance due to low environmental degradability of POPs, presenting long-term risks for human health and biodiversity in the major ecosystems. The anthropogenic derivation of these compounds, including PCBs, dioxins and endocrine disruptors, only adds to current disquiet over their distribution in different matrices such as food, water and sediments. Issues of particular concern with POPs in relation to human morbidity include the consequences of maternal exposure, transgenerational effects, endocrine disruption and relationship to carcinogenesis. Also under consideration is the possible link to asthma and diabetes. Furthermore, the biochemical mechanisms underlying the adverse effects of POPs remain complex issues despite advances in activation of receptors, signalling pathways and gene expression. The influence of trophic ecology on bioaccumulation of POPs in different wildlife species is under active investigation. Attempts are also under way to develop novel technologies for remediation employing microbial degradation.

Pollution in the rural environment remains an intractable problem due to multiple sources of contaminants, causing adverse human health and ecological effects. Of particular concern are pesticides and nutrient pollution with global implications for food safety and water quality. There are currently concerns over the pesticides Fipronil and pyrethroids in eggs and neonicotinoids in global honey supplies, but the issues of pesticide contamination of foods in general continue to be a matter of concern for a wide range of foods. In addition, the toxicology of organochlorine and organophosphate compounds continues to attract attention, justifying the inclusion of three chapters in this volume. Emerging issues relate to the effects of prenatal and early-life exposures in the development and exacerbation of morbidity. Current studies are designed to elucidate effects on the aetiology of asthma, neurodegenerative disorders and specific forms of cancer. Methodological considerations are also presented in this section of the *Handbook*. Furthermore, there is, at present, an active debate on the use of a major herbicide, glyphosate.

PART IV PETROLEUM POLLUTION. Crude oil pollution has, unfortunately, become a regular occurrence in recent times, arising from accidental discharges into the sea. The *Torrey Canyon* oil spill of 1967 arguably remains the worst marine contamination incident in UK history. Images of the *Exxon Valdez* oil spill in 1989 in Prince William Sound, Alaska, will readily be recalled by many readers of this volume. However, implications of the 2010 *Deepwater Horizon* oil spill in the Gulf of Mexico will reverberate in regulatory, legal and ecological circles for many years to come, and rightly so. The

effects of crude oil contamination on microbial and animal ecology are now emerging, although it is already apparent, from first principles, that detoxification pathways are limited in vertebrate species. Nevertheless, observations 24 years after the *Exxon Valdez* oil spill indicate that recovery is possible in the long term but remains somewhat patchy. Using biomarker evidence, efforts to establish timelines for different animal species exposed to crude oil contaminants are being undertaken.

With the emergence of novel exploration technologies in oil extraction such as hydraulic fracturing (fracking) come additional risks for human welfare, wildlife and associated habitats. Top predators may be exposed to or bioaccumulate via their macroinvertebrate food the chemical contaminants released into the ecosphere by fracking. Key areas of research and monitoring now need to be addressed to assist in the formulation of effective guidelines and policies to protect local communities and vulnerable animal species at fracking sites.

PART V TOXICOLOGY OF HEAVY METALS. Of all heavy metals, mercury pollution and toxicity continue to attract attention, due to widespread contamination associated with mining, burning of fossil fuels, deforestation and accidental discharges. Instances of mercury pollution have been reported in Brazil, China and parts of Africa. However, it is now generally accepted that mercury contamination is a global issue, even extending to US coastal fisheries. It is of concern that, 60 years after identification of the Minamata poisoning incident in Japan, steps are only now being undertaken to curb mercury contamination on a worldwide basis. The long-term neurological and behavioural effects of mercury toxicity as a result of prenatal and postnatal exposure are worth reviewing. Lead is also associated with neuropsychological and functional decline in humans, as indicated by a variety of manifestations including difficulties in intelligence, memory, attention and mood. The relationship between lead and autistic behaviours in children has been investigated, leading to recommendations to further reduce such exposure. The effects of lead during the early stages of brain development remain a primary area of research with neural stem cells in gene expression studies. Cadmium has been linked with toxic effects in plants and animals. Oxidative stress may be an underlying feature in chronic cadmium-induced hepatotoxicity and nephrotoxicity, while other research highlights the role of glutathione as a first line of defence against cadmium toxicity. Exposure and human health effects of cadmium are reviewed in this volume, but there is scope also to explore cardiovascular effects in a separate chapter.

PART VI PARTICULATES AND PLASTICS. Particulates from fire incidents and combustion of diesel in vehicles are emerging as major pollutants worldwide. Although particulates are associated with long-term morbidity in humans, interactions with gaseous pollutants and other ambient air contaminants add to the difficulties in interpretation of published data for these conditions. An attempt will be made in a subsequent chapter to summarize these interactions. In addition, assessment of the ecotoxicity of airborne particulate matter remains largely unexplored.

Marine litter comprising discarded plastic packaging constitutes a significant problem, as highlighted in the media. However, there are scientific issues in addition to wildlife ingestion and entanglement. For example, there is increasing evidence that plastics may act as ligands for a variety of chemical compounds, thereby contributing to persistence of pollutants in the marine environment. It is too early to evaluate the long-term ecotoxicity of these adsorption phenomena.

PART VII RADIATION RISKS. The incidence of non-melanoma skin cancer in white populations is increasing in many countries. Exposure to UV radiation is believed to be the underlying cause, though the pattern of exposure that promotes the different types of malignancy varies. Controversially, exponentially increasing incidence of cutaneous malignant melanoma in Europe correlates with low personal annual UV doses. It is suggested that intermittent UV exposures result in low cutaneous levels of vitamin D_3 and viral infections may possibly predispose to this incidence. Regarding radon, residential exposure is definitively linked with lung cancer incidence. For example, there are indications that high concentrations of radon progeny induce lung cancer in both underground miners and experimentally exposed laboratory animals, suggesting that ambient radon represents

an important health risk. The direction of current research is now focusing on possible links to leukaemia and interactions with ambient particulates. Recent assessments of the 30-year legacy of the Chernobyl nuclear accident indicate increased long-term risks of leukaemia and CVD among clean-up personnel as well as thyroid cancer in subjects exposed to radiation as children and adolescents. In addition, mental health effects appear to be the most significant public health issues in the heavily contaminated regions of Ukraine, Belarus and the Russian Federation. As might be anticipated, radioactive emissions following the Chernobyl nuclear accident continue to induce wildlife abnormalities. However, 30 years after the accident, there is still a lack of data relating to the genetic effects of radionuclide contamination on plant ecology. The human health and ecological impacts of the Fukushima nuclear accident are considered in this *Handbook*, supplementing evidence from the Chernobyl emissions.

PART VIII REMEDIATION. Diverse technologies are potentially available for environmental remediation of contaminated land and groundwater. Particular emphasis is currently being placed on the development of nanomaterials for removal of pollutants and biological contaminants. Nanomaterials are considered to be superior to other systems because of their higher surface-to-volume ratios. There is also interest in exploiting polymer-supported titanium dioxide photocatalysts for environmental remediation. Other methodologies include: the application of natural zeolites, by virtue of their ion-exchange properties in the separation, binding and chemical stabilization of hazardous substances; biochar; and iron-based applications in contaminated land and groundwater remediation. Of particular relevance also is the exploitation of plants for the removal of organics and other contaminants. Three chapters are included in this *Handbook* to exemplify the wide scope and likely constraints of new technologies currently available.

PART IX OUTLOOK AND CONCLUSIONS. The development and implementation of environmental regulations are under constant scrutiny, despite success in a number of high-profile cases. A potential concern relates to the impact of these regulations on industrial competitiveness, affecting international trade, employment, plant location and productivity, particularly in pollution-inducing and energy-intensive sectors. However, it is conceivable that environmental regulations may stimulate investment and innovation in clean technologies. It is also difficult to assess the relative stringency of international regulations, with the promotion, in some states, of lower standards in order to attract commercial investment. A case in point relates to a member of the World Trade Organization (WTO) who argued that the maximum residue limits (MRLs) for certain pesticides in food commodities were more stringent than the standards recommended by the *Codex Alimentarius* and were more trade-restrictive than necessary.

In addition, there are ongoing questions regarding auditing and compliance. It is maintained by some commentators that auditors' responsibilities in the context of detection and reporting of contraventions in environmental regulations are limited. Nevertheless, vigilance on the part of the regulatory agencies has reaped limited dividends for environmental protection. For example, the discharge of untreated sewage into the river Thames over several months by a major UK utility company has been labelled as an 'environmental disaster', deservedly attracting severe penalties. In 2016, a cruise-line operator incurred a substantial fine after illegally discharging oil and associated waste via a 'magic pipe' off the UK coast. The success of vigilance and surveillance is, arguably, best exemplified by the US Environmental Agency (EPA) findings that a number of German-manufactured cars were fitted with 'defeat software' designed to falsify emissions in performance tests.

The efficacy of regulatory agencies will depend upon the development of new methodologies to keep ahead of those who would seek to contravene environmental directives. A forward-looking chapter is, therefore, included to review future procedures for environmental toxicology and monitoring.

The aims in the concluding chapter are to collate and integrate the considerable advances linking pollution with human morbidity and ecological deterioration. This chapter is deliberately presented to appeal to a general audience in order to ensure wide dissemination of the central issues

emerging from recent research in environmental toxicology. Accordingly, the use of jargon has been minimized. There is a risk that a number of key findings may be 'lost in translation' due to lack of clarity in presentation. It is imperative that significant environmental health and ecological implications are perceived as action points for individuals as much as for corporate organizations and regulatory institutions at international and local levels. The evidence reviewed in this chapter relies on data obtained in epidemiological investigations, case studies linked to specific contamination incidents and fundamental experimentation designed to discern the underlying mechanisms of action of pollutants. It is worth considering whether, in the absence of political leadership, research scientists should exert a more forthright role in all matters relating to environmental protection.

Disclosure

It is self-evident that disclosure should be a central element in environmental protection policy. However, internet sources claim that communities on both sides of the Atlantic are unaware of radioactive contamination at nuclear power stations and naval bases. Phrases such as 'kept in the dark' and 'cover-up' are regularly associated with reports of such incidents. One Press article referred to 'dangerous radiation leaks from three-quarters of US nuclear power plants'. Furthermore, according to Tkavc *et al.* (2018), highly contaminated radionuclide waste stored in a strongly acidic medium mixed with heavy metals at US Department of Energy sites has been leaking since the 1950s. The response of the authorities is that such occurrences represent a public relations problem rather than a genuine health hazard. Others with intuitive scepticism might well disagree and insist on an independent environmental audit. This is essential as nuclear power is increasingly portrayed as a clean-energy source.

Expectations

With sustained funding and with participation of dedicated scientists, the discipline of environmental toxicology should evolve into a more exact science, underpinned by advances in medical research and quantitative methodologies, in place of anecdotal and qualitative risk assessments. Authors contributing to this edition are at the forefront of current developments to remove ambiguity, improve current models of analysis and elucidate biochemical mechanisms underlying epidemiological observations. Consequently, by reducing speculative theories and including more substantive evidence, future statements should become less tentative, leading to clarity in communication, improved regulatory measures and effective interventions. Going forward, however, I expect steady progress on environmental toxicology, akin to that in establishing the relationships between cigarette smoking and lung cancer/CVD or alcohol abuse and liver cirrhosis. Whatever the difficulties, we should not abandon our resolve but adopt an evangelical fervour in communication of research findings. In pursuing our objectives, it is salutary to recall the exhortation given by St Paul: 'The revelation of a mystery kept secret for endless ages, but now so clear that it must be broadcast' (*Romans* 16:25–27).

Acknowledgements

The publication of this edition of *A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology* is only possible by virtue of the expertise and cooperation of my international team of authors. They have an established reputation acquired by publishing original papers in peer-reviewed research journals. I am indebted to them for devoting valuable time and effort in the presentation of authoritative and comprehensive chapters in a readable format. I am convinced that their work will inspire students and staff alike for many years to come. In deference to their expertise, I decided that authors should be given freedom of expression in the preparation of individual chapters, while recognizing that the scientific terminology becomes increasingly more complex with successive advances in research in the various disciplines embodied in environmental toxicology.

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Disclaimer

A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology necessarily contains references to and descriptors of experimental protocols and commercial products. Authors were asked to refrain from excessive use of trade names unless there were compelling reasons for doing so. It is emphasized that no endorsement or criticism of these procedures and products is implied or should be attributed to the Editor or to CAB International, the publisher of this volume. We confirm our absolute impartiality in the choice of chapter titles and in the appointment of authors. Nevertheless, I should confirm my personal ownership of shares in oil and utility companies traded in the London Stock Exchange. These shares were purchased more than 15 years before my appointment as Editor of this *Handbook*.

The information set out in this volume is presented in good faith and in accordance with our understanding of the principles of 'best practice' and 'due diligence'. Although every effort has been made to verify the facts and figures, neither the Editor nor CAB International can accept responsibility for the data and conclusions presented in individual chapters or for any consequences of their use. The submission of signed contracts confers on each contributing author absolute responsibility to check all figures, facts and conclusions. All participating authors have undertaken to abide by stringent rules concerning submission of their chapters so as to avoid any 'material that might be deemed to be libellous, obscene, defamatory or improper' or incorrect. A number of products and methodologies are described by my team of authors. However, publication of this volume should not be interpreted as a recommendation for our readers to use these compounds or techniques for whatever purpose. It is particularly emphasized that data in this volume should not be used to extol or discredit the efficacy or competitiveness of any proprietary product cited or reviewed in individual chapters. The opinions expressed in this volume are exclusively those of the contributing authors, based on their data published in refereed journals, and should not be attributed to the Editor or CAB International. In selecting chapter titles, we have been guided entirely by the need to pursue diverse issues in environmental toxicology wherever it takes us, however unpalatable, but always based on robust evidence available in reputable research journals. This *Handbook*, therefore, is intended exclusively for use as a text in education and research in our collective efforts to protect and enhance human welfare and natural habitats.

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Terms and Acronyms

Introduction

Specific nomenclature and technical descriptors are now firmly embedded in the literature associated with environmental toxicology. Although many of the terms and acronyms appearing in this *Handbook* are already in the public domain, it is important to provide a comprehensive glossary to assist those readers who are new to this field. Additional definitions are available in a wide range of scientific dictionaries including, for example, the compilations of Parish *et al.* (2006), Singleton and Sainsbury (2006), Allaby (2010), Lackie (2013), Hodgson and Roe (2014) and Martin (2015). Readers will be aware that several free dictionaries are available and readily accessible online. Glossaries and other relevant information have also been provided in specialist monographs and handbooks such as those edited by D'Mello *et al.* (1991), D'Mello (1997), D'Mello (2012) and D'Mello (2015). These sources are recommended on the basis of a common vocabulary in the different disciplines of the life sciences. In addition, standard titles including works by Alberts *et al.* (2014), Lodish *et al.* (2013), Nelson and Cox (2013), Klug *et al.* (2014), Madigan *et al.* (2015) and Strelkauskas *et al.* (2016) are recommended as sources of in-depth information on different aspects of the biological sciences. Food toxicology is a recurring theme in this *Handbook* and the introduction by Shibamoto and Bjeldanes (2009) should be consulted for basic understanding of this expanding subject. Regarding epidemiology and clinical pathology, two volumes by Ward *et al.* (2016) and Carton (2017), respectively, may be relevant for the human health aspects of my *Handbook*. Fundamental principles of environmental toxicology and ecotoxicology are outlined for beginners in the works of Dong (2014) and Walker *et al.* (2012), respectively. It is assumed that readers will be conversant with general physiology, biochemistry, microbiology, pathology and molecular genetics to levels covered by these textbooks. However, the language associated with environmental toxicology is continually evolving and unremittingly complex, even to experienced researchers, but a highly effective way of updating information and relevant terminology is via the various research articles cited at the end of each chapter of this volume.

Definition of Terms and Acronyms

The important terms and acronyms appearing in *A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology* are listed and explained in Table 2. This compilation includes definitions

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Table 2. Explanation of acronyms and relevant terms used in A Handbook of Environmental Toxicology: Human Disorders and Ecotoxicology.

Abbreviation or term	Definition
AA	Amino acid
AAP	American Academy of Pediatrics (Ch 25)
Aβ	Amyloid beta (Ch 19)
ABA	Abscisic acid (Ch 4)
ABC	ATP-binding cassette (transporter) (Ch 4)
ACC	1-Amino-cyclopropane-1-carboxylic acid (Ch 4)
Ach	Acetylcholine (Ch 17)
AchE, AChE	Acetylcholine esterase (Ch 3, 17, 18)
ACGIH	American Conference of Governmental Industrial Hygienists(Ch 20)
AD	Alzheimer's disease (Ch 25 and 40)
ADC	Arginine decarboxylase (gene) (Ch 4)
ADHD	Attention deficit/hypersensitivity disorder (Ch 11, 26)
ADL	Activity of daily living (Ch 24)
ADME	Absorption, distribution, metabolism and excretion (Ch 17)
AFB_1	Aflatoxin B_1 (Ch 2)
AFB_2	Aflatoxin B_2 (Ch 2)
AFG_1	Aflatoxin G_1 (Ch 2)
AFG_2	Aflatoxin G_2 (Ch 2)
AFM_1	Aflatoxin M_1 (Ch 2)
Ah, AH	Aryl hydrocarbon (Ch 13, 14)
AhR/AHR	Aryl hydrocarbon receptor (Ch 11, 13, 39)
AKT	Protein kinase B (Ch 27)
Al	Aluminium (Ch 4 and 9)
AL	Acute leukaemia (Ch 33)
ALA	δ-Aminolevulinic acid (Ch 19)
ALA	American Lung Association (Ch 5)
AlaAT/ ALT	Alanine aminotransferase (Ch 4, 34)
ALK	Anaplastic lymphoma kinase (Ch 32)
ALP	Alkaline phosphatase (Ch 34)
ALRI	Acute lower respiratory infections (Ch 40)
ALS/PDC	Amyotrophic lateral sclerosis/Parkinsonism dementia complex (Ch 3, 19, 25)
AM	Arithmetic mean (Ch 24)
AMY	Amylase (Ch 34)
AOP	Adverse outcome pathway (Ch 10)
AP-1	Activator protein-1 (Ch 31)
APP	Amyloid precursor protein (Ch 19)
APX	Ascorbate peroxidase (Ch 9)
AQI	Air Quality Index (Ch 5)
AQSIQ	Administration of Quality Supervision, Inspection and Quarantine (China) (Ch 38)
AR	Acid rain (Ch 9)
AR	Androgen receptor (Ch 39)
ARDS	Acute respiratory distress syndrome (Ch 7)
ARE	Antioxidant-response element (Ch 31)
ARFY	Atherosclerosis risk factors in female youngsters (Ch 27)
ARGAH	Arginine amidohydrolase (Ch 4)
ArgE	*N*-Acetylornithine deacetylase gene in *E. coli* (Ch 4)
ARIC	Atherosclerosis Risk in Communities (Ch 14)
ARISA	Automated ribosomal intergenic spacer analysis (Ch 35)
ARLIS	Alaska Resource Library and Information Services (Ch 22)
ARNT	AHR nuclear translocator (Ch 13)
As	Arsenic

Continued

Table 2. Continued.

Abbreviation or term	Definition
ASD	Autism spectrum disorders (Ch 11)
AST	Aspartate aminotransferase (Ch 34)
ATP	Adenosine triphosphate (Ch 4, 8, 9)
ATSDR	Agency for Toxic Substances and Disease Registry (Ch 8, 25)
AWD	Atmospheric wet deposition (Ch 29)
Aze	Azetidine-2-carboxylic acid (Ch 19)
Ba	Barium
BA	Bioaugmentation (Ch 35)
BABA	β-Aminobutyrate (Ch 4)
BAL	Broncheoalveolara lavage (Ch 7)
BAM	Brewster Angle Mirror copy (Ch 6)
BaP	Benzo[a]pyrene (Ch10)
BAT	Best available technologies (Ch 12)
BBB	Blood brain barrier (Ch 25)
BChE	Butyrylcholinesterase (Ch 17)
BEIR	Biological Effects of Ionizing Radiation (conference) (Ch 32)
BEN	Balkan endemic nephropathy (Ch 2)
bHLH	Basic helix–loop–helix (Ch 13)
BHMSM	Bushnell–Haas mineral salt medium (Ch 35)
BLLs	Blood lead levels (Ch 25)
B2M	β-2-Microglobulin (Ch 26)
BMAA	β-*N*-Methylamino-l-alanine (Ch 3, 19)
BMI	Body mass index (Ch 34)
BOOP	*Bronchiolitis obliterans* organizing pneumonia (Ch 7)
BP	British Petroleum (Ch 20, 21)
Bq	Bequerel (Ch 32)
BR	Brassinosteroid (Ch 4)
BS	Biostimulation (Ch 35)
BTEX	Benzene, toluene, ethylbenzene and xylene (Ch 20, 23, 35)
BuCHE	Butyrylcholinesterase (Ch 18)
C	Carbon
Ca	Calcium
CAS	Chemical Abstract Service (Ch 23)
CAT	Catalase (Ch 9, 31)
CC	Case-control (study) (Ch 33)
Cd	Cadmium
CDC	Centers for Disease Control (and Prevention) (Ch 11, 14, 25)
CEC	Cation exchange capacity (Ch 37)
CFA	Coal fly ash (Ch 29)
ChB	Chafuroside B (Ch 31)
ChE	Choline esterase (Ch 34)
CI	Confidence interval (Ch 14, 26, 27, 32)
cJNKs	c-Jun N-terminal kinases (Ch 31)
CNS	Central nervous system (Ch 33, 40)
CO	Carbon monoxide
CO_2	Carbon dioxide
CoA	Coenzyme A
COD	Chemical oxygen demand (Ch 23)
COEH	Council on Environmental Health (Ch 25)
Cog	Cognitive (tests) (Chapter 18)
COHb	Carboxyhaemoglobin (Ch 28)
–COOH	Carboxyl group (Ch 37)

Continued

Table 2. Continued.

Abbreviation or term	Definition
COPD	Chronic obstructive pulmonary disease (Ch 5, 7, 8, 19, 28, 40)
COT	Committee on Toxicity (of Chemicals in Food, Consumer Products and the Environment) (Ch 18)
COX	Cytochrome c oxidase (Ch 8)
COX-2	Cyclooxygenase-2 (Ch 31)
CPC	Communist Party of China (Ch 38)
CPDs	Cyclobutane pyrimidine dimers (Ch 31)
CPK	Creatine phosphokinase (Ch 34)
Cr	Chromium
CRA	Chemical risk assessment (Ch 18)
CRD	Centre for Reviews and Dissemination (Ch 18)
CREB	Cyclic AMP response element binding protein (Ch 11)
CRP	C-reactive proteins (Ch 34)
Cs	Caesium
CSF	Cancer slope factor (Ch 23)
Cu	Copper
CVD	Cardiovascular disease (Ch 26, 40)
CvE	*Calluna vulgaris* extract (Ch 31)
CYPs	Cytochrome P450 enzymes (Ch 8, 13, 19)
DAS	Diacetoxyscirpenol (Ch 2)
DAT	Dopamine transporter (Ch 11, 16)
DCF	2′,7′-dichlorofluorescein (Ch 31)
DCRLs	Derived consideration reference levels (Ch 34)
DCM	Dichloromethane (Ch 29)
DDD	Dichlorodiphenyldichloroethane (Ch 40)
DDE	Dichlorodiphenyldichloroethylene (Ch 16, 40)
DDT	Dichlorodiphenyltrichloroethane/1,1,1-trichloro-2,2-*bis*(4-chlorophenyl) ethane (Ch 15, 16, 35, 40)
DEHP	Di (2-ethylhexyl) phthalate (Ch 30)
DES	Diethylstilbestrol (Ch 15)
DGGE	Denaturant gradient gel electrophoresis (Ch 35)
DGOMB	Deep Gulf of Mexico Benthos (Ch 21)
DIVER	Data Integration Visualization Exploration and Reporting (Ch 21)
DL	Dioxin-like (Ch 11)
dl-PCBs	Dioxin-like PCBs (Ch 13)
DLN	Draining lymph nodes (Ch 31)
DMF	Dimethylformamide (Ch 23)
DMSO	Dimethylsulfoxide (Ch 29)
DMT-1	Divalent metal transporter-1 (Ch 26)
DNA	Deoxyribonucleic acid (Ch 2, 3, 8, 10, 13, 25, 26, 30, 33, 34, 40)
DNT	Developmental neurotoxicity (Ch 11)
DOC	Dissolved organic carbon (Ch 23, 37)
DOM	Dissolved organic matter (Ch 37)
DON	Deoxynivalenol (Ch 2)
DOSS	dioctyl sulfosuccinate (Ch 21)
DPM	diesel exhaust particulate matter (Ch 29)
DPPC	Dipalmitoyl-*sn*-glycero-3-phosphtidylcholine (Ch 6)
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DREs	Dioxin response elements (Ch 13)
DSM-IV	Diagnostic and Statistical Manual of Psychiatric Disorders (Ch 18)
DTNB	5,5′-Dithio-bis-2-nitrobenzoic acid (Ch 17)
DWH	Deepwater Horizon (Ch 21)

Continued

Table 2. Continued.

Abbreviation or term	Definition
EA	Ellagic acid (Ch 31)
EaE	*Epilobium angustifolium* extract (Ch 31)
EBL	Erythroblast (Ch 34)
EC_{50}	Effect concentration required to elicit a negative 50% effect relative to control (Ch 21)
ECM	Extracellular matrix (Ch 31)
EDCs	Endocrine-disrupting chemicals (Ch 15)
EEG	Electroencephalogram (Ch 17)
EFSA	European Food and Safety Authority (Ch 10, 26)
EGCG	(-)-Epigallocatechin-3-gallate (Ch 31)
EGF	Epidermal growth factor (Ch 13)
EGFR	Epidermal growth factor receptor (Ch 31, 32)
eGFR	Estimated glomerular filtration rate (Ch 34)
EHQs	Exposure history questionnaires (Ch 18)
EIA	Environmental impact assessment (Ch 38)
EIARTR	Environmental impact assessment restriction targeting regions (Ch 38)
EIN2	Ethylene insensitive2 (Ch 4)
ELISA	Enzyme-linked immunosorbent assay (Ch 3 and 10)
EPA	Environmental Protection Agency (USA) (Ch 5, 40, 18)
EPBs	Environmental Protection Bureaus (China) (Ch 38)
EPL	Environmental Protection Law (China) (Ch 38)
EP&M	Environmental Protection & Management (Preface)
EPSP	5-Enolpyruvylshikimate-3-phosphate (Ch 19)
EREBP	Ethylene responsive-element binding protein (Ch 4)
ERF	Ethylene response factor (Ch 4)
ERKs	Extracellular signal-regulated kinases (Ch 31)
EROD	7-ethoxyresorufin-O-deethylase (Ch 22)
ET	Ethylene (Ch 4)
EU	European Union (Ch 2)
FAO	Food and Agriculture Organization (United Nations) (Ch 10, 30)
FB_1	Fumonisin B_1 (Ch 2)
FB_2	Fumonisin B_2 (Ch 2)
FB_3	Fumonisin B_3 (Ch 2)
FDA	Food and Drug Administration (USA) (Ch 17, 20)
FDNPP	Fukushima Dai-ichi Nuclear Power Plant (Ch 34)
Fe	Iron
Fe^0	Metallic/elemental iron (Ch 36)
FET	Fish embryo test (Ch 39)
FEV1	Forced expiratory volume in 1 second (Ch 5, 7)
FHB	Fusarium head blight
FPIA	Fluorescence polarization immunoassay (Ch 10)
FT_4	Free thyroxine (Ch 34)
FTIR	Fourier transform infrared spectrometry (Ch 35)
FVC	Forced vital capacity (Ch 5)
FYPs	Five-year plans (China) (Ch 38)
GABA	γ-Aminobutyrate/ γ-aminobutyric acid (Ch 4, 16, 25)
GAD	Glutamic acid decarboxylase (Ch 4)
Gas	Glycoalkaloids (Ch 1)
GB	Glycine betaine (Ch 4)
GC	Gas chromatography (Ch 35)
GC-MS	Gas chromatography-mass spectrometry (Ch 10, 35)
GDH	Glutamate dehydrogenase (Ch 4)

Continued

Table 2. Continued.

Abbreviation or term	Definition
GESAMP	Group of Experts on the Scientific Aspects of Marine (Environmental) Protection (Ch 30)
GFP	Green fluorescent protein (Ch 39)
GGT	Gamma-glutamyl transferase (Ch 14)
GLP	Glucagon-like-peptide (Ch 5)
GM	Geometric mean (Ch 24)
GOGAT	Glutamate synthase (Ch 4)
G6PD	Glucose-6-phosphate dehydrogenase (Ch 1, 4)
GPX	Guaiacol peroxidase (Ch 9)
GPx	Glutathione peroxidase (Ch 31)
GR	Glucocorticoid receptor (Ch 39)
GR	Glutathione reductase (Ch 9)
GS	Glutamine synthetase (Ch 4)
GSA	Glutamate-semialdehyde (Ch 4)
GSD	Geometric standard deviation (Ch 28)
GSH	Glutathione (Ch 31)
GSLs	Glucosinolates (Ch 1)
GST	Glutathione *S*-transferase (Ch 31, 32)
GTP	Green tea polyphenols (Ch 31)
HAQTS	(China) (Ch 38)
HAWS	(China) (Ch 38)
H2AX	Histone H2A (Ch 31)
HBH	(China) (Ch 38)
HBS	(China) (Ch 38)
HCC	Hepatocellular carcinoma (Ch 2)
β-HCH	beta-Hexachlorocyclohexane (Ch 16)
HCl	Hydrogen chloride (Ch 28)
HCN	Hydrogen cyanide (Ch 1, 28)
HDA	(China) (Ch 38)
HDL	High-density lipoprotein (Ch 14, 19)
HDM	House dust mite (Ch 5)
HEIQB	(China) (Ch 38)
HEPB	(China) (Ch 38)
HF	hydrogen fluoride (Ch 28)
Hg	Mercury
HHE	Health hazard evaluation (Ch 20)
HIITD	(China) (Ch 38)
HNO_2	Nitrous oxide (Ch 7)
HNO_3	Nitric acid (Ch 7)
HO-1	Heme oxygenase-1 (Ch 31)
H_2O_2	Hydrogen peroxide (Ch 4, 31)
HPEE	High pesticide exposure event (Ch 18)
HPLC	High-performance liquid chromatography (Ch 3, 6)
HR	Hazard ratio (Ch 26, 33)
H_2SO_4	Sulfuric acid (Ch 8)
HSP	Heat shock protein (Ch 13)
HSPGs	Heparin sulfate proteoglycans (Ch 19)
HULIS	Humic-like substances (Ch 29)
HWI	Hazardous waste incinerator (Ch 12)
HxCDF	
HY	(China) (Ch 38)
HyT	Hydroxytyrosol (Ch 31)

Continued

Table 2. Continued.

Abbreviation or term	Definition
I	Iodine
IAA	Indole acetic acid (Ch 4)
IAA-Trp	IAA-tryptophan conjugate (Ch 4)
IARC	International Agency for Research on Cancer (Ch 11, 13, 26, 32, 33)
IBI	International Biochar Initiative (Ch 37)
IC50	Inhibitory concentration of 50% of enzyme activity (Ch 31)
ICP-MS	Inductively coupled plasma-mass spectrometry (Ch 35)
ICRP	International Commission on Radiological Protection (Ch 34)
IDEA	Individuals with Disabilities Education Act (USA) (Ch 19)
IFN	Interferon (Ch 31)
IFNγ	Interferon gamma (Ch 31)
IKKα	IκB kinase α (Ch 31)
IL	Interleukin (Ch 5 and 31)
IL-12-KO	Interleukin-12p40 knockout (Ch 31)
Ile	Isoleucine (Ch 4)
iNOS	Inducible nitric oxide synthase (Ch 31)
IPCS	International Programme on Chemical Safety (Ch 24)
IQ	Intelligence quotient (Ch 25)
IQR	Interquartile range (Ch 14)
IRIS	Integrated Risk Information System (Ch 23)
IRS	Indoor residual spraying (Ch 16)
IS	Immune system (Ch 31)
IWI	Industrial waste incinerator (Ch 12)
JA	Jasmonic acid (jasmonate) (Ch 4)
JAQTS	(China) (Ch 38)
JAWS	(China) (Ch 38)
JBA	(China) (Ch 38)
JBDR	(China) (Ch 38)
JBH	(China) (Ch 38)
JBIIT	(China) (Ch 38)
JBPS	(China) (Ch 38)
JBS	(China) (Ch 38)
JBTT	(China) (Ch 38)
JCG	(China) (Ch 38)
JECFA	Joint (FAO/WHO) Expert Committee on Food Additives (Ch 24)
JEPB	(China) (Ch 38)
JNKS	c-Jun N terminal kinase (Ch 31)
K	Potassium
KD	(China) (Ch 38)
Keap 1	Kelch-like ECH-associated protein 1 (Ch 39)
KER	Key event relationship (Ch 10)
La	Lanthanum (Ch 9)
Laur-Hyt	Hydroxytyrosyl laurate (Ch 31)
LbE	Lemon balm extract (Ch 31)
LC	liquid chromotography (Ch 10)
LC_{50}	Lethal concentration required to kill 50% of a population (Ch 10)
LD_{50}	Lethal dose required to kill 50% of a population of organisms (Ch 2, 17)
LDH	Lactose dehydrogenase (Ch 34)
LDL	Low-density lipoprotein (Ch 34)
L-E	Long-Evans rat strain (Ch 13)
LeARG1 and *LeARG2*	Genes encoding arginase in tomato (Ch 4)
LH	(China) (Ch 38)

Continued

Table 2. Continued.

Abbreviation or term	Definition
LMW	Low molecular weight (Ch 26)
LNT	Linear non-threshold (Ch 34)
LOAEL	Lowest observed adverse effect level (Ch 23, 24)
LOC	Level of concern (Ch 20)
LMW	Low molecular weight (Ch 26)
LPS	Lipopolysaccharide (Ch 3)
LRRK	Leucine-rich repeat receptor kinase (Ch 4)
LTLL	Long-term low-level (Ch 18)
LV	Left ventricle (Ch 8)
MAPK	Mitogen-activated protein kinases (Ch 26, 31)
MBP	Myelin basic protein (Ch 19)
MCHC	Mean corpuscular haemoglobin concentration (Ch 34)
MCL	Maximum contaminant limits (Ch 23)
MC-LR	Microcystin-LR (Ch 3)
MCT 1	Monocarboxylase transporter 1 (Ch 19)
MCV	Mean corpuscular volume (Ch 34)
MD	Minimata disease (Ch 24)
MDA	Malondialdehyde (Ch 9)
MEE	Ministry of Ecology and Environment (China) (Ch 38)
MeHg	Methylmercury (Ch 11)
MEP	Ministry of Environmental Protection (China) (Ch 38)
MeV	Megaelectronvolt (Ch. 32)
Mg	Magnesium
mGy	Milligray (Ch 33)
MHW	Ministry of Health and Welfare (Japan) (Ch 24)
MIE	Molecular initiating event (Ch 10)
miRNA	MicroRNA
MITI	Minister of International Trade and Industry (Japan) (Ch 24)
MLOD	Maximum limit of detection (Ch 14)
MMAD	Mass median aerodynamic diameter (Ch 28)
MMP	Mitochondrial membrane potential (Ch 8)
MMPs	Matrix metalloproteinases (Ch 31)
MMPI	Minnesota multiphasic personality inventory (Ch 18)
MMSE	Mini mental state examination (Ch 18)
MoA	Ministry of Agriculture (China) (Ch 38)
MoA	Mode of action (Ch 10)
MOSSFA	Marine oil snow sedimentation and flocculent accumulation (Ch 21)
MPs	Microplastics (Ch 10)
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Ch 16)
MRI	Magnetic resonance imaging (Ch 18)
MRLs	Maximum residue limits (Ch 40)
mRNA	Messenger ribonucleic acid (Ch 13, 25)
mTOR	Mammalian target of rapamycin (Ch 27)
MS	Mass spectrometer/spectrometry (Ch 3 and 10)
MS	Multiple sclerosis (Ch 40)
MSH	Melanocyte stimulating hormone (Ch 31)
MSL	multi-soil layering (Ch 36)
mSv	millisievert (Ch. 33)
MSWI	municipal solid waste incinerator (Ch 12)
MT	Metallothionein (Ch 26)
Myr-Hyt	hydroxytyrosyl myristate (Ch 31)
N	Nitrogen

Continued

Table 2. Continued.

Abbreviation or term	Definition
NAAQS	National Ambient Air Quality Standard (Ch 7)
NAcc	Nucleus accumbens (Ch 11)
NaCl	Sodium chloride (Chapter 4)
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced) (Ch 4, 17, 40)
NALC	*N*-Acetyl-l-cysteine (Ch 8)
ncRNA	Non-coding RNA (Ch 25)
NDL	Non-dioxin-like (Ch 11)
NDRC	National Development and Reform Commission (China) (Ch 38)
NEC	No effect concentration (Ch 10)
NER	Nucleotide excision repair (Ch 31)
Neut	Neutrophil (Ch 34)
NF-κb	Nuclear factor kappa B (Ch 31)
NGO(s)	Non-governmental organisation(s) (Ch 15, 17, 38)
NGS	Next-generation sequence (Ch 32, 35)
NH_3	Ammonia
NHANES	National Health and Nutrition Examination Survey (Ch 11, 14, 15, 20, 25, 27)
NHEK	Normal human epidermal keratinocytes (Ch 31)
Ni	Nickel
NIEHS	National Institute of Environmental Health Sciences (Ch 20)
NIH	National Institutes of Health (Ch 20, 24)
NIMD	National Institute for Minamata Disease (Japan) (Ch 24)
NIOSH	National Institute for Occupational Safety and Health (Ch 7, 20)
NIV	Nivalenol (Ch 2)
NK	Natural killer (Ch 31)
NMDA	*N*-Methyl-d-aspartate (Ch 19)
NMDAR	*N*-Methyl-d-aspartic acid receptor (Ch 11)
NO	Nitric oxide (Ch 4, 5, 7, 31)
NO_X	Nitrogen oxides (Ch 5, 9)
NO_2	Nitrogen dioxide (Ch 7, 40)
NOAA	National Oceanographic and Atmospheric Administration (Ch 20, 21)
NOAEL	No observable adverse effect level (Ch 20)
NOEC	No observed effect concentration (Ch 10)
NOEL	No observable effect level (Ch 20)
NORM	Naturally occurring radioactive materials (Ch 23)
NOS	Nitric oxide synthase (Ch 4)
NPC	National Peoples Congress (China) (Ch 38)
NQO1	Quinone oxidoreductase 1 (Ch 31)
NR	Narrative review (Ch 18)
NRC	National Research Council (USA) (Ch 24 and 32)
NRDA	National Resource Damage Assessment (Ch 21)
NRF	Nuclear respiratory factor (Ch 8)
Nrf2	Nuclear factor erythroid 2-related factor 2 (Ch 31, 39)
NSCLC	Non-small cell lung cancer (Ch 32)
NSL	Nuclear translocation site (Ch 13)
3-NT	3-nitrotyrosine (Ch 7)
NTP	National Toxicology Program (USA) (Ch 25)
O_3	Ozone (Ch 7, 9)
OAT	Ornithine-δ-aminotransferase (Ch 4)
OC	Organic carbon (Ch 29)
OC	Organochlorine (Ch 40)
OCPs	Organochlorine pesticides (Ch 37)
ODC	Ornithine decarboxylase (Ch 4)

Continued

Table 2. Continued.

Abbreviation or term	Definition
OECD	Organization of Economic Cooperation and Development (Ch 10, 39)
OELs	Occupational exposure limits (Ch 20)
·OH	Hydroxyl radical (Ch 6, 37)
OP(s)	Organophosphorous / organophosphates (Ch 17, 18, 40)
OPAH	Oxygen-substituted PAH (Ch 40)
OR	Odds ratio (Ch 14, 33)
-OR	Ketone group (Ch 37)
OSAT	Operational Science Advisory Team (Ch 21)
OSHA	Occupational Safety and Health Administration (USA) (Ch 25)
OSIL	Ocean Scientific International Ltd (Ch 21)
OTA	Ochratoxin A (Ch 2)
OTB	Ochratoxin B (Ch 2)
5-OZT	5-Vinyl oxazolidinethione (Ch 1)
P	Phosphorus
PAC	Public Advisory Committee (Alaska) (Ch 22)
PAHs	Polycyclic aromatic hydrocarbons (Ch 10, 20, 21, 28, 29, 35, 40)
PAI-1	Plasminogen activator inhibitor-1 (Ch 5)
PAL	Phenylalanine ammonia-lyase (Ch 4)
PAzPC	1-Palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine (Ch 6)
Pb	Lead
PBDEs	Polybrominated diphenyl ethers (Ch 15, 37)
PBT	Persistent, bioaccumulative and toxic (Ch 25)
PCBs	Polychlorinated biphenyls (Ch 11, 13, 14, 15, 28, 35, 37, 40)
PCDDs	Polychlorinated dibenzo-*p*-dioxins (Ch 12, 13, 29, 37)
PCDFs	Polychlorinated dibenzofurans (Ch 12, 13, 15, 29, 37)
pCi	Picocurie (Ch 32)
PCP	Pentachlorophenol (Ch 37)
PCR	Polymerase chain reaction (Ch 3)
P5CR	Pyrroline-5-carboxylate reductase (Ch 4)
P5CS	Δ^1-Pyrroline-5-carboxylate synthetase (Ch 4)
PD	Parkinson's disease (Ch 40)
PDA	Photodiode array (Ch 3)
PE	Polyethylene (Ch 30)
PEC	Predicted environmental concentration (Ch 10)
PEG	Polyethylene glycol (Ch 4)
PELs	Permissible exposure limits (Ch 20)
PEP	Phosphoenolpyruvate (Ch 19)
PET	Positon emission tomography (Ch 18)
PG	Prostaglandin (Ch 31)
PGC	Peroxisome proliferator-activated receptor gamma coactivator (Ch 8)
PgE	*Punica granatum* extract (Ch 31)
PGF2 alpha	Prostaglandin F2 alpha (Ch 8)
PH	Phenylalanine hydroxylase (Ch 31)
PH_3	Phosgene (Ch 28)
PKC	Protein kinase C (Ch 11)
PLPC	1-Palmitoyl-2-linoleoyl-*sn*-glycero-3-phosphatidylcholine (Ch 6)
PM	Particulate matter (Ch 29, 40)
PNEC	Predicted no-effect concentration (Ch 10)
POD	Peroxidases (Ch 9)
POG	1-Palmitoyl-2-oleoyl-*sn*-glycerol (Ch 6)
PON1	Paraoxonase 1 (Ch 17, 18)
PonPC	1-Palmitoyl-2-(9′-oxo-nonanoyl)-*sn*-glycero-3-phosphocholine (Ch 6)

Continued

Table 2. Continued.

Abbreviation or term	Definition
POPC	1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphtidylcholine (Ch 6)
POPG	1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphtidylglycerol (Ch 6)
POPs	Persistent organic pollutants (Ch 12, 15, 40)
PP	Polypropylene (Ch 30)
PPAR	Peroxisome proliferator-activated receptor (Ch 14, 39)
PpE	Pomegranate polyphenolic extract (Ch 31)
PPE	Personal protection equipment (Ch 20)
Pref	Prefecture (in Japan) (Ch 24)
PRPs	Proline-rich proteins (Ch 1)
PSP	Progressive supranuclear palsy (Ch 3)
PST	Paralytic shellfish toxins (Ch 3)
PtE	*Passiflora tarminiana* extract (Ch 31)
PTFE	Polytetrafluoroethylene (Ch 28)
PTWI	Provisional tolerable weekly intake (Ch 24)
PVC	Polyvinyl chloride (Ch 30)
PXR	Pregnane-X-receptor (Ch 39)
QMS	Quadrupole spectrometer
qPCR	Quantitative polymerase chain reaction (Ch 3)
QSAR	Quantitative structure–activity relationship (Ch 23)
Ra	Radium
RADS	Reactive airway dysfunction syndrome (Ch 8, 28)
RANKL	Receptor activator of nuclear factor κb ligand (Ch 31)
RBP	Retinol-binding protein (Ch 26)
RBC	Red blood cell (Ch 8)
RDX	Hexahydro-1,3,5-trinitro-1,3,5-triazine (Ch 37)
REE	Rare-earth element (Ch 9)
REL	Recommended exposure limit (Ch 7)
REP	Relative effect potency (Ch 14)
RfC	Reference concentration (Ch 20, 23)
RfD	Reference dose (Chapter 20)
Rn	Radon
RNA	Ribonucleic acid (Ch 2)
RNS	Reactive nitrogen species (Ch 11)
ROS	Reactive oxygen species (Ch 4, 6, 9, 10, 11, 25, 29, 31, 39)
RR	(Ch 33)
RSDL	Reactive skin decontamination lotion (Ch 17)
RT	Response times (Ch 18)
RyR	Ryanodine receptors (Ch 11)
S	Sulfur (Ch 4)
SA	Salicylic acid (Ch 4)
SA-Asp	SA-aspartate (conjugate) (Ch 4)
SAM	*S*-Adenosylmethionine (Ch 4)
SAMDC	SAM decarboxylase (Ch 4)
SAR	Systemic acquired resistance (Ch 1)
SAWS	State Administration of Work Safety (China) (Ch 38)
SBS	Sick buildings syndrome (Ch 2)
SCD	(China) (Chapter 38)
SCLC	Small cell lung cancer (Ch 32)
SDG	Sustainable Development Goals, UN (Ch 38)
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Ch 6)
Se	Selenium
SETAC	Society of Environmental Toxicology and Chemistry (Ch 10)

Continued

Table 2. Continued.

Abbreviation or term	Definition
SIDS	Sudden infant death syndrome (Ch 40)
siRNA	Small interfering ribonucleic acid (Ch 11)
SMCO	*S*-Methylcysteine sulfoxide (Ch 1)
SMEs	Small and medium enterprises (Ch 38)
SMR	Standardized mortality ratio (Ch 33)
SNpc	Substantia nigra pars compacta (Ch 16)
SO_2	Sulfur dioxide (Ch 8, 9)
SOD	Superoxide dismutase (Ch 9, 31)
SP	Surfactant protein (Ch 6)
SPDS	Spermidine synthase (Ch 4)
SPMS	Spermine synthase (Ch 4)
SPR	Surface plasmon resonance (Ch 10)
SQT	Sediment quality triad (Ch 21)
Sr	Strontium
SR	Systematic review (Ch 18)
Src	Sarcoma
SSD	Species sensitivity distribution (Ch 10)
SSGM	Second Study Group on Minamata (Disease) (Ch 24)
ST	(Ch 33)
STAT3	Signal transducer and activator of transcription-3 (Ch 31)
STEL	Short-term exposure limit (Ch 28)
T3	Triiodothyronine (Ch 15)
T4	Thyroxine (Ch 15)
TBT	Tributyltin (Ch 15)
TCA	Trichloroacetic acid (Ch 19)
TCA	Tricarboxylic acid (as in TCA cycle) (Ch 4)
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Ch 12, 13, 14, 39, 40)
TCE	Trichloroethylene
TD	Threonine dehydratase (Ch 1)
TD	Toxico dynamics (Ch 10)
TD2	Threonine dehydratase 2 gene (Ch 1)
TDI	Tolerable daily intake (Ch 13)
TDS	Total dissolved solids (Ch 23)
TDP	Transactive-response DNA-binding protein (Ch 19)
Te	Tellurium (Ch 34)
TE	Trace element (Ch 29)
TEFs	Toxicity equivalent factors (Ch 10, 12, 13, 14)
TEL	Tetraethyl lead (Ch 25)
TENORM	Technologically-advised NORM (Ch 23)
TEQ	Toxicity equivalency (Cha 12, 13, 14, 28)
TFAM	Mitochondrial transcription factor A (Ch 8)
TG	Triglyceride (Ch 34)
TgAb	Anti-thyroglobulin antibody (Ch 34)
TGF-α	Transforming growth factor alpha (Ch 31)
TGFβ1	Transforming growth factor-beta (Ch 8)
TGGE	Temperature gradient gel electrophoresis (Ch 35)
TGIR	Thermogravimetric infrared spectrometry (Ch 35)
TH	Tyrosine hydroxylase (Ch 16)
T_h	T helper (cell) (Ch 8)
TK	Toxico kinetics (Ch 10)
TLR4	Toll-like receptor 4 (Ch 8)
TLVs	Threshold limit values (Ch 20)

Continued

Table 2. Continued.

Abbreviation or term	Definition
TMB-4	Trimedoxime (Ch 17)
TMPP	Trimethylolpropane phosphate (Ch 28)
TNB^-	Thionitrobenzoate
TNF	Tumour necrosis factor (Ch 5, 31)
TOPKAT	Toxicity Prediction by K(c)omputer Assisted Technology (Ch 23)
tPA	Tissue-type plasminogen activator (Ch 5)
TPH	Total petroleum hydrocarbons (Ch 21 and 35)
TPOAb	Anti-thyroid-peroxidase antibody (Ch 34)
TRFLP	Terminal restriction fragment length polymorphism (Ch 35)
TRPV	Transient receptor potential vanilloid (Ch 8)
TSH	Thyroid-stimulating hormone (Ch 15, 34)
TTT	Thymol turbidity test (Ch 34)
TUNEL	Terminal deoxynucleotidyl transferase (TDT) dUTP Nick-End Labelling (Ch 11)
TWI	Tolerable weekly intake (Ch 26)
UCA	Urocanic acid (Ch 31)
UFPs	Ultrafine particles (Ch 29)
UIBC	Unsaturated iron-binding capacity (Ch 34)
UK	United Kingdom (Ch 15)
UNEP	United Nations Environment Programme (Ch 24, 30)
UNSCEAR	UN Scientific Committee on the Effects of Atomic Radiation (Ch 34)
UOG	Unconventional oil and gas (Ch 23)
UPLC	Ultra-performance liquid chromatography (Ch 3)
USEPA/US EPA	United States Environmental Protection Agency (Ch 7, 10, 11, 20, 30, 39)
UV	Ultraviolet (Ch 2, 3, 10, 15, 31, 40)
VaD	Vascular dementia (Ch 40)
VDCC	Voltage-dependent calcium channel (Ch 11)
V_E	Volume (of air) exhaled (Ch 28)
VMAT/VMAT2	Vesicular monoamine transporter 2 (Ch 11 and 16)
VmE	*Vaccinium myrtillus* fruit extract (Ch 31)
VOCs	Volatile organic compounds (Ch 5, 20)
WHO	World Health Organization (of UN) (Ch 10, 13, 14, 17, 18, 25, 32)
WAIS	Wechsler adult intelligence scale (Ch 18)
WL	Working level (Ch 32)
WLM	Working level month (Ch 32)
WMS	Wechsler memory scale (Ch 18)
WOE	Weight of evidence (Ch 16)
WOR	Whole organism response (Ch 10)
WTC	World Trade Center
WTO	World Trade Organization
ZAWS	(China) (Chapter 38)
ZBIIT	(China) (Chapter 38)
ZEN	Zearalenone (Chapter 2)
ZEPB	(China) (Chapter 38)
ZJK	(China) (Chapter 38)
Zn	Zinc
ZVI	Zero-valent iron (Ch 36)

of standard as well as unique chapter-specific abbreviations or terms. Where appropriate, cross-referencing to individual chapters in this volume is included in order to facilitate a greater appreciation of the context of usage of particular terms. Alternative abbreviations for the same entry are listed here due to widespread use in research publications and in other literature.

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27 Cadmium II. Cardiovascular Effects of Human Exposure to Cadmium: Left Ventricular Structure and Function

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27.1 Abstract

Since the 1970s, the effect of cadmium perfusion on peak systolic contractility and cardiac atrioventricular conduction has been observed in rats and a growing body of evidence shows that cadmium exposure is associated with cardiovascular disease, including heart failure, in humans. However, few human studies linked the cadmium exposure to impaired left ventricular function. Due to the common coexistence of other poisoning heavy metals, such as lead, and the confounding effect of smoking, the causal relationship between cadmium exposure and left ventricular function in humans is still to be established.

27.2 Introduction

The heart is a muscular organ that pumps blood throughout the body, providing the tissues with oxygen and nutrients and removing metabolic waste. In mammals, including humans, the heart consists of four chambers: the upper left and right atria; and the lower left and right ventricles. In a healthy heart, the valves isolating the atria and ventricles, and linking ventricles and aorta or pulmonary, ensure that blood always flows in one direction through the heart. The heart pumps blood with a rhythm determined by pacemaker cells in the sinoatrial node, which generates a current travelling through the atrioventricular node and along the conduction system of the heart, and causing contraction of the heart. Incessant contraction of cardiac muscles to pump blood consumes more than 20% of oxygen and nutrients of the body, which is supplied by the coronary arteries. Any disorder of the aforementioned structures and tissues can lead to heart failure, defined as a condition or syndrome in which the heart is unable to pump enough blood to meet the demands of the body (Lilly, 2012; Mann *et al.*, 2014).

In general, the right atrium and ventricle are referred together as the right heart and their left counterparts as the left heart. The diseases causing right heart failure are usually very different from the ones leading to left heart failure. However, nowadays, left ventricular heart failure caused by tobacco use, obesity, lipid disorder, hypertension, diabetes, coronary artery disease and so on is much more prevalent than right heart failure, especially in developed countries (Mann *et al.*, 2014); therefore, if not specified, the term 'heart failure' usually refers to left ventricular dysfunction.

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Along with industrialization, population ageing and lifestyle changes, cardiovascular disease has become the leading cause of death worldwide (GBD2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). As the common final stage of all types of cardiovascular disease, heart failure is a major public problem with a prevalence of more than 23 million worldwide (Bui *et al.*, 2011). To improve life quality, industrialization for economic growth, rapidly progressing in developing countries, is inevitable. However, industrialization also leads to increased production and consumption of heavy metals, thus exacerbating global metal pollution, including cadmium, which is now a big threat to public health. The parallel increase in the incidence of heart failure and cadmium contamination suggests a possible association. Indeed, a growing body of evidence has shown that exposure to cadmium is associated with cardiovascular diseases, including heart failure in humans (Tellez-Plaza *et al.*, 2013a). However, heart failure is a syndrome that can be aetiologically caused by a variety of heart diseases. An association between cadmium exposure and heart failure does not necessarily indicate a causal toxic effect of cadmium on the heart muscle, as has been showed in animal studies (Hawley and Kopp, 1975; Kopp *et al.*, 1978) The relationship between cadmium and different cardiovascular diseases (Tellez-Plaza *et al.*, 2013b) might be explained by residual confounding through traditional cardiovascular risk factors such as age, sex, smoking (Olsson *et al.*, 2002), hypertension (Gallagher and Meliker, 2010; Staessen *et al.*, 2000) and dyslipidaemia (Cho *et al.*, 2016; Zhou *et al.*, 2016). This chapter will focus on the association of cadmium with left ventricular function and heart failure, covering the above aspects (Fig 27.1).

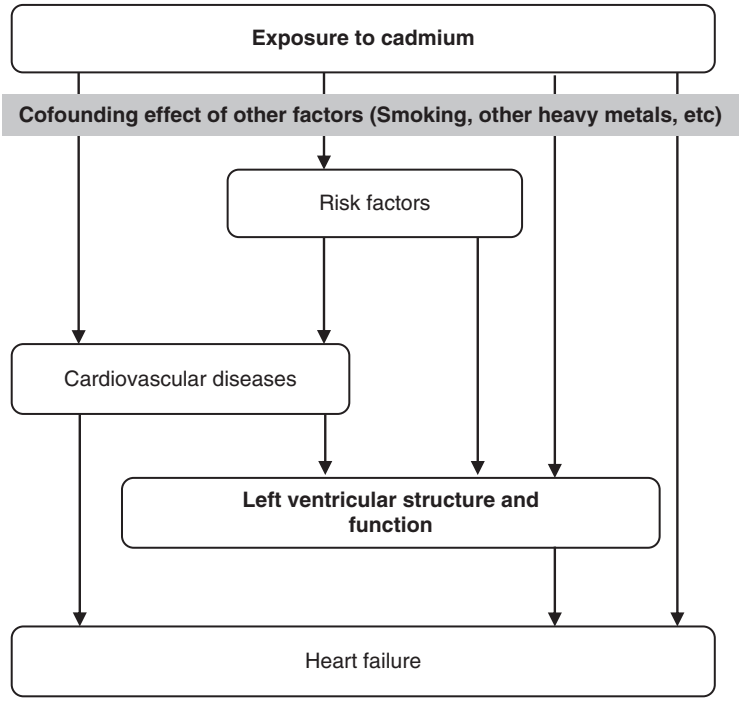

Fig. 27.1. Outline of the relationship between cadmium exposure and left ventricular structure and function and heart failure. The arrow lines indicate the potential mechanisms or the evidenced links between the cadmium exposure with risk factors, left ventricular function, heart failure and cardiovascular diseases. However, concerning the cofounding effect of age, sex, smoking and exposure to other pollutants, caution should be used when interpreting these data.

27.3 Cadmium and Left Ventricular Function

Hawley and Kopp first applied the perfusion of the cadmium ion in a purpose of competition with calcium in isolated rat heart and observed prolonged electrophysiological PR interval in 1975 (Hawley and Kopp, 1975). Kopp *et al.* (1978) also confirmed that the atrioventricular conduction block after application of chemical composition perfusion with cadmium in a concentration of 0.03 mmol l^{-1} to the isolated Langendorff rat heart occurred in A-H interval (atrioventricular nodal depression). With an effect of decreasing heart rate, perfusion of cadmium ions also largely depressed ventricular systolic tension (Kopp *et al.*, 1978). The underlying mechanism was illustrated in a further experiment: the cadmium ions can inhibit phosphorylation level of light chain-2 of myofibrillar proteins and suppress positive inotrope induced by calcium or isoproterenol (Kopp and Barany, 1980). Kopp and colleagues then moved to animal studies *in vivo*, and studied female hooded rats fed 5 ppm cadmium via drinking-water for 15 months (Kopp *et al.*, 1980a, b). Growth and food and water intake were comparable with controls. Perfused hearts of exposed animals showed depressed myocardial contractility and reduced positive inotropic responsiveness to isoproterenol (Kopp *et al.*, 1980a). The depressed myocardial contractility was not due to altered β-receptor function, but to depressed phosphorylation of the myocardial contractile proteins (Kopp *et al.*, 1980a). In anaesthetized rats exposed to cadmium and lead for 20 months according to a similar protocol, cadmium selectively slowed conduction proximal to the His bundle (Kopp *et al.*, 1980b). Phosphorus-31 nuclear magnetic resonance spectroscopy revealed depressed high-energy phosphate and glycerol-3-phosphorylcholine concentrations in hearts of cadmium-exposed rats (Kopp *et al.*, 1980b). In the cultured cardiomyocytes, cadmium treatment induced dramatic endoplasmic reticulum stress and impaired energy haemostasis (Chen *et al.*, 2015). Moreover, cadmium may inhibit the protein kinase B (AKT)–mTOR (mammalian target of rapamycin) pathway to reduce energy production, by either disrupting the glucose metabolism (Chen *et al.*, 2015) or inhibiting mitochondrial respiratory (Kisling *et al.*, 1987) and related gene expressions (Chen *et al.*, 2015). Another important line of the potential cadmium cardiotoxic effect refers to cardiac fibrosis: experiments *in vitro* demonstrated a cadmium-induced depolarization of the mitochondrial membrane and permeabilization of the plasma membrane (Türkcan *et al.*, 2015). In further ApoE–/– mice models, Türkcan *et al.* (2015) illustrated that treatment with western diet or cadmium results in necrotic cardiomyocyte death and myocardial fibrosis. These experiments (Hawley *et al.*, 1975; Kopp *et al.*, 1978, 1980a, b; Kopp and Barany, 1980; Prentice and Kopp, 1985) produced evidence for direct pathophysiological changes in the absence of overt cadmium toxicity, the main mechanisms being suppressing conductivity in the heart and dysregulation of energy metabolism.

Concerning the evidence in humans, only one population study reported on the association of left ventricular structure and function with cadmium exposure (Yang *et al.*, 2017b). In 179 participants (50.3% women; mean age, 39.1 years) randomly recruited from a Flemish population, baseline 24 h urinary cadmium and other risk factors (1985–2000) and follow-up echocardiographic left ventricular structure and systolic and diastolic function (2005–2010) were assessed with a median interval of 11.9 years (Yang *et al.*, 2017b). After adjustment for sex, age, mean arterial pressure, heart rate, body mass index, fasting plasma glucose, total-to-high-density lipoprotein–cholesterol ratio, serum creatinine, γ-glutamyltransferase, smoking and anti-hypertensive treatment, Yang *et al.* (2017b) observed that a doubling of baseline 24 h urinary cadmium was significantly ($P \leq 0.015$) associated with decreased regional longitudinal strain rate (–0.066 s^{-1}) and regional radial strain (–2.848%) during follow-up. Meanwhile, the blood lead level was also associated with reduced left ventricular systolic function. However, models including both cadmium and lead exposure indexes did not allow differentiating whether left ventricular systolic dysfunction was predominantly related to blood lead or urinary cadmium. None of the left ventricular diameter, wall thickness or diastolic function parameters was associated with 24 h urinary cadmium excretion ($P \geq 0.16$) (Yang *et al.*, 2017b). Of course, caution should be taken when interpreting these results. Indeed, confounding by the coexistence of other

heavy metals as toxic agents, such as lead, cannot be excluded. Furthermore, there might be some residual confounding by the common determinants of cadmium exposure (Olsson *et al.*, 2002) and left ventricular structure and function, such as sex, age and smoking (Kuznetsova *et al.*, 2008, 2009; Lang *et al.*, 2015).

Therefore, although the experimental studies provided strong evidence of a direct cardiotoxic effect of cadmium, more data are required to confirm this effect in humans. Of note, in the Flemish studies, the left ventricular ejection fraction was not associated with either lead or cadmium exposure (Yang *et al.*, 2017b) or low-level residential air pollution (Yang *et al.*, 2017a). As highlighted in a recent systematic review (Kalam *et al.*, 2014), this might be explained by the inaccurate assessment of systolic function using left ventricular ejection fraction in people with a value within the normal range (> 45%). Therefore, for future studies focusing on low-to-moderate environmental cadmium exposure in relation to left ventricular systolic function, a longitudinal design assessing left ventricular function by a state-of-the-art technique (for instance, strain and strain rate) and accounting for other heavy metals and nicotine would be favoured.

27.4 Cadmium and Heart Failure

Although cadmium studies directly focusing on left ventricular function in humans are scarce (Yang *et al.*, 2017b), there is mounting evidence supporting a link between the incidence or prevalence of heart failure and cadmium exposure. Among inhabitants aged ≥ 50 years in the Kakehashi river basin, Ishikawa Prefecture, Japan, Nishijo and colleagues compared cause-specific mortality between subjects (n = 2408) with positive (≥ 4 mg dl^{-1}) and negative (< 4 mg dl^{-1}) urinary retinol-binding protein (Nishijo *et al.*, 1995) and between individuals (n = 3178) with higher (≥ 1000 μg g^{-1} creatinine) and lower (< 1000 μg g^{-1} creatinine) creatinine-standardized urinary β_2-microglobulin (Nishijo *et al.*, 2006). During the 15-year follow-up in the retinol-binding protein study, 52 and 86 cases of fatal heart failure were identified in men and women, respectively (Nishijo *et al.*, 1995). The corresponding incidences in the β_2-microglobulin study were 60 in men and 87 in women (Nishijo *et al.*, 2006). Using the total Japanese population as the standard population, the standardized heart failure mortality amounted to 302.6% and 122.5% (P < 0.01) in men with positive and negative urinary retinal binding protein, respectively. In women, the corresponding rates were 353.0% and 155.9% (P < 0.05) (Nishijo *et al.*, 1995). For the comparison of higher versus lower urinary β_2-microglobulin, the estimated standardized heart failure mortality ratios were 179% versus 93% in men and 248% versus 104% in women (Nishijo *et al.*, 2006). Compared with the risk of fatal heart failure among the subjects with a urinary β_2-microglobulin of < 300 μg g^{-1} creatinine, the hazard ratio of those with a β_2-microglobulin level of 300–1000, 1000–10,000 and ≥ 10,000 μg g^{-1} creatinine were 0.88 (95% confidence interval (CI): 0.41–1.89), 1.45 (0.74–2.84) and 3.69 (1.62–8.39) in males and 1.94 (1.08–3.48), 3.05 (1.73–5.35) and 3.19 (1.19–5.52) in females (Nishijo *et al.*, 2006). The dose–response relationship between urinary β_2-microglobulin and cadmium (Ishizaki *et al.*, 1989) and between the frequency of inhabitants with urinary retinol-binding protein of ≥ 4 mg dl^{-1} and the average concentration in rice of the hamlets where the subjects were living (Nogawa *et al.*, 1978) suggested a causal association between heart failure and cadmium exposure (Nishijo *et al.*, 1995, 2006) .

By using National Health and Nutrition Examination Survey (NHANES, 1999–2006), Peters *et al.* (2010) assessed the association between blood and urinary cadmium and the prevalence of heart failure in the general population. Among 12,049 participants aged 30 years or older, 471 persons reported a history of heart failure at the time of their interviews. The geometric mean cadmium concentration was 3.8 nmol l^{-1} in blood and 2.7 nmol l^{-1} in urine. After adjusting for age, sex, race/ethnicity, body mass index, education level, poverty income ratio, alcohol consumption, smoking status and blood cotinine, the odds ratios of prevalent heart failure were 1.48 (95% CI: 1.17–1.87) and 1.12 (1.03–1.20) in relation to a 50% increase in blood and urinary cadmium, respectively (Peters *et al.*, 2010). The retrospective design, cross-sectional analysis and self-reported outcome of heart failure were the major limitations and made the interpretation of this study difficult. However, in

3348 American Indian adults aged 45–74 years who participated in the Strong Heart Study in 1989–1991 and were followed up until 2018, the overall median and geometric mean urinary cadmium concentration at baseline were 0.92 and 0.94 μg g^{-1} creatinine, respectively (Tellez-Plaza *et al.*, 2013a). During follow-up, 328 subjects developed heart failure. In animal models solely adjusted for gender, the incidence of heart failure was not significantly related to urinary cadmium. Only in multivariable-adjusted models, the risk of heart failure in the second, third and fourth cadmium quartiles increased significantly compared with the first quartile group (Tellez-Plaza *et al.*, 2013a) .

A single cigarette typically contains 1–2 μg of cadmium (Menden *et al.*, 1972; Sugita *et al.*, 2001). When burned, more than 50% of the cadmium, present at a level of 1000–3000 ppb in the smoke, is inhaled and absorbed into the blood through the lung. Then, the question arises whether part of the cardiovascular risk associated with smoking is due to the inhaled cadmium. The odds ratio of heart failure prevalence associated with smoking decreased from significant 2.28 (95% CI: 1.66–3.12) to insignificant 1.40 (0.88–2.24) after additional adjustment for blood cadmium (Peters *et al.*, 2010). Additional adjustment for urinary cadmium produced similar results (Peters *et al.*, 2010). These findings are consistent with the hypothesis that smoking increases the risk of heart failure through exposure to cadmium (Peters *et al.*, 2010) .

27.5 Cadmium and Cardiovascular Disease and Associated Risk Factors

Cardiovascular disease, especially coronary heart disease, is the common aetiological cause of left ventricular dysfunction and heart failure (Mann *et al.*, 2014). Over the past two decades, increasing evidence has indicated that cadmium exposure is a cardiovascular risk factor (Nawrot *et al.*, 2008; Tellez-Plaza *et al.*, 2013b; Tinkov *et al.*, 2018). Tellez-Plaza *et al.* (2013) meta-analysed seven prospective and five cross-sectional studies that evaluated the association of cardiovascular disease with low to moderate environmental cadmium exposure in general populations. The pooled relative risks of cardiovascular and coronary heart diseases comparing the highest to lowest cadmium exposure categories were 1.36 (95% CI: 1.11–1.66) and 1.30 (1.12–1.52), respectively. These risk estimates were 1.23 (1.05–1.44) and 1.21 (1.07–1.37) if only the prospective studies were included in the meta-analysis. These relative risks were consistent for urinary cadmium 1.36 (95% CI: 1.11–1.66) and blood cadmium 1.41 (1.18–1.70) as exposure biomarkers. All the aforementioned analyses accounted for age, sex and smoking status, as they are the main determinants of cadmium exposure (Olsson *et al.*, 2002) and major contributing risk factors for cardiovascular disease (Mann *et al.*, 2014). By adding four newly emerging prospective and two cross-sectional studies, another meta-analysis conducted in 2017 confirmed these findings (Tinkov *et al.*, 2018). Residual confounding effect by smoking and sex is a common concern when interpreting the association between cadmium exposure and cardiovascular disease. However, the pooled relative risks for cardiovascular disease were of similar magnitude in men, women (Tellez-Plaza *et al.*, 2013b) and never-smokers (Tellez-Plaza *et al.*, 2013b; Tinkov *et al.*, 2018). In addition, the associations remained largely similar after adjustment for cigarette pack-year and serum nicotine, in addition to smoking status (Tellez-Plaza *et al.*, 2013b). All these analyses (Tellez-Plaza *et al.*, 2013b; Tinkov *et al.*, 2018) support a causal relationship between cadmium exposure and cardiovascular disease, which potentially leads to left ventricular dysfunction and heart failure.

In addition to age, sex and smoking, cadmium exposure was associated with atherogenic changes in lipid profile. In a meta-analysis of several available studies (Kim, 2012; Ettinger *et al.*, 2014; Tangvarasittichai *et al.*, 2015; Zhou *et al.*, 2016) higher cadmium exposure was associated with higher total cholesterol levels, higher low-density lipoprotein cholesterol levels and lower high-density lipoprotein cholesterol levels (Tinkov *et al.*, 2018). Among 195 young healthy females enrolled in the Atherosclerosis Risk Factors in Female Youngsters (ARFY) study, a 1-SD increment in serum cadmium was associated with an odds ratio of 1.6 (95% CI: 1.1.–2.3) for early atherosclerotic vessel wall thickening after multivariable adjustment (Messner *et al.*, 2009). Blood cadmium was also significantly associated with the number of plaques in carotid

arteries (P = 0.001) and with intima–media thickness (P = 0.005) (Lind *et al.*, 2012). Bergström *et al.* (2015) also demonstrated a significant relationship between blood cadmium level and area of atherosclerotic plaques. Moreover, plaque cadmium content was 50-fold higher than that in blood. The highest concentration of cadmium in plaques was observed in the upstream sections of carotid plaques, being more than twofold higher than that in stenosis and downstream sections (Bergström *et al.*, 2015). These studies suggest that cadmium exposure can cause atherosclerosis, thereby leading to coronary heart disease and left ventricular dysfunction.

A growing body of evidence supports the suggestion that cadmium exposure plays a role in the development of hypertension (Tellez-Plaza *et al.*, 2008; Lee *et al.*, 2011; Caciari *et al.*, 2013) and chronic kidney disease (Navas-Acien *et al.*, 2009; Hwangbo *et al.*, 2011). It is well known that at all ages and across all ethnicities, high blood pressure is the major driver of cardiovascular complications (Lewington *et al.*, 2002). The causal relationship between blood pressure and left ventricular hypertrophy (Schmieder *et al.*, 1996) and diastolic dysfunction (Redfield *et al.*, 2003; Nadruz *et al.*, 2017) is beyond doubt. Renal function may be one of the contributors to this relationship (Yang *et al.*, 2013). However, evidence showing an association between cardiovascular disease or left ventricular function and cadmium exposure through the pathway of hypertension and/or chronic kidney disease is lacking.

27.6 Conclusions

Experimental or animal studies (Hawley *et al.*, 1975; Kopp *et al.*, 1978, 1980a, b; Kopp and Barany, 1980; Prentice *et al.*, 1985) had suggested a direct cardiotoxic effect of cadmium for more than three decades. Moreover, mounting evidence supports a causal relationship between cadmium exposure and cardiovascular disease, in particular heart failure (Tellez-Plaza *et al.*, 2013b; Tinkov *et al.*, 2018) The association of cadmium exposure with left ventricular structure and function through its relationship with hypertension (Tellez-Plaza *et al.*, 2008; Lee *et al.*, 2011; Caciari *et al.*, 2013), lipid profile (Kim, 2012; Ettinger *et al.*, 2014; Tangvarasittichai *et al.*, 2015; Zhou *et al.*, 2016) and chronic kidney function (Navas-Acien *et al.*, 2009; Hwangbo *et al.*, 2011) is highly speculative. However, studies directly linking cadmium exposure to left ventricular structure and function are very rare (Yang *et al.*, 2017b). Well designed longitudinal studies assessing left ventricular function by state-of-the-art technique (for instance, systolic strain and strain rate) and accounting for other heavy metals and nicotine are warranted.

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