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Pim de Voogt *Editor*

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Editor
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Foreword

International concern in scientific, industrial, and governmental communities over traces of xenobiotics in foods and in both abiotic and biotic environments has justified the present triumvirate of specialized publications in this field: comprehensive reviews, rapidly published research papers and progress reports, and archival documentations These three international publications are integrated and scheduled to provide the coherency essential for nonduplicative and current progress in a field as dynamic and complex as environmental contamination and toxicology. This series is reserved exclusively for the diversified literature on "toxic" chemicals in our food, our feeds, our homes, recreational and working surroundings, our domestic animals, our wildlife, and ourselves. Tremendous efforts worldwide have been mobilized to evaluate the nature, presence, magnitude, fate, and toxicology of the chemicals loosed upon the Earth. Among the sequelae of this broad new emphasis is an undeniable need for an articulated set of authoritative publications, where one can find the latest important world literature produced by these emerging areas of science together with documentation of pertinent ancillary legislation.

Research directors and legislative or administrative advisers do not have the time to scan the escalating number of technical publications that may contain articles important to current responsibility. Rather, these individuals need the background provided by detailed reviews and the assurance that the latest information is made available to them, all with minimal literature searching. Similarly, the scientist assigned or attracted to a new problem is required to glean all literature pertinent to the task, to publish new developments or important new experimental details quickly, to inform others of findings that might alter their own efforts, and eventually to publish all his/her supporting data and conclusions for archival purposes.

In the fields of environmental contamination and toxicology, the sum of these concerns and responsibilities is decisively addressed by the uniform, encompassing, and timely publication format of the Springer triumvirate:

Reviews of Environmental Contamination and Toxicology [Vol. 1 through 97 (1962–1986) as Residue Reviews] for detailed review articles concerned with any aspects of chemical contaminants, including pesticides, in the total environment with toxicological considerations and consequences.

Bulletin of Environmental Contamination and Toxicology (Vol. 1 in 1966) for rapid publication of short reports of significant advances and discoveries in the fields of air, soil, water, and food contamination and pollution as well as methodology and other disciplines concerned with the introduction, presence, and effects of toxicants in the total environment.

Archives of Environmental Contamination and Toxicology (Vol. 1 in 1973) for important complete articles emphasizing and describing original experimental or theoretical research work pertaining to the scientific aspects of chemical contaminants in the environment.

The individual editors of these three publications comprise the joint Coordinating Board of Editors with referral within the board of manuscripts submitted to one publication but deemed by major emphasis or length more suitable for one of the others.

Coordinating Board of Editors

Preface

The role of *Reviews* is to publish detailed scientific review articles on all aspects of environmental contamination and associated (eco)toxicological consequences. Such articles facilitate the often complex task of accessing and interpreting cogent scientific data within the confines of one or more closely related research fields.

In the 50+ years since *Reviews of Environmental Contamination and Toxicology* (formerly *Residue Reviews)* was first published, the number, scope, and complexity of environmental pollution incidents have grown unabated. During this entire period, the emphasis has been on publishing articles that address the presence and toxicity of environmental contaminants. New research is published each year on a myriad of environmental pollution issues facing people worldwide. This fact, and the routine discovery and reporting of emerging contaminants and new environmental contamination cases, creates an increasingly important function for *Reviews.* The staggering volume of scientific literature demands remedy by which data can be synthesized and made available to readers in an abridged form. *Reviews* addresses this need and provides detailed reviews worldwide to key scientists and science or policy administrators, whether employed by government, universities, nongovernmental organizations, or the private sector.

There is a panoply of environmental issues and concerns on which many scientists have focused their research in past years. The scope of this list is quite broad, encompassing environmental events globally that affect marine and terrestrial ecosystems; biotic and abiotic environments; impacts on plants, humans, and wildlife; and pollutants, both chemical and radioactive; as well as the ravages of environmental disease in virtually all environmental media (soil, water, air). New or enhanced safety and environmental concerns have emerged in the last decade to be added to incidents covered by the media, studied by scientists, and addressed by governmental and private institutions. Among these are events so striking that they are creating a paradigm shift. Two in particular are at the center of ever increasing media as well as scientific attention: bioterrorism and global warming. Unfortunately, these very worrisome issues are now superimposed on the already extensive list of ongoing environmental challenges.

The ultimate role of publishing scientific environmental research is to enhance understanding of the environment in ways that allow the public to be better informed or, in other words, to enable the public to have access to sufficient information. Because the public gets most of its information on science and technology from internet, TV news, and reports, the role for scientists as interpreters and brokers of scientific information to the public will grow rather than diminish. Environmentalism is an important global political force, resulting in the emergence of multinational consortia to control pollution and the evolution of the environmental ethic. Will the new politics of the twenty-first century involve a consortium of technologists and environmentalists, or a progressive confrontation? These matters are of genuine concern to governmental agencies and legislative bodies around the world.

For those who make the decisions about how our planet is managed, there is an ongoing need for continual surveillance and intelligent controls to avoid endangering the environment, public health, and wildlife. Ensuring safety-in-use of the many chemicals involved in our highly industrialized culture is a dynamic challenge, because the old, established materials are continually being displaced by newly developed molecules more acceptable to federal and state regulatory agencies, public health officials, and environmentalists. New legislation that will deal in an appropriate manner with this challenge is currently in the making or has been implemented recently, such as the REACH legislation in Europe. These regulations demand scientifically sound and documented dossiers on new chemicals.

Reviews publishes synoptic articles designed to treat the presence, fate, and, if possible, the safety of xenobiotics in any segment of the environment. These reviews can be either general or specific, but properly lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, (eco)toxicology, and regulation. Certain affairs in food technology concerned specifically with pesticide and other food-additive problems may also be appropriate.

Because manuscripts are published in the order in which they are received in final form, it may seem that some important aspects have been neglected at times. However, these apparent omissions are recognized, and pertinent manuscripts are likely in preparation or planned. The field is so very large and the interests in it are so varied that the editor and the editorial board earnestly solicit authors and suggestions of underrepresented topics to make this international book series yet more useful and worthwhile.

Justification for the preparation of any review for this book series is that it deals with some aspect of the many real problems arising from the presence of anthropogenic chemicals in our surroundings. Thus, manuscripts may encompass case studies from any country. Additionally, chemical contamination in any manner of air, water, soil, or plant or animal life is within these objectives and their scope.

Manuscripts are often contributed by invitation. However, nominations for new topics or topics in areas that are rapidly advancing are welcome. Preliminary communication with the Editor-in-Chief is recommended before volunteered review manuscripts are submitted. *Reviews* is registered in WebofScience™.

Inclusion in the Science Citation Index serves to encourage scientists in academia to contribute to the series. The impact factor in recent years has increased from 2.5 in 2009 to almost 4 in 2013. The Editor-in-Chief and the Editorial Board strive for a further increase of the journal impact factor by actively inviting authors to submit manuscripts.

Amsterdam, The Netherlands Pim de Voogt
January 2015

Contents

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Letter to the Editor

Contents

1 Response to the Citation in the Manuscript Entitled "Pore Water Collection, Analysis, and Evolution: The Need for Standardization"

James Fish

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Dear Editor-in-Chief,

I am writing in regard to the chapter published by Gruzalski et al. in *Reviews of Environmental Contamination and Toxicology*, Vol. 237, pp. 37–51, Nov 2015 (DOI: 10.1007/978-3-319-23573-8_2), entitled "Pore Water Collection, Analysis, and Evolution: The Need for Standardization." My work with the Alaska Department of Environmental Conservation is cited with the following quoted text: "Fish (2011) compared pore water data from samples collected in discharge zones to groundwater cleanup levels to evaluate the effectiveness of a nearby groundwater remediation project. That type of comparison contradicts the stated goal of groundwater cleanup levels since pore water is not 'usable' in this context without accounting for the dilution of discharged pore water by groundwater or surface

P. de Voogt (ed.), *Reviews of Environmental Contamination and Toxicology Volume 244*, Reviews of Environmental Contamination and Toxicology 244,
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waters." This mischaracterizes how pore water data was interpreted in this project. First, there was no groundwater remediation project referenced in the chapter, but rather a combined sub-slab depressurization and soil vapor extraction system that was installed as vapor intrusion mitigation. As some mass of contaminant is removed from the subsurface by operating this system, arguably there is some remediation of smear-zone soils, but these systems are not used to remediate groundwater. They were installed to mitigate the vapor intrusion pathway in nearby impacted buildings and take advantage of any possible removal of contamination from soils. This was clearly identified in the chapter. Second, it is appropriate to compare pore water data to groundwater cleanup levels, since Alaska regulations (18 AAC 75.345 Groundwater and surface water cleanup levels) indicate that contaminated groundwater (which includes hyporheic zone groundwater) should not cause a violation of surface water quality standards. ADEC's Contaminated Site Program acknowledges that if contaminated pore water discharges into a surface water body (the Chena River in this case), it is diluted by the receiving surface water body and likely poses little risk to human or ecological receptors, and may not render a water body as impaired. Third, the major reason to use groundwater cleanup levels as a benchmark for pore water data is to assess the fate and transport of the contaminated groundwater. Fish (2011) clearly states, "Pore water was collected from the banks of the Chena River to investigate contaminant migration into the river and the viability of the sediment and surface water contact and ingestion exposure pathways." Fourth, I acknowledge pore water may not necessarily neatly "fit" into various regulatory mandates and regulations. But Alaska Water Quality Standards are meant to be protective of multiple water uses, including drinking water, and all groundwaters of the State are considered as drinking water sources, unless explicitly reclassified. Thus it is very appropriate to examine pore water data in light of Federal MCLs, as well as groundwater cleanup levels and surface water quality standards of the State, to inform investigators not only of exceedances or violations, but also of contaminant exposure pathways where receptors may be at risk. I do agree with the concept that the authors are promoting, in that use of pore water data needs some standardization. Regardless of defined standards, however, pore water data is still useful to examine contaminant fate and transport and receptor exposure risks, as long as investigators recognize the limitations of the pore water data.

2 Reply: Response to Dr. Fish's Comments Regarding "Pore Water Collection, Analysis, and Evolution: The Need for Standardization" by Gruzalski et al.

Jacob G. Gruzalski, James T. Markwiese, Neil E. Carriker, William J. Rogers, Rock J. Vitale, and David I. Thal

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Dear Editor-in-Chief,

The authors wish to thank Dr. Fish for his interest and comments (*Reviews of Environmental Contamination and Toxicology*, Vol. 244, this issue) regarding our paper (*Reviews of Environmental Contamination and Toxicology*, Vol. 237, pp. 37–51, Nov 2015 DOI: 10.1007/978-3-319-23573-8_2). We apologize for our mischaracterization of his work with the Alaska Department of Environmental Conservation and are grateful for his clarification on realistic uses of pore water data for his project and others of similar scope. In the context of our experience comparing pore water data from fairly stable sediment on the bottom of a constantly flowing river to drinking water limits without considering realistic dilution factors provides, at best, minimal useful information for resource management decisions beyond simply identifying a contaminant transport pathway. Dr. Fish's final sentence is well stated and one with which we fully agree.

Reference

Fish J (2011) Use of pore water as part of contaminated sites management: case studies in Kotzebue and Fairbanks, Alaska. In: The fourth interagency conference of research in the watersheds, Fairbanks, AK, 26–30 Sept 2011, pp 2–8

A Global Perspective of Fine Particulate Matter Pollution and Its Health Effects

Arideep Mukherjee and Madhoolika Agrawal

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P. de Voogt (ed.), *Reviews of Environmental Contamination and Toxicology Volume 244*, Reviews of Environmental Contamination and Toxicology 244,
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Abbreviations

CI	Confidence interval
CPCB	Central Pollution Control Board
HR	Hazard ratio
IQR	Interquartile range
NAAQS	National ambient air quality standard
OR	Odds ratio
PI	Posterior interval
PM	Particulate matters
$PM_{2.5}$	Particulate matters of 2.5 μm size or less
WHO	World Health Organization

1 Introduction

The particulate matter (PM) pollution is a global burden, which not only affects the physical atmosphere, but also has drastic effects on human civilization since the beginning of anthropogenic interferences to the natural ecosystems. The greatest concern lies over the negative impact on human health as exposure to ambient PM pollution is ranked 12th among the Global DALYs (disability-adjusted life-years) risk factors according to Global burden of disease study in 2013 (Forouzanfar et al. 2015). An aerosol is a suspension of a solid or liquid particle in the air. For health purposes, aerosol or particulate matter (PM) is typically defined by size, with the smaller particles having more health impacts. Particles with a diameter <10 μm are called PM_{10} and with a diameter <2.5 μm $PM_{2.5}$.

Climate change combined with air pollution reduces the healing capacity (intrinsic ability to restore back to its earlier state in time) of natural systems, and causes extreme variability (variations over a wide range) leading to more serious health effects (Fig. 1). PM in air is cosmopolitan in distribution in all types of ecosystems from desert to oceans. PM has both direct and indirect effects on the earth by both cooling and heating of the atmosphere. Aerosols in the atmosphere impact both climate and biogeochemistry in the earth's surface after deposition (Von Schneidemesser et al. 2015). It is estimated that anthropogenic changes in aerosols contribute to ~40.0 % change in short wave radiative forcing and ~60.0 % increase in the number of Cloud Condensation Nuclei (CCN), the small particles on which water vapor condenses (Mahowald et al. 2011). Aerosols have a short atmospheric lifetime (about a week), so their effects are more evident than greenhouse gases (GHGs) (Kopp and Mauzerall 2010). Most PM occurs naturally in the environment as desert dust, forest fire, sea salt, and sulfates from volcanoes, but increasing anthropogenic interferences in the environment have significantly increased the PM burden (Zhang et al. 2015). Large cities with higher traffic and poor air pollutant dispersion are more susceptible to negative health effects due to PM. High traffic density in urban areas contributed up to 140 % higher $PM_{2.5}$ levels compared to suburban background area (Dongarra et al. 2010).

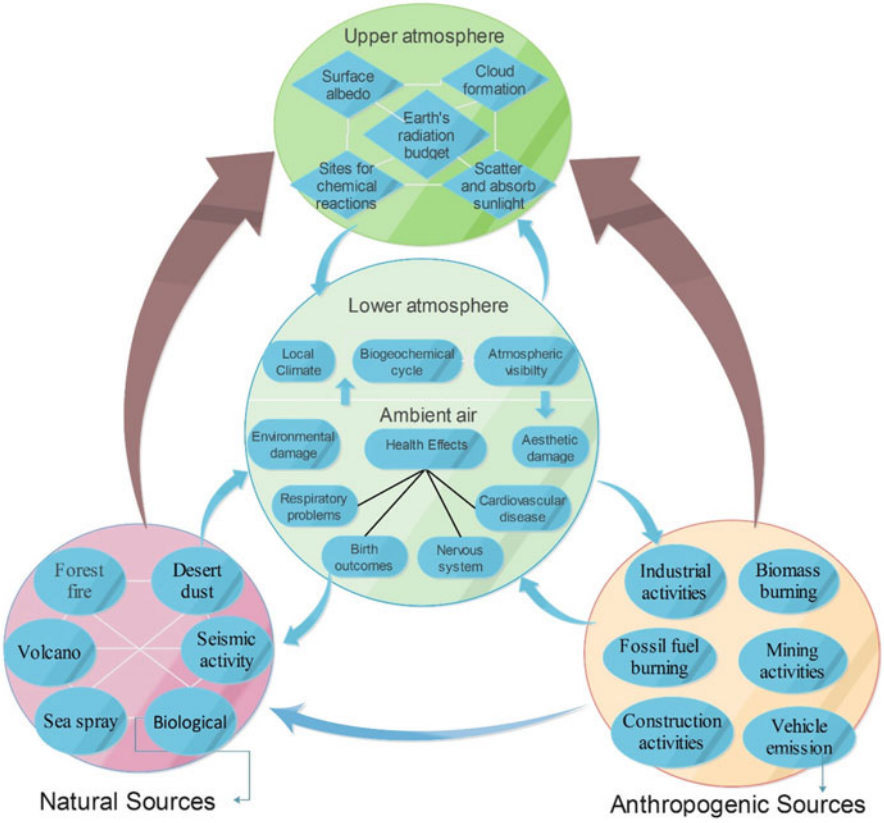

Fig. 1 Effects of particulate matter on different components of the atmosphere

The major component of PM having potential negative health effects are traffic and combustion related fine PM (Mills et al. 2009; Pope and Dockery 2013). Earlier reports have mostly highlighted PM exposure and short- or long-term effects with PM-related hospital admissions, mortality and morbidity (Samet et al. 2000; Pope et al. 2002; Dominici et al. 2006), but recent scientific findings have identified several health effects of PM as fine particles trigger inflammatory response, plaque formation in the blood vessels, lung cancer, term low birth weight, mutagenicity, changes in gene expression, and immune responses (Coronas et al. 2009; Wichmann et al. 2009; Raaschou-Nielsen et al. 2013; Dadvand et al. 2014; Ding et al. 2014; Hennig et al. 2014; Apte et al. 2015; Chafe et al. 2014).

As fine PM is one of the major air pollutants in the world and most severe to health, it is of utmost important to summarize a global scenario of PM status and its health effects. So considering these points the manuscript attempts to cover a global perspective of the current status of fine particulate matter pollution ($PM_{2.5}$) particles with an aerodynamic diameter of 2.5 μm or less. Their range of concentrations and

sources and their health effects in urban, suburban, rural, and remote areas of the world are well documented and analyzed. The major objective of this review is to collate the information on spatial variations in fine PM concentrations and their exceedances in different continents of the world, with special reference to country and city specific variations. Since fine PM is mainly responsible for negative health impacts, source apportionment of fine PM, its constituents, and different health impacts were also reviewed.

2 Method

World Wide Web was searched for combinations of key words such as fine particulate matter pollution, $PM_{2.5}$, source apportionment of fine PM, constituents of $PM_{2.5}$, health effects of fine PM in PubMed, Scopus, Google scholar, and SciVerse. We selected 500 peer-reviewed articles published after year 2000 containing information on fine PM concentrations and related health effects. Among the articles searched, only those satisfying the criteria such as measurement of fine PM and source apportionment by standard methodology, health effects using human subjects and relevant statistical analyses for health assessment were further screened for the review. Local studies with only limited data for specific season or location were excluded with exception of a few studies having no long-term data available for comparison at such locations. For global and country specific variations in fine PM, databases from government organizations like Central Pollution Control Board (CPCB) in India, United States Environmental Protection Agency (US EPA) in the USA, Chinese National Environmental Monitoring (CNEM) in China, European Environment Agency (EEA) for Europe, and World Health Organization (WHO) for global database were also screened (CPCB 2013; CNEM 2013; EEA 2013, US EPA 2015; WHO 2014). Relevant published reviews and meta-analysis were also searched to identify the health effects of $PM_{2.5}$ and its constituents.

3 $PM_{2.5}$ Guidelines and Standards

$PM_{2.5}$ and below in ambient air significantly cause severe health concern, even in low concentrations. Several national and international monitoring agencies have proposed guideline values to reduce health effects caused by $PM_{2.5}$. The values above the guidelines are suggested to be toxic or causing severe negative effects on breathing for both short and long durations, but no concentration is identified at which no health effect is recorded (WHO 2005). These values are suggested based on scientific evidences of toxicity of specific pollutant, geographic location, emission sources, economic conditions, and monitoring duration. These guidelines are implemented to reduce or control the pollutant under the specific conditions of a country. Selected $PM_{2.5}$ guideline values for 24-h average (short term) and annual average (long term) of national and international agencies are given in Table 1.

Table 1 $PM_{2.5}$ ambient air quality guideline values (μg m^{-3})

Agency/country	24-h	Annual	References
WHO	25.0	10.0	WHO (2005)
	75.0 (IT-1)	35.0 (IT-1)	
	50.0 (IT-2)	25.0 (IT-2)	
	37.5 (IT-1)	15.0 (IT-1)	
US EPA	35.0	12.0 (Primary)	US EPA (2015)
		15.0 (Secondary)	
China	35.0 Class 1	15.0 Class 1	GB-3095 (2012)
	75.0 Class 2	35.0 Class 2	
India	60.0	40.0	CPCB (2009)
Europe		25.0	EEA (2013)
Australia	25.0	8.0	NEPM (2002)
Canada	30.0 (Old)	10.0 (2015)	ECC (2013)
	28.0 (2015)	8.80 (2020)	
	27.0 (2020)		
Mexico	65.0	15.0	NOM (2005)
Bangladesh	65.0	15.0	Begum et al. (2013)
Thailand	50.0	25.0	PCD (2010)
Japan	35.0	15.0	EQSJ (2009)

IT-1 interim target-1, *IT-2* interim target-2, *IT-3* interim target-3

4 Global $PM_{2.5}$ Status and Exceedance

4.1 Asia

Asia is the largest and most populated continent in the world with varying landscapes. Most of the developing countries in Asia have very high levels of air pollutants (WHO 2014). West and South Asia are the most populated and polluted zones in the world. In South Asia, Pakistan, Bangladesh, and Afghanistan have very high $PM_{2.5}$ concentration and values were 8.00–10.0 times above the World Health Organization (WHO) annual mean standard of 10.0 μg m^{-3} (WHO 2005). In India, fine PM level was 5.00 times higher than the WHO annual mean standard. In West Asia, fine PM levels were very high in Qatar, Iran, and in United Arab Emirates although levels were significantly lower in Oman, Lebanon, and Israel (Fig. 2). In East Asia, Mongolia has very high PM level of 64.0 μg m^{-3} followed by China (41.0 μg m^{-3}), whereas Japan is the only country having $PM_{2.5}$ levels below the WHO annual mean standard (Fig. 2d). South-East Asia is comparatively less polluted by fine PM as most of the countries showed values below 25.0 μg m^{-3} except Vietnam and Myanmar (WHO 2014).

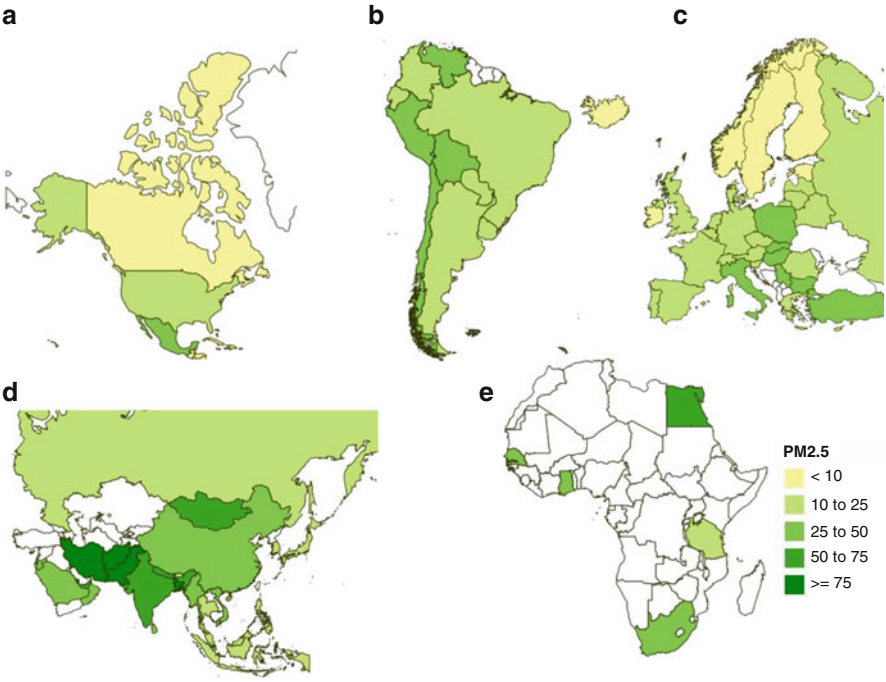

Fig. 2 Global distribution of $PM_{2.5}$ concentration (μg m^{-3}) in different continents of the world (**a**) North America, (**b**) South America, (**c**) Europe (**d**) Asia, and (**e**) Africa. (Data source WHO 2014)

4.1.1 India

Most of the major metropolitan cities in India violate the annual mean WHO and national mbient air quality standard (NAAQS) of India (CPCB 2009) for $PM_{2.5}$ (CPCB 2013) (Fig. 3). Major cities like Delhi, Ahmedabad, and Patna showed levels higher than 100 μg m^{-3} (CPCB 2013). Southern and northeastern part of India showed lower levels of $PM_{2.5}$ compared with other regions mostly due to higher vegetation cover, lower emissions, and planned urbanization (CPCB 2013; Tian et al. 2014). Most cities in north India are unplanned with huge population and poor road conditions that are ideal conditions for higher particulate episodes throughout the year. Seasonal variations were distinct with higher pollution load in winter and lower in rainy season (CPCB 2013). Chennai was found to be the least polluted with $PM_{2.5}$ and maximum levels were found in Delhi. Traffic is identified as a major cause of such higher $PM_{2.5}$ level in India (CPCB 2013).

Northern parts of India are highly polluted with PM levels in ambient air (Fig. 4). New Delhi, the capital of India, showed very high $PM_{2.5}$ levels ranging between 27.0 and 227 μg m^{-3} in urban atmosphere which exceeded the annual mean NAAQS of India (CPCB 2009) by 2.40 times (Tiwari et al. 2009). Further Tiwari et al. (2013) reported a higher annual mean of 122 μg m^{-3}, with variations between

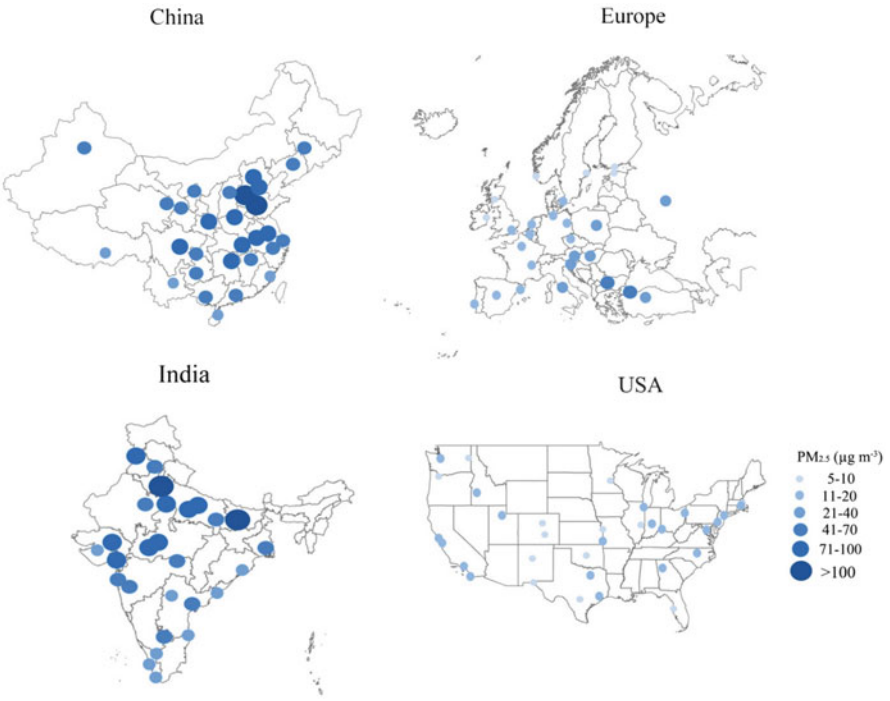

Fig. 3 Mean annual $PM_{2.5}$ concentrations for year 2013 in China and the USA and for 2011 for India and Europe (Data Source CPCB 2013; CNEM 2013; EEA 2013, US EPA 2015, WHO 2014)

54.3 and 338 μg m^{-3} in New Delhi. Higher concentration of fine PM in northern India is a direct result of excessive biomass burning, coal burning, traffic, and dust storms in summer from Thar Desert of Rajasthan (Kulshrestha et al. 2009; Tiwari et al. 2013). Mean $PM_{2.5}$ concentrations in both urban and rural areas in Agra were more than double the annual mean NAAQS of India (CPCB 2009), and annual average levels were 10.5 and 9.10 times higher than annual mean WHO standard, respectively (Kulshrestha et al. 2009). Similarly, in Kanpur ambient $PM_{2.5}$ levels in commercial, residential, and control sites were well above the annual mean national standard of India and 14.0, 9.50, and 6.00 times of WHO annual mean standard at respective sites (Sharma and Maloo 2005).

$PM_{2.5}$ levels ranged between 34.5 and 112 μg m^{-3} in the largest city of eastern India, Kolkata, with annual mean value, almost 1.80 times the annual mean national standard (CPCB 2009), and maximum exceedance occurred during winter season (2.30–2.80 times) (Chatterjee et al. 2012). In Raipur, another growing urban center in eastern India, $PM_{2.5}$ levels ranging from 24.0 to 269 μg m^{-3} with a mean value of 150 μg m^{-3}, which was more than three times higher than annual mean NAAQS (CPCB 2009). But the most concerning factor was that $PM_{2.5}$ levels exceeded the annual mean standard for 94.0 % of sampling days (Deshmukh et al. 2013).

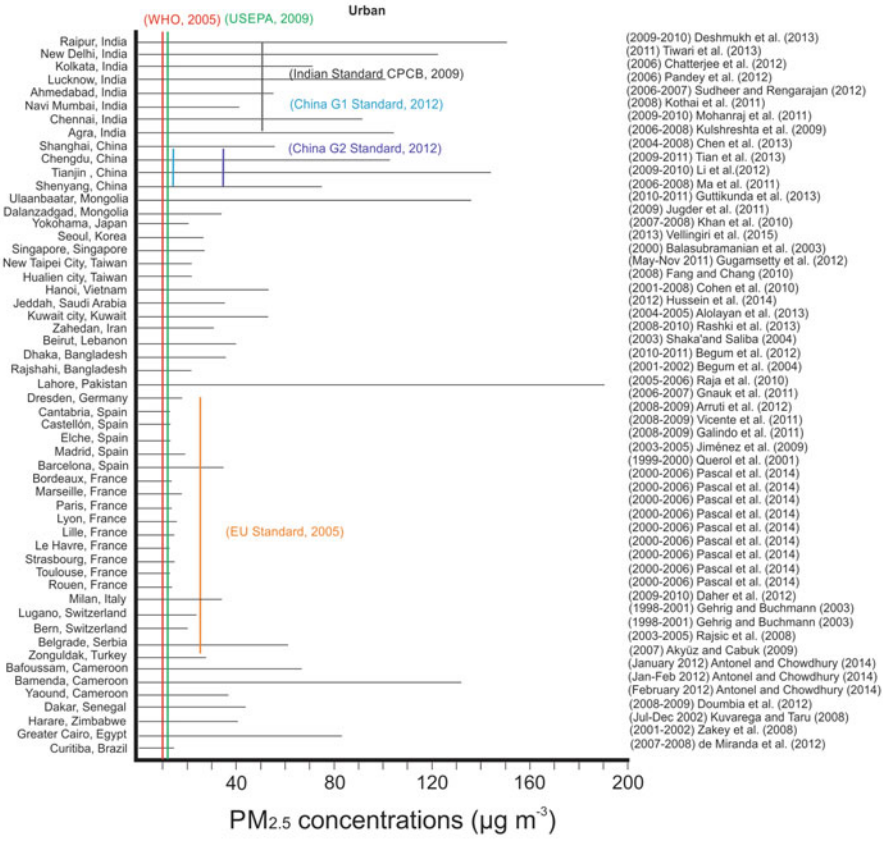

Fig. 4 Variations in $PM_{2.5}$ concentrations at different urban locations throughout the world. Concentrations are mean values based on measurements performed in different years (varying from 1999 to 2013)

Monitoring data from heavily urbanized area of Ahmedabad, one of the largest city in western India, revealed $PM_{2.5}$ concentrations to be 1.30 times the NAAQS and 5.00 times of WHO annual mean standard during the study period from 2006 to 2007 (Sudheer and Rengarajan 2012). A study based on different land use patterns in Mumbai city by Joseph et al. (2012) reported 59.0, 76.0, 67.0, and 80.0 % exceedance of NAAQS (CPCB 2009) for $PM_{2.5}$ at control, kerb, residential, and industrial sites, respectively.

4.1.2 China

China showed higher $PM_{2.5}$ concentrations in all major cities with violation of annual mean Class I Chinese ambient air quality standards (CAAQS) of 15.0 µg m^{-3} and Class II standard of 35.0 µg m^{-3} (GB3095 2012) (Fig. 3). Shijiazhuang and Jinan showed

values above 100 μg m^{-3} in north, whereas apart from Haikou and Fuzhou in south-east and Yinchuan, Lhasa, and Kunming in western China, all other cities showed $PM_{2.5}$ levels above 50.0 μg m^{-3} (WHO 2014). Seasonal variations were distinct with maximum concentration during winter and lowest during summer season. Higher exceedance levels of $PM_{2.5}$ concentrations were mostly in northern part compared to south-east and west and exceedance rates were more in winter than in summer season.

In urban and suburban areas in Tianjin, $PM_{2.5}$ mass concentration was above CAAQS (GB3095 2012) and almost 13.0 times the WHO annual mean standard (Li et al. 2012). $PM_{2.5}$ mean concentrations were just above 24-h CAAQS at suburban sites near two largest cities, Beijing and Shanghai (Zhou et al. 2009), however, at an urban site in Shanghai, concentrations varied from 8.00 to 389 μg m^{-3} with annual mean level exceeding annual mean CAAQ Class II standard by 1.60 times during the study period of 2004–2008 (Chen et al. 2013). Hu et al. (2014) studied short-term $PM_{2.5}$ levels during June–August 2013, in 13 cities located in North China Plain (NCP) and in 20 cities in Yangtze River Delta (YRD). Average $PM_{2.5}$ levels were 77.0 μg m^{-3} in NCP region and 42.8 μg m^{-3} in YRD region and in both the regions, annual mean CAAQ Class I standard was exceeded by 83.0 % and 51.0 % of times, respectively. Mean annual level of $PM_{2.5}$ in Chengdu was 10.0 times of the WHO annual mean standard and almost three times of annual mean CAAQ Class II standard of 35.0 μg m^{-3}.

4.1.3 Other Asian Countries

$PM_{2.5}$ levels were recorded very high in Lahore, Pakistan with annual average concentration of 194 μg m^{-3} during 2007–2008, and $PM_{2.5}$ levels were above 100 μg m^{-3} for 84.0 % of sampling days (Stone et al. 2010). Khwaja et al. (2015) reported $PM_{2.5}$ concentrations varying between 30.0 and 279 μg m^{-3} with an annual mean of 101 μg m^{-3} in the megacity of Karachi, Pakistan during 2008–2009. Long-term monitoring results of $PM_{2.5}$ concentrations from 1996 to 2011 in Dhaka, Bangladesh showed values ranging between 5.26 and 240 μg m^{-3} with a mean value of 36.7 μg m^{-3}, which was 3.70 times higher than WHO annual mean standard and 2.40 times of Bangladesh annual standard of 15.0 μg m^{-3} (Begum et al. 2013) (Fig. 4). In an urban traffic-influenced site in Dhaka, annual mean $PM_{2.5}$ concentration level was 82.5 μg m^{-3}, which was ascribed to high traffic under urban influence (Begum et al. 2012). Alolayan et al. (2013) in Kuwait City reported $PM_{2.5}$ levels to be 5.00 times the WHO annual mean standard and exceedance of 78.0 % days above WHO 24-h mean value. In Jeddah, Saudi Arabia, $PM_{2.5}$ levels were 3.40 times of the WHO annual mean standard (Hussein et al. 2014). $PM_{2.5}$ concentrations varied between 23.0 and 186 μg m^{-3} with an average of 74.2 μg m^{-3} during 2000–2001 in Jeddah, Saudi Arabia (Hussain et al. 2014).

Compared to other Asian megacities, $PM_{2.5}$ levels were comparatively lower in Singapore with annual mean $PM_{2.5}$ concentrations of 27.2 μg m^{-3} and levels exceeded only 30.0 % times, the value of 30.0 μg m^{-3}, although the mean level was 2.70 times higher than WHO annual mean standard (Balasubramanian et al. 2003). In urban residential site in Karachi, Pakistan, $PM_{2.5}$ concentration varied

from 27.4 to 175 μg m^{-3} with annual mean level, 8.35 times higher than the annual mean WHO standards (Mansha et al. 2012). Han et al. (2011) monitored $PM_{2.5}$ levels at a rural site in Chuncheon, Korea and reported that about 37.0 % of samples exceeded 24-h US NAAQS of 35.0 μg m^{-3} and annual mean level was 3.00 times the annual mean WHO standard (Fig. 6). Urban residential site in Kaohsiung City, Taiwan showed $PM_{2.5}$ levels ranging from 0.80 to 162 μg m^{-3} with annual mean value three times of the annual mean WHO standard during 2006–2010 (Cheng et al. 2014).

4.2 Africa

In the African continent, fine PM levels were above 30 μg m^{-3} in Senegal, Mauritius, and Ghana whereas in South Africa, level was below 30 μg m^{-3} (Fig. 2e). Compared to other countries in Africa, Ghana showed high mean $PM_{2.5}$ value of around 49 μg m^{-3} (WHO 2014). Due to lack of data in the most of the countries in this region, limited information is available on fine PM levels in Africa. Poor air quality in African continent is not new with excessive biomass burning for cooking and dusty roads. African dust storms add more concern to the already severely affected continent.

High $PM_{2.5}$ levels were observed by Doumbia et al. (2012) at a traffic-influenced site in Dakar, the capital and the largest city of Senegal in West Africa, where daily mean levels varied between 24.0 and 80.0 μg m^{-3} and annual mean concentration was several times higher than WHO annual mean standard. Dionisio et al. (2010) reported about 8.00–14.0 μg m^{-3} higher $PM_{2.5}$ levels in roadside compared to residential site in Accra, the capital of West African country of Ghana. Fine PM levels ranged between 3.00 and 53.0 μg m^{-3} at an urban background site and from 1.90 to 36.0 μg m^{-3} at a suburban site in Nairobi, Kenya, and both sites exceeded the 24-h WHO standard by 29.0 and 7.00 %, respectively (Gaita et al. 2014). $PM_{2.5}$ at a kerb side in Dares Salaam, the largest city of Tanzania ranged between 5.10 and 66.0 μg m^{-3} (Mkoma et al. 2010). Around an urban industrial area in Harare, Zimbabwe Kuvarega and Taru (2008) found mean $PM_{2.5}$ concentration of 40.5 μg m^{-3}, which exceeded the WHO annual mean limit throughout the monitoring period. Owoade et al. (2015) found fine PM ranging between 14.4 and 986 μg m^{-3} around scrap iron and steel smelting industries in South Western Nigeria during 2011–2012, with a mean value of 300 μg m^{-3} around the main production unit.

4.3 Europe

Europe seems to have much better air quality related to fine PM concentration compared to other regions of the world primarily due to planned development, green technology, reduction in emissions, and lower population density (Maas and Grennfelt 2016). Fine PM levels were least in Northwestern Europe with only United Kingdom, Denmark, and Lithuania having values above WHO guideline (Fig. 2c). In Western Europe, most of the countries have $PM_{2.5}$ values ranging between 15.0 and 20.0 μg m^{-3} (WHO 2014). In Eastern Europe, fine PM values above 20.0 μg m^{-3} were recorded in most of the countries except Romania and Belarus and maximum concentration was reported from Turkey, with annual average level of 39.0 μg m^{-3} (WHO 2014). In Southern European countries, annual fine PM values were just above the annual mean WHO levels of 10.0 μg m^{-3} in Spain, Portugal, and Malta, above 20.0 μg m^{-3} in Slovenia and Italy, above 30.0 μg m^{-3} in Serbia, and above 40.0 μg m^{-3} in Bulgaria (WHO 2014).

$PM_{2.5}$ levels in most European cities were well below the annual mean European Union (EU) $PM_{2.5}$ standard of 25.0 μg m^{-3} (Fig. 4). In some of the cities like Dublin (Ireland), Stavanger (Norway), Stockholm (Sweden), and Helsinki (Finland), the levels were even below the annual mean WHO $PM_{2.5}$ standard of 10.0 μg m^{-3}. In Madrid (Spain), Lisbon (Portugal), and Glasgow (UK), levels were just above or around the annual mean WHO standard. Only few cities showed values above the annual mean EU $PM_{2.5}$ standard like Sofia (Bulgaria) and Istanbul (Turkey), where annual mean levels were twice the EU permissible limit. Larger European cities like Paris, Berlin, Barcelona, Prague, Moscow, and London also showed $PM_{2.5}$ values below EU permissible limit, but were well above WHO, $PM_{2.5}$ annual mean standard.

Rajšić et al. (2008) reported $PM_{2.5}$ concentration to be three times higher than the European Commission (EC) annual limit of 20.0 μg m^{-3} and six times of the WHO annual limit in Belgrade, Serbia. Roadside monitoring of $PM_{2.5}$ in Athens, Greece, showed levels ranging from 8.00 to 135 μg m^{-3} with annual mean level almost four times of the annual mean WHO and 1.60 times of the annual mean European Union (EU) standards (Chaloulakou et al. 2005). In dense traffic area around a highway in Istanbul, Turkey, Onat et al. (2013) found $PM_{2.5}$ levels ranged from 23.8 to 81.5 μg m^{-3} whereas $PM_{2.5}$ value was observed above 35.0 μg m^{-3} during 60 % of the total monitoring period.

Mean annual $PM_{2.5}$ concentration was twice the EU and five times of the WHO annual mean standards in industrialized city of Bursa, Turkey (Kendall et al. 2011). Mean $PM_{2.5}$ concentrations were 24.11 and 64.3 μg m^{-3}, respectively, in suburban and urban areas in Izmir, Turkey during 2004–2005 (Yatkin and Bayram 2008). In three cities, Pavia, Verona, and Torino in Northern Italy, $PM_{2.5}$ levels were 1.4, 1.5, and 1.9 times of the annual mean EU standard whereas exceedance in daily air quality value was more than 50 % in all these cities (Traversi et al. 2009). Lazaridis et al. (2008) found $PM_{2.5}$ concentration close to the EU annual mean, but were 2.50–2.70 times higher than the annual WHO standard at Akrotiri station, an urban

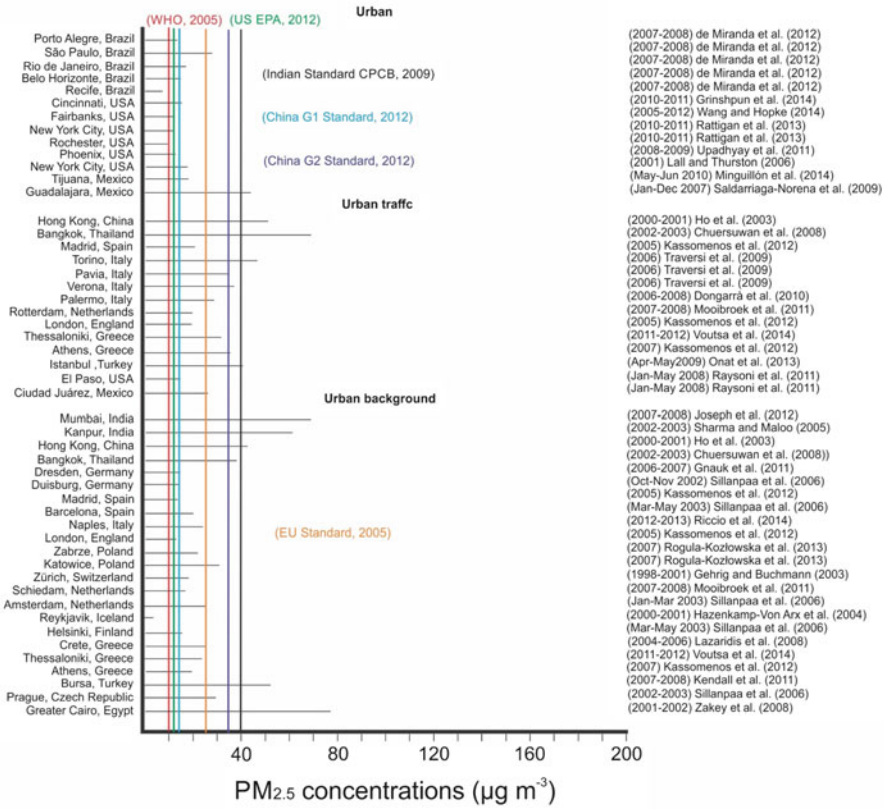

Fig. 5 Variations in $PM_{2.5}$ concentrations at different urban, urban traffic, and urban background locations throughout the world. Concentrations are mean values based on measurements performed in different years (varying from 1998 to 2013)

background area of the island of Crete, Greece (Fig. 5). In suburban areas in Cartagena, Spain, $PM_{2.5}$ concentrations ranged from 7.00 to 47.0 μg m^{-3} with annual mean below the EU standard and 2.20 times the annual mean WHO standard (Fig. 6) (Negral et al. 2008). Long-term monitoring results from 2003 to 2012 at a rural site in Melpitz, Germany showed that $PM_{2.5}$ levels were consistently above the annual mean WHO standard (Spindler et al. 2013) (Fig. 6). Hazenkamp-Von Arx et al. (2004) monitored $PM_{2.5}$ levels in 21 cities in Europe for 1 year and found $PM_{2.5}$ levels ranging from 3.70 to 44.9 μg m^{-3} with lowest concentration in Reykjavik, the capital of Iceland and maximum in Turin, Italy. In most of the major cities like Paris, Barcelona, and Antwerp, $PM_{2.5}$ levels were above the annual mean WHO standard. A similar study from 20 European sites during 2008–2011 found that 16 out of 20 sites showed $PM_{2.5}$ levels above the WHO annual limit, whereas except Turin, Italy, all other cities were below the EU annual limit (Eeftens et al. 2012).

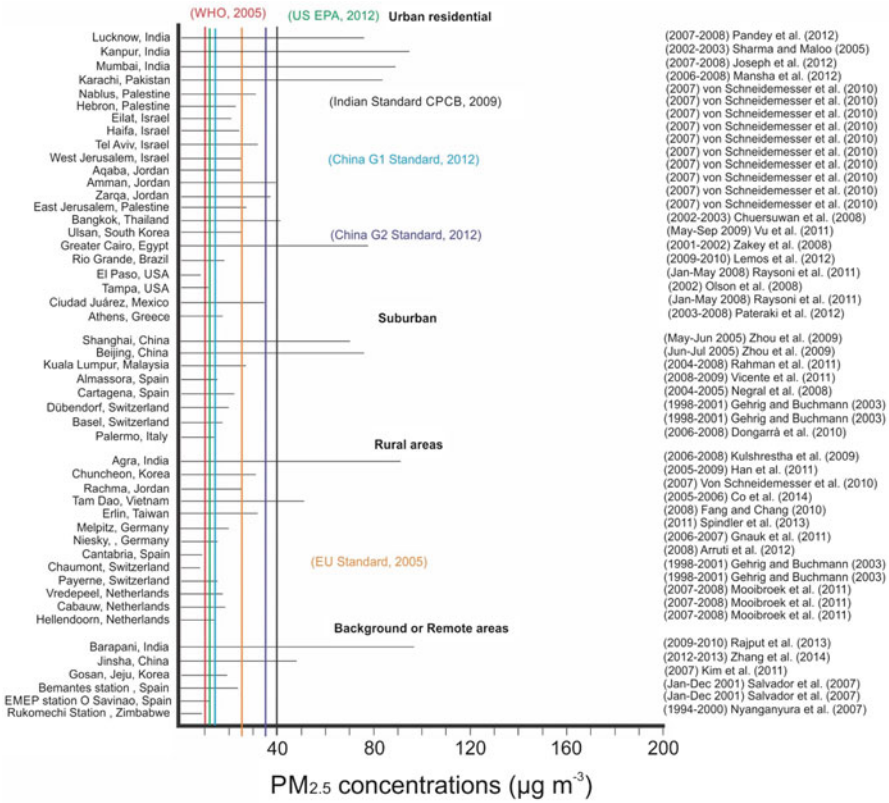

Fig. 6 Variations in $PM_{2.5}$ concentrations at different urban residential, suburban, rural, and remote location throughout the world. Concentrations are mean values based on measurements performed in different years (varying from 1994 to 2013)

4.4 South America

Unlike Asia and Africa, South American countries have regulated fine PM levels up to a significant level (WHO 2014). In most of the countries, $PM_{2.5}$ levels were below 30.0 µg m^{-3} with exception of Peru where concentration was 39.0 µg m^{-3}. In Brazil and Columbia, values were below 25.0 µg m^{-3}, whereas in Uruguay, Argentina, Ecuador, and Paraguay levels were even below 20.0 µg m^{-3} (Fig. 2b). $PM_{2.5}$ estimation in highly traffic area in six Brazilian state capitals revealed that concentration was maximum in Sao Paulo (28.1 µg m^{-3}) and least in Recife (7.10 µg m^{-3}). In all the cities except Recife, levels were higher than the annual mean WHO and USEPA standards (de Miranda et al. 2012).

Mariani and de Mello (2007) reported $PM_{2.5}$ concentration of 17.0 µg m^{-3} at a costal urban site in Rio de Janeiro, Brazil. Short-term study of $PM_{2.5}$ levels by Lemos et al. (2012) in urban, industrial, and residential areas in Rio Grande city,

Brazil showed that levels were below the Brazilian standard, but higher than 24-h WHO standard on few occasions during the study period. $PM_{2.5}$ mean concentration was 71.0 and 61.0 μg m^{-3} in urban and semiurban areas of the Córdoba, the second largest city of Argentina which was three times higher than the EU and seven times higher than the annual mean WHO standards during the period of July 2009–April 2010 (López et al. 2011).

4.5 North America

$PM_{2.5}$ levels in North American continent were variable with countries. Levels in Canada were below the WHO annual mean standard and were just above the standard in the USA (WHO 2014). In countries like Mexico levels were 2.50 times higher than the annual mean WHO standard (Fig. 2a).

According to US EPA dataset for $PM_{2.5}$ (Weighted Annual Mean) for year 2013 (US EPA 2015), levels in most of the areas in the USA were below NAAQS (US EPA 2012) annual mean standard of 15.0 μg m^{-3} (Fig. 3). Only few areas having higher $PM_{2.5}$ levels are Bakersfield, CA; Fairbanks, AK; Fresno, CA based on Core Based Statistical Area (CBSA) in the USA. The database clearly showed that $PM_{2.5}$ is under control in most of the areas in the USA. In many areas values were even below 5.00 μg m^{-3}. When 98th percentiles of the daily average measurement values for the whole period were compared, exceedance of 24-h NAAQS of 35 μg m^{-3} was more prominent (US EPA 2012). It indicates that short-term effects of $PM_{2.5}$ are more realized than the long-term ones. Results of 537 monitoring sites for $PM_{2.5}$ from 2000 to 2013 indicate a 34.0 % national decrease in fine PM concentration in the USA (US EPA 2014).

Saldarriaga-Noreña et al. (2009) in Guadalajara, Mexico found $PM_{2.5}$ levels to be 2.90 and 3.50 times the annual mean Mexican standard of 15.0 μg m^{-3} in industrial and traffic-influenced sites, with values ranging from 2.00 to 181 μg m^{-3} during the study period (Fig. 4). Raysoni et al. (2011) analyzed $PM_{2.5}$ levels outside schools in US-Mexican border and found higher concentrations at schools in Ciudad Juárez, Mexico compared to El Paso, USA during January to May 2008. A short-term study by Olson et al. (2008) at a residential outdoor in Tampa, USA showed that $PM_{2.5}$ level was three times below the USEPA 24-h standard during October and November 2002. Long-term monitoring results in both New York City and Rochester, USA showed decreasing pattern of $PM_{2.5}$ level from 2003 to 2012 with values within the annual mean WHO and US EPA levels in Rochester and just above WHO level in New York City (Rattigan et al. 2013). In four cities in Connecticut and one in Massachusetts, $PM_{2.5}$ levels ranged between 11.9 and 17.0 μg m^{-3} with maximum concentration of 18.3 μg m^{-3} during cold season in New Heaven and lowest concentration of 11.6 μg m^{-3} at Hartford (Lee et al. 2011). Qin et al. (2006) found average $PM_{2.5}$ concentration of 13.0–15.0 μg m^{-3} in different urban commercial area in New York City.

5 Source Apportionment for $PM_{2.5}$

Source apportionment studies help to recognize or characterize those factors that contribute to pollution levels. The composition of PM depends upon its origin and transformations that happen under different environmental conditions (Hyder et al. 2014). An effect of PM is elicited based on its chemical nature and toxicity. $PM_{2.5}$ is mostly generated due to combustion and emissions from automobiles (Fleisch et al. 2014). Major components of $PM_{2.5}$ are black carbon (BC), polycyclic aromatic hydrocarbons (PAHs), heavy metals, organic carbon, hydrocarbons, volatile organic hydrocarbons (VOCs), minerals, inorganic ions, and biological material (Tiwari et al. 2009; Traversi et al. 2009; de Miranda et al. 2012; Fleisch et al. 2014).

5.1 Asia

In New Delhi, India, Tiwari et al. (2009) reported that $PM_{2.5}$ was made up of undetermined fractions (40.9 %), secondary inorganic aerosols (27.1 %), salt aerosols (23.3 %), and mineral matter (8.70 %) indicating sources such as biomass and fossil fuel burning and soil derived particles. Source apportionment through principal component analysis (PCA) of $PM_{2.5}$ revealed that major contributors were vehicular emission (38.0 %), biomass burning (27.0 %), dust aerosols (18.0 %), and secondary anthropogenic components (11 %) in the eastern Indian megacity of Kolkata in 2006 (Chatterjee et al. 2012). $PM_{2.5}$ mass was mostly contributed by organic matter (36.0–52.0 %), secondary inorganic aerosols (21.0–27.0 %), crustal (6.00–12.0 %), non-crustal (4.0–8.00 %), and sea salt (6.00–11.0 %) in Mumbai, India (Joseph et al. 2012). Sudheer and Rengarajan (2012) in urban atmosphere of Ahmedabad, India reported that anthropogenic sources (80.0 %) contributed to $PM_{2.5}$ mass and identified industrial emission, biomass burning, vehicular emissions, and resuspended or long range transported dust as the major sources of particulate pollution.

Major contributors to high $PM_{2.5}$ in Karachi, Pakistan were industrial emissions (53.0 %), road dust (16.1 %), and secondary aerosols (12.4 %) (Mansha et al. 2012). Source apportionment study by Raja et al. (2010) in Lahore, Pakistan detected secondary particles (30.2 %), diesel emissions (28.3 %), biomass burning (14.8 %), coal combustion (13.3 %), and two-stroke vehicles (7.70 %) as the major contributors to observed $PM_{2.5}$ mass. Alolayan et al. (2013) in Kuwait City found maximum contribution of soil/sand dust (54.0 %) followed by oil combustion (18.0 %), petrochemical industry (12.0 %), local traffic (11.0 %), and transported traffic/smelter emissions (5.0 %) to $PM_{2.5}$, indicating that major sources in Kuwait city are of crustal origin which is approximately 50.0 % mass of $PM_{2.5}$, and were attributed to dust storm events in this area (Alolayan et al. 2013). Major sources of fine particles in Kuala Lumpur, Malaysia were two-stroke engines (35.7 %), motor vehicles (31.9 %), smoke/biomass burning (17.5 %), soil dust (8.30 %), and

industry (16.7 %) (Rahman et al. 2011). At a traffic site in Bangkok Metropolitan Region, Thailand, Chuersuwan et al. (2008) observed maximum contribution from automobiles (32.0 %), followed by biomass burning (26.0 %). PCA analysis revealed six major sources of $PM_{2.5}$ in Singapore as soil dust, metallurgical industry, emissions from biomass fires and local traffic, sea spray, and fuel oil combustion processes (Balasubramanian et al. 2003).

5.2 *Europe and Africa*

Rogula-Kozłowska et al. (2013) found that apart from industrial, power plants, and soil/road dust, combustion of fuels in domestic uses and automobiles contributed to 36.0–78.0 % $PM_{2.5}$ mass at two sites in Poland. In urban traffic and background sites, Voutsa et al. (2014) found secondary inorganic aerosols (SIA) to be a major part of $PM_{2.5}$ mass and identified local sources and long range transport as major contributors to SIA formation in Thessaloniki, Greece. In Barcelona Metropolitan area, Spain, vehicular-secondary sources contributed 73.0 % of $PM_{2.5}$ mass (Querol et al. 2001). Rajšić et al. (2008) reported combustion sources from traffic and resuspended road dust mostly contribute to trace metals in coarse and fine fraction of PM in a central urban area in Belgrade, Serbia. Negral et al. (2008) identified sources of $PM_{2.5}$ as crustal, traffic, secondary, marine, Zn metallurgy industry, and shipyard in Cartagena, Spain. Source profile of fine PM using positive matrix factorization (PMF) technique, in Izmir, Turkey, showed contributions of unidentified fraction (38.0 %), fuels and steel (37.0 %), traffic (12.0 %), mineral (9.00 %), and marine (4.00 %) sources in suburban area whereas unidentified (48.0 %), fuels and steel (22.0 %), traffic (15.0 %), marine (14.0 %), and mineral (1.00 %) in urban area Yatkin and Bayram (2008).

Zakey et al. (2008) identified waste burning to be a significant source of $PM_{2.5}$ in different environments of Greater Cairo area in Egypt. In Nairobi, Kenya, source apportionment by PMF identified five major sources of fine PM as traffic (39.0 %), mineral dust (35.0 %), mixed factor (13.0 %), industrial (7.0 %), and combustion (6.0 %) (Gaita et al. 2014). Around scrap iron and steel smelting industries in South Western Nigeria, Owoade et al. (2015) identified coking coal (83 %) as the major source of fine PM followed by soil (10.0 %), metallurgical industry (6.00 %), and electronic waste processing (1.00 %).

5.3 *North and South America*

Source apportionment analysis by Olson et al. (2008) in residential outdoors of Tampa, Florida identified sulfate (55.0 %), gasoline-powered motor vehicles (32.0 %), diesel-powered vehicles (8.00 %), and road dust (5.00 %) as major sources of $PM_{2.5}$ by using EPA Chemical Mass Balance Model. Pancras et al.

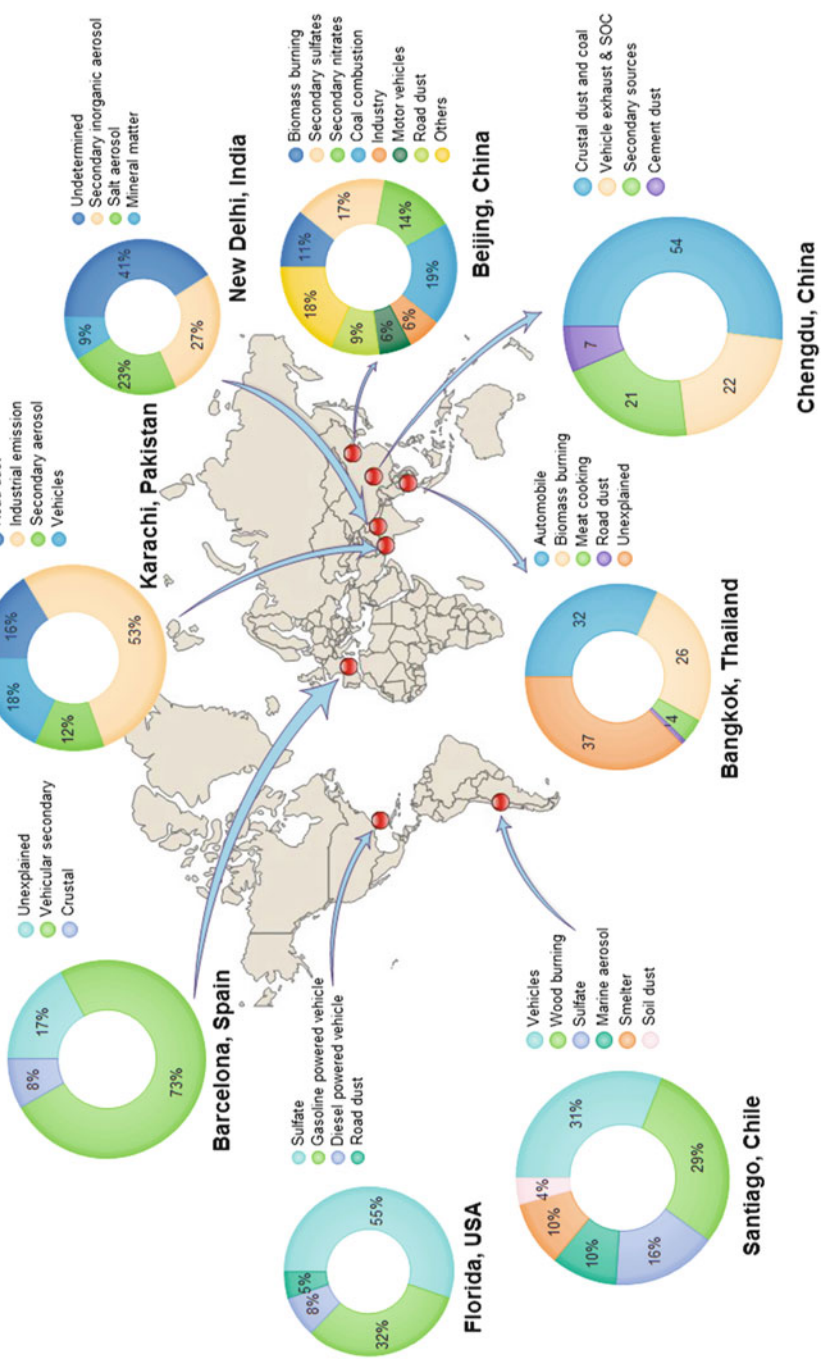

Fig. 7 Source apportionment of $PM_{2.5}$ in selected cities of the world

(2013) in Dearborn, Michigan, USA identified automobiles, road dust, and industries, secondary sources as the major sources of $PM_{2.5}$ pollution. Sources of $PM_{2.5}$ in four cities in Connecticut and one in Massachusetts in the USA were sulfur-related pollution, motor vehicle, road dust, oil combustion, and sea salt (Lee et al. 2011).

A study by Murillo et al. (2013) to identify sources of EC and OC in $PM_{2.5}$ mass characterized gasoline vehicles (10.0 %), on-road diesel emissions (16.0 %), railroad traffic (4.0 %), industrial combustion (9.0 %), and wood smoke (5.0 %) as major contributors to $PM_{2.5}$ in Costa Rica, Central America. Major sources of $PM_{2.5}$ in urban area of Córdoba City, Argentina were traffic (32.0 %), urban dust (54.0 %), soil dust (1.00 %), metallurgical industries and diesel (13.0 %), whereas in suburban site major contributors were urban dust (56.0 %) followed by traffic (28.0 %) and metallurgical industries and diesel (11.0 %) (López et al. 2011).

Different sources of fine PM in different regions of the world mostly depend on local activities, population density, atmospheric condition, and land use pattern. In Fig. 7 a detailed source profile of $PM_{2.5}$ at selected cities of the world, where exceedances are high is shown.

6 Gas to Particle Conversion and Secondary Aerosol Formation in Atmosphere

PM in the atmosphere is either directly generated through primary sources or by secondary formation due to gas to particle conversion. Secondary generation of PM contributes significant portion of fine PM in the atmosphere, as most of the secondary aerosols are formed from particles of size 0.10–2.50 μm (Baek et al. 2006; Hallquist et al. 2009; Zhang et al. 2015; Yao et al. 2016).

Major secondary aerosols in the atmosphere are organics, sulfate, nitrate, ammonium, and other inorganic salts, which are formed either by gas to particle conversion or by particle phase reactions (Zhang et al. 2015; Huang et al. 2016). Primary emitted gases in the atmosphere such as sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ammonia (NH_3), ozone (O_3), and VOC_s undergo photochemical oxidation, hydration, peroxyradical self-reaction, and condensation to produce various short lived intermediate molecules, which by process of nucleation, transformation, and coagulation ultimately produce secondary aerosols (Baek et al. 2006; Hallquist et al. 2009; Zhang et al. 2015). Secondary aerosol formation is a complex process controlled by concentrations of precursor atmospheric gases, particle size of existing PM, relative humidity, temperature, wind speed and direction, boundary layer height, and solar radiation (Huang et al. 2016). Higher relative humidity increases higher secondary formation by increasing oxidation of sulfur and nitrogen species in the atmosphere (Huang et al. 2016).

Secondary aerosol formation and their lifetimes in the atmosphere is variable with higher concentrations during day time which is correlated with higher

emissions of precursor gases and suitable atmospheric conditions for secondary aerosol formation. Mancilla et al. (2015) found 32.0 % higher organic carbonaceous aerosol during day hours compared to night time in an urban area of Monterrey, Mexico.

Inorganic aerosols such as sulfate and nitrate are formed through initial reactions of hydroxyl radicals (OH) with SO_2 and NO_2 by intermediate formation of sulfuric and nitric acid. Nitric acid may further react with ammonia gas to form ammonium nitrate aerosol. Sulfuric acid may further nucleate or may be absorbed at existing particle surfaces or form salts with other inorganic species such as ammonia (Baek et al. 2006; Hallquist et al. 2009; Zhang et al. 2015). In Beijing, China, secondary inorganic aerosols such as sulfate, nitrate, and ammonium contributed almost 82.8 % of total inorganic mass of water soluble inorganics in fine PM compared to 61.8 % contribution in coarse particle fraction, indicating higher secondary formation in fine mode aerosols (Zhang et al. 2015). Further, during polluted days contributions of secondary inorganic aerosols (sulfate, nitrate, and ammonium) were much higher (82.0–90.0 %) than in non-polluted days (64.0–81.0 %) in total PM inorganic mass.

In comparison to inorganic aerosols, reaction mechanisms of VOCs are much more complicated. Different VOCs released into the atmosphere undergo further oxidation to produce less volatile organics, such as aldehydes, carboxylic acids, ketones, and hydroperoxides, by photo-oxidation in the presence of hydroxyl radicals, ozone, nitrate, water vapor through several chemical reactions such as aldol condensation, ozonolysis, and peroxyradical self-reaction to form secondary organic species (Zhang et al. 2015). Significant contributions of around 11.0–52.0 % of secondary organic aerosols in $PM_{2.5}$ were observed in an urban metropolitan area of Monterrey, Mexico by Mancilla et al. (2015), whereas in an urban area of Ahmedabad city, 34.6 % and 45.0 % contributions to the total carbonaceous aerosol mass in $PM_{2.5}$ were reported by Sudheera et al. (2015), respectively, during day and night time.

7 Health Effects of $PM_{2.5}$

Among outdoor air pollutants, $PM_{2.5}$ is the most prevailing contributor to the global health liability (Anenberg et al. 2010). $PM_{2.5}$ has the ability to cross the alveoli of the lung and can finally enter into the blood stream to produce inflammatory or oxidative damage, leading to more drastic and long-term secondary effects on both cardiovascular and nervous systems (Araujo 2011; Breysse et al. 2013; Øvrevik et al. 2015). These health effects mostly depend upon age, lifestyle, health status, medical care, and exposure concentrations of the pollutants and climate. Percentage change in $PM_{2.5}$ mean annual exposure data between 1990 and 2010 showed a global increase of $PM_{2.5}$ exposure by 9.90 % (World Bank 2015). This global increase is directly correlated with 8.00 % increase in South Asia and 34.0 % increase in East Asia and Pacific. Significant reductions have, however, occurred in

European Union (42.0 %), Latin American countries (7.00 %), and the USA (29.0 %) in the last two decades (Fig. 8). A detailed summary of studies examining the association between $PM_{2.5}$ and health effects is presented in Table 2. It is beyond the scope of this article to assess all the health effects of $PM_{2.5}$, therefore in this section we have only discussed recent studies suggesting association of $PM_{2.5}$ and health effects from article published between 2004 and 2017.

7.1 *Evidences from Recent Reviews and Meta-Analysis of Health Effects of Fine PM*

Sun et al. (2015) assessed a relationship between fine particulate matter exposure during pregnancy and preterm birth based on 18 studies before 2014 and found a positive association between fine PM and preterm birth. Hamra et al. (2014) suggested outdoor air pollution and PM to be classified as Group-1 carcinogen based on the systematic review and meta-analysis of outdoor particulate matter exposure and lung cancer risk. In a systematic review and meta-analysis of short-term exposure to PM Bell et al. (2013) reported a higher risk of PM associated hospitalization and death for elderly persons and indicative evidence of higher risk of death for lower education and income group individuals. In a systematic review and meta-analysis of epidemiological time-series studies (61 studies, 40 investigated daily mortality, and 27 hospital admissions)

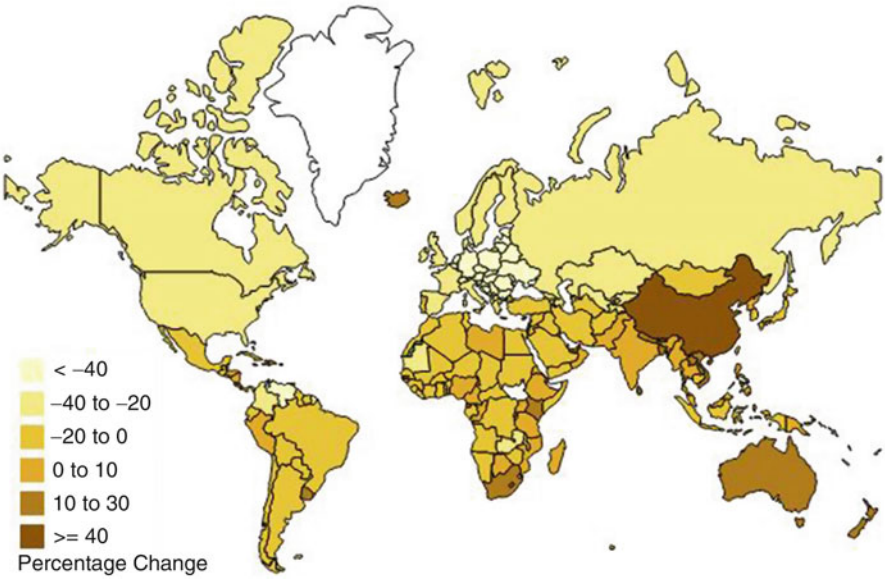

Fig. 8 Percentage change in mean annual exposure concentration of $PM_{2.5}$ between 1990 and 2010. Darker region indicates positive increase in $PM_{2.5}$ exposure, whereas lighter region indicates decrease in $PM_{2.5}$ exposure in the last two decades (World Bank 2015)

Table 2 Summary of studies examining the association between $PM_{2.5}$ and health impacts

Study	Data collection period	Location	Sample size	Age	Method/model	Results	Findings	References
Global burden of mortality due to $PM_{2.5}$		Global		All ages	Global atmospheric chemical transport model	3.50 ± 0.90 million cardiopulmonary and 220,000 ± 80,000 lung cancer mortalities annually	Anthropogenic $PM_{2.5}$ contributes substantially to global premature mortality	Anenberg et al. (2010)
Source-specific daily $PM_{2.5}$mass and hospital admissions	2001–2002	New York City, USA		≥65.0	Time-series generalized linear model	Source-related $PM_{2.5}$ (specifically steel and traffic) was significantly associated with hospital admissions	Toxicity of $PM_{2.5}$ depends on the source	Lall et al. (2011)
Mortality effects from PM size fractions	2005–2009	Beijing, China			Poisson generalized additive models	10.0 μg m^{-3} increase in $PM_{2.5}$ levels is associated with a 0.65 % (95 % CI: 0.29–0.80 %), 0.63 % (95 % CI: 0.25–0.83 %), and 1.38 % (95 % CI: 0.51–1.71 %) increase in non-accidental, respiratory and circulatory mortality, respectively	Significant associations between daily mortality with $PM_{2.5}$	Li et al. (2013)

(continued)

Table 2 (continued)

Study	Data collection period	Location	Sample size	Age	Method/model	Results	Findings	References
Short-term associations between $PM_{2.5}$ and mortality	2000–2006	9 French cities	548,474	15.0–74.0, >74.0	Poisson regression model	10.0 μg m^{-3} increase in $PM_{2.5}$ results in increase of (+0.7 % [−0.1; 1.6]) on all-ages non-accidental mortality	Significant association between short-term impacts of $PM_{2.5}$ on mortality	Pascal et al. (2014)
Traffic related air toxics and low birth weight (LBW)	2004–2006	Los Angeles, USA	220,528		Logistic regression	Approximately 5.00 % increase in adjusted odds of term LBW per IQR increase was associated with exposures to $PM_{2.5}$	Significant association between $PM_{2.5}$ with fetal growth	Wilhelm et al. (2012)
PM exposure with arterial BP and hypertension	2000–2003	Bochum, Essen, and Mülheim, Germany	4291	45.0–75.0	Generalized additive models	IQR increase in $PM_{2.5}$ (2.40 μg m^{-3}) was associated with estimated increases in mean systolic and diastolic BP of 1.40 mmHg (95 % CI: 0.5, 2.3) and 0.9 mmHg (95 % CI: 0.4, 1.4), respectively	Significant association between long-term exposure to PM with increased arterial BP and hypertension	Fuks et al. (2011)

Ambient air and traffic pollution and the presence of depressive symptoms	2005–2008	Boston, USA	765	≥65.0	Epidemiological studies depression scale	OR of CESD-R score ≥ 16.0 of 0.67 (95 % CI: 0.46, 0.98) per IQR (3.04 μg m^{-3}) increase in $PM_{2.5}$ over the 2 weeks preceding assessment	No association between exposure to ambient air pollutants with depressive symptoms	Wang et al. (2014)
Fine particulate air pollution and hospital admission	1999–2002	204 US urban counties	11.5 Million	> 65.0	Bayesian 2-stage hierarchical models and single lag and distributed lag over dispersed Poisson regression models	1.28 % (95 % CI, 0.78 %–1.78 %) increase in risk of heart failure per 10.0 μg m^{-3} increase in same-day $PM_{2.5}$	Significant association between short-term exposure to $PM_{2.5}$ with increases the risk for hospital admission for cardiovascular and respiratory diseases	Dominici et al. (2006)
Association between ambient air pollution and stillbirth	1998–2004	New Jersey, USA	1719	20.0–40.0	Time-stratified case-crossover design and conditional logistic regression	The relative odds of stillbirth increased with IQR increases in the mean concentrations of $PM_{2.5}$ (OR = 1.07, 95 % CI = 0.93–1.22) 2 days before delivery	Significant association between increased risk of stillbirth with short-term increases in air pollutants in the previous few days	Faiz et al. (2013)

(continued)

Table 2 (continued)

Study	Data collection period	Location	Sample size	Age	Method/model	Results	Findings	References
Long- and short-term effects of $PM_{2.5}$ exposures on population mortality	2000–2008	Massachusetts, USA			Time-series analysis	10.0 μg m^{-3} increase in $PM_{2.5}$ exposure was associated with a 2.80 % increase in PM-related mortality (95 % CI = 2.0–3.5) for short-term exposure and 1.6 (CI = 1.50–1.80) for long-term exposure	Short-term effects of $PM_{2.5}$ exposures was more severe on population mortality	Kloog et al. (2013)
Reduction in (traffic policy-related) air pollution concentrations with changes in respiratory health	2008, 2010		661		Eight busy urban and four suburban background locations were selected for air pollution and respiratory health measurement	Airway resistance decreased with a decline in PM (9.0 % per IQR)	Reduction in (traffic policy-related) air pollution concentrations may lead to small improvements in respiratory health	Boogaard et al. (2013)
Long-term exposure to ambient air pollution and lung cancer incidence	2008–2011	9 European countries	312,944		Cox regression models	Hazard ratio of 1·18 (0·96–1·46) with per 5.00 μg m^{-3} increase in $PM_{2.5}$	Significant association between long-term exposure to ambient air pollution and lung cancer	Raaschou-Nielsen et al. (2013)

Long-term exposure to fine PM and all cause, lung cancer and cardiovascular mortality	1979–1983 and 1999–2000	Columbia and Puerto Rico	1.2 Million	≥30.0	Cox proportional hazards survival model	Each 10.0 μg m^{-3} increase in fine particulate air pollution was associated with approximately a 4.0, 6.0, and 8.0 % increase risk of all cause, cardiopulmonary and lung cancer mortality	Significant association between long-term exposure to fine particulate air pollution and lung cancer and cardiovascular mortality	Pope et al. (2002)
Association between particulate air pollution and cardiovascular diseases	2008–2009	Karachi, Pakistan		$40.0 < \text{Age} < 60.0$	Generalized linear model (GLM) using negative binomial regression	1.60 % Increase in both hospital admissions and emergency room visits for cardiovascular disease with each 10.0 μg m^{-3} increase in $PM_{2.5}$ concentration	Higher levels of fine PM were associated with a striking elevation in rates of ER visits and hospitalizations for cardiovascular diseases	Khwaja et al. (2012)

IQR interquartile range, *CI* confidence interval, *HR* hazard ratio, *PI* posterior interval, *OR* odds ratio

Atkinson et al. (2015) assessed daily mortality and hospital admissions due to PM pollution. Morakinyo et al. (2016) identified the role of biological and chemical components of inhalable and respirable PM toxicity.

7.2 *Evidences from Recent Health Effects Studies of Fine PM*

In a recent study by Wu et al. (2017) in Chinese men, sperm concentration and count were found to be adversely effected by fine PM whereas no changes were observed in sperm motility. The study concludes that fine PM pollution effects sperm development specifically semen quality. Lu et al. (2017) identified a positive association between $PM_{2.5}$ exposure and glucose homeostasis during pregnancy in 3589 pregnant women in Chiayi City, Taiwan although short-term effect was non-significant. Chen et al. (2017) reported association between ambient $PM_{2.5}$ and influenza incidence in China and found that a 10.0 μg m^{-3} increase in $PM_{2.5}$ was associated with relative risk (RR) of 1.01 (95 % CI: 1.00, 1.02), of influenza incidence that appeared at lag day 2. The authors also estimated that exposure to fine PM may contribute to 10.7 % of incident influenza cases. Ajmani et al. (2016) reported significant association between worsening of olfactory function with $PM_{2.5}$, 6-month average exposure (per 1-IQR increase in $PM_{2.5}$: OR 1.28, 95 % CI 1.05, 1.55) in home-dwelling US adults age 57–85 years. Mehta et al. (2016) studied long-term $PM_{2.5}$ exposure effects on renal function in a cohort of older men in the Boston Metropolitan area and found a 2.10 μg m^{-3} interquartile range higher 1-year $PM_{2.5}$ was associated with a 1.87 mL $min^{-1}/1.73$ m^2 lower estimated glomerular filtration rate [95 % confidence interval (CI): −2.99, −0.76] suggesting a reduction in renal function due to fine PM. In Seoul, Korea, Kim et al. (2016) assessed the relationship between long-term $PM_{2.5}$ exposure and major depressive disorder in 27,270 participants 15–79 years of age from 2002 to 2010 and found risk of major depressive disorder was positively associated with long-term exposure to $PM_{2.5}$.

Results of meta-analysis by Flores-Pajot et al. (2016) found changes in autism spectrum disorder of 1.34 (95 % CI: 0.83, 2.17) with a 10.0 μg m^{-3} increase in $PM_{2.5}$ exposure. In a short-term $PM_{2.5}$ exposure and infant mortality study in Japan Yorifuji et al. (2016) reported odds ratios of 1.06 (95 % confidence interval: 1.01–1.12) for infant mortality and 1.10 (1.02–1.19) for post-neonatal mortality for a 10.0 μg m^{-3} increase in $PM_{2.5}$. Luo et al. (2015) in their systematic review and meta-analysis of short-term exposure to particulate air pollution and risk of myocardial infarction (MI) identified that 10.0 μg m^{-3} increment in $PM_{2.5}$ was associated with risk of MI (OR = 1.02; 95 % CI 1.01–1.03). Meta-analysis of 25 published epidemiological studies between maternal exposure to $PM_{2.5}$ and pregnancy outcomes found a positive association between increase in $PM_{2.5}$ concentrations and increase in the risk of low birth weight, preterm birth (PTB), and

small for gestational age (SGA) whereas the association was non-significant for stillbirth (Zhu et al. 2015). In a 5-year study from 2005 to 2009, in six counties in South-western Pennsylvania, authors found an increase in risk of childhood autism spectrum disorder for both prenatal and postnatal exposure to $PM_{2.5}$ (Talbott et al. 2015).

7.3 *Evidences from Global Health Effects Estimates of Fine PM*

Evans et al. (2013) derived global $PM_{2.5}$ exposure levels by utilizing remote sensing data of MODIS and MISR satellites, and found that the anthropogenic component of $PM_{2.5}$ was responsible for a global fraction of adult mortality by 8.00 % (5.30–10.5) due to cardiopulmonary disease and 9.40 % (6.60–11.8) due to ischemic heart disease. Climate change can modify these effects more strongly than what was expected. Fang et al. (2013) found that twenty-first century climate change results in approximate global increases of 100,000 premature mortalities associated with $PM_{2.5}$. Satellite derived pollution data showed that the anthropogenic component of $PM_{2.5}$ (95 % CI) was solely responsible for 12.8 % (5.90–18.5) increase in lung cancer-based adult mortality in the world (Evans et al. 2013). According to estimates of a global atmospheric chemical transport model (CTM) and health impact function, 75.0 % of excess mortalities in Asia and 17.0 % in Europe occurred because of high $PM_{2.5}$ concentrations (Anenberg et al. 2010).

7.4 *Evidences from Fine PM Exposure Health Effects Estimates*

Hennig et al. (2014) found significant associations between long-term exposure to $PM_{2.5}$ with high-sensitive C-reactive protein (hs-CRP), a marker of systemic inflammation with 4.53 % increase in hs-CRP concentration (95 % CI: 2.76, 6.33 %) per 1.00 μg m^{-3} increase in total $PM_{2.5}$ in three German cities (Table 1). The study on short-term associations between $PM_{2.5}$ and mortality in nine French cities by Pascal et al. (2014) clearly indicated that $PM_{2.5}$ had a significant impact on cardiovascular mortality and the impact was highest during summer season. Fleisch et al. (2014) evaluated the association of second trimester and $PM_{2.5}$ exposure in pregnant women in Boston, USA and found that $PM_{2.5}$ exposure was significantly associated with impaired glucose tolerance (IGT), but not with gestational diabetes mellitus (GDM) and indicated the direct effect of PM in abnormal glycemia during pregnancy.

Harrison et al. (2004) found a significant association between long-term exposures to $PM_{2.5}$ and mortality due to lung cancer based on American Cancer Society

cohort study. A significant association was found between long-term exposures to $PM_{2.5}$ with cardiovascular events in women in 36 US metropolitan areas (Miller et al. 2007). A 24.0 % increase in the risk of a cardiovascular event [Hazard Ratio (HR) = 1.24; 95 % CI, 1.09 to 1.41] and 76.0 % increase in the risk of death from cardiovascular disease (HR = 1.76; 95 % CI, 1.25 to 2.47) were associated with a 10 μg m^{-3} increase in $PM_{2.5}$ (Miller et al. 2007). In Karachi, Pakistan, Khwaja et al. (2012) found an increase in hospital admissions by 1.60 % and emergency room visits for cardiovascular disease by 1.60 % with each 10.0 μg m^{-3} increase in $PM_{2.5}$ concentrations. The Heinz Nixdorf Recall Study, a population-based prospective cohort in Germany found a positive association between long-term urban background $PM_{2.5}$ and arterial BP and hypertension, which may induce atherosclerosis (Fuks et al. 2011). Short-term effects of $PM_{2.5}$ on cause-specific hospital admission were investigated by Dominici et al. (2006) in 204 US urban counties and they reported that reducing $PM_{2.5}$ concentrations by 10.0 μg m^{-3} would reduce the number of hospitalizations for heart failure by 3156.

7.5 Evidences from Genotoxic Health Effects Estimates of Fine PM

Human bronchial epithelial (HBE) cells when exposed to $PM_{2.5}$ samples collected from Wuhan, China showed changes in 970 and 492 genes at lower and higher exposures (Ding et al. 2014). These changes were mostly associated with genes of inflammatory and immune responses, oxidative stress response, and response to DNA damage. Similar variable responses in inflammation-related genes in the bronchial epithelial cell line were also observed by Øvrevik et al. (2009). Baulig et al. (2009) and Cachon et al. (2014) also found associations between pro-inflammatory response in airway epithelial cells and aqueous extracts of $PM_{2.5}$. Cachon et al. (2014) observed cell cycle alterations by fine PM in human bronchial epithelial cells.

8 Health Effects of Chemical Constituents of $PM_{2.5}$

Major components present in the fine PM are typically similar in different geographic regions of the world but proportions of different components vary significantly with different emissions and local sources (Chatterjee et al. 2012; Gaita et al. 2014; Raja et al. 2010). The composition and properties of PM influence its toxicity apart from its aerodynamic diameter, exposure pathway, and alveolar deposition capacity (Mazzoli-Rocha et al. 2010). PM contains a diverse array of chemical and biological constituents such as carbonaceous (organic and elemental carbon, aldehydes, PAH, nitro-PAH, ketones, quinones, hydrocarbons), inorganic

(sulfate, nitrate, ammonia, quartz, silica, sea salt, mineral oxides), and biological (bacteria, pollen, fungi, virus, plant debris) components (Ghio et al. 2012) (Fig. 9).

Rohr and Wyzga (2012) reviewed 48 independent epidemiological studies to assess different health effects of PM components. Among different PM components studied, carbonaceous components of PM were found to be maximally associated with negative health effects. The study also identified that effects were more prominent for cardiovascular anomalies. Metals such as nickel (Ni), vanadium (V), zinc (Zn), copper (Cu), silicon (Si), and potassium (K) showed maximum negative health effects. V and Ni were found to be more toxic for both respiratory and cardiovascular diseases whereas Al and Si were more prominent in respiratory anomalies. Iron (Fe), Zn, sulfur (S), and lead (Pb) showed the least associations with negative health effects amongst the metals studied. Authors also found contradictions in health effects related to sulfate which were probably due to spatial variations in those studies. Cakmak et al. (2014) reported acute changes in cardiovascular and respiratory physiology with metals in $PM_{2.5}$. There were significant increases in heart rate and blood pressure and decrease in lung function with IQR increases in calcium (Ca), cadmium (Cd), Pb strontium (Sr), tin (Sn), V, and Zn levels in fine PM. Greene and Morris (2006) found lifetime excess lung cancer risk due to chromium (Cr) and arsenic (As) in $PM_{2.5}$ in Washington, DC, USA (Fig. 9).

Mazzoli-Rocha et al. (2010) reviewed the association between oxidative stress and impairment of the function of the lung exposed to PM and found PM constituents specifically PAH and HM as the major elicitors of oxidative stress and respiratory diseases. Breysse et al. (2013) identified BC, OC, SVOCs, Ni, and V as important components of PM toxicity and also concluded that the secondary aerosol formation may enhance PM toxicity. Miyata and van Eeden (2011) identified major soluble metals such as Fe, V, Ni, and Zn to be mainly responsible for ROS generation. de Kok et al. (2006) reported PAH concentration as the most important factor in determining the radical generating capacity compared to total metal content or transition metal content in PM.

In a review Valavanidis et al. (2008) identified almost 500 different organic compounds with mutagenic potential. Mutagenicity was mostly due to the presence of polar or highly polar compounds with an aromatic nitro group, amines, and aromatic ketones. DNA-reactivity was found to be positively correlated with concentrations of total PAH and transition metals indicating that chemical components of PM directly influence DNA strand break (de Kok et al. 2006). Significant quantitative and qualitative differences in cytokine/chemokine responses to PM components in bronchial epithelial cell line were observed when effects of PM components were assessed on the expression of 84 inflammation-related genes Øvrevik et al. (2009).

Stanek et al. (2011) examined relationships between PM components and health effects from 29 epidemiological studies and found vehicular emission, biomass burning, and road dust sources contributing maximally to cardiovascular diseases but no such clear associations were observed with metals, secondary sulfate, and salt components in PM. SOA represents a significant part of $PM_{2.5}$, as we have already discussed in Section 6 but health effects of SOA are limited and only

reported from a few regions of the world. Rappazzo et al. (2015) studied associations between chemical component of $PM_{2.5}$ with risk of preterm birth (PTB) in three cities of the USA and found consistent associations between EC and sulfate with risk of PTB, whereas for nitrate, an association was only found for the first trimester and no significant association was observed for organic carbon. Nitrate levels in $PM_{2.5}$ showed an association with an increase in monthly mortality in a 7-year study of 12.5 million Medicare enrollees in eastern USA for the age group above 65 years (Chung et al. 2015). In a traffic related air toxic study, major components of SOAs such as organic carbon and ammonium nitrate in $PM_{2.5}$ showed a positive association with preterm birth in women living in Southern California, USA (Wilhelm et al. 2011).

Exposure to airborne PAHs was found to be adversely affecting the children's cognitive development by 5 years of age in a prospective cohort study in Krakow, Poland (Edwards et al. 2010). Results of a New York City cohort study showed distinct effects in child behavior with prenatal exposure to PAH (Perera et al. 2012) (Fig. 9). Perera et al. (2009) observed a significant inverse relationship between high/low PAH exposure and full-scale and verbal IQ score (Fig. 10). Hong et al. (2016) estimated the lung cancer risk of atmospheric PAH in five Asian countries and found a higher lung cancer risk in China and Vietnam compared to India, Japan, and South Korea.

Biological components in PM can also cause severe health effects directly through allergic pollens in PM or by the presence of bacterial or fungal toxin in PM that after inhalation can induce several inflammatory responses (Morakinyo et al. 2016). Degobbi et al. (2011) reviewed the role of endotoxin (cell wall component of gram-negative bacteria) in PM toxicity and found endotoxin as a modulator for immunological response by increasing pro-inflammatory cytokine expression. The study also identified an increment in response of several cytokines and chemokine's expressions due to the presence of endotoxin in PM.

Krall et al. (2015) reviewed the current methods and challenges in epidemiological studies on associations between PM constituents and health effects and found three major challenges like spatial–temporal variations in exposure, identifying effects of individual PM components and error in measurement techniques. Based on the epidemiological and toxicological findings it is clear that the toxicity of PM depends on the combination of all PM components and their interactions with each other. The information is still limited due to heterogeneity in PM components concentrations in different studies, exposure doses, and specific measurement techniques. Therefore, further researches are required to identify stronger associations between PM components and health effects.

9 Mechanism of Fine PM Toxicity

Most of the studies have reported oxidative stress as the primary effect of PM-related toxicity (Salvi and Holgate 1999; Øvrevik et al. 2015). Reactive oxygen species (ROS) cause significant damage to tissues and further induce different signaling cascades in this process. The mechanism follows the activation of transcription factors which induce genes of pro-inflammatory response in most cases. The intensity of oxidative stress depends upon the size of fine PM as well as its chemical constituents. PAH, organic constituents, and heavy metals severely intensify these effects (Bai et al. 2007; Øvrevik et al. 2015). When PM interacts with airway epithelial cells and alveolar macrophages it raises the levels of cytokine like IL-interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor (GMCF), IL-1b which results in local or systematic inflammation (Block and Calderón-Garcidueñas 2009).

Araujo (2011) reviewed the association of PM and its components with systemic oxidative stress, inflammation, and atherosclerosis based on epidemiological and experimental evidences. The author suggested three different mechanisms by which PM causes systemic cardiovascular irregularities; pulmonary and systemic inflammation; activation of receptors of pulmonary receptors that alters the autonomic nervous system, and entree of PM components to systemic circulation. It was further suggested that the effects of PM and its components are collaborating and even gaseous pollutants play a significant role in health effects.

Mazzoli-Rocha et al. (2010) reviewed the role of oxidative stress in signaling and inflammation by PM. It was found that PM-induced generation of ROS activates the redox responsive signaling pathway (mitogen-activated protein kinase (MAPK) family) and Ca^{++} influx, which further stimulate transcription factor and expression of genes related to inflammation or DNA damage in inflammatory cells and alveolar macrophages that ultimately result in cell injury or apoptosis, leading to respiratory morbidity and mortality. Similar observations were also made by Ghio et al. (2012) and Breysse et al. (2013) in their studies of uncertainties in the health effects caused by airborne particulate matter. Major outcomes of the studies were (1) identification of the role of epigenetic mechanisms in PM-induced toxicity, (2) role of respiratory inflammation by fine PM induces asthmatic responses, (3) ROS as an important modulator in induction of cellular response, (4) increment in pro-inflammatory and immune responses, (5) changes in concentrations of plasma high-density lipoprotein, (6) increase in coronary vascular resistance and decrease in myocardial perfusion causing acute myocardial infraction, (7) induction in expression of genes related to innate immunity, genes of complement system pathways and chemotaxis, (8) intrusion of eosinophil and neutrophil to airways, and (9) elevated secretions of cytokines (Breysse et al. 2013).

Ghio et al. (2012) further identified PM-induced responses such as the role of kinase cascade (ERK, p38, and Jun kinases) in PM-induced cell responses, oxidant generation by activation of NADPH oxidases, the role of metals in electron transport and ROS generation, induction in expression of stress response enzymes

(glutathione transferase, heme oxygenase, and superoxide dismutase) in epithelial cells and macrophages, mitochondrial dysfunction, and increased expression of cytochrome P-450.

In their review on the toxicological assessment of airborne PM, Valavanidis et al. (2008) identified several different mechanisms of toxicity such as ROS generation, DNA oxidative damage, mutagenicity, and induction of pro-inflammatory factors (cytokines and chemokines). Valavanidis et al. (2008) in their review concluded that all the studied relationships between PM and genotoxicity showed positive DNA damage, oxidative DNA damage, micronuclei sister chromatid exchange, and single-strand breaks. de Kok et al. (2006) also found fine PM to exert high DNA-reactivity.

Miyata and van Eeden (2011) reviewed the immunological interactions between alveolar macrophages and PM and found fine PM to induce innate immune responses by ROS generation through activation of different transcription factors. After particles are internalized, adaptive immunity is induced through expression of major histocompatibility complex Class II and modulation in response of T helper cells. Feng et al. (2016) identified oxidative stress and inflammation with alteration in immune responses as the major mechanism behind fine PM-induced respiratory effects. Oxidative stress and inflammation in hypothalamus may cause alteration in its neuroendocrine function and ultimately may lead to neuroendocrine disorders. Alteration in immune response in pregnant women due to PM exposure may induce adverse effects in childhood or at maturity (Feng et al. 2016). Increase in expression of phase I xenobiotic-metabolizing cytochrome P450 enzymes due to organic components of fine PM and inflammatory response in other organs such as spleen, heart, kidney, and liver due to fine PM are reported (Feng et al. 2016) (Fig. 9).

Øvrevik et al. (2015) identified interactions of particles with lipid bilayer, cell surface receptors, intracellular molecules, and direct formation of ROS, resulting in activation of genes responsible for process of inflammation in airway mucosa cells. This inflammation itself can trigger cardiovascular effects by transport of inflammatory mediators through circulation (Øvrevik et al. 2015). Laing et al. (2010) observed that $PM_{2.5}$ exposure resulted in endoplasmic reticulum stress and unfolded protein response (UPR) signaling pathway in lung and liver tissues and in mouse macrophage cells and they concluded that $PM_{2.5}$ can activate UPR-related branches which further lead to apoptosis by the PERK-eIF2-CHOP pathway. The mechanisms of toxicity of PM and their effects are shown in Fig. 10.

Based on the above evidences, it can be concluded that the actual mechanisms and components of fine PM responsible for such health effects after exposure of biological systems to PM are still not completely known and further evidences at gene and molecular levels should be studied.

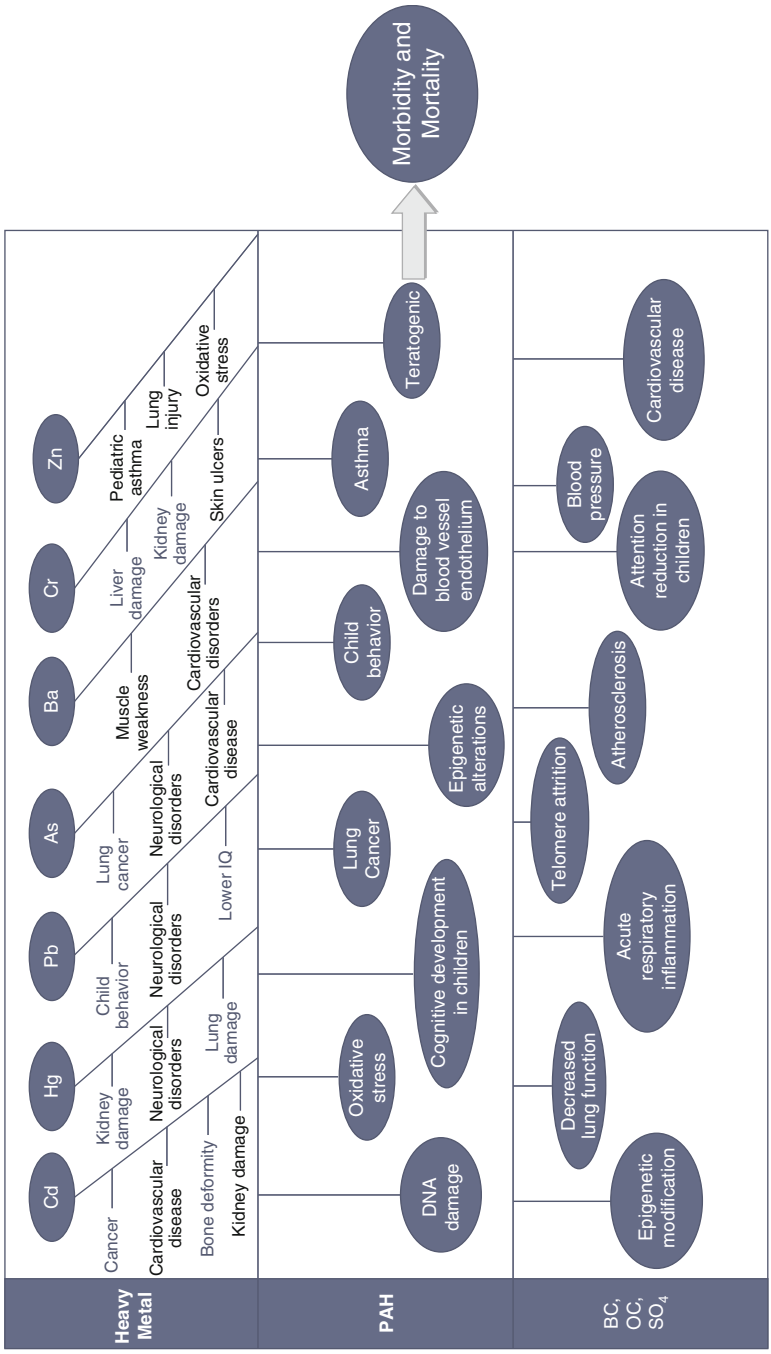

Fig. 9 Health effects of different $PM_{2.5}$ chemical constituents

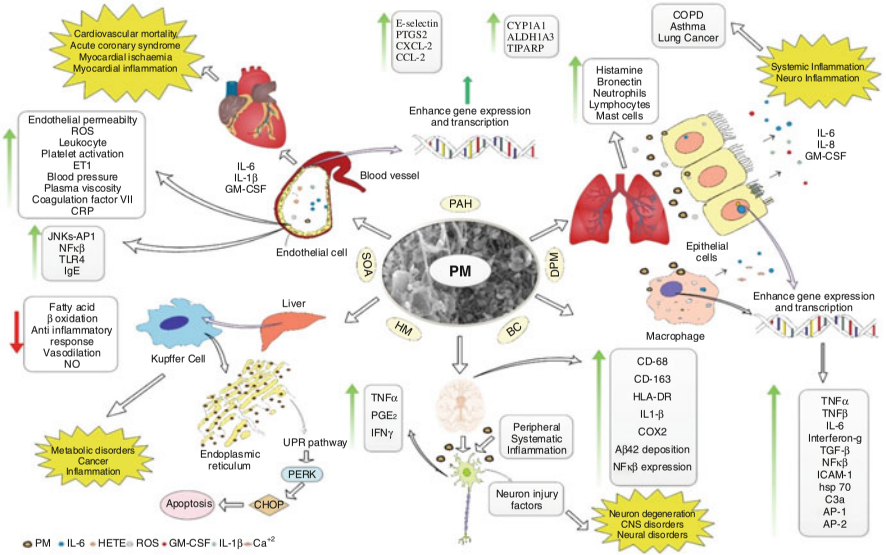

Fig. 10 Different pathways of PM toxicity and their effects in different organ systems. *PM* particulate matter, *PAH* polycyclic aromatic hydrocarbons, *DPM* diesel particulate matter, *SOA* secondary organic aerosol, *HM* heavy metal, *BC* black carbon, *ROS* reactive oxygen species, *ET-1* endothelin-1, *CRP* C-reactive protein, *JNKs-AP1* c-Jun N-terminal kinases activation protein 1, *NO* nitric oxide, *NF-κB* nuclear factor-κB, *TLR-4* toll-like receptor 4, *IgE* immunoglobulin E, *UPR* unfolded protein response, *PERK* protein kinase-like ER kinase, *CHOP* C/EBP homologous protein, *IL-6* interleukin 6, *IL-1β* interleukin 1β, *GM-CSF* granulocyte-macrophage colony stimulating factor, *TNFα* tumor necrosis factor α, PGE_2 prostaglandin E2, *IFNγ* interferon γ, *CCL-2* chemokine (C-C motif) ligand 2, *CXCL-2* chemokine (C-X-C motif) ligand 2, *PTGS2* prostaglandin-endoperoxide synthase 2, *CYP1A1* cytochrome P450, family 1, subfamily A, polypeptide 1, *ALDH1A3* aldehyde dehydrogenase 1 family, member A3, *TIPARP* TCDD-inducible poly(ADP-ribose) polymerase, *AP-1* activator protein 1, *AP-2* activator protein 2, *C3a* complement component 3a, *HSP70* heat shock protein 70, *ICAM1* intercellular adhesion molecule-1, *TGF-β* transforming growth factor beta, *NFκβ* nuclear factor κβ, $A\beta_{42}$ amyloid beta-42, COX_2 cyclooxygenase 2, *HLA-DR* human leukocyte antigen-D related, *HETE* hydroxyicosatetraenoic acid. (Modified from Bai et al. 2007; Block and Calderón-Garcidueñas 2009; Laing et al. 2010; Aung et al. 2011)

10 Suggestions

Cleaning our environment is the biggest and topmost priority in the current scenario; choices should be economical and implementable with long-term solutions. Identifying problems is the first step to solution. We know the consequences that we are facing every day, so we must bring new ideas to overcome this burden. The following suggestions can help to mitigate the PM levels and consequently improve human health. Suggestions are proposed from best to least effective measure:

1. Strict emission standards for fine PM emission from vehicles and industries.
2. Prevention of biomass burning.
3. More emphasis should be given on health effects study especially in Asian and African countries.
4. School building should not be near highway or any major roadway.
5. More scientific research on passive monitoring techniques should be conducted as it is economical and easy to implement in developing countries.
6. Large urban forestry development programs.
7. Use of bio-filters to reduce emissions from industry or around traffic sites.
8. Creating a global PM_{10}, $PM_{2.5}$, and PM_1 standards for different regions based on its topography and history.
9. Epidemiological monitoring of air quality effects as a part of national ambient air quality monitoring program especially for developing countries.
10. Creating a global database of PM levels and their sources.

11 Conclusion

Fine PM has become a major public health issue, particularly in large cities. Most of the large cities in the world showed PM levels above the respective standards of their own countries as well as the WHO standards. Levels were less elevated in the USA and European cities. Asian cities are mostly critical with consistently higher $PM_{2.5}$ levels and exposure. Most of the major cities in Asia have exceeded the threshold levels. Even rural and remote areas have higher PM levels, which indicate a rapid dispersion from urban centers. High population density and urbanization are the major drivers of poor air quality around the world. Automobiles along with combustion activities are major sources of $PM_{2.5}$.

Epidemiological studies provided evidence that there is an increasing trend of fine PM-related health issues all over the world. Traffic seems to be the major factor behind health anomalies around the globe with children and pregnant women being most vulnerable. Several studies indicated the carcinogenic or mutagenic nature of chemical constituents associated with fine PM that have severe health consequences even at lower concentrations. African and Asian countries require more epidemiological studies to provide a broader perspective of health effects. More scientific

studies on gene and metabolic levels will further be able to discover the yet hidden health effects of fine PM.

12 Summary

Global status, trend, and health effects of fine particulate matter ($PM_{2.5}$) were reviewed. Asian and African continents have higher exceedance of fine PM than the standards compared to Europe and the USA. Traffic, biomass burning, road dust, and local sources affect fine PM concentrations. Epidemiological studies provided clear evidence of increasing fine PM-related health issues all over the world. Fine PM causes several health effects such as increase in inflammatory responses, lung cancer, heart rate variability, term low birth weight, mutagenicity, changes in gene expression, and immune responses. Chemical constituents of fine PM such as polycyclic aromatic hydrocarbons, heavy metals, and elemental carbon are mostly responsible for $PM_{2.5}$ toxicity. Emission reduction policies should be more emphasized with epidemiological studies to combat negative effect of fine PM.

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A Review of the Environmental Degradation, Ecotoxicity, and Bioaccumulation Potential of the Low Molecular Weight Polyether Polyol Substances

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Contents

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Abbreviations

DEG	Diethylene glycol; 2,2′-oxy-diethanol
EO	Ethylene oxide; oxirane
GLY	Glycerol; propane-1,2,3-triol
MPG	Mono-propylene glycol; propane-1,2-diol
NTE	2,2′,2″-Nitrilotriethanol; triethanol amine
o-TDA	Methyl-phenylene-2,3-diamine and methyl-phenylene-3,4-diamine, mixture of isomers
PEC	Predicted environmental concentration
PEG	Polyethylene glycol
PENT	Pentaerythritol; 2,2-bis(hydroxymethyl)propane-1,3-diol
PNEC	Predicted no-effect concentration
PO	Propylene oxide; methyloxirane
SOR	Sorbitol; glucitol; 1,2,3,4,5,6-hexahydroxy-cyclohexane
SUC	Sucrose; α,β-1,4-gluco-fructopyranose
TMP	1,1,1-Trimethylolpropane; propylidyne-1,1,1-trimethanol

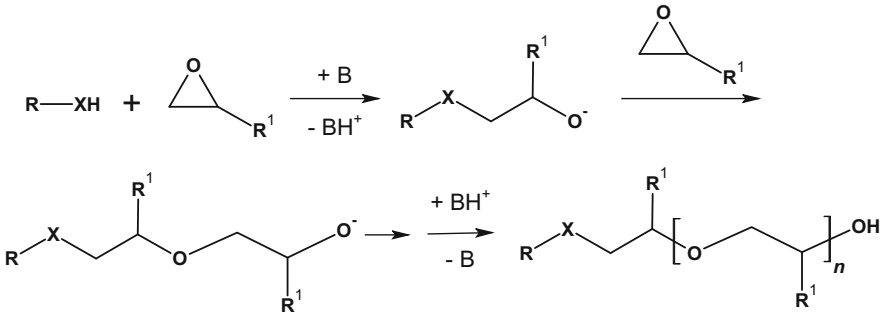
1 Introduction

1.1 Background and Purpose

"Polyalkylene glycol" is the name given to a broad class of synthetic organic chemicals which are produced by polymerization of one or more alkylene oxide (epoxide) monomers, such as ethylene oxide (EO) and propylene oxide (PO), with various initiator substances which possess amine or alcohol groups. A generalization of this polymerization reaction is illustrated in Fig. 1.

The structures of the polyalkylene glycol substances can be simply described as containing repeating ether linkages (-R-O-R-), and two or more terminal hydroxyl groups (-R-OH); thus lending to their identification by other common names such as polyalkylene oxides, polyglycols, polyethers, or polyether polyols. The names, chemical descriptors, and Chemical Abstract Registry Numbers for these substances are summarized in Table 1. A seemingly infinite variety of polyalkylene glycol substances can be synthesized, which along with their versatility and varied properties, lends to production volumes which are among the highest for synthetic organic chemicals. It is estimated that global production of these substances approaches 8 million metric tons (17 billion lbs.) annually (Chinn et al. 2006, 2007). Of this production, approximately 80 % is consumed in the manufacture of polyurethane foams, coatings, and sealants (Chinn et al. 2006); and the remainder is consumed in formulation of surfactants, lubricants, and other functional fluids (Chinn et al. 2007).

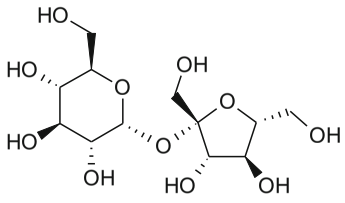
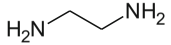
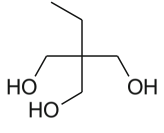
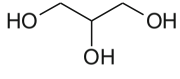
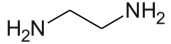
Because of the sheer volumes of polyalkylene glycols which are produced, transported, and used around the world, there is interest among industry, regulatory authorities, and non-governmental organizations to assess the potential impact of these substances on the environment. The accuracy and reliability of these assessments can

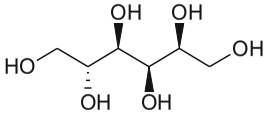
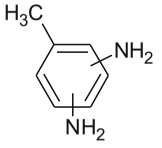
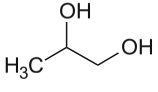
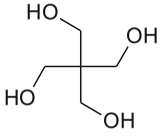
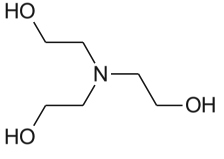


X = NH, O; R^1 = H, CH_3

Fig. 1 Generalized schematic of base-catalyzed polyalkylene glycol synthesis

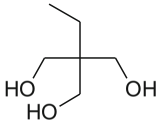
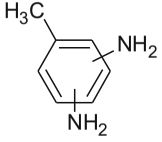
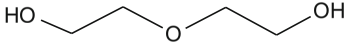
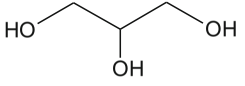
Table 1 Identity, composition, and representative homologues of the predominant commercial polyether polyol (PEPO) substances

CAS name	CAS no.	Initiator	Alkoxylate	Molecular weight (M_n)	Representative homologue
Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, ether with β-D-fructofuranosyl α-D-glucopyranoside	9049-71-2	 Sucrose (SUC)	Propylene oxide (1–6.5 mol)	580	SUC + 5 PO
Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″,α‴-[1,2-ethanediylbis[nitrilobis (methyl-2,1-ethanediyl)]]tetrakis [ω-hydroxy-	25214-63-5	 Ethylenediamine (EDA)	Propylene oxide (1–8.5 mol)	280	EDA + 3 PO
Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)	25723-16-4	 Trimethylolpropane (TMP)	Propylene oxide (1–6.5 mol)	310	TMP + 3 PO
Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-hydroxy-	25791-96-2	 Glycerol (GLY)	Propylene oxide (1–6.5 mol)	260	GLY + 2 PO
Oxirane, 2-methyl-, polymer with oxirane, 1,2-ethanediylbis(nitrilodialkylene) ether	26316-40-5	 Ethylenediamine (EDA)	Propylene oxide + Ethylene Oxide (1–8.5 mol)	280	EDA + 1 EO + 2 PO

Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, ether with D-glucitol (6:1)	52625-13-5	 Sorbitol (SOR)	Propylene oxide (1–12.5 mol)	600	SOR + 6 PO
Benzenediamine, ar-methyl-, polymer with 2-methyloxirane	63641-63-4	 o-Toluenediamine (TDA)	Propylene oxide (1–5.5 mol)	510	TDA + 3 PO
Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-	25322-69-4	 1,2-propanediol (MPG)	Propylene oxide (1–4.5 mol)	230	MPG + 3 PO
Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, ether with 2,2-bis (hydroxymethyl)-1,3-propanediol (4:1)	9051-49-4	 Pentaerythritol (PENT)	Propylene oxide (1–8.5 mol)	400	PENT + 3 PO
Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α-″-(nitrilotri-2,1-ethanediyl)tris[ω-hydroxy-	37208-53-0	 2,2′,2″-nitrilotris(ethanol) (NTE)	Propylene oxide (1–6.5 mol)	340	NTE + 2 PO

(continued)

Table 1 (continued)

CAS name	CAS no.	Initiator	Alkoxylate	Molecular weight (M_n)	Representative homologue
Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)	50586-59-9	 Trimethylolpropane (TMP)	Ethylene oxide (1–6.5 mol)	222	TMP + 2 EO
Benzenediamine, ar-methyl-, polymer with 2-methyloxirane and oxirane	67800-94-6	 o-Toluenediamine	Propylene oxide + ethylene oxide (1–8.5 mol)	282	o-TDA + 2 PO + 1 EO
Poly[oxy(methyl-1,2-ethanediyl)], α,α-′-(oxydi-2,1-ethanediyl)bis[ω-hydroxy-	9051-51-8	 Diethyleneglycol	Propylene oxide (1–4.5 mol)	222	DEG + 2 PO
Poly(oxy-1,2-ethanediyl), α,α′,α″-1,2,3-propanetriyltris[ω-hydroxy-polymer	31694-55-0	 Glycerol	Ethylene oxide (1–6.5 mol)	180	GLY + 2 EO

be aided by collection and evaluation of all relevant information on the physical–chemical properties, environmental fate, and ecotoxicity. Recognizing this need, we are presenting a compilation and review of this information from currently available experimental studies, structure–activity relationships, and computational models. This information can be used to inform assessments of potential environmental exposure and effects across this family of substances; thereby facilitating assessments which are based on a complete, credible, and transparent weight-of-evidence.

1.2 Substance Description

1.2.1 Nomenclature

The polyalkylene glycol substances which are used within the polyurethanes industry are commonly referred to as "polyether polyols," a name which is hereafter abbreviated as "PEPO." Amongst all commercial PEPO substances, those having the lowest average molecular weight (i.e., M_n = 200–800 g/mol) and at least two hydroxyl groups per molecule are typically used in production of rigid polyurethane foams, such as those used for thermal insulation. The PEPO substances of intermediate molecular weight (i.e., M_n = 400–3000 g/mol) are used in the production of adhesives, coatings, elastomers, sealants, etc. The highest molecular weight PEPOs (i.e., M_n = 2000–6000 g/mol) are used to produce the flexible polyurethane foams commonly used in mattresses, upholstered furniture, and automotive seating. Typical production volumes for any given PEPO substance can range from 100 to more than 1000 metric tons/year. Whereas the PEPO substances are produced over this wide range of molecular weight, this review will focus primarily on those having $M_n < 1000$ g/mol because:

1. PEPO substances having $M_n > 1000$ g/mol generally meet the Organisation for Economic Co-operation and Development (OECD) definition of "polymer" (OECD 2007), and are thus assessed differently than other discrete organic substances under most chemical regulatory programs of the OECD member countries.
2. Due to their high molecular weight, the PEPO polymers exceeding a mean molecular weight of 1000 g/mol are expected to show low bioavailability (Lipinski et al. 1997).
3. Much of the available physical property and hazard data for the PEPO substances have been generated from the low molecular weight representatives, for the above reasons.

Because most of the PEPO substances do not meet the OECD definition of "polymer," they are regulated as "no longer polymer" (NLP) substances (European

Commission 2006). These PEPOs have been assigned specific NLP identification numbers, which correspond to Chemical Abstracts Registry Numbers for the more broadly defined polyalkylene glycol substance families. The most common NLP PEPOs, which are subject of this review, are given in Table 1.

1.2.2 Characterization

Both the NLP and polymer PEPO substances are composed of mixtures of similar molecules (i.e., homologues), and these components of a given PEPO substance differ only in their number of alkoxylate repeating units. In some limited cases, two initiator substances may be simultaneously reacted with an epoxide monomer (e.g., PO), producing what is essentially a binary blend of two distinct PEPO substances. In such cases, the physical–chemical and ecotoxicological properties of the PEPO blend can be inferred from the individual component PEPOs, and therefore the properties of the bulk blends are not typically evaluated. The various PEPO substances identified by a specific CAS registry or NLP number are often characterized and differentiated from each other on the basis of their average molecular weight (M_n). The M_n represents the arithmetic mean of molecular mass for all component molecules of the PEPO mixture, and is typically determined by gel permeation chromatography (GPC).

For step-addition polymerizations that are employed in the manufacture of the PEPO substances, the mole fraction and the molecular weight fraction of a single component PEPO homologue can be calculated on the basis of statistical consideration from (Flory 1940):

$$N_x = \frac{e^{-\upsilon} \times \nu^{x-1}}{(x-1)!}; \quad W_x = \frac{x + \frac{M(s)-M}{M}}{\nu + \frac{M(s)}{M}} \times \frac{e^{-\nu} \times \nu^{x-1}}{(x-1)!} \tag{1}$$

where
N_x = mole fraction of the molecule with x units
W_x = weight fraction of the molecule with x units
x = number of monomer units
M = molecular weight of repeating monomer unit
$M(s)$ = molecular weight of the starter molecule
ν = stoichiometric number of monomers per starter molecule.

Using Eq. 1, a theoretical molecular weight distribution can be determined for a given PEPO substance, as shown in Fig. 2. As can be seen, the calculated weight distribution is comparable to the measured molecular weight distribution determined by GPC. Deviations are attributable to the fact that for the calculate distribution, all –OH groups are assumed to have equal reactivity. This is not always the case, as primary –OH groups are more reactive than secondary –OH groups against the epoxide monomer. With another electrophilic reagent, the aromatic isocyanate group, primary alcohols react about four times faster than secondary alcohols

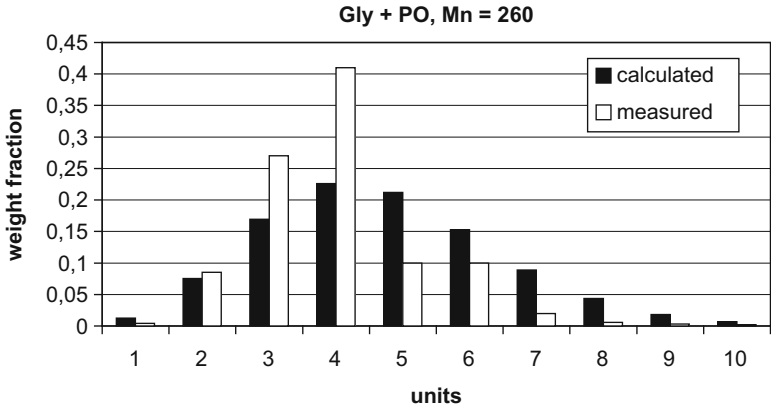


Fig. 2 Illustration of molecular weight distribution of component homologues of a GLY + PO PEPO substance (M_n = 260) as measured by gel permeation chromatography (GPC) and by calculation from Eq. 1

(Lovering and Laidler 1962). It needs to be mentioned that the use of sucrose, sorbitol, or pentaerythritol as initiator requires the addition of a co-initiator, as these molecules are solids at ambient temperatures. The addition reaction of propylene oxide and/or ethylene oxide to these solids would be difficult to start, but after initiation could progress violently. Therefore, glycerol, monopropylene glycol, diethylene glycol, or other liquid polyfunctional alcohols are added as solvents. As a result, propoxylated sucrose, as an example, always contains another propoxylated compound. The test reports, however, typically just mention "Sucrose, propoxylated," but not the co-initiator. The co-initiator may make up to 50 % by weight of the main initiator. As the main initiator provides more reaction sites for the alkylene oxide to be added, the weight proportion of the molecules derived from the co-initiator decrease, while its molar fraction remains constant. The resulting PEPO is a mixture of two different PEPOs.

The relative reactivity of the initiators against alkylene oxides is $(Alkyl)_2NH > (Alkyl)NH_2 > (Aryl)NH_2 > RCH_2\text{-}OH > R_2CH\text{-}OH$. Therefore, a PEPO produced by the reaction of EDA with PO, theoretically first all N-H functions will react before further PO units are added to the newly formed OH-groups (Lovering and Laidler 1962; Flammersheim 1998).

1.2.3 Identification of Representative PEPO Homologues

As the PEPO substances are widely varied in composition, and are themselves mixtures of homologous molecules, it is virtually impossible to assess the physical–chemical and toxicological properties of every individual component of every possible PEPO substance. Therefore, the assessment and comparison of degradation, accumulation, and toxicity potentials for these substances can be facilitated by

assessing these properties for discrete homologues which are most representative of the ecotoxicological properties of a given PEPO mixture, or even of a broader PEPO family. This representative homologue approach was applied in this review for predicting selected physical–chemical and toxicological properties of the PEPO substances, the rationale for which is described below.

The potential hazard (toxicity) of a mixture of similar substances is a function of the combined concentration, reactivity, and bioavailability of the individual components of that mixture. For the PEPO substances, this premise is based on the following principles and assumptions:

- The component homologues of a given PEPO substance are assumed to exhibit equivalent reactivity potential, as these components all possess the same reactive functional groups which are associated with their common initiator and alkoxylate repeating unit(s). Therefore, the chemical and biological reactivity exhibited by a single homologue of a PEPO substance is assumed to be representative of other associated homologues of a bulk PEPO substance.
- The uptake of substances via routes of absorption across the skin, intestine, blood–brain barrier, fish gills, etc. is commonly described using models which are based on the fundamental principle of passive diffusion, and is largely influenced by chemical properties such as molecular size (i.e., molecular mass), hydrophobicity (i.e., $\log K_{ow}$), and water solubility (Potts and Guy 1992; Lipinski et al. 1997; Abraham et al. 1999; Jaworska et al. 2002). That is, uptake of substances via these routes generally decreases with increased molecular weight, increased water solubility, and decreased $\log K_{ow}$. As discussed below, water solubility is generally decreased, while $\log K_{ow}$ is generally increased, with increased molecular weight of the PEPO substances. Values of $\log K_{ow}$ for PEPO homologues can be calculated from chemical structure, using the widely accepted structure-fragment methods described below.
- The concentration of each component homologue in a PEPO substance can be calculated from the molecular weight distribution for that substance, as described above.
- A derivation of relative bioavailability among PEPO components allows identification of the most bioavailable and potentially toxic of the individual PEPO homologues.

Potts and Guy (1992) have proposed a means of estimating the skin permeability coefficient (Kp) for a substance, based on molecular weight and $\log K_{ow}$:

$$\log K_p = 0.71 \log K_{ow} - 0.0061\,\mathrm{MW} - 6.3 \qquad (2)$$

where Kp is the skin permeation coefficient (cm/s) of an aqueous solute, Kow is the octanol-water partition coefficient, and MW is molecular weight (g/mol). Where Kp is used as a generic metric of bioavailability, the contribution to potential toxicity of a PEPO homologue can be determined by multiplying this calculated Log Kp (from Eq. 2) by its mole fraction in the bulk PEPO substance (from Eq. 1). Using this approach—which assumes that the inherent toxicity is the same for all

homologues due to identical functional groups—the representative homologue making the largest contribution to toxicity potential was identified for each of the PEPO families, as shown in Table 1. For the environmental behavior, however, the smallest and the largest homologue, contributing at least 1 mol% to the respective PEPO, were modeled to cover the range of $\log K_{ow}$ and vapor pressure values. Further, the $\log K_{ow}$ is an important parameter in ecotoxicity QSAR models (Escher and Schwarzenbach 2002; Endo et al. 2011), so the range of values needs to be considered.

2 Physical–Chemical Properties

2.1 Structural Properties

The physical–chemical properties of the PEPOs are expected to be dictated by structural contributions of the initiator, total moles of alkoxylate added (molecular wt.), and the ratio and order of EO and PO units (i.e., random or block) incorporated in the structure. The initiator molecule determines the functionality, or number of hydroxyl-terminated chains, imparted to the PEPO substance. As illustrated in Table 1, use of 1,2-propanediol as an initiator results in a bi-functional polypropylene glycol polyol, whereas glycerol and trimethylolpropane give tri-functional polyols (three –OH groups per molecule). Generally, as the molecular weight (i.e., moles of alkoxylate) of the PEPO increases, any influence of the initiator on the overall physical–chemical properties becomes less pronounced. Thus, a remarkable uniformity in physical–chemical properties is exhibited across the family of PEPO substances (Table 2). The number of average molecular weight (M_n) of the PEPOs was measured by either gel permeation chromatography (GPC), ^{1}H-NMR or by end-group analysis via the hydroxyl number (OHN). The reaction of an initiator with EO results in the formation of a primary alcohol-terminated PEPO, whereas reaction with PO can result in termination with either a primary or a secondary alcohol group. When EO and PO are both reacted to form a PEPO, the ratio of EO:PO employed in the alkoxylate chain typically ranges over 10-20 EO to 80-90 PO units (wt:wt). The order and proportion of EO:PO incorporation into the alkoxylate chains can influence PEPO properties in several ways (Schmolka 1977):

1. Incorporation of EO generally imparts hydrophilic properties (increased water solubility), whereas PO contributes toward PEPO hydrophobicity. This is demonstrated experimentally with TDA + 3 PO and TDA + 2 PO + EO (water solubility 21 g/L and 275 g/L at 20 °C), and also by the pair TMP + 3 PO and TMP + 2 EO (water solubility about 100 g/L and total miscibility at 20 °C; Table 2).
2. Co-reaction of EO and PO may initially result in preferential reaction of EO with the initiator, but ultimately gives a random distribution of EO and PO units across the alkoxylate chain, thereby producing a random copolymer.

3. Sequential reaction of the PO and EO monomers typically involves reaction of PO first, followed by end-capping with the more reactive EO to give a block copolymer PEPO. The ethoxylate and propoxylate blocks impart distinct hydrophilic and hydrophobic moieties to the PEPO molecules. This amphiphilic structure confers surface-active (surfactant) properties to the block copolymer PEPOs, as exhibited by the similarly nonionic and amphiphilic alcohol ethoxylate surfactants.

2.2 *Physical Properties*

The distribution and transport of an organic substance in the environment can largely be determined from a small set of key physical–chemical properties. Table 2 summarizes the key physical–chemical properties which are expected to influence the environmental fate and distribution of the polyether polyols. These and other key physical–chemical properties which are used to assess potential hazard of these substances, such as reported in material safety data sheets, are also briefly discussed below.

2.2.1 Melting/Freezing Point

All of the PEPOs described in Table 2 are liquids at 20 °C. Exact determination of the melting (freeze) point is not performed on a regular basis as all these PEPO substances have freeze points well below 0 °C. Values reported in Table 2 were generated either by the capillary method or by DTA according to OECD test guideline no. 102.

2.2.2 Boiling Point

The boiling point of PEPO substances is also not routinely measured. All PEPOs listed in Table 2 show boiling points above 200 °C, and attempts to measure them often result in thermal decomposition before boiling is observed.

2.2.3 Water Solubility

Water solubility of the PEPOs is highly influenced by the molecular weight and proportion of propoxylate units in the molecule. The oligomeric PEPOs (NLPs) show high water solubility, for example, the propoxylated 1,2-propanediol ($M_n = 230$) and propoxylated glycerol ($M_n = 260$) are miscible with water, while the propoxylated trimethylolpropane ($M_n = 340$) is soluble to 100 g/L, ethoxylated

Table 2 Summary of selected physical–chemical properties of the PEPO substances

Formulation	Molecular weight (M_n) [118][a]	Melting point [102][a]	pKa_1/ pKa_2[b]	Density (g/cm^3) [109][a]	Vapor pressure (Pa) [104][a]	Surface tension (mN/m) [115][a]	Water solubility [105][a]	logK_{ow} (HPLC) [117][a]	logK_{oc} [121][a]
SUC + 5.2 PO	650 (GPC)	−50 °C	n.a.	1.122 at 20 °C	3.02×10^{-2} at 20 °C; 3.47×10^{-2} at 50 °C[c]	56	240 g/L at 20 °C	<0.5	<1.25
EDA + 3.3 PO	250 (H-NMR)	−40 °C	5.3/ 8.8	1.034 at 20 °C	1000 at 20 °C; 2200 at 50 °C[d]	64	Miscible in water in any ratio at 22 °C	<0.3…1.6; 0.0[e]	<1.25 …>5.63 at pH 5.5 & 7.5
TMP + 3.6 PO	340 (GPC)	−18 °C	n.a.	1.048 at 20 °C	2.64×10^{-4} at 20 °C; 4.23×10^{-4} at 50 °C[c]	57	100 g/L at 22 °C	0.5…1.6	<1.25
GLY + 3 PO	250 (GPC)	<−150 °C	n.a.	1.08 at 20 °C	200 at 20 °C; 600 at 50 °C [d]	53	Miscible at any ratio[f]	<0…1.6	<1.25
EDA + 0.7 EO + 2.8 PO	240 (H-NMR)	<−150 °C	5.3/ 8.8	1.055 at 20 °C	1000 at 20 °C 2100; at 50 °C[d]	63	Miscible at any ratio at 23 °C	<0.3…1.5	>5.63 at pH 5.5 & 7.5
SOR + 7.2 PO	640 (GPC)	<−150 °C	n.a.	1.1014/at 20 °C	No data	56	Miscible at any ratio	<0…2.0	<1.25
o-TDA + 3 PO	340 (GPC)	<−150 °C	1.4/ 6.2	1.06 at 23 °C	700 at 20 °C; 2100 at 50 °C[d]	51	21 g/L at 20 °C	<0.3…2.8	2.7… 5.5 at pH 5.4; 2.54… 4.77 at pH 7.6
MPG + 2.7 PO	260 (OHN)	150 °C	n.a.	1.012 at 20 °C	600 at 20 °C; 1000 at 50 °C[d]	64	Miscible at any ratio at 22 °C	<0.3…0.9	<1.25
PENT +4.9 PO	420 (GPC)	−50 °C	n.a.	1.086 at 20 °C	400 at 20 °C; 1300 at 50 °C[d]	37	Miscible at any ratio at 22 °C	<0.3…1.3	<1.25

(continued)

Table 2 (continued)

Formulation	Molecular weight (M_n) [118][a]	Melting point [102][a]	pKa_1/ pKa_2[b]	Density (g/cm^3) [109][a]	Vapor pressure (Pa) [104][a]	Surface tension (mN/m) [115][a]	Water solubility [105][a]	logK_{ow} (HPLC) [117][a]	logK_{oc} [121][a]
NTE + 3 PO	320 (H-NMR)	<−150 °C	7.4	1.078 at 20 °C	600 at 20 °C; 1500 at 50 °C[d]	51	Miscible at any ratio at 20 °C	<0.3	<1.25…>5.63 at pH 5.5 & 7.5
DEG + 3.8 PO	222 (OHN)	<−50 °C	n.a.	1.046 at 20 °C	No data	58	Miscible at any ratio at 20 °C	<0.5…1.1	No data
GLY + 4.9 EO	308 (OHN)	<−49 °C	n.a.	1.1635 at 20 °C	3.89×10^{-4} at 20 °C; 5.96×10^{-4} at 25 °C[d]	61	Miscible at any ratio at 20 °C	<0.3…0.5	<1.5
o-TDA + 5.2 PO + 2.6 EO	540 (OHN)	−10…−11 °C	1.4/ 6.2	No data	2.01×10^{-4} at 20 °C; 2.83×10^{-4} at 25 °C[d]	43	275 g/L at 20 °C	0.7…5.2	1.97 at pH = 5.4; 1.99 at pH = 7.6
TMP + 3.2 EO	275 (OHN)	−33…−22	n.a.	1.1192 at 20 °C	5.36 at 20 °C[g]	63	Miscible at any ratio at 20 °C	<0.3…1.1	No data

n.a. = not applicable; number average molecular mass by ^{1}H-NMR, gel permeation chromatography (GPC) or end-group analysis (OHN, the hydroxyl number)

[a]Number of OECD guideline for testing of chemicals

[b]Calculated with ACD Labs p*K*a DB software (v5.12, October 2001)

[c]Knudsen effusion method

[d]Static method

[e]Shake flask method OECD 107

[f]Temperature not reported

[g]Static method at elevated temperature

trimethylolpropane (M_n = 222) is miscible in any ratio. With an increasing propylene oxide to ethylene oxide ratio and with increasing molecular weight, water solubility is generally reduced. As the degree of polymerization (i.e., molecular weight) is increased, the mixing of a PEPO with water becomes essentially an extraction of the low molecular weight components, rather than complete dissolution of the entire homologous mixture. Therefore, the amount of PEPO which can be dissolved in water becomes a function of the mass of PEPO added to water (Schmolka 1977). For this reason, the PEPO oligomers are expected to be worst case representatives for higher molecular weight PEPOs.

2.2.4 Dissociation Constant

Dissociation constants for the corresponding acids of the amine-based PEPOs were calculated with ACD Labs p*K*a DB software (v. 5.12, October 2001). Data are listed in Table 2. In the environment, a considerable proportion of the amine-based PEPOs are protonated. Attempts to derive p*K*a values by acid-base titration for the EDA initiated polyols were unsuccessful as curves were gradually inclining without sharp equivalent points. A representative substitute, *N*,*N*,*N*′,*N*′-Tetrakis (1-hydroxy-2-propyl)-ethane-1,2-diamine, which is a component in the EDA + PO polyol and can be synthesized by careful reaction of ethylene-1,2-diamine with four equivalents of propylene oxide (EDA + 4 PO; no molecular weight distribution), delivered p*K*a-values by acid-base titration:

$$[\mathrm{EDA} + 4\mathrm{PO}]\mathrm{H}_2^{2+} = [\mathrm{EDA} + 4\mathrm{PO}]\mathrm{H}^{+} + \mathrm{H}^{+} : \mathrm{p}K\mathrm{a}_1 : 2.2$$

$$[\mathrm{EDA} + 4\ \mathrm{PO}]\mathrm{H}^{+} = [\mathrm{EDA} + 4\ \mathrm{PO}] + \mathrm{H}^{+} : \mathrm{p}K\mathrm{a}_2 : 7.2$$

The p$K\mathrm{a}_2$ is in the range of the calculated value, but p$K\mathrm{a}_1$ is much lower than predicted. For ethylenediamine, the values are 7.33 for p$K\mathrm{a}_1$ and about 10 for p$K\mathrm{a}_2$ (ECHA 2017a). The lower p*K*a values for the propoxylated ethylenediamine against ethylenediamine can be explained by sterically hindrance of the nitrogen which reduces stabilization of the ammonium ion by hydrogen bonds. For o-toluenediamine, the measured p$K\mathrm{a}_2$ is 6.86 (ECHA 2016), which is close to the calculated value of 6.2 for oTDA +3 PO and o-TDA + 2 PO + EO. The measured p*K*a of nitrilotriethanol (NTE) is 7.86 (ECHA 2017b), the calculated value for NTE + 2 PO is 7.4. For o-TDA as for NTE as well it is expected that alkoxylation reduces the p*K*a values of the corresponding ammonium ions. With these p*K*a values, it is obvious that at ambient pH values in environmental compartments, a significant proportion of the amine-initiated PEPOs are single protonated, charged species. The proportion protonated is calculated as

$$\alpha = \frac{1}{1 + 10^{(\mathrm{pH} - \mathrm{p}K)}} \tag{3}$$

where pKa$_2$ has to be taken for the EDA and o-TDA initiated PEPOs. Results are summarized in Table 3. For the EDA initiated PEPOs, the measured pKa$_2$ of *N,N,N′,N′*-Tetrakis(2-hydroxypropyl)-1,2-diaminoethane was chosen. For the o-TDA and NTE initiated PEPOs, the calculated pKa$_2$ and pKa values were used, respectively.

2.2.5 Density

The PEPOs have densities which span a range of 1.0–1.2 g/cm^3 (Table 2), and they are thus equally or slightly more dense than water ($\delta = 1.0$ g/cm^3, 4 °C) or seawater ($\delta = 1.025$ g/cm^3, 20 °C). Therefore, if spilled in freshwater or marine environments, the viscous PEPOs would tend to remain suspended in the water column as they slowly dissolve, rather than forming a floating slick on the surface or rapidly sinking to cover the bottom sediments.

2.2.6 Vapor Pressure

As shown in Table 2, the vapor pressures of these substances are typically 100–2000 Pa at 20 °C. The largest contribution to vapor pressure is typically expected from low molecular weight components (oligomers). This is probably true for high molecular weight PEPOs. For the NLPs, the increase in molecular weight with increasing number of repeating units may be countered by the "dilution" of hydrogen bonds. For example, MPG + 3 PO has a vapor pressure of 600 Pa at 20 °C (Table 2), propylene glycol (propane-1,2-diol), however, has a vapor pressure of 11 Pa at 20 °C (Ullmann 1993).

At 20 °C, the vapor pressures listed in Table 2 span a range from 2×10^{-4} to 700 or even 2000 Pa. The effusion method with the Knudsen cell delivered comparatively low vapor pressures, whereas data exceeding 100 Pa were generated by the static method. The difference in these findings can be explained by the fact that the PEPOs are mixtures of homologue oligomers, where small molecules are expected to exert a higher vapor pressure than larger molecules. Further, the PEPOs are hygroscopic. The effusion method allows the removal of minor components having a high vapor pressure, whereas this is unlikely to happen in the static method. Therefore, it can be concluded that the PEPOs have initial vapor pressures of about 500 Pa at 20 °C due to a limited content of small oligomers and water, whereas the bulk material has a vapor pressure in the range of 10^{-2} to 10^{-4} Pa.

2.2.7 Surface Tension

Surface tension is not routinely measured, or reported in a regulatory context, for substances which are not intended to be used as commercial surfactants. The surface tension of the PEPOs has an influence on the assessment of their environmental distribution and bioaccumulation potential. Table 2 summarizes the measured surface tensions (0.1 % aq. solution, 20 °C) for several of the PEPO substances having $M_n < 700$. Whereas the surface tension of distilled water at 20 °C is 72.5 mN/m, the surface tensions of the PEPO substances in Table 2 range from 37.35 to 63.62 mN/m. For comparison purposes, a range of secondary alcohol ethoxylate surfactants ($C_{12...14}$ alkyl chain, 7–20 mol EO) exhibit surface tensions ranging from approximately 30 to 40 mN/m at 20 °C (The Dow Chemical Company 2008). Many definitions for a surface-active substance, or surfactant, have been introduced for various commercial or regulatory purposes. For example, the EU Detergent Regulation 648/2004 states that a surfactant must "consist of one or more hydrophilic and one or more hydrophobic groups of such a nature and size that it is capable of reducing the surface tension of water" (European Commission 2004). The Harmonized Tariff Schedule of the United States defines a surface-active agent as a substance giving a transparent solution or suspension at 0.5 % (wt) in water, that lowers the surface tension to below 45 mN/m (U.S. ITC 2005). Similarly, Franke et al. (1994) recommended a surface tension criterion of 50 mN/m for a 0.1 % (wt) aqueous solution. Although the addition of PEPOs to water lowers the surface tension, based on the definitions given above, the PEPOs are not classified as surface active with the exemption of PENT +4.9 PO and *o*-TDA + 5.2 PO + 2.6 EO.

2.2.8 Octanol-Water Partition Coefficient ($\log K_{ow}$)

The $\log K_{ow}$ can be measured using the OECD Guideline 107: Shake flask method (OECD 1995), estimated by the OECD 117 HPLC method (OECD 2004), or calculated using various fragment constant methods (Meylan and Howard 1995; Hansch and Leo 1979; Rekker and Mannhold 1992). Tables 3 and 4 provide a summary of the available measured, estimated, and calculated $\log K_{ow}$ values for a

Table 3 Fraction α of single protonated, amine-initiated PEPO at different pH values

Representative homologue	p*K*a[a]	pH of environmental compartment		
		5	7	9
EDA + 3 PO	7.2	0.994	0.613	0.016
EDA + EO + 2 PO	7.2	0.994	0.613	0.016
NTE + 2 PO	7.4	0.996	0.715	0.025
o-TDA + 3 PO	6.2	0.941	0.137	0.002
o-TDA + 2 PO + 1 EO	6.2	0.941	0.137	0.002

[a]p*K*a of the mono-protonated compound

wide variety of polyether polyol substances. Because these various methods can give widely varied logK_{ow} values, the relevance and reliability of each method is briefly discussed.

The shake flask method is impossible to use with surface-active materials due to emulsion formation which is difficult to break down. The OECD has acknowledged this in their Test Guideline 107 and suggests that a calculated value or an estimated based on the individual solubilities in *n*-octanol and water should be provided in these circumstances. A further difficulty arises as the PEPOs are actually mixtures of homologues molecules, and every single component is expected to show a different distribution constant. An exemption are the EDA initiated PEPOs when they are reacted with not more than four equivalents EO/PO; as the aliphatic primary and secondary amines are more reactive against the alkoxides than hydroxyl groups, the amine N-H groups react successively. With ^{1}H-NMR, it could be shown that the product EDA + 3.3 PO consisted of about 20–30 % *N,N,N′,N′*-Tetrakis(2-hydroxypropyl)-1,2-diaminoethane and about 70–80 % *N,N,N-′*-Tris(2-hydroxypropyl)-1,2-diaminoethane. For this substance, the shake flask method (OECD 107) delivered a logK_{ow} of 0.0.

The reverse-phase HPLC method for estimation of logK_{ow} (OECD 2004) involves comparison of the HPLC capacity factor (k) of an unknown substance against a plot of k vs. logK_{ow} for a series of reference substances. However, as with the "shake flask" method, the OECD advises against using the HPLC method to determine logK_{ow} for surface-active substances, without providing a cut-off level with regard to surface activity. Because the HPLC method provides a practical means of experimentally estimating logK_{ow} for mixtures, and it was validated for surface-active, ethoxylated alcohols (Eadsforth et al. 2014), the method has been applied in the estimation of logK_{ow} for several of the polyether polyols (Tables 3 and 4).

The OECD recommends various structure-fragment calculation methods for estimating logK_{ow}, when neither of the above experimental methods can be applied (OECD 1995, 2004). The most recommended logK_{ow} calculation procedures include those of Rekker and Mannhold (1992), Hansch and Leo (1979), and Meylan and Howard (1995). Unlike the experimental measurement techniques, the calculation methods generate a theoretical value of logK_{ow} for single representative structures.

For the calculation of the logK_{ow}, the molecular distribution was calculated against the nominal composition of the respective PEPO, i.e., starter plus number of monomer units per starter. For every molecule contributing at least 1 mol% to the mixture, the logK_{ow} was calculated using the KOWWIN software tool (v. 1.68, United States Environmental Protection Agency 2010), SPARC (ARChem LLC, http://archemcalc.com/sparc-web/calc#/multiproperty; 2017), and the ACDlabs phys-chem suite percepta (Advanced Chemistry Development, Inc., release 2016). The ACDlabs suite offers two calculation methods for the logK_{ow}: the classical method, similar to the KOWWIN and SPARC method, makes use of structural increments. The "GALAS" compares the structure under investigation with similar compounds with measured logK_{ow} data and provides a reliability index depending on the structural similarity between the

Table 4 Measured and calculated logK_{ow} values for polyether polyols

Product tested	logK_{ow} by OECD 117 [eluent][a]	logK_{ow} by					Surface tension (mN/m)
		KOW-WIN	ACD classic	ACD GALAS	ACD consensus	SPARC	
SUC + 5.2 PO	<0.5 [A/W]	−4.0…−2.7	−2.6…−1.3	<−2.0…0.2	−2.5…−0.7	−6.7…3.2	56
SOR + 7.2 PO	<0.3…2.0 [A/W]	−4.1…−3.2	−2.4…−1.3	−2.0…3.4	−2.1…1.1	−5.0…6.4	56
PENT +4.9 PO	<0.3…1.3 [A/W]	−2.5…−1.0	−1.2…−0.6	−1.4…3.2	−1.3…1.4	−3.7…6.0	37
MPG + 2.7 PO	<0.3…0.9 [n. d.]	0.6…1.8	−0.3…0.4	−0.1…3.5	−0.1…2.5	−0.2…5.6	64
DEG + 3.8 PO	<0.5…1.1 [A/W]	−1.3…0.0	−1.6…−1.5	−0.8…2.8	−1.0…0.6	−1.0…5.9	58
GLY + 3 PO	0.5…1.6; [A/W]	−2.0…−1.2	−1.7…−1.3	−1.1…2.3	−1.3…0.9	−2.2…3.7	53
GLY + 4.9 EO	<0.3…0.5 [M/W][b]	−5.5…−2.1	−5.8…−2.0	−1.4…−0.2	−2.1…−1.5	−2.5…0.0	61
TMP + 3.6 PO	0.5…1.6 [A/W]	−0.7…0.6	−0.2…0.0	−0.5…3.2	−0.5…2.0	−1.5…5.7	57
TMP + 3.2 EO	<0.3…1.7 [M/W][b]	−3.3…−1.1	−3.2…−0.6	−0.7…0.0	−1.0…−0.4	−1.8…−0.1	63
o-TDA + 5.2 PO + 2.6 EO	0.7…5.2 [M/W][c]	0.4…1.2	0.4…1.4	0.7…3.5	0.6…2.2	−0.8…2.2	43
o-TDA + 3.8 PO	<0.3...2.8 [A/W][c]	0.7…1.9	0.7…2.0	1.2…3.2	1.0…2.4	−0.1…2.3	51
EDA + 3.3 PO	<0.3…1.6; [A/W][c]; (0.0)[d]	−2.1…−1.4	−3.1…0.1	−1.0…1.4	−1.1…−0.5	−2.7…1.5	64
EDA + 0.7 EO + 2.8 PO	<0.3...1.5 [A/W][c]	−3.0…−1.4	−4.2…−0.2	−1.0…1.4	−1.2…−0.6	−3.1…1.8	63
NTE + 3 PO	<0.3 [A/W][c]	−2.3…−1.3	−3.6…−1.9	−1.4…2.2	−1.5…−0.4	−2.4…4.0	51

[a]*A* acetonitrile, *M* methanol, *W* water
[b]Tailing
[c]Tailing of peaks; mobile phase did not contain buffer
[d]OECD 107

different substances. The ACD consensus method is a linear combination between the "classical" and the "GALAS" method. The complete set of chemical structures, their respective SMILES codes, and calculation results are summarized in (Supplementary Data 1).

As most of the PEPOs are not surface active, and because the HPLC-method was shown to be applicable for surface-active alcohol ethoxylates (Eadsforth et al. 2014), this method has been applied to the PEPOs. Results are given in Table 4. For EDA + 3.2 PO, the HPLC-result for logK_{ow} is in acceptable agreement with the result derived from the shake flask method (<0.3. . .1.6 against 0.0; see Table 4). Concerning the preferred calculation method, by comparison with measured data SPARC seems to be best applicable for PEPOs with a high content of EO units and/or when the initiator is either ethylene diamine or ortho-toluene diamine. If the initiator is not an amine, and the main monomer is PO, SPARC tends to overestimate the logK_{ow} by 2–4 units. In these cases, the ACD consensus model seems to provide better calculation data, but these may be 1.0 units below to 0.5 units above the values measured with HPLC. For o-TDA + 5.2 PO + 2.6 EO, the discrepancy between calculated and measured logK_{ow} is extreme (0.4. . .0.7 against 0.7. . .5.2). For this molecule, the HPLC run showed a strong tailing which was not observed with the other PEPOs. Therefore, it is assumed that in this case the calculated logK_{ow} values with SPARC and ACD consensus model are a better predictor of environmental behavior than the experimental result; both calculation models delivered data in acceptable agreement with experimental data generated for TDA + PO. The surface tension below 50 mN/m cannot be the sole explanation for the strange chromatogram of o-TDA + PO + EO, as the PEPO with the lowest surface tension, PENT + PO, delivered a chromatogram with symmetrical peaks and without any tailing in the RP-18 HPLC run. In general, the results of the HPLC runs are an indication that not only linear (Eadsforth et al. 2014), but also branched surface-active substances are not necessarily incompatible with this screening method. Visual inspection of the chromatograms revealed that the combination methanol/water as mobile phase resulted in more tailing of the peaks when compared to acetonitrile/water. Therefore, for measuring the logK_{ow} of PEPO substances by OECD 117, acetonitrile/water should be chosen as mobile phase.

Over all it is concluded that the OECD 117 HPLC-method can be used to estimate the logK_{ow} values for PEPOs. As mobile phase, acetonitrile/water should be used. Only in case of strong tailing, data generated by SAR models shall be preferred, and between those used in this report, SPARC should be chosen if the initiator is anamine or the main monomer is EO. The ACD consensus model should be used for the other PEPOs.

2.2.9 Soil Adsorption Coefficient (K_{oc})

Determination of adsorption coefficients (K_{oc}) was carried out using the HPLC screening method (OECD test guideline 121, 2001). A summary of the K_{oc} data generated using this method is provided together with other K_{oc} data generated by

QSAR in Table 5. LogK_{oc} data have been calculated using the PCKOCWIN model which is part of the EpiSuite software version 2.00 (U.S. EPA 2010) and the SPARC K_{oc} calculator (ARChem LLC, http://archemcalc.com/sparc-web/calc#/multiproperty; 2017). For the QSAR methods, logK_{oc} for the smallest and the largest molecule making up at least 1 mol% of the homologue mixtures as given in (Supplementary Data 1) were calculated. Concerning the low molecular weight homologues, calculation data are not in contradiction to measured data for the neutral PEPOs. The high molecular weight homologues, however, have much higher calculated logK_{oc} values by the PCKOCWIN MCI method and the SPARC method than the HPLC-runs. No K_{oc} data have been generated for the PEPOs using the batch equilibrium method according to OECD guideline no. 106 (OECD 1981). Other authors made use of this method and found logK_{oc} values of 1.94, 2.30, and 3.12 for diethylene glycol, tri-ethylene glycol, and polyethylene glycol 600 (Podoll et al. 1987) and 3.24, 3.39, and 3.19 for tetra-, hexa-, and octa-ethylene glycol, respectively (Traverso-Soto et al. 2014). Cation exchange capacity of the soil has a greater influence on the partitioning of these glycols than the content of organic carbon (Podoll et al. 1987). As Traverso-Soto et al. (2014) reported the adsorption of ethoxylated alcohols does increase with the number of EO units, as these interact with mineral phases whereas the alkyl chain interacts with organic matter. Concerning ethoxylated alcohols, the specific surface of the clay minerals has a positive influence on the distribution constant; for probing the inner surface of clay minerals, ethylene glycol-mono-methyl ether is better suited than N_2 as the glycol can intercalate into the minerals (Droge et al. 2009). Against this background it is debatable in how far the HPLC screening method can provide reliable data for the PEPOs; it can simulate effects originating from cavity formation for the solute in the solvent, hydrogen-donor and -acceptor effects and interaction with n-electrons (Poole and Poole 1999), but intercalation in minerals is not covered. If it is assumed that the EO-rich PEPOs do not deviate strongly from PEGs in soil, the HPLC test method delivers too low values and, therefore, is of limited use only. For further clarification, the PCKOCWIN MCI method and SPARC were applied to ethylene glycols with published, experimental K_{oc} data (Traverso-Soto et al. 2014), and calculated logK_{oc} data are compared to experimental data in Table 6. As can be seen there are considerable differences between measured and calculated data.

For the amine-initiated PEPOs, the PCKOCWIN software is not suitable as it does not allow to include charged species, which are present in amine-initiated PEPOs at pH = 5 and 7 (Table 3). The SPARC method takes the pH value and charged species into consideration, and pH has a much stronger influence on the result than the molecular weight (logK_{oc} versus pH plots for amine-initiated PEPOs are given in annex 1, Supplementary Data 1). However, as can be seen in Table 5, there are clear deviations between data generated by the HPLC method and calculated data. LogK_{oc} for polyethylene imine generated by the shake flask method is about 3.8 (Podoll et al. 1987); again, cation exchange capacity is a more important factor for the distribution than the content of organic carbon.

Table 5 Measured and calculated logK_{oc} values for polyether polyols

Substance tested	logK_{oc} by OECD 121	logK_{oc} by PCKOCWIN (v.2.00)		logK_{oc} by SPARC
		MCI[a]	Via logK_{ow}	
SUC + 5.2 PO	<1.25	0.02...9.27	−2.04...−2.05	0.31...24.11
SOR + 7.2 PO	<1.25	1.04...9.52	−2.24...−2.32	−0.81...18.94
PENT +4.9 PO	<1.25	1.00...5.84	−0.88...−1.11	−2.75...20.46
TMP + 3.6 PO	<1.25	1.00...3.89	−0.36...−0.19	−0.95...20.10
TMP + 3.2 EO	No data	1.00...1.11	−0.59...−2.35	−1.74...10.06
GLY + 3 PO	<1.25	1.00...2.17	−0.93...−1.06	−2.52...15.7
GLY + 4.9 EO	<1.5	0.00...2.73	−1.16...−3.60	−2.88...11.19
MPG + 2.7 PO	<1.25	0.00...1.65	0.45...0.44	−0.54...17.0
DEG + 3.8 PO	No data	1.00...3.48	−0.82...−0.55	−1.10...20.05
o-TDA + 5.2 PO + 2.6 EO	1.31...2.99 at pH = 5.4 1.40...2.93 at pH = 7.6	1.20...7.35	0.84...0.27	6.19...30.91 at pH = 5.6; 4.26...30.24 at pH = 7.6;
o-TDA + 3.8 PO	2.70 ... 5.51 at pH 5.4 2.54 ... 4.77 at pH 7.6	1.20...2.92	0.84...0.49	6.19...22.65 at pH = 5.6; 4.26...21.22 at pH = 7.6;
EDA + 0.7 EO + 2.8 PO	>5.63 at pH = 5.5 >5.63 at pH = 7.5	0.61...1.68	−0.50...−1.95	2.97...20.43 at pH = 5.6; 2.28...19.60 at pH = 7.6;
EDA + 3.3 PO	<1.25 ... >5.63 at pH 5.5 <1.25 ... >5.63 at pH 7.5	0.61...3.28	−0.50...−1.18	3.99...24.9 at pH = 5.6; 3.35...23.9 at pH = 7.6;
NTE + 3 PO	<1.25 ... >5.63 at pH 5.5 <1.25 ... >5.63 at pH 7.5	1.00...2.58	−1.34...−1.26	4.04...22.16 at pH = 5.6; 3.68...21.11 at pH = 7.6;

[a]Calculation via molecular connectivity index

Against these experiences the use of K_{oc} as descriptor for the PEPO distribution in the environment is questionable. For better understanding of the behavior of PEPOs in soil, data according to OECD test guideline no. 106 need to be generated.

3 Environmental Fate

The environmental fate of the PEPOs depends on physical–chemical properties described in the previous chapter and on potential degradation pathways. Though adsorption/desorption is a property that is usually addressed under "environmental fate," we regarded it more appropriate to list and discuss the data together with other physical properties in Chap. 2. This chapter deals with data on biodegradation, estimates of atmospheric photodegradation, and will then proceed to environmental distribution modeling.

3.1 Aquatic Fate

3.1.1 Biodegradation Studies

Data from degradation simulation tests are of importance concerning the PBT/vPvB assessment in the European Union (ECHA 2014). Substances showing ready biodegradability, i.e., either at least 70 % DOC removal, 60 % CO_2 evolution, or 60 % O_2 consumption within a 10 days window in OECD 301 tests are regarded as readily biodegradable, and as biodegradable if they fulfil the criteria but miss the 10 days window. For the PEPOs, tests on inherent biodegradability were almost exclusively performed according to the OECD 302B test guideline. When there is at least 70 % DOC removal within 7 days after a lag time of not more than 3 days with not more than 15 % DOC removal within that lag time, the substance is regarded as inherently biodegradable (ECHA 2012). For convenience, this information is summarized in Table 7. Data on biodegradation of the PEPOs are summarized in Table 8.

For SUC + PO, results are diverging. Sucrose initiated polyether polyols typically contain another initiator, like glycerol or diethylene glycol, which serves as a

Table 6 Measured and calculated logK_{oc} data for ethylene glycols and linear alkylalcohol-ethoxylates

Substance	Experimental	PCKOCWIN MCI	SPARC
Diethylene glycol	1.94[a]	0	−1.67
Triethylene glycol	2.30[a]	1	−1.61
Tetraethylene glycol	3.24[b]	1	−0.63
Hexaethylene glycol	3.39[b]	1	2.44
Octaethylene glycol	3.17[b]	1	5.53
Polyethylene glycol 600	3.12...3.74[a]	1	16.33
$C_{12}(EO)_2$	5.27[b]	2.45	7.31
$C_{12}(EO)_8$	5.98[b]	2.78	16.63

[a]Podoll et al. (1987)
[b]Taverso-Soto et al. (2014)

solvent for the sucrose. Differences in the non-disclosed co-initiators, different inocula, and differences in test methods may be responsible for results ranging from "readily biodegradable" to "not inherently biodegradable." Increase in PO monomer units is also a potential explanation for decreased biodegradability.

For EDA + PO + EO, a degradation test in close orientation to the OECD test guideline no. 303 was conducted where a median removal of 70 % non-purgeable organic carbon (NPOC) was achieved (Dow Chemical Company 2017).

SOR + 6 PO was also investigated in the SCAS-test (OECD 302A) where a DOC removal of 2 % was achieved. Six out of the ten PEPOs show neither ready nor inherent biodegradability. For SOR + 6 PO the DOC removal in the OECD 302 B test was below 20 %, meaning this substance is rated as persistent based on these test results. For o-TDA + PO and TMP + EO test data on inherent biodegradability are required before a conclusion on potential persistency can be drawn.

Because the PEPO substances exhibit similarity in physical–chemical properties such as molecular weight, water solubility, and $\log K_{ow}$, their apparent differences in biodegradability likely arise from structural and/or conformational differences imparted by their initiator. Generally speaking, the PEPO substances that have amine-initiators, and/or alcohol initiators with a functionality of at least three or more (branched PEPOs), appear to have reduced biodegradability. The poly(propylene glycol) substances (i.e., 1,2-propanediol + PO) have been shown to be readily biodegradable over molecular weights ranging from about 350 to 2000 g/mol (West et al. 2007). Likewise, the poly(ethylene glycol) substances have been shown to biodegrade rapidly over molecular weights of up to 20,000 g/mol (Bernhard et al. 2008). Thus, the alkoxylate fragments of the PEPO substances are not intrinsically resistant to microbial degradation, and the mechanisms for their degradation are well-understood. Several research groups have extensively studied the biodegradation mechanisms for polyether substances (White et al. 1996; Kawai 2002; Tachibana et al. 2003). The polyether substances are apparently metabolized via oxidation of the terminal alcohol groups to ketone, aldehyde, and carboxylate groups, followed by cleavage of the adjacent terminal ether bond. Thus, the biodegradation of these substances appears to occur via a stepwise depolymerization mechanism, with each oxidative step initiated at the terminal ends of the molecules, and presumably catalyzed by various related alcohol dehydrogenase enzymes (Tachibana et al. 2003). An additional or alternate mechanism of degradation would appear to be operative for the poly(ethylene glycol) substances, which can result in random scission of the polyethylene glycol chains to form shorter polyether oligomers (Zgola-Grzeskowiak et al. 2006; Bernhard et al. 2008). The prevalence of this apparent mechanism appears to be dependent upon both molecular weight of the polyether and the organisms (e.g., freshwater vs. seawater) involved in their degradation.

Table 7 Rating of biodegradation tests in the European Union (ECHA 2012, 2014)

Test result	Rate constant (h^{-1})		Persistency evaluation
	STP (h^{-1})	Surface water (d^{-1})	
Readily biodegradable	1	0.047	Not P, not vP
Readily biodegradable, failing 10 days window	0.3	0.014	Not P, not vP
Inherent biodegradable, fulfilling specific criteria	0.1	0.0047	Not P, not vP
Inherently biodegradable, missing specific criteria	0	0	Potentially P or vP
Not biodegradable (p.e. <20 % DOC removal)	0	0	Sufficient information to confirm persistence

Table 8 Results of biodegradability tests of PEPO substances

Product tested	M_n	Test results (%)		Comment	Rate constant k	
		OECD 301 (A...F)	OECD 302B		STP (h^{-1})	surface water (d^{-1})
SUC + PO	440	91 (F)	66	Readily biodegradable	1	0.047
SUC + PO	500	No data	35	Not inherently biodegradable	0	0
SUC + PO	720	32 (D)	No data	Not biodegradable	0	0
EDA + PO	360	9 (F)	36	Not biodegradable	0	0
TMP + PO	310	84 (F)	97	Readily biodegradable	1	0.047
TMP + PO	1000	76 (BOD_{10})	97	Readily biodegradable	1	0.047
GLY + PO	260	38 (B)	99	Inherently biodegradable	0.1	0.0047
EDA + EO + PO	280	2 (F)	61	Not biodegradable	0	0
SOR + PO	700	8 (D)	14	Not biodegradable	0	0
o-TDA + PO	510	9 (F)	No data	Not biodegradable	0	0
MPG + PO	230	87 (D, F)	No data	Readily biodegradable	1	0.047
MPG + PO	450	70...80 (F)	>90	Readily biodegradable	1	0.047
PENT + PO	400	51 (F)	No data	Not biodegradable	0	0
NTE + PO	340	49 (F)	No data	Not biodegradable	0	0
DEG + PO	222	75 (F)	No data	Readily biodegradable	1	0.047
Gly + EO	180	55[a]	35	Not biodegradable	0	0
o-TDA + PO + EO	282	No data	35	Not biodegradable	0	0
TMP + EO	222	<10 (A)	No data	Not biodegradable	0	0

[a]OECD 310

3.1.2 Abiotic Degradation

Data on direct or indirect photolysis of the PEPOs in water are not available. Direct photolysis is not expected as the PEPOs do not show absorption above 300 nm, with the exemption of o-TDA-initiated PEPPOs which have a weak band at 305 nm. Some indirect photolysis may be expected, as the PEPOs are expected to show a high reactivity against OH radicals in air (see Chap. 3.2), and their high water solubility indicates that the aquatic phase should be an important compartment within which the PEPOs are expected to be present if released into the environment. With the lack of experimental data, a photolytic decay of PEPOs in water cannot be incorporated into environmental models.

There are no data concerning hydrolytic behavior of the PEPOs. Due to the lack of appropriate groups like ester-, amide-, nitrile-, or organo-halide structures, hydrolysis is not expected to play a role in environmental decay of the parent PEPOs.

Non-photolytic, oxidative decay of polypropylene glycols at elevated temperature is reported by Yang et al. (1996). At 150 °C in the dark, PPG loses 25 % of weight after 268 h (about 11 days). Release of small molecules like ethylene or propylene glycol formate and acetate indicates the scission of the polyether chain. For a detectable oxidative decay, polyethylene and polypropylene glycols need to be in a liquid state (Gallet 2001; Gallet et al. 2002). As there are no experimental data for the PEPOs, oxidative decay cannot be incorporated into environmental fate modeling.

3.2 Atmospheric Fate

The fate of the PEPO substances in the atmosphere has not been directly studied. The potential for persistence and long-range transport of the PEPO substances can be assessed on the basis of accepted structure–activity relationships. The molecular structures of the PEPO substances lack functional groups or chemical bonds which appreciably absorb light at above the 290 nm cut-off for solar radiation penetrating the troposphere. The only exemptions are o-TDA-initiated PEPOs which show a small shoulder at 305 nm in the UV spectrum. Therefore, direct photolysis is not expected to be an important or relevant process affecting their atmospheric fate. Conversely, indirect photolysis, via reaction with photochemically generated hydroxyl radicals, is the predominant process affecting fate of organic substances, such as the PEPO substances, in the troposphere. The rate at which this indirect photolysis process occurs for a specific substance can be accurately predicted from molecular structure, using the AOPWIN model (v1.92) developed by Meylan and Howard (1993) for the US EPA (2010). This version of AOPWIN model has been shown to estimate second-order rate constants for reaction with hydroxyl radicals within a factor of two of the experimental value for >90 % of circa 640 chemicals

(U.S. EPA 2010). The rate constants for this reaction have been estimated for representative homologues of the PEPO substances (listed in Table 1), and are summarized in Table 9. OH radicals have a very short atmospheric lifetime of about 1 s. As a result, there is no photodegradation in absence of sun light. This fact is taken into consideration by averaging the 12 h light period OH radical concentration over the 24 h. Therefore, the corresponding half-lives calculated for the PEPOs substances assume an average tropospheric hydroxyl radical concentration of 1.5×10^6 molecules/cm^3 and 12-h photo-day.

The predicted atmospheric half-lives for representative homologues of the PEPO substances range from 0.5 to 2.5 h. (Table 9). The reaction of hydroxyl radical with these substances is predicted to be dominated by a hydrogen abstraction mechanism, whereby the oxidative radical chain reaction can be initiated at any of a number of C–H bonds. Lesser contributions to the overall reaction rate arise from hydroxyl radical attack at the amino and hydroxyl groups, or by its addition to the aromatic ring of the o-toluenediamine-initiated PEPOs. Accordingly, sensitivity analyses with the AOPWIN (v1.92) model showed that each additional ethoxylate or propoxylate repeating unit results in an incremental decrease in predicted reaction half-life, typically by 0.1–0.3 h, which is independent of the ordering/positioning of these repeating units. Therefore, the predicted atmospheric half-lives given in Table 9 for the representative PEPO homologues can be regarded as representative of all homologues of the corresponding PEPO. GLY + PO, GLY + EO, TMP + EO, and DEG + PO have half-lives just above 2 day, which is the cut-off for suspicion for long-range transport potential in the European Union (ECHA 2014). However, due to generally low vapor pressures, high water solubility, and biodegradation data, only GLY + EO and TMP + EO are left over as substances that deserve follow-up.

3.3 Terrestrial Fate

Degradation data on the PEPO substances in soil are not available. However, polyethylene glycols and polypropylene glycols (PPGs) are degraded by bacterial strains found to be present in soil, e.g., *Pseudomonas aeruginosa* and *Pseudomonas stutzeri,* to name two (White et al. 1996). Kawai et al. (1977) isolated bacteria from activated sludge and from soil which could use PPG diols and triols as the sole carbon source. The enriched cultures grew faster on higher molecular weight PPGs than on the easily degradable monopropylene glycol; the authors argue that the assumed recalcitrance of the PPGs to microbial degradation may at least partly be attributable to the lack of previous exposure. Based on the results of biodegradation tests with activated sludge, branched and also amine-initiated PEPOs are expected to show poorer biodegradation results in soil than non-amine and linear PEPOs.

Table 9 Summary of second-order reaction rate constants and associated half-lives predicted by AOPWIN for reaction of the PEPO substances with hydroxyl radical

CAS no.	Representative homologue	Estimated second-order rate constant (cm^3/molecule × s) × 10^{12}	Estimated atmospheric half-life (h)[a]
25791-96-2	GLY + 2 PO	50.5	2.5
9051-49-4	PENT +3 PO	72.2	1.8
25311-69-4	MPG + 3 PO	74.8	1.7
25214-63-5	EDA + 3 PO	231	0.6
26316-40-5	EDA + 1 EO + 2 PO	204	0.6
25723-16-4	TMP + 3 PO	77.4	1.7
52625-13-5	SOR + 6 PO	180	0.7
9049-71-2	SUC + 5 PO	198	0.6
63641-63-4	o-TDA + 3 PO	258	0.5
37208-53-0	NTE + 2 PO	187	0.7
9051-51-8	DEG + 2 PO	59.4	2.2
31694-55-0	GLY + 2 EO	50.5	2.5
67800-94-6	o-TDA + 2 PO + 1 EO	254	0.5
50586-59-9	TMP + 2 EO	50.8	2.5

[a]Assuming a 24 h average hydroxyl radical concentration of 1.5 × 10^6 molecules/cm^3 and 12-h photo-period

3.4 Environmental Release

Monitoring data for the PEPO substances are not available. Concerning structurally similar compounds, Traverso-Soto et al. (2013, 2014) detected alcohol ethoxylates and polyethylene glycols in marine sediments, the latter achieving levels of 1.6–8.8 ppb.

To our knowledge, PEPOs are exclusively used for the production of polyurethanes. As water is a powerful trace reactant in the polyurethane reaction, storage of PEPOs is done under strict control of exposure to air as gaseous water can be absorbed by the PEPOs. This, and the fact that the PEPOs have

comparatively low vapor pressures, leads to the assumption that any release happens into sewers, only. In 2014, the total market volume of polyether polyols was 2.4 million tons in Europe and Middle East (ISOPA 2016). The amount to be allocated to Europe is expected to be 80 %. Due to the use patterns in polyurethane production, about 40 % of this amount can be allocated to the lower molecular polyether polyols as presented in this document. About 80 % of the polyols are transported by tank truck and the remaining material is delivered in drums and integrated bulk containers (IBCs). It is expected that drums with PEPOs are handled similar to drums with di-isocyanates, meaning that about 0.5 % of the drum content is left after emptying (ISOPA 2014). Because the PEPOs are not classified as hazardous to the environment, the reasonable worst case assumption is that this material is discharged into sewers. For tank truck transport as well a loss of 0.5 % of the transported PEPO to sewers due to cleaning activities is assumed; this as well is worst case as—between others—dedicated tank trucks are in use to avoid contamination of the polyol with water as this would seriously impact the polyurethane reaction these PEPOs are used for. Due to the generally low vapor pressures, atmospheric losses are expected to be negligible. Overall, the estimated loss of PEPOs into the aquatic system in Europe is estimated as

$$\text{Emission}_{\text{aqua, europe}} = 2.4 \times 10^6 \frac{t}{a} \times 0.8 \times 0.4 \times 0.005 = 3840 \frac{t}{a} = 10.52 \frac{t}{d} = 0.44 \frac{t}{h}.$$

For modeling purposes, it is assumed that for an individual PEPO up to 10 % of this amount can be emitted, which is 440 kg/h, split over 10 locations in Europe, which gives an regional release of 44 kg/h or about 1 t/d and a continental release of 10 t/d.

3.5 Environmental Distribution

The distribution and fate of the PEPOs was modeled with the EUSES program v.2.1 (European Union 2016). The general release estimate was 1 t/d into regional wastewater, and 10 t/d into continental wastewater. This program limits the indirect atmospheric degradation by reaction with OH radicals to a maximum rate constant of 10^{-10} s^{-1}, and water solubility is limited to 100 g/L. The PEPOs are mixtures of oligomers. As discussed earlier, the low molecular weight homologues show a comparatively high vapor pressure of about 400 Pa (25 °C) and a low $\log K_{ow}$ (set to 0), whereas the high molecular weight homologues have a low vapor pressure of about 0.004 Pa (25 °C) and the high-end $\log K_{ow}$ as given by the OECD test method no. 117. Modeling is done for the low and the high molecular weight homologues. The $\log K_{oc}$ was fixed to 4. Data concerning regional predicted environmental concentrations (PECs) in freshwater, its sediment, soil, and air are summarized in Table 10. The EUSES calculation results for the environment are listed in Appendix 2 (Supplementary Data 2).

For the amine-initiated polyols, the high vapor pressure (400 Pa at 25 °C) was linked with the low logK_{ow} of 0.0 and a logK_{oc} of 4, and the low vapor pressure was combined with the highest measured logK_{ow} and a logK_{oc} of 6 because measured data for the latter were >5.6. For reasons outlined in Chap. 2.2.8, for o-TDA + PO + EO the logK_{ow} data of o-TDA + PO were used. Results are listed in Table 11.

Calculated values for marine water were typically a factor of 10 below the surface water values reported in Tables 10 and 11. Similarly, calculated continental concentrations were about a factor of 10 or more below the regional values. Sediment and agricultural soil are the compartments that show the highest levels for the predicted environmental concentrations (PECs). Especially for the amine-initiated PEPOs, the strong influence of the logK_{oc} is obvious. Experimental logK_{oc} data for the PEPOs generated by the OECD 121 test method are of limited reliability, and data for polyethylene glycols generated by the OECD 106 test guideline (batch method) were taken as surrogate (see Chap. 2.2.9); the results listed in Tables 10 and 11 underline the need for generating logK_{oc} data by the batch method according to OECD test guideline no. 106. Once these data have been generated, the EUSES (v.2.1) calculations should be revisited.

4 Ecotoxicity

A compilation of all the available ecotoxicity data for the polyols has been made. A short overview is given in Table 10. For all test species (fish, invertebrates, algae, and microorganisms) only data of validity 1 ("valid without restrictions") or 2 ("valid with restrictions") according to Klimisch et al. (1997) and which after careful review are appropriate for risk assessment purposes were included. In many cases there was no definite ecotoxicity value reported and in these cases data were presented as greater than (>) values.

4.1 Acute Aquatic Toxicity

Data on acute aquatic toxicity of the PEPOs are summarized in Table 12, and further data are given in Appendices 3, 4, and 5 (Supplementary Data 3). In summary, all acute fish, daphnia, algae, and microorganism ecotoxicity values are greater than 100 mg/L, with one exception, the acute fish data on *Danio rerio* for o-TDA + 3 PO, where the highest concentration tested was 77.8 mg/L (measured concentration) without showing mortality. In conclusion, these data confirm the low acute toxicity of the NLPs toward aquatic organisms. This collection of toxicity data demonstrates that the polyether polyols are "practically non-acute toxic" to freshwater and marine organisms according to the GESAMP acute toxicity criterion (EC50, LC50 > 100 mg/L) (GESAMP 2002).

Table 10 Predicted environmental concentrations (PEC) on regional scale for non-amine PEPOs in surface water, seawater, agricultural soil, and air calculated by EUSES v.2.1; $\log K_{oc} = 4$ for all substances

Substance	$\log K_{ow}$	VP (Pa)	PEC surface water (mg/L)[a]	PEC sediment (mg/kg)[a] wet weight	PEC air (mg/m^3)	PEC agricultural soil (mg/kg)[a] wet weight
Suc + PO[b]	0.5	0.004	1.15E-03	0.465	7.83E-12	2.94
	0.0	400	5.53E-04	0.224	1.06E-06	1.64
SUC + PO[c]	0.0	400	3.35E-03	1.35	2.64E-06	2.12
	0.5	0.004	0.0107	4.33	1.86E-11	3.81
SOR + PO	0.0	400	3.63E-03	1.36	1.63E-06	2.12
	2.0	0.004	0.0107	4.33	1.79E-11	3.81
PENT + PO	0.0	400	3.75E-03	1.52	3.19E-06	2.13
	1.3	0.004	0.0107	4.33	7.91E-12	3.81
TMP + PO	0.5	400	6.10E-04	0.247	1.20E-06	1.66
	1.6	0.004	1.15E-03	0.465	4.83E-14	2.94
TMP + EO	0.0	400	4.46E-03	1.80	3.65E-06	2.16
	1.7	0.004	0.0107	4.33	2.26E-12	3.81
GLY + PO	0.5	400	6.24E-03	2.52	4.19E-14	3.47
	1.6	0.004	6.24E-03	2.52	4.16E-14	3.47
GLY + EO	0	400	7.82E-03	7.10E-03	3.30E-06	2.31E-05
	0.5	0.004	0.0161	0.0177	2.16E-13	4.70E-05
MPG + PO	0	600	3.71E-04	3.37E-04	2.16E-07	9.04E-06
	0.9	0.004	5.25E-04	7.16E-04	2.95E-14	8.30E-05
DEG + PO	0.0	400	4.12E-04	3.74E-04	1.83E-07	9.25E-06
	1.1	0.004	5.26E-04	8.17E-04	2.53E-14	1.29E-04

[a]Sum of adsorbed and dissolved compound; lowest $\log K_{ow}$ set to 0.0; vapor pressure set to 400 Pa (high) or 0.004 Pa (low)
[b]Readily biodegradable
[c]Not biodegradable

Table 11 Predicted environmental concentrations (PEC) on a regional scale for amine-initiated PEPOs in surface water, sediment, agricultural soil, and air calculated by EUSES v.2.1

Substance	logK_{ow}	logK_{oc}	VP (Pa)	PEC surface water (mg/L)[a]	PEC sediment (mg/kg)[a]	PEC air (mg/m^3)	PEC agricultural soil (mg/kg)[a]
o-TDA + 5.2 PO + 2.6 EO	0.7	4	400	3.51E-03	1.42	2.58E-06	2.12
	2.8	6	0.004	1.71E-03	29.7	2.87E-12	88.5
o-TDA + 3.8 PO	0	4	400	2.84E-03	1.15	4.14E-06	2.10
	2.8	6	0.004	2.24E-03	38.9	1.55E-11	88.5
EDA + 3.3 PO	0	4	400	4.32E-03	1.75	2.31E-06	2.15
	1.6	6	0.004	1.71E-03	29.7	6.22E-13	88.5
EDA + 2.8 PO + 0.7 EO	0	4	400	4.36E-03	1.76	2.30E-06	2.15
	1.5	6	0.004	1.71E-03	29.7	5.74E-13	88.5
NTE + 3 PO	0	4	400	4.04E-03	1.63	2.41E-06	2.14
	0	6	0.004	1.71E-03	29.7	1.02E-12	88.5

[a]Total concentration, sum of adsorbed and dissolved; concentrations in sediment and soil on the basis of wet weight

Escher et al. (2010) described different mechanisms and modes of action in ecotoxicity, targeting membrane structure and functions (non-polar and polar narcosis, degradation by reactive intermediates, uncoupling/blocking of transmembrane transport or electron transport chains), proteins and peptides (alkylation, oxidation, binding to enzymes or receptors, binding to peptides that interact with DNA), and DNA/RNA reactive (base modification and damage). Test methods to scrutinize into these mechanisms are published (Escher et al. 2005) but were not applied to the PEPOs. The PEPOs were not mutagenic in in-vitro bacterial reverse mutation tests (OECD test guideline no. 471), in-vitro chromosomal aberration test (OECD test guideline no. 473), and in-vitro point mutation in mammalian cells (OECD test guideline no. 476), either in presence or absence of metabolic activation. This issue will be subject of a separate review.

Because those polyether polyols based on other starters than amines are nonionic and non-reactive, any acute toxicity associated with these substances is expected to occur through a narcotic mode of action. It has been shown that this baseline toxicity, or narcosis, of neutral organic chemicals is directly related to bioconcentration in aquatic organisms (McCarty and Mackay 1993; McCarty et al. 1993). Escher (2001) asserts that most nonionic surfactants exhibit a narcotic

mode of toxicity. More specifically, Muller et al. (1999) postulate that at low surfactant concentrations this narcosis occurs via initial adsorption of the surfactant monomer onto membrane surfaces, with subsequent absorption into the membrane lipids.

For QSAR models, the membrane-water partition coefficient was shown to relate to acute toxicity in fish (Könemann 1981), *Daphnia magna* and *Vibrio fischeri* (Zhao et al. 1998), and the green algae *Chlorella vulgaris* (Verhaar et al. 1999). An algorithm to transform $\log K_{ow}$ into $\log K_{mw}$ was published by Vaes et al. (1997) and further extended by Escher and Schwarzenbach (2002), Escher and Hermens (2002), and Endo et al. (2011). Some of the equations are listed below:

$$\log K_{mw} = 1.01 \times \log K_{ow} + 0.12 \quad \text{for neutral compounds;} \tag{4}$$

$$\log K_{mw} = 0.9 \times \log K_{ow} + 0.52 \quad \text{for polar compounds;} \tag{5}$$

$$\log \mathrm{LC50} = -0.83 \times \log K_{mw} - 1.46 \quad \text{for } \textit{Poecilia reticulata}, \tag{6}$$

$$\log\{\mathrm{EC}_{50}\} = -0.91 \times \log\{K_{mw}\} - 0.63 \quad \text{for } \textit{Chlorella vulgaris}, \text{ and} \tag{7}$$

$$\log\{\mathrm{EC}_{50}\} = -0.77 \times \log\{K_{mw}\} - 1.89 \quad \text{for } \textit{Daphnia magna}. \tag{8}$$

where EC_{50} or LC_{50} are calculated in mole/L, and K_{mw} is the membrane-water partition coefficient. The calculated data using the algorithms for algae and daphnia are matched against experimental values in Table 13; the amine-initiated PEPOs are regarded as polar substances due to the p*K*a values of the corresponding acids. For the PEPOs, the range of calculated EC_{50} values covers, or is above the measured

Table 12 Acute aquatic toxicity data of PEPOs, LC_{50}, EC_{50} or IC_{50}, mg/L

CAS no.	Representative homologue	Fish[a]	Daphnia[a]	Algae[a]	Bacteria[a]
9049-71-2	SUC + 5 PO	>1000	≥100[b]	≥100 (E_rC_{10})	>720
25214-63-5	EDA + 3 PO	≥2200[b]	≥ 100[b]	No data	≥10,000
25723-16-4	TMP + 3 PO	≥100[b]	≥100[b]	≥100 (E_rC_{10})	≥10,000
25791-96-2	GLY + 2 PO	≥1000[b]	≥100[b]	≥100 (E_rC_{10})	≥10,000
26316-40-5	EDA + 1 EO + 2 PO	4230	≥100[b]	≥100 (E_rC_{10})	≥10,000
52625-13-5	SORB +6 PO	≥1000[b]	≥100[b]	≥1000[c]	≥10,000
63641-63-4	o-TDA + 3 PO	≥77.8[b]	≥100[b]	≥100 (E_rC_{10})	≥10,000
25322-69-4	MPG + 3 PO	≥100[b]	105.8	≥100 (E_rC_{10})	≥1000
9051-49-4	PENT +3 PO	≥100[b]	≥100[b]	≥100 (E_rC_{10})	≥10,000
37208-53-0	NTE + 2 PO	≥100[b]	≥100[b]	≥100 (E_rC_{10})	≥10,000
9051-51-8	DEG + 2 PO	≥100[b]	≥100[b]	≥100 (E_rC_{10})	>1000
31694-55-0	GLY + 2 EO	No data	≥100[b]	No data	>1000
67800-94-6	o-TDA + 2 PO + 1 EO	No data	≥100[b]	No data	>110
50586-59-9	TMP + 2 EO	No data	No data	No data	≥36[d]

[a] LC_{50}/96 h for fish, EC_{50}/48 h for daphnia, EC_{50}/72 h for algae, and IC_{50}/30 min for activated sludge, if not indicated otherwise

[b] No mortality, immobility, or inhibition was observable

[c] Marine species *Skeletonema costatum*

[d] No inhibition of decay of reference substance in OECD 301A

values. These results imply that the PEPOs can be regarded as substances acting via baseline narcosis.

Recently, Austin et al. (2015) updated the acute fish model, which is applicable for compounds with $\log K_{ow}$ values between −1 and 5.

$$\log\{LC_{50}\} = 1.833 - (0.9362 \times \log K_{ow}). \quad (9)$$

LC_{50} is calculated as mmole/L. Using this formula for the PEPOs would correctly predict EC_{50} and LC_{50} values above 100 mg/L. When the lower and upper end of measured $\log K_{ow}$ values is used for the calculation of the acute fish LC_{50}, the interval covers the measured values, as shown in Table 14.

All of these observations lead to the conclusion, that the PEPOs are most likely acting via baseline narcotic toxicity. In addition, the QSAR model Toxtree (v2.66) (Verhaar et al. 1999) predicts the non-amine PEPOs belonging to the class 1 - (non-polar narcotics). The program rates the amine-initiated PEPOs as class 5 - (non-classifiable); one reason is the calculated $\log K_{ow}$ being out of the range from 0 to 6, or the molecular mass is beyond 600 g/mol. However, experimental data indicate that the amine-initiated polyols can be regarded as belonging to class 2 substances (polar narcotics), as they are partly protonated at ambient pH levels (see Sect. 2.2.4).

The mechanism of action of baseline narcotic toxicity is regarded as showing a high degree of reversibility, and differences between species are expected to be small (Escher et al. 2010). Therefore, it is assumed that in case of lacking data concerning acute aquatic toxicity, read across between different PEPOs is possible.

4.2 Chronic Aquatic Toxicity

For the conduction of chronic daphnia tests, four PEPOs (TMP + 3 PO, EDA + EO + 2 PO, SORB +5 PO, and *o*-TDA + 3 PO) were selected. These PEPOs span a grid from low to high water solubility, low to high functionality, aromatic to non-aromatic, and neutral to basic/charged molecular fragments in the aquatic phase. Chronic daphnia and algae data are summarized in Table 15.

In general, the PEPOs show little to limited chronic toxicity; o-TDA + 3 PO and EDA + EO + 2 PO, however, are the exception. The 21-days daphnia NOAEC for o-TDA + 3 PO may be explained by the toxicity of the initiator. o-TDA (CAS-No.: 26966-75-6) shows a 21-days NOEC of 0.282 mg/L, and a LOEC of 0.963 mg/L in a chronic daphnia test (3(or 4)-methylbenzene-1,2-diamine; (ECHA 2016)). For EDA, the 21-days daphnia NOEC is 0.16 mg/L (Kühn et al. 1989), and the 72-h E_rC_{10} for algae is >100 mg/L (Kühn and Pattard 1990). That means, the alkoxylation of EDA with PO reduces the chronic toxicity to daphnia while increasing the toxicity to algae. The chronic toxicity observed may therefore become apparent as biodegradation or metabolic degradation occurs and the initiator molecules become more bioavailable. When categorized using the OASIS®

Table 13 Calculated versus measured EC_{50} data (mmole/L) for daphnia and algae

Product tested	$\log K_{ow}$ by OECD 117	$\log K_{mw}$		Daphnia		Algae	
		Low[a]	High	Calc.	Meas.	Calc.	Meas.
SUC + 5.2 PO	<0.5	0.12	---	10.4	>0.15	182	>0.15
SOR + 7.2 PO	<0.3...2.0	0.12	2.14	10...0.29	>0.16	182...2.6	>0.16
PENT + 4.9 PO	<0.3...1.3	0.12	1.43	10...1.0	>0.24	182...11.7	>0.24
MPG + 2.7 PO	<0.3...0.9	0.12	1.03	10...2.1	>0.36	182...27	>0.36
DEG + 3.8 PO	<0.5...1.1	0.12	1.23	10...1.5	>0.45	182...18	>0.45
GLY + 3 PO	0.5...1.6;	0.21	1.74	8.9...0.6	>0.4	82...6.1	>0.4
GLY + 4.9 EO	<0.3...0.5	0.12	0.63	10...4.2	>0.3	182...63	>0.3
TMP + 3.6 PO	0.5...1.6	0.21	1.74	8.9...0.6	>0.29	82...6.1	>0.29
TMP + 3.2 EO	<0.3...1.7	0.12	1.84	10...0.5	>0.45	182...5.0	>0.45
o-TDA + 5.2 PO + 2.6 EO	0.7...2.8[b]	1.15	2.95	1.7...6.9E-02	>0.19	21...0.5	>0.19
o-TDA + 3.8 PO	<0.3...2.8	0.12	2.95	10...6.9E-02	>0.29	182...0.5	>0.29
EDA + 3.3 PO	<0.3...1.6	0.12	1.74	10...0.6	>0.4	182...6.1	>0.4
EDA + 0.7 EO + 2.8 PO	<0.3...1.5	0.12	1.64	10...0.7	>0.42	182...7.5	>0.42
NTE + 3 PO	<0.3	0.12	----	10	>0.31	182	>0.31

[a]0 for values "<X"
[b]Upper value in analogy to o-TDA + PO

MoA (Mode of Action) predictor contained within the OECD Toolbox, o-TDA, and EDA were categorized as "reactive unspecified" and "narcotic amine," respectively; molecules which fall into these categories are expected to have slightly higher than baseline toxicity. Additionally, as shown in Appendix A5, some of the metabolites predicted to be most prevalent were categorized similarly; it is therefore possible these may have contributed to any chronic toxicity.

For those NLPs for which no long-term toxicity has been determined low chronic ecotoxicity is expected. However, o-TDA + PO + EO is expected to be comparable to o-TDA + PO, meaning the 21-days NOEC for daphnia toxicity is 1.0 mg/L, and NTE + PO—in absence of substance-specific data—is expected to be comparable to EDA + PO with an E_rC_{10} of 4.25 mg/L.

Chronic tests with fish have not been performed with the PEPOs. Austin and Eadsforth (2014) developed a model for predicting chronic fish toxicity for substances acting via non-polar narcosis and which have $\log K_{ow}$ values between 0.45 and 5.30. For Verhaar scheme class 1 compounds (neutral narcotics) the relation is

$$\log \mathrm{NOEC} = 0.711 - 0.914 \times \log K_{ow}, \tag{10}$$

where the no effect concentration has the dimension mmole/L. For the non-amine PEPOs which belong to Verhaar class 1 substances, the calculated NOEC for chronic fish toxicity is at maximum 7.64×10^{-5} mol/L, which is about 20–40 mg/L.

Table 14 Calculated versus measured LC_{50} data for fish (mmole/L), using the lower and upper limits of measured $\log K_{ow}$ values

PEPO tested	M_n	$\log K_{ow}$[a]		LC50		
		Low[b]	High[c]	Experimental	Calc. low	Calc. high
EDA + 5 PO	350	<0.3	1.6	4870	12,480	757
MPG + 6 PO	424	<0.3	0.9	6760	15,190	4167
EDA + EO + 2 PO	220	<0.3	1.5	4230	8201	617

[a]HPLC-method values for EDA + 3.3PO, MPG + 2.7 PO, and EDA + 0.7 EO + 2.8 PO
[b]Lower limit of the method
[c]Maximum value from the HPLC-run

4.3 Toxicity to Marine Organisms

Of the PEPOs discussed in this paper, only SOR + 6 PO was tested with marine organisms. The 48-h EC_{50} for *Acartia tonsa* and the 72-h EC_{50} for *Skeletonema costatum* were greater than 1000 mg/L, the highest concentration tested.

4.4 Sediment Organisms

The effect of the PEPOs against sediment organisms was not investigated. Distribution modeling revealed that sediment is an important compartment where concentrations of PEPOs are magnitudes higher than in the aquatic phase (see Chap. 3.5). The performance of cursory tests with selected PEPOs should be considered. Based on the results, the need for further steps can be discussed.

4.5 Toxicity to Terrestrial Organisms

No terrestrial studies have been carried out for the PEPO substances with the exemption of mammalian toxicity. This will be subject of a separate review. Distribution modeling revealed that agricultural soil is an important compartment where concentrations of PEPOs are magnitudes higher than in the aquatic phase (see Chap. 3.5). The performance of toxicity tests with soil organisms for selected PEPOs is recommended. Based on the results, the need for further steps can be discussed.

Table 15 Summary of chronic ecotoxicity (in mg/L) for the PEPOs

Representative homologue	CAS number	Daphnia magna (21d-NOEC)	Algae (72 h–E_rC_{10})
SUC + 5 PO	9049-71-2	–	≥100
EDA + 3 PO	25214-63-5	–	4.25
TMP + 3 PO	25723-16-4	≥8.5[a]	≥100
Gly + 2 PO	25791-96-2	–	≥100
EDA + EO + 2 PO	26316-40-5	≥10	≥100
SOR + 6 PO	52625-13-5	≥10	≥100
o-TDA + 3 PO	63641-63-4	1.0	≥100
MPG + 3 PO	25322-69-4	–	≥100
PENT + 3 PO	9051-49-4	–	≥100
NTE + 2 PO	37208-53-0	–	≥100
DEG + 2 PO	9051-51-8	–	≥100

[a]Nominal concentration 10 mg/L; measured concentration 8.5 mg/L

4.6 Environmental Risk Evaluation

In the EUSES program (European Union 2016), predicted no effect concentrations (PNECs) are calculated by applying safety factors to the lowest available (no-) effect data for ecotoxicity. These factors—used as divisors—are smaller with increasing number of species tested. With acute data for three trophic levels and chronic data points for two trophic levels covering the most sensitive species in acute tests, this factor is 50. PNECs are also calculated for compartments without toxicity test data by assuming similar sensitivity of the organisms between compartments and a similar distribution behavior of the substance between water, air, and solids. By read across, the PEPOs are grouped together as shown in Table 16. The full set of the EUSES calculations concerning the environment is given in (Supplementary Data 2). A summary of results is listed in Table 17, matching the highest PECs against the PNECs. There is no compartment showing a PEC/PNEC ratio of 1 or above, so "no risk for the environment" is the first conclusion. However, as outlined above, the logK_{oc} values for the PEPOs need some further evaluation, and calculation results may change. Further, especially for the o-TDA initiated PEPOs, but also for some others the PEC/PNEC ratio in soil is less than a factor of 10 below 1. As a precautionary measure, toxicity tests with soil organisms for selected PEPOs are recommended; based on the results, the need for tests with sediment organisms can be discussed.

5 Bioaccumulation Potential

5.1 Measured and Calculated logK_{ow} and BCF Values

Measured logK_{ow} values for the PEPOs (see Chap. 2.2.8) do not indicate a critical bioconcentration potential with the exemption of o-TDA + 5.2 PO + 2.6 EO. However, the latter is surface active, and the HPLC-chromatogram showed a considerable tailing of the peak, so the measured logK_{ow} is considered as of low reliability (see Chap. 2.2.8). The calculated logK_{ow} values for o-TDA initiated PEPOs using the SPARC or ACD algorithms, showing an acceptable agreement with measured data for o-TDA + 3 PO, do not indicate a critical bioaccumulation potential.

Di Toro et al. (2000) have proposed relationships between toxicity, partition coefficient, and bioconcentration of narcotic substances:

$$\log(EC_{50}) \sim -\log(K_{ow}) + 1.7 \quad (11)$$

$$\log(BCF) \sim \log K_{ow} - 1.3 \quad (12)$$

According to these relationships, the measured LC50 values in fish (LC50 > 100 mg/L) correlate to a logK_{ow} value of −0.3 by Eq. 11. Insertion of the calculated logK_{ow} values of <3.0 in Eq. 12 equates to log BCF values of 1.7 (BCF < 50). Therefore the low toxicity of the polyether polyols is indicative of a low bioaccumulation potential for these substances.

5.2 Biotransformation and Elimination

5.2.1 General Considerations and Data from Structural Analogues

Metabolism was not investigated for the PEPOs. As logK_{ow} values for the PEPOs are below 3, and water solubility is at least 21 g/L, the PEPOs are not expected to accumulate in fish for simple physical reasons. In addition, the PEPOs are not inert to metabolism. Radiolabeled tripropylene glycol methyl ether (TPM; CAS-No. 25498-49-1), which is structurally very similar to MPG + 3 PO, was given via gavage to rats (OECD 2003). Within 48 h, more than 60 % was excreted in the urine, and about 16 % was excreted with feces as well as exhaled as CO_2. In the

Table 16 Grouping and PNECs (aqua) of the PEPOs

PEPO group	$NOEC_{chronic}$ daphnia (mg/L)	$NOEC_{chronic}/E_rC_{10}$ algae (mg/L)	PNEC (mg/L)
Non-amine	10	100	0.2
o-TDA initiated	1	100	0.02
Aliphatic amine initiated	100	4...10	0.08...0.2

Table 17 Regional scale PEC/PNEC ratios

Substance	PEC/PNEC surface water	PEC/PNEC sediment	PEC/PNEC agricultural soil
SUC + PO[a]	5.66E-03	1.07E-02	8.33E-02
SUC + PO[b]	5.28E-02	9.93E-02	0.108
SOR + PO	5.28E-02	9.93E-02	0.108
PENT + PO	5.28E-02	9.93E-02	0.108
TMP + PO	6.66E-03	1.25E-02	9.80E-02
TMP + EO	5.28E-02	9.93E-02	0.108
GLY + PO	3.62E-02	6.80E-02	0.116
GLY + EO	8.05E-02	7.39E-02	5.18E-04
MPG + PO	2.63E-03	2.47E-03	6.29E-04
DEG + EO	2.63E-03	2.50E-03	7.94E-04
o-TDA + PO + EO	0.173	0.325	0.602
o-TDA + PO	0.14	0.263	0.594
EDA + PO	5.00E-02	8.19E-02	0.143
EDA + PO + EO	2.15E-02	4.04E-02	6.10E-02
NTE + PO	4.68E-02	8.81E-02	0.143

[a]Readily biodegradable
[b]Not biodegradable

urine, the metabolites were propylene glycol, di- and tripropylene glycol, derivatives of propanoic acid, and TPM-sulfate. As Nabb et al. (2006) have demonstrated, the basic metabolism is the same in rat and fish liver, but the turnover rate in fish is up to 20 times slower than in rat. Therefore, metabolic degradation pathways observed in mammals like rat can be expected to take place in fish as well.

The pathways for microbial metabolism of polyethylene glycol (PEG) and polypropylene glycol (PPG) have been well elucidated (Kawai 2002), and involve rather simple metabolic pathways which are expected to be conserved across higher organisms. PEG was shown to be aerobically metabolized by stepwise oxidation of the terminal alcohol group to aldehyde and carboxylic acid groups, followed by terminal ether cleavage which results in a stepwise depolymerization of PEG. This terminal oxidation of PEG has been shown to be carried out by NAD-dependent alcohol dehydrogenases (ADH) of diverse origins. For example, the transformations were observed with ADH isolated from a variety of microbes which did not grow on PEG, as well as ADH isolated from equine liver. A similar mechanism has been shown for the metabolism of PPG, and these microbial transformations of diol (i.e., propoxylated 1,2-propanediol) and triol (i.e., propoxylated glycerol) forms of PPG have been observed for molecular weights up to 4000 and 3000 g/mol, respectively (Kawai 2002). The "ready biodegradability" of propoxylated 1,2-propanediols has been demonstrated over a similar molecular weight range, as have their biodegradability in seawater (West 2003a, b). Based on these known pathways in microorganisms and rat, the metabolism of polyether polyols in fish is expected to result in daughter products having decreased hydrophobicity (e.g.,

carboxylates, ketones) and decreased molecular weight (via stepwise depolymerization). In addition to these Phase I metabolic processes, Phase II conjugations of the terminal alcohol groups of the polyols and metabolites with sulfate (*o*-sulfation, Testa and Jenner 1976) and glucuronic acid (Clarke et al. 1991) are also possible, which would enhance excretion of the substances from fish. The polyether polyols therefore appear to possess structural features which would lend to their rapid metabolism and excretion in fish.

5.2.2 OASIS Calculations

The metabolic transformation of EDA + PO + EO, SOR + PO and o-TDA + PO was modeled with the OASIS® programme; summarized results are added as Appendix A6 (Supplementary Data 4). These examples were chosen to represent a variety of PEPO initiators. Candidates for these calculations were some of the PEPOs with poor biodegradation data, namely o-TDA + 3 PO, EDA + 2 EO + 4 PO, EDA + 1 EO + 2 PO, EDA + 3 PO, SOR + 6 PO. For the PEPOs based on EO and PO monomers, substructures were defined where the order of the monomer units was changed. In agreement with expectations, the program predicts secondary OH-groups to be oxidized to ketone functions, whereas primary OH-groups end up as carboxyl groups. Chain scission is predicted which, by the interpretation of the structures, is a result of α-hydroxylation of ethers, with subsequent decay of the intermediate semi-acetal. All metabolites have low logK_{ow} values, usually lower than the parent compound. As far as the toxicity is governed by general narcosis, the decay of the polyether chains should generate molecules of lower toxicity. The predicted metabolites were categorized by the OASIS® MoA tool within the OECD Toolbox. As shown in Table 18 of Appendix A6 (Supplementary Data 4), a number of the metabolites fall into the categories "Reactive unspecified" or "Narcotic amine," compounds that fall into these categories are expected to exert toxicity greater than expected via non-polar narcosis. The biodegradation of the PEPOs may therefore release some smaller toxic metabolites, however, based on the predicted logK_{ow} values and structure (Appendix A6, Supplementary Data 4) and the biodegradation studies performed on the PEPOs, these generally more reactive molecules are not expected to bioaccumulate or to persist in the environment. For the o-TDA initiated PEPO, the decay of the polyether chain may release finally a primary aromatic amino group which raises a structural alert for toxicity. This may explain why this polyol shows the lowest NOEC of all tested PEPOs in the chronic daphnia tests (see Sect. 4.2) (Fig. 3 and 4).

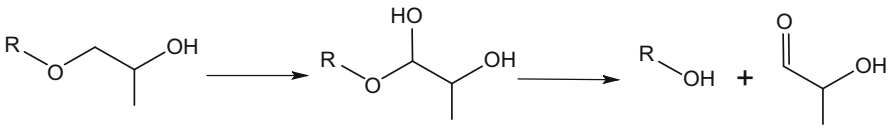


Fig. 3 Decay of the polyether chain via α-hydroxylation

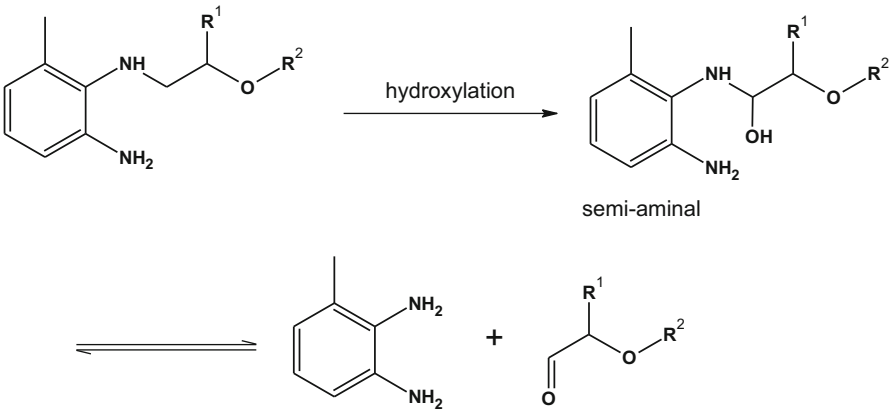


Fig. 4 Release of aromatic amine by α-hydroxylation

6 Conclusion

Polyether polyols (PEPOs) are important oligomeric or polymeric substances and intermediates for the production of polymers like polyurethanes. The PEPOs are produced by a polyaddition reaction of propylene oxide and/or ethylene oxide to alcohols or amines, leading to bi-, tri-, or polyfunctional alcohols. The product is a mixture of homologues which differ in the number of repeating units and show a molecular weight distribution. The substances dealt with in this paper are in a molecular weight range of 230–800. Melting points are below 0 °C, boiling points are above 200 °C and in most cases associated with thermal decomposition, and vapor pressures range from 0.0002 to 2000 Pa at 20 °C; low values are achieved with the effusion method which allows "purification" of the PEPOs from small amounts of high vapor pressure components; the static method, however, includes these components and results in higher vapor pressure values.

The PEPOs are readily soluble in water, and the measured logK_{ow} values are typically below 3, for the lower molecular weight homologues in many cases below 0.3. o-TDA initiated polyols show higher logK_{ow} values by the HPLC-method. Aqueous solutions (0.1 % by weight) of a few of the PEPOs have surface tensions below 50 mN/m at 20 °C and these PEPOs can be regarded as surface active. Nevertheless, the OECD test guideline no. 117, HPLC screening method is suitable for the PEPO substances, provided the chromatograms do not show a strong tailing. For the mobile phase, acetonitrile/water turned out to be more suitable than methanol/water to avoid tailing. In case of tailing of peaks in the chromatograms, logK_{ow} shall be calculated by the SPARC program for PEPOs initiated with amines and/or where the main monomer is EO, and by ACDLabs percepta program for the others.

Concerning water-soil distribution, the HPLC screening method according to OECD test guideline no. 121 is regarded as of poor reliability. Published data for alcohol ethoxylates and polyethylene glycols by other authors showed that cation exchange capacity plays a crucial role in soil-water distribution. Therefore, the PEPOs should be analyzed by the batch method (OECD test guideline no. 106).

In biodegradation studies some of the PEPOs are readily biodegradable, some are inherently biodegradable, others show only poor biodegradation. Biodegradability seems to decrease with the degree of branching, the amine-initiated PEPOs show poor biodegradability and SOR + 6 PO is suspected to be persistent; for o-TDA + 3 PO and TMP + 2 EO, data on inherent biodegradability are required to draw a conclusion with respect to persistency. There are no data concerning biodegradation in soil or sediment. All PEPOs are expected to react rapidly with OH radicals, but data on indirect photodegradation in water are not available. The poor biodegradability of GLY + EO and TMP + EO combined with atmospheric half-lives just above the critical cut-off of 2 day (ECHA 2014) calls for further investigation into these substances.

Environmental modeling with the program EUSES (v.2.1) shows that, on a regional scale with respect to predicted environmental concentrations, freshwater sediment and agricultural soil are the main compartments where highest concentrations of PEPOs are to be expected, followed by surface water followed by air. To run the calculation, the range of isomers and homologues in a PEPO was covered by either a high vapor pressure of 400 Pa at 25 °C and a low $\log K_{ow}$ of 0.0, or a low vapor pressure of 0.004 Pa at 25 °C and a high $\log K_{ow}$ as given as the upper value in the OECD test guideline no. 117 chromatograms. The $\log K_{oc}$ was fixed at 4, and for amine-initiated PEPOs it was set to either 4 or 6. Monitoring data concerning emission of PEPOs in the environment are not available. The regional and continental release in Europe was estimated on the basis of market data. Monitoring data as well as experimental data concerning soil-water distribution generated by the batch method would allow to run a more robust modeling.

The aquatic ecotoxicity of the PEPOs is low, with EC50/LC50 values, often greater than 100 mg/L. NOECs for chronic toxicity to daphnia for selected PEPOs are above the top concentration tested, which was 8.5 or 10 mg/L; only for o-TDA + 3 PO the NOEC was as low as 1 mg/L. For algae, the lowest $NOAEC_r$ was 4.7 mg/L for EDA + 3 PO; all other PEPOs showed $NOEC_r$ of 100 mg/L. With respect to the mode of action and mechanism of action, the non-amine PEPOs do belong to the non-polar narcotics, whereas the amine-initiated PEPOs can be classified as polar narcotics. Therefore, differences in species sensitivity and compartment sensitivity are expected to be small.

For environmental risk assessment, in the EUSUS program PEC values were matched against the predicted no effect concentrations (PNEC). As there are no ecotoxicity data for the PEPOs against sediment and soil organisms, the program calculated the toxicity for these compartments on the basis of the equilibrium partitioning, assuming comparable sensitivity of soil, sediment, and water organisms. A PEC/PNEC ratio ≥ 1 would indicate the need for further data or risk reduction measures. For all compartments, the PEC/PNEC ration was below one.

However, values of up to about 0.6 were reached for the agricultural soil compartment, and also for the sediment PEC/PNEC ratios higher than 0.1 were calculated. As a precautionary measure, running toxicity tests with soil and sediment organisms with selected PEPOs shall be considered.

Due to their logK_{ow} values, PEPOs are not likely to accumulate in fish. In addition, literature data on structurally similar compounds indicate that PEPOs are substrates for phase I and phase II metabolism. Taken together, the PEPOs described in this paper do not fulfil the criteria either for persistent and bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) as defined by the European Union (ECHA 2008).

7 Summary

This article deals with polyether polyols (PEPOs) produced by poly addition reactions of ethylene oxide and/or propylene oxide to two- or polyfunctional alcohols or amines, delivering oligomers with mean molecular weights below 700 g/mol. The products show the following environmental and ecotoxicological properties:

- Water solubility is high, vapor pressure is low, whereas for the latter experimental data depend on the method chosen. The effusion method—allowing small amounts of high vapor pressure components to escape—generates vapor pressure data below 10 Pa/20 °C, whereas the static method generates data in the range of 100–2000 Pa/20 °C.
- For establishing the logK_{ow} the OECD guideline no. 117 screening method is applicable, unless surface activity in combination with strong peak tailing is observed. In that case, the logK_{ow} shall be calculated by established QSAR methods.
- For better understanding of the environmental behavior, logK_{oc}, or better logK_d data should be generated with the batch method (OECD test guideline No. 106).
- Some PEPOs are readily biodegradable, others are inherently or not biodegradable. Increases in branching or amine-initiators result in decreased biodegradability.
- The acute aquatic toxicity is low. LC_{50} and EC_{50} values are above 100 mg/L.
- For the chronic aquatic toxicity with daphnia, four PEPOs were selected spanning the grid from low to high functionality, low to high logK_{ow} values, and amine- or no amine-initiator. 21-days NOECs for daphnia coincided with the top-concentrations tested, 10 mg/L, with the exemption of TDA + 3 PO where the NOEC was 1 mg/L. The algae 72-h $NOEC_r$ was 100 mg/L; only for EDA + 3 PO, it was as low as 4.25 mg/L.
- Sediment and agricultural soil turned out to be important compartments for the PEPOs. Toxicity tests with soil and perhaps sediment organisms should be

considered. Also, better and more robust release estimates of PEPOs in the environment would increase the reliability of the modeling results.
- Based on logK_{ow} values, the PEPOs are not expected to show a significant bioaccumulation potential.

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Conflict of Interest

T. Schupp worked for BASF, a Polyether-polyol producer, until 2012.

B.T.A. Bossuyt is working for Huntsman, a Polyether-polyol producer.

R.J. West and S.M. Shen are working for Dow Chemical Company, a Polyether-polyol producer.

T. Austin and C.V. Eadsforth are working for Shell Chemical Company, a Polyether-polyol producer.

This work was sponsored by ISOPA, the European Isocyanate, and Polyol Producer Association. The authors declare that all data of the PEPOs available to them are evaluated and presented in good faith. The views presented are those of the authors and do not necessarily coincide with the views of ISOPA.

Appendix 1: Toxicity to Fish; 96 h LC_{50}

Composition	CAS-no.	M_n (g/mol)	Species	Value
TMP + PO	50586-59-9	340	*Danio rerio*	>100 mg/L
SUC + GLY + PO	9049-71-2	720	*Pimephales promelas*	27.2 g/L
SUC + PO	9049-71-2	440	*Danio rerio*	>4.2, <7.5 g/L
EDA + PO	25214-63-5	360	*Danio rerio*	>3.1, <7.5 g/L
EDA + PO	25214-63-5	480	*Leuciscus idus*	4.6 g/L
EDA + EO + PO	26316-40-5	280	*Danio rerio*	>100 mg/L
EDA + EO + PO	26316-40-5	280	*Pimephales promelas*	4.23 g/L
GLY + PO	25791-96-2	300	*Leuciscus idus*	>1 g/L
SOR + PO	52625-13-5	700	*Leuciscus idus*	>1 g/L
o-TDA + PO	63641-63-4	340	*Danio rerio*	>77 mg/L (LC_0)
MPG + PO	25322-69-4	230	*Danio rerio*	>100 mg/L (LC_0)
MPG + PO	25322-69-4	400	*Poecelia reticulata*	>100 mg/L (LC_0)
MPG + PO	25322-69-4	450	*Leuciscus idus*	>4.6, <10 g/L
PENT + PO	9051-49-4	420	*Danio rerio*	>100 mg/L (LC_0)
NTE + PO	37208-53-0	320	*Danio rerio*	>100 mg/L (LC_0)
DEG + PO	9051-51-8	280	*Danio rerio*	>100 mg/L (LC_0)

Appendix 2: Acute Toxicity to Crustacea (48 h EC_{50})

Composition	CAS-No.	M_n (g/mol)	Species	Value
TMP + PO	50586-59-9	340	*Daphnia magna*	>100 mg/L (EC_0)
SUC + PO	9049-71-2	440	*Daphnia magna*	>100 mg/L (EC_0)
SUC + GLY + PO	9049-71-2	720	*Daphnia magna*	9.89 g/L
EDA + PO	25214-63-5	360	*Daphnia magna*	>100 mg/L (EC_0)
EDA + EO + PO	26316-40-5	280	*Daphnia magna*	>100 mg/L (EC_0)
EDA + EO + PO	26316-40-5	280	*Daphnia magna*	305[a] and 103[b] mg/L
GLY + PO	25791-96-2	300	*Daphnia magna*	>100 mg/L (EC_0)
SOR + PO	52625-13-5	700	*Daphnia magna*	>100 mg/L (EC_0)
SOR + PO	52625-13-5	600	*Acartia tonsa*	>1000 mg/L (EC_{10})
o-TDA + PO	63641-63-4	340	*Daphnia magna*	>100 mg/L (EC_0)
o-TDA + PO + EO	67800-94-6	520	*Daphnia magna*	>100 mg/L (EC_0)
MPG + PO	25322-69-4	230	*Daphnia magna*	105 mg/L
PENT + PO	9051-49-4	420	*Daphnia magna*	>100 mg/L (EC_0)
NTE + PO	37208-53-0	320	*Daphnia magna*	>100 mg/L (EC_0)
DEG + PO	9051-51-8	280	*Daphnia magna*	>100 mg/L (EC_0)
GLY + EO	31694-55-0	310	*Daphnia magna*	>100 mg/L (EC_0)

[a]Non-neutralized
[b]Neutralized

Appendix 3: Toxicity to Algae (72 h)

Composition	CAS-No.	M_n (g/mol)	Species	E_rC50 (mg/L)	NOECr (mg/L)
TMP + PO	50586-59-9	340	Desmodesmus subspicatus	>100	≥100
SUC + PO	9049-71-2	580	Desmodesmus subspicatus	>100	100
EDA + EO + PO	26316-40-5	280	Desmodesmus subspicatus	>100	100
GLY + PO	25791-96-2	300	Desmodesmus subspicatus	>100	100
SOR + PO	52625-13-5	600	*Skeletonema costatum*	>1000	1000
o-TDA + PO	63641-63-4	340	Desmodesmus subspicatus	>100	100
MPG + PO	25322-69-4	230	Desmodesmus subspicatus	>100	100
PENT + PO	9051-49-4	420	Desmodesmus subspicatus	>100	100
NTE + PO	37208-53-0	320	Desmodesmus subspicatus	>100	100
DEG + PO	9051-51-8	280	Desmodesmus subspicatus	>100	100

Appendix 4: Toxicity to Microorganisms

Composition	CAS-no.	M_n (g/mol)	Test	Value
TMP + PO	50586-59-9	340	Resp. inhib. activated sludge (OECD 209)	IC_{50}/ 30 min > 10 g/L
SUC + PO	9049-71-2	500	Resp. inhib. activated sludge (OECD 209)	IC_{50}/ 30 min > 0.72 g/ L
EDA + PO	25214-63-5	360	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_{10})
EDA + EO + PO	26316-40-5	280	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_{10})
GLY + PO	25791-96-2	300	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_0)
GLY + PO	25791-96-2	300	*Pseudomonas putida* growth inhibition[a)]	LOEC = 6.6 g/L
SOR + PO	52625-13-5	600	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_0)
SOR + PO	52625-13-5	700	*Pseudomonas putida* growth inhibition[a]	LOEC = 2.4 g/L
o-TDA + PO	63641-63-4	340	Resp. inhib. activated sludge (OECD 209)	IC_{50} = 10 g/L
o-TDA + PO + EO	67800-94-6	520	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 2 g/L (IC_0)
MPG + PO	25322-69-4	230	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 1 g/L (IC_0)
MPG + PO	25322-69-4	450	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 700 mg/L (IC_0)
MPG + PO	25322-69-4	450	*Pseudomonas putida* growth inhibition[a)]	LOAEC > 10 g/ L (IC_0)
PENT + PO	9051-49-4	420	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_5)
NTE + PO	37208-53-0	320	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 10 g/L (IC_0)
DEG + PO	9051-51-8	280	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 1 g/L (IC_0)
GLY + EO	31694-55-0	310	Resp. inhib. activated sludge (OECD 209)	IC_{50} > 640 mg/L (IC_{10})

Water quality—Pseudomonas putida growth inhibition test (Pseudomonas cell multiplication inhibition test). https://www.iso.org/obp/ui/#iso:std:iso:10712:ed-1:v1:en. Accessed at: June 23rd, 2016

[a]German Umweltbundesamt: "Bewertung wassergefaehrdender Stoffe, LTwS Nr. 10, 1979." See also: ISO 10712:1995(en)

Appendix 5: Metabolic Transformation of EDA + PO + EO, Modeled with OASIS®

Prediction of Biodegradation and Metabolites of Polyols

Chemicals Assessed:

Propoxylated/ethoxylated ethylenediamine polyol (EDA+EO+PO)

Sorbitol propoxylated polyol (Sorbitol+PO)

o-Diaminotoluene, propoxylated (TDA+PO)

The Dow Chemical Company

Date of Assessment:

May 12, 2016

Prediction of Biodegradation Metabolites of Polyols

Objective: The objective of this study is to identify potential metabolites from aerobic biodegradation of propoxylated/ethoxylated ethylenediamine polyol (EDA + EO + PO, CAS No. 26316-40-5), sorbitol propoxylated polyol (SOR + PO,

CAS No. 52625-13-5), and propoxylated o-diaminotoluene (TDA + PO, CAS No. 63641-63-4) using prediction software.

Software: Prediction software OASIS Catalogic (v5.11.16) was selected. The Kinetic 301F Model (v12.15) implemented in OASIS Catalogic was deemed appropriate for this study. The model was developed based on a training database of catabolic pathways for more than 551 organic compounds. Training set data and expert knowledge were used to determine the principal transformations and to train the system to simulate aerobic catabolism of training chemicals. The documented pathways of microbial catabolism were collected from scientific papers, monographs, and databases accessible over the Internet.

Method: Seven representative molecular structures of these polyols (Tables 18–20) representing various alkoxylation configurations were used for the prediction of their potential metabolites from aerobic biodegradation. The seven molecular structures included three variations from EDA + EO + PO (Table 18), two variations from SOR + PO (Table 19), and two variations from TDA + PO (Table 20). These seven representative molecular structures are in the applicability domain of the model defined by its parametric domain, structure fragment domain, and metabolic domain. Potential metabolites from aerobic biodegradation of the seven molecular structures were predicted using Kinetic 301F Model in OASIS Catalogic (v5.11.16). The metabolites with a predicted quantity of greater than or equal to 5 % (i.e., 0.05) were reported in this study.

Results: Potential metabolites from aerobic biodegradation of the seven representative molecular structures of the polyols are summarized in Tables 21–27. Predicted quantities, octanol-water partition coefficient ($\log K_{ow}$) values, and the predicted mode-of-action (predicted using the Verhaar Scheme (modified) and OASIS®) of the potential metabolites as well as their parent compounds are also shown in Tables 21–28. Predicted metabolites have $\log K_{ow}$ values similar or less than their corresponding parent compounds. As far as the ecotoxicity and bioaccumulation potential of these polyols and their metabolites correlate with their $\log K_{ow}$, the metabolites are not expected to be more toxic or more bioaccumulative than their parent compounds. However, it cannot be excluded that EDA and TDA-based PEPOs might release the core substance (initiator), which shows a higher ecotoxicity than the respective PEPO. Additionally, after mode of action prediction, a number of the metabolites fall into the categories "Reactive unspecified" or "Narcotic amine"; compounds that fall into these categories are expected to exert toxicity greater than expected via non-polar narcosis.

Conclusion: Predicted metabolites have $\log K_{ow}$ values similar or less than their corresponding parent compounds. The bioaccumulation potential of these polyols and their metabolites correlate with their $\log K_{ow}$, therefore, the metabolites are not expected to be more bioaccumulative than their parent compounds although some metabolites appear to be generally more reactive and may have higher aquatic toxicity.

Appendix 6: QPRFs of the Seven Representative Molecular Structures

Table 18 Representative structures for propoxylated/ethoxylated ethylenediamine polyol (EDA + EO + PO)

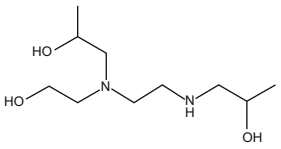
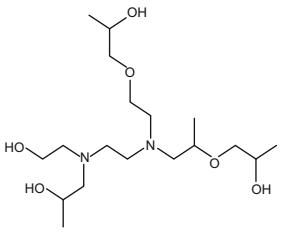
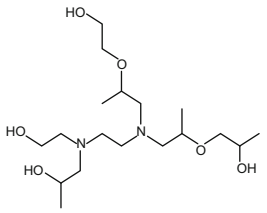
Material: propoxylated/ethoxylated ethylenediamine polyol (EDA + EO + PO)		
Representative structures analyzed:		
EDA + 1EO + 2PO	EDA + 2EO + 4PO (a)	EDA + 2EO + 4PO (b)
		

Table 19 Representative structures for sorbitol propoxylated polyol (SOR + PO)

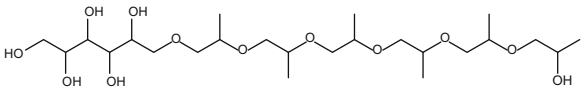
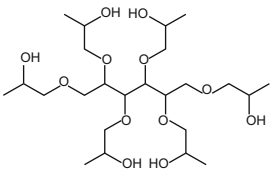
Material: sorbitol propoxylated polyol (SOR + PO)	
Representative structures analyzed:	
SOR + 6PO (a)	SOR + 6PO (b)
	

Table 20 Representative structures for propoxylated o-diaminotoluene (TDA + PO)

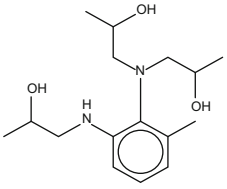
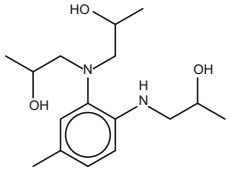
Material: o-Diaminotoluene, propoxylated (TDA + PO)	
Representative structures analyzed:	
TDA + 3PO (a)	TDA + 3PO (b)
	TDA + 3PO (b) 

Table 21 Predicted quantities and logK_{ow} values for metabolites of EDA + 1EO + 2PO

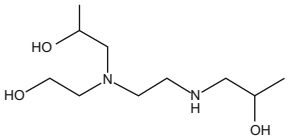
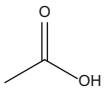
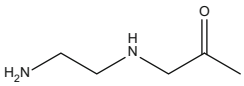
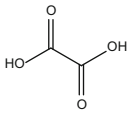
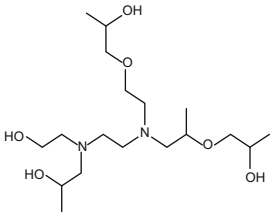
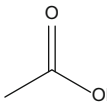
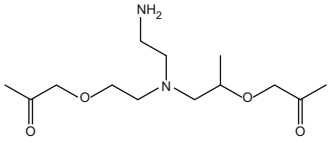
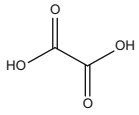
Parent: EDA + 1EO + 2PO log$K_{ow} = -2.15$ 		
Predicted metabolites with quantities of >5 %:		
Metabolite 1.1 SMILES: C(C)(=O)O Quantity: 0.28 log$K_{ow} = 0.087$ 	*Metabolite 1.2* SMILES: C(C)(=O)CNCCN Quantity: 0.87 log$K_{ow} = -1.46$ 	*Metabolite 1.3* SMILES: C(=O)(O)C(=O)O Quantity: 0.19 log$K_{ow} = -1.74$ 

Table 22 Predicted quantities and logK_{ow} values for metabolites of EDA + 2EO + 4PO (a)

Parent: EDA + 2EO + 4PO (a) log$K_{ow} = -2.63$ 		
Predicted metabolites with quantities of >5 %:		
Metabolite 2.1 SMILES: C(C)(=O)O Quantity: 0.42 log$K_{ow} = 0.087$ 	*Metabolite 2.2* SMILES: C(C)(=O)COC(C)CN(CCN)CCOCC(C) = O Quantity: 0.27 log$K_{ow} = -2.21$ 	*Metabolite 2.3* SMILES: C(=O)(O)C(=O)O Quantity: 0.37 log$K_{ow} = -1.74$ 

(continued)

Table 22 (continued)

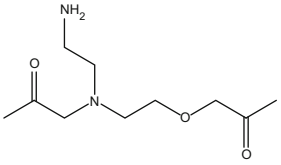
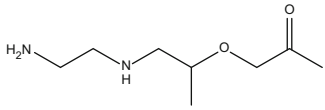
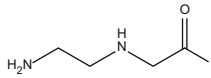
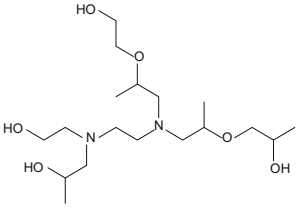
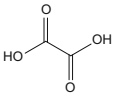
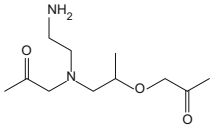
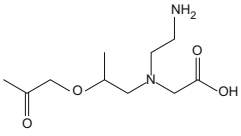
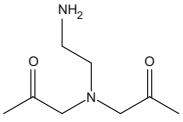
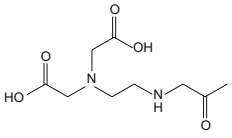
Metabolite 2.4 SMILES: C(C)(=O)CN(CCN)CCOCC(C) = O Quantity: 0.087 logK_{ow} = −2.09 	*Metabolite 2.5* SMILES: C(C)(=O)COC(C)CNCCN Quantity: 0.14 logK_{ow} = −1.58 	*Metabolite 2.6* SMILES: C(C)(=O)CNCCN Quantity: 0.27 logK_{ow} = −1.46 

Table 23 Predicted quantities and logK_{ow} values for metabolites of EDA + 2EO + 4PO (b)

Parent: EDA + 2EO + 4PO (b)
logK_{ow} = −2.63



Predicted metabolites with quantities of >5 %:

Metabolite 3.1 SMILES: C(C)(=O)O Quantity: 0.28 logK_{ow} = 0.087 	*Metabolite 3.2* SMILES: C(=O)(O)C(=O)O Quantity: 0.43 logK_{ow} = −1.74 	*Metabolite 3.3* SMILES: C(C)(=O)CN(CC(C)OCC(C) = O)CCN Quantity: 0.27 logK_{ow} = −1.67 
Metabolite 3.4 SMILES: C(C)(=O)CN(CC(C)OCC(C) = O)CCN Quantity: 0.13 logK_{ow} = −4.14 	*Metabolite 3.5* SMILES: C(C)(=O)CN(CC(C) = O)CCN Quantity: 0.087 logK_{ow} = −1.55 	*Metabolite 3.6* SMILES: C(=O)(O)CN(CC(=O)O)CCNCC(C) = O Quantity: 0.18 logK_{ow} = −3.88 

(continued)

Table 23 (continued)

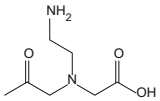
Metabolite 3.7 SMILES: C(=O)(O)CN(CC(C) = O)CCN Quantity: 0.15 logK_{ow} = −4.02 		

Table 24 Predicted quantities and logK_{ow} values for metabolites of SOR + 6PO (a)

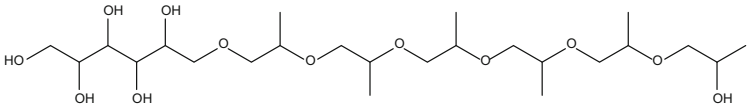
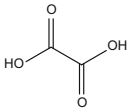
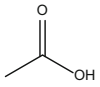
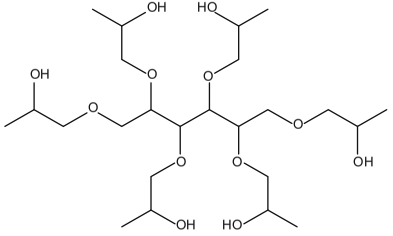
Parent: SOR + 6PO (a) logK_{ow} = −2.75 	
Predicted metabolites with quantities of >5 %:	
Metabolite 4.1 SMILES: C(=O)(O)C(=O)O Quantity: 0.94 logK_{ow} = −1.74 	*Metabolite 4.2* SMILES: C(C)(=O)O Quantity: 0.44 logK_{ow} = 0.087 

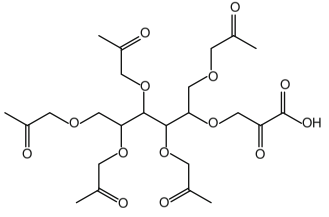
Table 25 Predicted quantities and logK_{ow} values for metabolites of SOR + 6PO (b)

Parent: SOR + 6PO (b)
logK_{ow} = −4.53

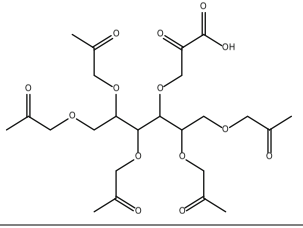


Predicted metabolites with quantities of >5 %:

Metabolite 5.1
SMILES: C(=O)(O)C(=O)COC(C(C(C(COCC(C) = O)OCC(C) = O)OCC(C) = O)OCC(C) = O)COCC(C) = O
Quantity: 0.33
logK_{ow} = −6.51



Metabolite 5.2
SMILES: C(=O)(O)C(=O)COC(C(C(COCC(C) = O)OCC(C) = O)OCC(C) = O)C(COCC(C) = O)OCC(C) = O
Quantity: 0.33
logK_{ow} = −6.51



Metabolite 5.3
SMILES: C(=O)(O)C(=O)COCC(C(C(C(COCC(C) = O)OCC(C) = O)OCC(C) = O)OCC(C) = O
Quantity: 0.33
logK_{ow} = −6.51

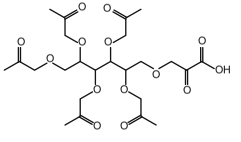
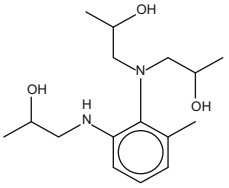


Table 26 Predicted quantities and logK_{ow} values for metabolites of TDA + 3PO (a)

Parent: TDA + 3PO (a)
logK_{ow} = 1.09



Predicted metabolites with quantities of >5 %:

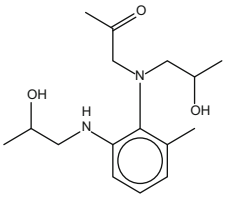
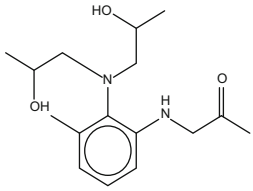
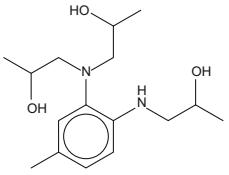
Metabolite 6.1	*Metabolite 6.2*
SMILES: c1(NCC(C)O)c(N(CC(C) = O)CC (C)O)c(C)ccc1 Quantity: 0.67 logK_{ow} = 1.34	SMILES: c1(NCC(C) = O)c(N(CC(C)O)CC (C)O)c(C)ccc1 Quantity: 0.33 logK_{ow} = 1.34
	

Table 27 Predicted quantities and logK_{ow} values for metabolites of TDA + 3PO (b)

Parent: TDA + 3PO (b)
logK_{ow} = 1.09



Predicted metabolites with quantities of >5 %:

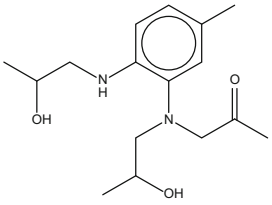
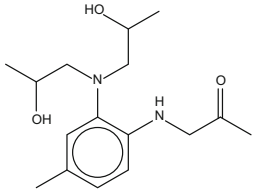
Metabolite 7.1	*Metabolite 7.2*
SMILES: c1(NCC(C)O)c(N(CC(C) = O)CC (C)O)cc(C)cc1 Quantity: 0.67 logK_{ow} = 1.34	SMILES: c1(NCC(C) = O)c(N(CC(C)O)CC (C)O)cc(C)cc1 Quantity: 0.33 logK_{ow} = 1.34
	

Table 28 Metabolite mode of action as predicted by the Verhaar scheme (modified) and OASIS®

Metabolite	Verhaar scheme (modified) MOA	MOA by OASIS®
1.1	1	Reactive unspecified
1.2	5	Narcotic amine
1.3	1	Reactive unspecified
2.1	1	Reactive unspecified
2.2	5	Narcotic amine
2.3	1	Reactive unspecified
2.4	5	Narcotic amine
2.5	5	Narcotic amine
2.6	5	Narcotic amine
3.1	1	Reactive unspecified
3.2	1	Reactive unspecified
3.3	5	Narcotic amine
3.4	5	Narcotic amine
3.5	5	Narcotic amine
3.6	5	Reactive unspecified
3.7	5	Reactive unspecified
4.1	1	Reactive unspecified
4.2	1	Reactive unspecified
5.1	5	Reactive unspecified
5.2	5	Reactive unspecified
5.3	5	Reactive unspecified
6.1	5	Base surface narcotics
6.2	5	Base surface narcotics
7.1	5	Base surface narcotics
7.2	5	Base surface narcotics

References

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Impacts of Sublethal Mercury Exposure on Birds: A Detailed Review

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Contents

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1 Introduction

Environmental mercury concentrations are predicted to continue to increase worldwide, while climate change is expected to exacerbate the impact of this ubiquitous contaminant (Sunderland et al. 2009; Stern et al. 2012). The effects of mercury on wildlife have been studied extensively, but until recently the majority of birds investigated have been either piscivorous species or domesticated breeds, such as the white leghorn chicken. Recent experiments and field studies have begun to include songbirds, as it has recently been discovered that mercury is not restricted to aquatic environments but also impacts terrestrial species (Cristol et al. 2008). Additionally, recent experimental studies have tended to use lower concentrations of mercury in an effort to understand the sublethal impacts that most exposed wildlife are experiencing, such as those involving behavior. The overall number of studies on sublethal effects has increased dramatically, with only 34 published articles found during the decades before 1999, 44 identified in the first decade of the 2000s, and already 76 located with publication dates since 2010. Given the expected worsening of the mercury pollution problem, and the realization that mercury affects more types of birds than previously suspected, a review of the burgeoning literature on sublethal effects of mercury on birds is overdue.

2 Methods

To determine which level of mercury to consider "sublethal," we searched for evidence of a lowest lethal dose and concentrations that actually occur in prey items in the environment. Domestic zebra finches (all scientific names given in Table 1, along with American Ornithological Society Alpha codes) chronically exposed to 5 μg/g dietary mercury experienced 25% mortality within 10 weeks, making it a lethal dose for some individuals (Scheuhammer 1988). Environmental mercury concentrations as high as 5 μg/g are rare in wild prey items of birds, including both fish and terrestrial arthropods; in fact, these rarely exceed 2 μg/g (Henny et al. 2002; Merrill et al. 2005; Cristol et al. 2008; Burgess and Meyer 2008). Therefore, experimental studies were included in this review of sublethal exposure only if some birds in the study were exposed to <5 μg/g methylmercury. For dosing studies, and field studies that measured mercury concentrations in prey items, we defined four categories of exposure that are referenced with each citation: trace (≤0.5 μg/g), low (0.5–1.0 μg/g), medium (1.0–2.0 μg/g), and high (>2.0 μg/g). All concentrations for exposure are on a wet weight basis unless otherwise noted as being reported in dry weight (dw). Resulting concentrations in bird tissues are

Table 1 Common and scientific names of all species referenced, with American Ornithological Society alpha abbreviations in parentheses

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
Low sensitivity species				
American avocet (AMAV)	*Recurvirostra americana*	Ackerman et al. (2008b)		L
		Herring et al. (2010)		R
		Herring et al. (2017)		C
American black duck (ABDU)	*Anas rubripes*	Finley and Stendell (1978)	R	
Black-necked stilt (BNST)	*Himantopus mexicanus*	Ackerman et al. (2008b)		L
		Herring et al. (2010)		R
		Herring et al. (2017)		C
Black-bellied plover (BBPL)	*Pluvialis squatarola*	Hargreaves et al. (2010)	R	C
Common eider (COEI)	*Somateria mollissima*	Provencher et al. (2016)	E	I, B, C
		Provencher et al. (2017)		L, R
		Wayland et al. (2002)		I, C
Common merganser (COME)	*Mergus merganser*	Kalisińska et al. (2010)	C	
Domestic mallard (MALL)	*Anas platyrhynchos domesticus*	Ji et al. (2006)	O	
		Snelgrove-Hobson et al. (1988)	O	
Double-crested cormorant (DCCO)	*Phalacrocorax auritus*	Clarkson et al. (2012)		C
		Gibson et al. (2014)	OX	
		Heinz et al. (2012b)	R	
		Henny et al. (2002)	I, G	
		Loerzel et al. (1999)	N	
Greater scaup (GRSC)	*Aythya marila*	Hoffman et al. (1998)	I	
King eider (KIEI)	*Somateria spectabilis*	Wayland et al. (2008)		L
Laughing gull (LAGU)	*Leucophaeus atricilla*	Jenko et al. (2012)	R, OX, GE	
Lesser scaup (LESC)	*Aythya affinis*	Anteau et al. (2007)		C
		Custer et al. (2000)	OX	
		Pollock and Machin (2009)	E	

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
Mallard (MALL)	*Anas platyrhynchos*	Heinz (1974)	R	
		Heinz (1975)	B	
		Heinz (1976a)	R	B
		Heinz (1976b)	R, B	
		Heinz (1979)	R, B	
		Heinz (1980)		R
		Heinz et al. (2010a)		R (hormesis)
		Heinz et al. (2010b)	R	
		Heinz et al. (2011)	R	
		Heinz et al. (2012a)		R (hormesis)
		Heinz et al. (2012b)	R	
		Heinz and Locke (1976)	N	
		Hoffman and Moore (1979)	R	
		Klimstra et al. (2012)	R	
		Pass et al. (1975)		N
Ruddy duck (RUDU)	*Oxyura jamaicensis*	Hoffman et al. (1998)	C, OX	
Semipalmated plover (SEPL)	*Charadrius semipalmatus*	Hargreaves et al. (2010)	R	C
Surf scoter (SUSC)	*Melanitta perspicillata*	Hoffman et al. (1998)	C, OX	
White-winged scoter (WWSC)	*Melanitta deglandi*	Wayland et al. (2008)	L	
Medium sensitivity species				
Acadian flycatcher (ACFL)	*Empidonax virescens*	Rowse et al. (2014)	R	C
American dipper (AMDI)	*Cinclus mexicanus*	Henny et al. (2005)		R
Arctic tern (ARTE)	*Sterna paradisaea*	Braune et al. (2012)	R	N
Atlantic puffin (ATPU)	*Fratercula arctica*	Fort et al. (2015)	C	
Black skimmer (BLSK)	*Rynchops niger*	King et al. (1991)		R
Black-footed albatross (BFAL)	*Phoebastria nigripes*	Finkelstein et al. (2007)	I	
Black-legged kittiwake (BLKI)	*Rissa tridactyla*	Fort et al. (2015)	C	
		Tartu et al. (2013)	R, E	
Brown skua (BRSK)	*Stercorarius antarcticus*	Goutte et al. (2014b)	R	

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
California clapper rail (CLRA)	*Rallus longirostris obsoletus*	Ackerman et al. (2012)	C	
Carolina wren (CARW)	*Thryothorus ludovicianus*	Hallinger et al. (2010)	B	
		Jackson et al. (2011)	R	
Caspian tern (CATE)	*Hydroprogne caspia*	Herring et al. (2017)		C
		Hoffman et al. (2011)	OX	
Clark's grebe (CLGR)	*Aechmophorus clarkii*	Elbert and Anderson (1998)	I, M	R
Common guillemot (COMU)	*Uria aalge*	Fort et al. (2015)	C	
Common loon (COLO)	*Gavia immer*	Barr (1986)	R	
		Burgess and Meyer (2008)	R	
		Evers et al. (2003)	R	
		Evers et al. (2008)	R, B, C	
		Franceschini et al. (2017)	E	
		Hamilton et al. (2011)		N
		Kenow et al. (2003)		L, I, B, G
		Kenow et al. (2007)		I
		Kenow et al. (2008)	I, OX	
		Kenow et al. (2010)	B	
		Kenow et al. (2011)	R, B	
		Merrill et al. (2005)	B	
		Meyer et al. (1998)	R	L
		Mitro et al. (2008)		L
		Nocera and Taylor (1998)	B	
		Olsen et al. (2000)	B	
		Pollentier et al. (2007)		R
		Scheuhammer et al. (2008)	N	
		Schoch et al. (2014)	R	
Eastern bluebird (EABL)	*Sialia sialis*	Bouland et al. (2012)	R	
		McCullagh et al. (2015)	R, C	

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
European starling (EUST)	*Sturnus vulgaris*	Carlson et al. (2014)	C	
		Nicholson and Osborn (1984)	I	
Forster's tern (FOTE)	*Sterna forsteri*	Ackerman et al. (2008a)	R	L
		Herring et al. (2010)	R	
		Herring et al. (2012)	E	
		Herring et al. (2017)	C	
		Hoffman et al. (2011)	OX	
		King et al. (1991)		R
Great egret (GREG)	*Ardea alba*	Bouton et al. (1999)	B	
		Herring et al. (2009)		E
		Herring et al. (2014)	E, I	C
		Hoffman et al. (2005)	OX, M	
		Sepúlveda et al. (1999)	I	L, R
		Spalding et al. (2000a)	I, B	
		Spalding et al. (2000b)	G	
Great skua (GRSK)	*Stercorarius skua*	Thompson et al. (1991)		L, R
Great tit (GT[a])	*Parus major*	Costa et al. (2014)	R	I
Leach's storm-petrel (LESP)	*Oceanodroma leucorhoa*	Pollet et al. (2017)		L, R
Herring gull (HEGU)	*Larus argentatus*	Rutkiewicz et al. (2010)		N
House wren (HOWR)	*Troglodytes aedon*	Custer et al. (2007)		R
		Hallinger et al. (2010)	B	
Japanese quail (JAQU)	*Coturnix japonica*	Hill and Soares (1984)	E	E
		Rutkiewicz et al. (2013)	B, N	
Nelson's sparrow (NESP)	*Ammodramus nelsoni*	McKay and Maher (2012)	B	
Northern waterthrush (NOWA)	*Parkesia noveboracensis*	Seewagen (2013)		M
Rock pigeon (ROPI)	*Columba livia*	Evans et al. (1982)	B, N	
		Laties and Evans (1980)	B	

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
Razorbill (RAZO)	*Alca torda*	Fort et al. (2015)	C	
Red-winged blackbird (RWBL)	*Agelaius phoeniceus*	Gillet and Seewagen (2014)		G
Ruddy turnstone (RUTU)	*Arenaria interpres*	Hargreaves et al. (2010)	R	C
Saltmarsh sparrow (SASP)	*Ammodramus caudacutus*	Scoville and Lane (2013)	N	
Snow petrel (SNPE)	*Pagodroma nivea*	Tartu et al. (2014)	E	
		Tartu et al. (2015)	R, E	
Song sparrow (SOSP)	*Melospiza melodia*	Hallinger et al. (2010)	B	
South polar skua (SPSK)	*Stercorarius maccormicki*	Goutte et al. (2014b)	R	
Thick-billed murre (TBMU)	*Uria lomvia*	Braune et al. (2012)	R	N
Tree swallow (TRES)	*Tachycineta bicolor*	Brasso and Cristol (2008)	R	
		Bouland et al. (2012)	R	
		Custer et al. (2006)	OX	R, GE
		Custer et al. (2007)		R
		Custer et al. (2008)	OX	R
		Custer et al. (2012)		R
		Franceschini et al. (2009)	E	
		Gerrard and St. Louis (2001)		R
		Hallinger and Cristol (2011)	R	
		Hallinger et al. (2011)	L	
		Hawley et al. (2009)	I	
		Longcore et al. (2007)	G	
		Taylor and Cristol (2015)	R	L
		Wada et al. (2009)	E	G
Wandering albatross (WAAL)	*Diomedea exulans*	Bustamante et al. (2016)		L, R
		Costantini et al. (2014)	OX	I
		Goutte et al. (2014a)	R	L

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
Western grebe (WEGR)	*Aechmophorus occidentalis*	Elbert and Anderson (1998)	I, M	R
White leghorn (REJU)	*Gallus gallus domesticus*	Heinz et al. (2012b)		R
		Lundholm (1995)	R, E, M	
		Rutkiewicz et al. (2013)	B, N	
Zebra finch (ZEFI)	*Taeniopygia guttata*	Caudill et al. (2015)		I
		Henry et al. (2014)	OX	
		Kobiela et al. (2015)	B	
		Lewis et al. (2013)	I	
		Maddux et al. (2014)	E	
		Moore et al. (2014)	E	
		Scheuhammer (1988)	B	
		Varian-Ramos et al. (2014)	R	
		Wolf et al. (2017)	N	
		Swaddle et al. (2017)	B	
		Yu et al. (2016)	R	I, B
		Yu et al. (2017)	N	B
High sensitivity species				
American kestrel (AMKE)	*Falco sparverius*	Albers et al. (2007)	R, C	
		Bennett et al. (2009)		R, B, N
		Fallacara et al. (2011a)	R, I	G
		Fallacara et al. (2011b)	I	
Bald eagle (BAEA)	*Haliaeetus leucocephalus*	Anthony et al. (1999)	R	
		Bowerman et al. (1994)		R
		Rutkiewicz et al. (2011)	E	
		Scheuhammer et al. (2008)	N	
		Weech et al. (2006)		R, C
		Wiemeyer et al. (1984)	R	
Belted kingfisher (BEKI)	*Megaceryle alcyon*	Bouland et al. (2012)	R	
		White and Cristol (2014)	C	

(continued)

Table 1 (continued)

Common name (AOS alpha)	Scientific name	Citation	Endpoint impact	
			Detected	Not detected
Black-crowned night heron (BCNH)	*Nycticorax nycticorax*	Henny et al. (2002)	I, G	R
		Hill et al. (2008)	R	
		Hoffman et al. (2009)	I	
Glossy ibis (GLIB)	*Plegadis falcinellus*	Clarkson et al. (2012)		C
Great blue heron (GBHE)	*Ardea herodias*	Champoux et al. (2017)	E	
		Custer et al. (1997)	OX	R
Great white heron (GBHE)	*Ardea herodias occidentalis*	Spalding et al. (1994)	I	
Red-tailed hawk (RTHA)	*Buteo jamaicensis*	Fimreite and Karstad (1971)		N
Snowy egret (SNEG)	*Egretta thula*	Henny et al. (2002)	I, R, G	
		Henny et al. (2017)		L, B
		Hill et al. (2008)	R	
		Hoffman et al. (2009)	I	
		Olivero-Verbel et al. (2013)	R, E	
White ibis (WHIB)	*Eudocimus albus*	Adams and Frederick (2008)	B	
		Adams et al. (2009)	E	
		Frederick et al. (2011)		L
		Frederick and Jayasena (2010)	R	
		Heath and Frederick (2005)	R, E	C
		Herring et al. (2009)		E
		Herring et al. (2014)		I, E, C
		Jayasena et al. (2011)	E	
White-tailed sea eagle (WTEA)	*Haliaeetus albicilla*	Helander et al. (1982)		R

Species are organized by low, medium, and high sensitivity based on the results of Heinz et al. (2009). Endpoints reported in each publication are categorized as statistically negatively impacted by mercury or not statistically impacted. *B* behavior, *C* condition, *E* endocrine function, *G* growth, *GE* gene expression, *I* immune function, *L* longevity, *M* metabolism, *N* neurological function, *OX* oxidative stress, *R* reproduction

[a]British Trust for Ornithology banding code

Table 2 Citations with AOS alpha codes for species, total mercury concentrations (μg/g) in tissues, and dietary exposure (μg/g) when known

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Ackerman et al. (2008a) (FOTE)	0.3[a]; 6.4[b] (body)		
Ackerman et al. (2008b) (AMAV)	4.0[b] (natal down)		
Ackerman et al. (2008b) (BNST)	10[b] (natal down)		
Ackerman et al. (2012) (CLRA)	0.6[a]; 9.9[b] (head), 9.0[b] (body); 0.6[c]		
Adams and Frederick (2008) (WHIB)	Data not reported	0.05, 0.1. 0.3	Diet, MeHgCl
Adams et al. (2009) (WHIB)	~8–23[b] (scapular)	0.05, 0.1, 0.3	Diet, MeHgCl
Albers et al. (2007) (AMKE)	2.0–19.1[c]	0.6, 1.7, 2.8, 3.9, 5.0	Diet, MeHgCl, dw
Anteau et al. (2007) (LESC)	1.0[d]		
Anthony et al. (1999) (BAEA)	~1–2.5[c] (dw)		
Barr (1986) (COLO)	0.5–1.4[c]; 5.1–29.7[d] (adult), 0.8–1.3[d] chick (ww); *	0–0.53, 0.04–5.16	Prey items
Bennett et al. (2009) (AMKE)	21.3–44.9[a]; 275–542[b] (adult P), 4.4[b] (chick P); *	1.24, 2.65, 5.02	Diet, MeHgCl
Bouland et al. (2012) (BEKI)	~2.5[a]		
Bouland et al. (2012) (EABL)	~1[a]		
Bouland et al. (2012) (TRES)	~1.5[a]		
Bouton et al. (1999) (GREG)	Data not reported	0.5, 5.0	Force-fed, MeHgCl
Bowerman et al. (1994) (BAEA)	21[b] (P), 23[b] (S), 19[b] (T), 21[b] (adult body); *		
Brasso and Cristol (2008) (TRES)	3.7[a] (adult), 0.2[a] (nestling); 13.6[b] (P)	0.97	Prey items, dw
Braune et al. (2012) (ARTE)	*	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4	Egg injection, MeHgCl
Braune et al. (2012) (TBMU)	*	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.5	Egg injection, MeHgCl
Burgess and Meyer (2008) (COLO)	0.4–7.4[a] (adult), <0.1–1.3[a] (juvenile)	0.09, 0.16	Prey items
Bustamante et al. (2016) (WAAL)	23.9[b] (body)		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Carlson et al. (2014) (EUST)	4.9–9.8[a]	0.75, 1.5	Diet, MeHgCys
Caudill et al. (2015) (ZEFI)	~4–32[a]	0.3, 0.6, 1.2, 2.4	Diet, MeHgCys
Champoux et al. (2017) (GBHE)	0.55 (plasma), 8.4[b] (mix of P, S, T, body)		
Clarkson et al. (2012) (DCCO)	10.9–12.6[b] (P) (dw)		
Clarkson et al. (2012) (GLIB)	3–4.4[b] (P) (dw)		
Costa et al. (2014) (GT)	0.1–0.2[a] (dw); 0.1–1.1[b] (T) (dw); *		
Costantini et al. (2014) (WAAL)	~2.5–19 (red blood cells) (dw)		
Custer et al. (1997) (GBHE)	0.1[c]		
Custer et al. (2000) (LESC)	~0.1–1.6[d]		
Custer et al. (2006) (TRES)	0.2–0.3[c] (dw); 0.1–0.2[d]	0.04–0.07	Prey items, dw
Custer et al. (2007) (HOWR)	2.7[c] (dw); 2.9[d]		
Custer et al. (2007) (TRES)	7.3[c] (dw); 3.8[d]		
Custer et al. (2008) (TRES)	0.2[c] (dw); 0.2[d]; *	Low–0.091	Prey items, dw
Custer et al. (2012) (TRES)	<0.1[a]; 0.3[c] (dw); 0.3[d]	0.02–0.14	Prey items, dw
Elbert and Anderson (1998) (CLGR)	1.2–4.4[d]; *		
Elbert and Anderson (1998) (WEGR)	1.2–4.4[d]; *		
Evans et al. (1982) (ROPI)	~12[a]; 20–82.3[d]; *	1, 1.5, 2	Force-fed, MeHgCys
Evers et al. (2003) (COLO)	0.1–4.4[c]		
Evers et al. (2008) (COLO)	1.7[a]; 16.7[b] (S); 1.6[c]		
Fallacara et al. (2011a) (AMKE)	2.2–62[a]; *	0.6, 3.9	Diet, MeHgCl, dw
Fallacara et al. (2011b) (AMKE)	0.1–9.1[a]; *	0.6, 3.9	Diet, MeHgCl, dw
Fimreite and Karstad (1971) (RTHA)	<0.2–20[d]; *	2.6, 5.2, 7.8	Diet, MeHgDicyan
Finkelstein et al. (2007) (BFAL)	4.5[a]		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Finley and Stendell (1978) (ABDU)	40.8–65.6[c] (P); 3.9–6.1[c]; 10.2–14.5[d] (ww); *	3	Diet, MeHgDicyan
Fort et al. (2015) (ATPU)	7.1[a] (dw); 8.6[d]; *		
Fort et al. (2015) (BLKI)	8.6[a] (dw); 10.8[d]; *		
Fort et al. (2015) (COGU)	6.3[a] (dw); 5.5[d]; *		
Fort et al. (2015) (RAZO)	9.4[a] (dw); 10.1[d]; *		
Franceschini et al. (2009) (TRES)	~0.1–1[a] (adult), <0.1[a] (chick) ; ~0.5–2.7[b] (T); 0.1[c]		
Franceschini et al. (2017) (COLO)	1.8–2.2[a], 9.9–15[b] (S)	0.4, 1.2	Fish, MeHgCl
Frederick and Jayasena (2010) (WHIB)	0.7–4[a]; 4.3–51.3[b] (scapular)	0.05, 0.1, 0.3	Diet, MeHgCl
Frederick et al. (2011) (WHIB)	0.7–4[a]; 4.3–51.3[b] (scapular)	0.05, 0.1, 0.3	Diet, MeHgCl
Gerrard and St. Louis (2001) (TRES)	1.7[b] (adult), 0.8–1.3[b] (chick); ~0.3[d] (chick); *		
Gibson et al. (2014) (DCCO)	9–17.5[a] (dw)		
Gillet and Seewagen (2014) (RWBB)	<0.1–0.3[a] (nestlings), <0.1–0.7[a] (adults)		
Goutte et al. (2014a) (WAAL)	2.0–18.7 (red blood cells) (dw)		
Goutte et al. (2014b) (BRSK)	8.2 (red blood cells) (dw)		
Goutte et al. (2014b) (SPSK)	2.2 (red blood cells) (dw)		
Hallinger and Cristol (2011) (TRES)	3.0[a]		
Hallinger et al. (2010) (CARW)	~0.2–5.9[a]		
Hallinger et al. (2010) (HOWR)	~0.1–8.4[a]		
Hallinger et al. (2010) (SOSP)	~<0.1–4.9[a]		
Hallinger et al. (2011) (TRES)	2.8[a]		
Hamilton et al. (2011) (COLO)	22.8[d]; *		
Hargreaves et al. (2010) (BBPL)	~0.3–0.5[a]; ~1.5[b] (P); ~0.1[c] (dw)		
Hargreaves et al. (2010) (RUTU)	~0.3[a]; ~0.5[b] (P); ~0.2[c] (dw)		
Hargreaves et al. (2010) (SEPL)	~0.5–0.7[a]; ~2.0[b]; ~0.2[c] (dw)		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Hawley et al. (2009) (TRES)	0.8–7.4[a]		
Heath and Frederick (2005) (WHIB)	0.3–20[b] (scapular)		
Heinz and Locke (1976) (MALL)	0.8–7.2[c]; *	3	Diet, MeHgDicyan
Heinz (1974) (MALL)	1–9.2[c]	0.5, 3	Diet, MeHgDicyan
Heinz (1975) (MALL)	1–9.2[c]	0.5, 3	Diet, MeHgDicyan
Heinz (1976a) (MALL)	11.2–68.7[b] (P); 0.8–7.4[c]; 1.6–11.1[d] (ww); *	0.5	Diet, MeHgDicyan
Heinz (1976b) (MALL)	9.0[b] (P); 0.9[c]; 0.9[d] (ww); *	0.5, 3	Diet, MeHgDicyan
Heinz (1979) (MALL)	9.0–11.2[b] (P); 0.8–0.9[c]; 0.9–1.6[d] (ww); *	0.5	Diet, MeHgDicyan
Heinz (1980) (MALL)	Data not reported	1, 5	Diet, MeHgCl
Heinz et al. (2010a) (MALL)	0.8[c]	0.5	Diet, MeHgCl
Heinz et al. (2010b) (MALL)	1.6–6[c]	1, 2, 4, 8	Diet, MeHgCl
Heinz et al. (2011) (MALL)	Data not reported	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4	Egg injection, MeHgCl
Heinz et al. (2012a) (MALL)	Data not reported	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4	Egg injection, MeHgCl
Heinz et al. (2012b) (DCCO)	Data not reported	0.2, 0.4, 0.8, 1.6	Egg injection, MeHgCl
Heinz et al. (2012b) (MALL)	Data not reported	0.2, 0.4, 0.8, 1.6	Egg injection, MeHgCl
Heinz et al. (2012b) (REJU)	Data not reported	0.2, 0.4, 0.8, 1.6	Egg injection, MeHgCl
Helander et al. (1982) (WTEA)	0.8–12.4[c] (dw)		
Henny et al. (2002) (BCNH)	6.6[a] (adult), 3.3[a] (fledgling); 32.3[b] (body); *	0.03–0.97	Stomach contents, >71% MeHg
Henny et al. (2002) (DCCO)	17.1[a] (adult), 5.4[a] (juvenile); 66.3[b] (body); 1.1[c], *	0.82–2.23	Stomach contents, >71% MeHg
Henny et al. (2002) (SNEG)	5.9[a] (adult), 2.7[a] (fledgling); 30.6[b] (body); *	0.2–1.96	Stomach contents, >71% MeHg
Henny et al. (2005) (AMDI)	0.2–2.2[b] (S, T, body); <0.1[c]	0.1979, 0.0193, 0.0478	Prey, 8–103% MeHg, dw
Henny et al. (2017) (SNEG)	1.5–3.4[a]		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Henry et al. (2014) (ZEFI)	2.5–30.4[a]; ~5–105[d]	0.3, 0.6, 1.2, 2.4	Diet, MeHgCys
Herring et al. (2009) (GREG)	1.6–6.2[b] (scapular)		
Herring et al. (2009) (WHIB)	0.2–1.5[b] (scapular)		
Herring et al. (2010) (AMAV)	Data not reported		
Herring et al. (2010) (BNST)	Data not reported		
Herring et al. (2010) (FOTE)	~0.1–5[c]		
Herring et al. (2012) (FOTE)	0.5[a]; 20.3[b] (natal down)		
Herring et al. (2014) (GREG)	4.1 (red blood cells) (dw)		
Herring et al. (2014) (WHIB)	0.6 (red blood cells) (dw)		
Herring et al. (2017) (AMAV)	0.3[a], 2.4[b] (body)		
Herring et al. (2017) (BNST)	1.0[a], 8.6[b] (body)		
Herring et al. (2017) (CATE)	1.4[a], 10.9[b] (body)		
Herring et al. (2017) (FOTE)	1.4[a], 9.7[b] (body)		
Hill and Soares (1984) (JAQU)	Data not reported	0.125, 0.5, 2, 8	Diet, MeHgCl
Hill et al. (2008) (BCNH)	0.8–7.4[a]; 0.2–1.0[c]		
Hill et al. (2008) (SNEG)	0.8–5.5[a]; 0.2–1.9[c]		
Hoffman and Moore (1979) (MALL)	<0.1–0.5[c]	0.3, 1, 3, 9, 27, 90	MeHg applied to egg
Hoffman et al. (1998) (GRSC)	3–66[d]		
Hoffman et al. (1998) (RUDU)	2–9[d]		
Hoffman et al. (1998) (SUSC)	5–35[d]		
Hoffman et al. (2005) (GREG)	0.6–102[a]; 11–160[d] (ww); *	0.5, 5	Diet, MeHgCl
Hoffman et al. (2009) (BCNH)	0.6–16[b] (body)		
Hoffman et al. (2009) (SNEG)	0.8–12[a]; 20.5–36.4[b] (body); 2–4.5[d] (ww); *		
Hoffman et al. (2011) (CATE)	8.9[d]; *		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Hoffman et al. (2011) (FOTE)	6.8–15.6[d] (adult), 3.4[d] (chick); *		
Jackson et al. (2011) (CARW)	0.6–8.4[a]		
Jayasena et al. (2011) (WHIB)	0.7–4[a]; 4.3–51.3[b] (scapular)	0.05, 0.1, 0.3	Diet, MeHgCl
Jenko et al. (2012) (LAGU)	Data not reported	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2	Egg injection, MeHgCl
Ji et al. (2006) (MALL, domestic)	4.5[d]; *		
Kalisińska et al. (2010) (COME)	12.6[d]; *		
Kenow et al. (2003) (COLO)	~0.1–20[a]	0.1, 0.5, 1.5	Diet, MeHgCl
Kenow et al. (2007) (COLO)	~0.1–15[a]	0.08, 0.4, 1.2	Diet, MeHgCl
Kenow et al. (2008) (COLO)	0.1–2.3[a]	0.08, 0.4, 1.2	Diet, MeHgCl
Kenow et al. (2010) (COLO)	~0.1–15[a]	0.08, 0.4, 1.2	Diet, MeHgCl
Kenow et al. (2011) (COLO)	1.7–12[a]; 0.6–4.2[c]; ~0.8–10[d]; *	0.5, 1.3, 2.9	Egg injection, MeHgCl
King et al. (1991) (BLSK)	0.5[c]		
King et al. (1991) (FOTE)	0.4[c]		
Klimstra et al. (2012) (MALL)	Data not reported	0.2, 0.4, 0.8, 1.6	Egg injection, MeHgCl
Kobiela et al. (2015) (ZEFI)	13.9[a]	1.2	Diet, MeHgCys
Laties and Evans (1980) (ROPI)	16.0[a]	1.5, 2, 2.5	Force-fed, MeHgCys
Lewis et al. (2013) (ZEFI)	5–12[a]	0.5, 1.0	Diet, MeHgCl, & MeHgCys
Loerzel et al. (1999) (DCCO)	*	0.5, 3.5	Fish, MeHgCl
Longcore et al. (2007) (TRES)	*		
Lundholm (1995) (REJU)	Data not reported	1, 5	Force-fed, MeHg
Maddux et al. (2014) (ZEFI)	Data not reported	0.5, 1.0	Diet, MeHgCl
McCullagh et al. (2015) (EABL)	~0.5–0.7[a]; ~2.2–3.4[b] (P), ~1.5[b] (S), ~1.7[b] (T); *		
McKay and Maher (2012) (NESP)	2.9[a]		
Merrill et al. (2005) (COLO)	0.3[a]	0.53	Prey items, dw

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Meyer et al. (1998) (COLO)	0.6–4.2[a]; 3–21[b]; 0.9[c]		
Mitro et al. (2008) (COLO)	<0.1–7.4[a]; 2.2–46[b] (S)		
Moore et al. (2014) (ZEFI)	~2–58[a]	0.3, 0.6, 1.2, 2.4	Diet, MeHgCl
Nicholson and Osborn (1984) (EUST)	6.6[d]; *	1.1	Diet, unspecified
Nocera and Taylor (1998) (COLO)	0.2–1.3[a]		
Olivero-Verbel et al. (2013) (SNEG)	<0.1[c]; <0.1 (eggshell)		
Olsen et al. (2000) (COLO)	Data not reported		
Pass et al. (1975) (MALL)	1.8–5.7[a]; 4.7–11.7[d]; *	1.53, 2.78	Diet, MeHgDicyan
Pollentier et al. (2007) (COLO)	0.03 (eggshell)		
Pollet et al. (2017) (LSPE)	0.2–2.3[a]		
Pollock and Machin (2009) (LESC)	1.3[d]		
Provencher et al. (2016) (COEI)	0.2[a]		
Provencher et al. (2017) (COEI)	0.4–0.5[a]		
Rowse et al. (2014) (ACFL)	<0.1–0.6[a] (adult), <0.1[a] (nestling) (dw)		
Rutkiewicz et al. (2010) (HEGU)	*		
Rutkiewicz et al. (2011) (BAEA)	15.3[b] (P), 15.8[b] (body); 8[d]; *		
Rutkiewicz et al. (2013) (JAQU)	*	0.17, 0.62, 2.0, 3.2, 6.4	Egg injection, MeHgCl, & MeHgCys
Rutkiewicz et al. (2013) (REJU)	*	0.17, 0.62, 2.0, 3.2, 6.4	Egg injection, MeHgCl, & MeHgCys
Scheuhammer (1988) (ZEFI)	~9–45[d]; *	1, 2.5, 5	Diet, MeHgCl, dw
Scheuhammer et al. (2008) (BAEA)	0.5–104[d]; *		
Scheuhammer et al. (2008) (COLO)	0.5–670[d]; *		
Schoch et al. (2014) (COLO)	2.0[a] (adult), 0.2[a] (chicks);16.4[b] (S, T); 0.8[c]		

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Scoville and Lane (2013) (SASP)	1.5[a]; 20.7[b] (adult P); 3.4[b] (juvenile)		
Seewagen (2013) (NOWA)	0.4[a]		
Sepúlveda et al. (1999) (GREG)	<0.1–3.9[a] (undosed nestlings); *	1.54	Force-fed, MeHgCl
Snelgrove-Hobson et al. (1988) (MALL, domestic)	*	0.5, 5, 15	Diet, MeHgCl
Spalding et al. (1994) (GBHE, white)	9.8[d] (ww)		
Spalding et al. (2000a) (GREG)	1.1–74.4[a]; 19–770[b] (P)	0.5, 5.0	Force-fed, MeHgCl
Spalding et al. (2000b) (GREG)	12–93[a]; 40–150[b] (scapular); 15–140[d]; *	0.5, 5.0	Force-fed, MeHgCl
Swaddle et al. (2017) (ZEFI)	17.8[a]	1.2	Diet, MeHgCys
Tartu et al. (2013) (BLKI)	~0.5–3.3 (red blood cells) (dw)		
Tartu et al. (2014) (SNPE)	2.7 (red blood cells) (dw)		
Tartu et al. (2015) (SNPE)	1.9 (red blood cells) (dw)		
Taylor and Cristol (2015) (TRES)	2.2–3.2[a] (adult); 7.4–12.9[b] (nestling body)		
Thompson et al. (1991) (GRSK)	7[b] (adult scapular), 1.3[b] (nestling); 11.6[d]; *		
Varian-Ramos et al. (2014) (ZEFI)	~4–32[a]	0.3, 0.6, 1.2, 2.4	Diet, MeHgCys
Wada et al. (2009) (TRES)	0.4[a]		
Wayland et al. (2002) (COEI)	1.3–6.5[d]		
Wayland et al. (2008) (KIEI)	0.2[a]		
Wayland et al. (2008) (WWSC)	0.2[a]		
Weech et al. (2006) (BAEA)	1.6–9.4[a] (adult), 0.1–0.8[a] (chick); 0.8–65[b] (adult)		
White and Cristol (2014) (BEKI)	0.6–3.4[a]; 9.4–26.3[b] (body)		
Wiemeyer et al. (1984) (BAEA)	<0.1–1.2[c]		
Wolf et al. (2017) (ZEFI)	Data not reported	1.2	Diet, MeHgCys

(continued)

Table 2 (continued)

Citation (AOS alpha)	Tissue mercury concentration	Exposure concentration	Form of exposure
Yu et al. (2016) (ZEFI)	0.1[a]	0.2, 3.2	Egg injection, MeHgCl
Yu et al. (2017) (ZEFI)	Data not reported	0.2, 3.2	Egg injection, MeHgCl

Concentrations in blood (a), feathers (b), eggs (c), and exposure are expressed as wet/fresh weight unless otherwise noted. Concentrations in liver (d) are expressed as dry weight unless otherwise noted. The type of feather is indicated in parentheses, including primaries (P), secondaries (S), tail (T), body (i.e., breast and back), and down. Asterisk denotes additional tissue concentration information reported in cited paper but not included here
MeHgCl methylmercury chloride, *MeHgCys* methylmercury cysteine, *MeHgDicyan* methymercury dicyandiamide

presented for all studies where reported, in Table 2, and are indicated as being on a wet or dry weight basis. The form and mode of mercury exposure varied across studies reviewed, from unknown in many field studies to dietary methylmercury chloride in most dosing studies. In general, only total residues (rather than particular species of mercury) were reported from the tissues of exposed birds. We provide the mode of exposure (e.g., diet, egg injection, etc.), for each dosing study, and include the details of form of methylmercury when available. (Table 2 is organized by citation and referenced to Table 1 by AOS Alpha code for each species). This review incorporates all peer-reviewed literature discussing the effect of sublethal doses of mercury on birds of all taxa that was in English and detected by the authors using reasonable diligence on standard online search engines through May 2017. It is intended to serve as a detailed summary of the state of knowledge concerning sublethal effects of mercury on birds.

3 Reproduction

3.1 Overview

Depressed reproductive success is the most widely investigated and reported consequence of mercury exposure, but the endpoints measured have varied widely between studies, from eggshell structure to timing of breeding. Dozens of different species have been studied, both in the field and in laboratories (all experimental dosing results are denoted as such throughout the text of this review, and all unspecified studies were correlational field studies). Across a wide range of concentrations and methodologies, mercury exposure clearly has deleterious impacts on many aspects of avian reproduction. We refer to all forms of the element as "mercury" throughout this review, but we assume that impacts on wild birds were from methylmercury, which is the form most abundant in their tissues and many prey items. Although laboratory studies used a variety of forms of mercury, we are

unable to ascertain which form caused any observed effects because of unstudied reactions during digestion or metabolism.

3.2 Clutch Size

The number of eggs laid in a clutch appears to be impacted by mercury in some species. Mercury contamination was associated with the reduced numbers of eggs in free-living black-legged kittiwakes (Tartu et al. 2013), as well as dosed American kestrels (Albers et al. 2007: trace, low, medium, and high in diet), dosed mallards (Heinz 1974: trace, high in diet), and dosed white leghorn chickens (Lundholm 1995: 1 mg methylmercury/day over 50 days in diet). Female eastern bluebirds with higher feather mercury, indicating long-term exposure from a nearby contaminated river, had smaller clutches (McCullagh et al. 2015). However, no differences were detected in the number of eggs laid by reference or environmentally exposed tree swallows (Brasso and Cristol 2008: low in prey (dw); Gerrard and St. Louis 2001: trace in prey (dw)), common eiders (Provencher et al. 2017), dosed black ducks (Finley and Stendell 1978: high in diet), or dosed zebra finches (Varian-Ramos et al. 2014: trace, low, medium, and high in diet; Yu et al. 2016: trace, high injected in egg). Great tits laid larger clutches in a contaminated site, but nestling blood mercury concentrations were not significantly different than in the reference site, suggesting that mercury was an unlikely cause of this difference (Costa et al. 2014). Thus, there is an equal weight of evidence, from free-living and dosed birds, supporting the hypothesis that mercury does reduce clutch size, or that it has no effect on clutch size.

3.3 Eggshells and Embryos

Eggshell thinning has been related to mercury in free-living snowy egrets (Olivero-Verbel et al. 2013) and domestic white leghorn chickens (Lundholm 1995: 1 mg methylmercury/day over 50 days in diet). Bald eagles exposed to more mercury had thinner eggshells in one study (Wiemeyer et al. 1984), but not in another (Anthony et al. 1999). Eggs of mallards maintained on a methylmercury-contaminated diet did not have thinner shells (Heinz 1974: trace, high in diet; Heinz 1976a: trace, high in diet; Heinz 1976b: trace in diet; and Heinz 1980: low, high in diet) until the third generation of exposure (Heinz 1979: trace in diet). Eggshell thinning was not related to mercury exposure for free-living great blue herons (Custer et al. 1997), common loons (Pollentier et al. 2007, note that eggshell thickness was related to lake pH, a proxy for mercury), Forster's terns, or black skimmers (King et al. 1991), but it should be noted that these three studies reported relatively low mercury concentrations. Thus, it appears that mercury is associated with eggshell thinning,

although the effect is difficult to detect under some circumstances, such as low-dose environmental exposure.

Other attributes of eggs may also be affected by mercury. Free-living egrets with higher mercury levels had wider eggs with decreased weight (Olivero-Verbel et al. 2013). Lundholm (1995: 1 mg methylmercury/day over 50 days in diet) reported eggshell defects and shorter egg length in mercury-dosed chickens, while Heinz (1974: trace, high in diet) found decreased egg weight in dosed mallards. Common loons exposed to mercury had decreased egg volume (Evers et al. 2003). Egg volume was also lower for contaminated tree swallows in one study (Brasso and Cristol 2008: low in prey, dw) but did not differ between reference and contaminated birds in a larger study on the same population (Hallinger and Cristol 2011). Egg volume was not related to mercury in Leach's storm-petrels (Pollet et al. 2017).

Several studies indicate the effects of mercury on embryos as well. Applying mercury to the surface of mallard eggs caused teratogenicity, including skeletal defects and incomplete ossification (Hoffman and Moore 1979: trace, low, and high). When injected into eggs, mercury was teratogenic to varying degrees in 22 of 25 different species (Heinz et al. 2011: trace, low, medium, and high), including mallards and double-crested cormorants (Heinz et al. 2012b: trace, low, and medium injected in egg; Klimstra et al. 2012: trace, low, and medium injected in egg). It should be noted, however, that, injected mercury is potentially more toxic than maternally deposited mercury because an embryo is likely to encounter a larger proportion of the dose over a shorter span of time. Injection of methylmercury lengthened the necessary incubation period of common loon eggs in a dose-dependent manner (Kenow et al. 2011: trace, medium, and high). Eggs of dosed mallards experienced increased embryo mortality (Heinz 1974: trace, high in diet), with fewer viable eggs produced (Heinz 1979: trace in diet). Thick-billed murre and arctic tern eggs injected with mercury also had reduced embryo survival (Braune et al. 2012: trace, low, medium, and high). Forster's tern eggs collected from the wild showed a positive relationship between number of malpositioned embryos and mercury concentration, but no relationship between embryo deformities and mercury. However, there was no relationship between mercury concentration and occurrence of either embryo malpositioning or deformation in free-living black-necked stilts or American avocets (Herring et al. 2010). Finally, no relationship was found between mercury and embryonic development in wild-collected eggs of white-tailed sea eagle (Helander et al. 1982) or common loons (Evers et al. 2003). A clear majority of studies from both the field and laboratory indicate that mercury is embryotoxic in a variety of ways.

3.4 Hatching and Hatchlings

Numerous studies have examined whether there is an effect of mercury exposure on survival of baby birds in the nest and around fledging time. There was a mercury-related decline in the proportion of eggs hatching in free-living tree swallows

(Hallinger and Cristol 2011), as well as dosed laughing gulls (Jenko et al. 2012: trace, low, medium, and high injected in egg), zebra finches (Varian-Ramos et al. 2014: trace, low, medium, and high in diet; Yu et al. 2016: trace, high injected in egg), American kestrels (Albers et al. 2007: trace, low, medium, and high in diet), and common loons (Kenow et al. 2011: trace, medium, and high injected in egg). There was a suggestive association between paternal mercury level and hatching success in a study of three species of Arctic-nesting shorebirds (Hargreaves et al. 2010). In a set of experimental studies on mallards, hatching success declined in three studies (Hoffman and Moore 1979: applied methylmercury to eggshell resulting in egg concentrations of 0.05–0.53 μg/g; Heinz et al. 2009: trace, low, medium, and high injected in egg; Klimstra et al. 2012: trace, low, and medium injected in egg) but improved in another (Heinz et al. 2010a: trace in diet). This latter result, an apparent case of hormesis, is perhaps based on a mild antibiotic effect of mercury and was reproduced in an egg injection experiment (Heinz et al. 2012a: trace, low, medium, and high). It should be noted here that injection of mercury into eggs produces higher toxicity than the same concentration of mercury deposited by a female (Heinz et al. 2009: trace, low, medium, and high injected in egg). Blood mercury concentration in breeding female tree swallows was not associated with the hatching success of their broods (Taylor and Cristol 2015). Mercury-related changes in hatching rate were not observed for great skuas (Thompson et al. 1991), Forster's terns, black skimmers (King et al. 1991), Leach's storm-petrels (Pollet et al. 2017), tree swallows, or house wrens (Custer et al. 2007: trace-high in prey (dw); Custer et al. 2006: trace in prey (dw); Custer et al. 2008: trace in prey (dw); Custer et al. 2012: trace in prey (dw)), nor dosed black ducks (Finley and Stendell 1978: high in diet) or mallards (Heinz 1976b: trace in diet; Heinz et al. 2010b: low, medium, and high in diet). However, mercury concentrations were near background levels for Forster's terns, black skimmers (King et al. 1991), and tree swallows (in 3 of the 4 tree swallow studies: Custer et al. 2006: trace in prey (dw); Custer et al. 2008: trace in prey (dw); Custer et al. 2012: trace in prey (dw)), so those negative results are not highly relevant.

In a series of landmark dosing studies on female mallards, Heinz (1974: trace, high in diet; Heinz 1976a: trace, high in diet; Heinz 1976b: trace in diet; and Heinz 1979: trace in diet) reported a reduction in the number of ducklings hatching, findings that were replicated decades later (Heinz et al. 2010b: low, medium, and high in diet). Mercury exposure also resulted in fewer hatchlings for free-living snowy egrets (Henny et al. 2002: trace, low, medium, and high in prey; Hill et al. 2008), common loons (Barr 1986; Schoch et al. 2014), and dosed black ducks (Finley and Stendell 1978: high in diet), American kestrels (Albers et al. 2007: trace, low, medium, and high in diet), and white ibises (Frederick and Jayasena 2010: trace in diet). The probability of hatching was lower for wandering albatross with higher mercury (Goutte et al. 2014a). Anthony et al. (1999) reported fewer nestlings from free-living bald eagles exposed to mercury, but Bowerman et al. (1994) and Weech et al. (2006) reported no correlations between environmental mercury exposure and the number of bald eagle nestlings. Contamination from mercury used in mining did not correlate with the number of black-crowned night-

heron nestlings either (Henny et al. 2002: trace, low in prey), and Elbert and Anderson (1998) reported an unclear relationship for western grebes in the same situation. Of eggs that hatched, mercury did not reduce nestling survival in dosed zebra finches (Yu et al. 2016: trace, high injected in egg). Mercury concentrations near background levels did not reduce tree swallow nestling survival (Custer et al. 2012; trace in prey (dw)). Thus, many studies have shown that survival through the nestling period is reduced by mercury exposure beginning in ovo, but several studies failed to find this effect, and one notably found an increase in hatching rate as the result of mercury exposure.

3.5 Fledging and Fledglings

Reduction in the number of fledged or independent offspring is the effect of mercury exposure with the most robust support. This includes several reports of fewer common loon chicks in broods that had survived to late in the season (Evers et al. 2008; Burgess and Meyer 2008: trace in prey; Meyer et al. 1998), which may result in a negative population growth rate (Schoch et al. 2014). Field studies on loons are now well-established for determining the magnitude of reproductive harm that mercury may have, although studies on lakes with low pH should recognize the potential confounding impacts of reduced fish abundance and availability (Meyer et al. 1998). Reduced fledging success has been reported in free-living birds: tree swallows (Brasso and Cristol 2008: low in prey (dw); Hallinger and Cristol 2011), wandering albatross (Goutte et al. 2014a), and Acadian flycatchers (Rowse et al. 2014, trace in prey items), as well as dosed American kestrels and dosed zebra finches (Albers et al. 2007: trace, low, medium, and high in diet; Varian-Ramos et al. 2014: trace, low, medium, and high in diet). Male eastern bluebirds with higher blood mercury, indicating recent exposure from a nearby contaminated river, fledged a lower proportion of their young than males with lower blood mercury (McCullagh et al. 2015). For tree swallows hatched near a contaminated river, the feather mercury of nestlings that died in the nest was almost twice as high as that of nestlings from nests in which all nestlings fledged (Taylor and Cristol 2015). There was a nonsignificant trend of fewer fledglings among mercury-dosed white ibis in an aviary study (Frederick and Jayasena 2010: trace in diet). (Hereafter, for all nonsignificant trends reported by authors we provide sample size of the smallest treatment group, to allow assessment of one aspect of statistical power; in this case, $n = 20$.) There was an uncertain relationship between fledgling numbers and mercury exposure in free-living American dippers (Henny et al. 2005: trace, low, and medium in prey (dw)). The only such studies not reporting reduced numbers of offspring in birds with higher mercury were on great skuas (Thompson et al. 1991), wandering albatrosses (Bustamante et al. 2016), Leach's storm-petrels (Pollet et al. 2017), and common loons (Barr 1986), all exposed through their natural fish diets. However, a recent study of long-term data from Antarctic colonies of two species of skua indicates an effect of tissue mercury concentration in 1 year on reproductive

success the following year, an effect severe enough that it is predicted to lead to population declines (Goutte et al. 2014b). Finally, great tits fledged more offspring in a contaminated site, but nestling blood mercury concentrations did not differ significantly from the reference site so the effect is unlikely to have been due to mercury (Costa et al. 2014).

3.6 Other Measures of Reproductive Output

The literature suggests that mercury may impact a number of other reproductive endpoints, but there are too few examples of each of these to allow generalized conclusions. Nestlings from contaminated sites were more sensitive to high ambient temperatures (Hallinger and Cristol 2011), and primary sex ratios of offspring on mercury-contaminated sites were female biased in belted kingfishers, tree swallows, and eastern bluebirds, relative to reference sites (Bouland et al. 2012). No impact on sex ratio was found in dosed zebra finches (Yu et al. 2016: trace, high injected in egg).

Other metrics of reproductive success have yielded equivocal results. A model for Carolina wrens developed from field results indicated reduced nest survival, due primarily to nest abandonment, with small increases in maternal blood mercury concentration (Jackson et al. 2011). Common loons were more likely to desert nest sites in lakes contaminated with mercury (Barr 1986). However, for bald eagles, nest success, as defined by the percent of breeding territories producing at least one fledgling (Bowerman et al. 1994), did not relate to mercury contamination. Similarly, the probability of wandering albatross breeding in a given year did not change with mercury exposure (Bustamante et al. 2016). Common eiders with higher blood mercury had a higher propensity to nest, but this was not significant ($n = 74$) (Provencher et al. 2017).

3.7 Timing of Breeding

Studies of the effect of mercury on timing of reproductive events, such as laying and fledging, have yet to produce any consensus. The potential effect of mercury on laying date is especially unclear. Studies of dosed birds revealed increased latency to renest (zebra finches, Varian-Ramos et al. 2014: trace, low, medium, and high in diet) and delay in onset of egg laying (American kestrels, Albers et al. 2007: trace, low, medium, and high in diet), in contrast to free-living tree swallows (Hallinger and Cristol 2011) and great tits (Costa et al. 2014), where earlier onset of laying occurred on contaminated sites (although great tit nestling blood mercury concentrations did not differ from reference sites). However, the onset of laying in the same population of tree swallows was reported to be unaffected in a different study of the same mercury-contaminated sites (Brasso and Cristol 2008: low in prey

(dw)). Neither great skuas (Thompson et al. 1991), black-legged kittiwakes (Tartu et al. 2013), Leach's storm-petrels (Pollet et al. 2017), nor dosed black ducks (Finley and Stendell 1978: high in diet) exhibited a relationship between mercury concentration and onset of egg laying. Blood mercury concentration was negatively related to date of hatching in Forster's terns (Ackerman et al. 2008a), while a positive relationship between mercury and interval from laying to hatching was observed for dosed American kestrels (Albers et al. 2007: trace, low, medium, and high in diet). No relationship between mercury and the timing of post-fledging dispersal of juvenile snowy egrets was found (Henny et al. 2017).

4 Longevity

Mercury does not appear to directly decrease longevity at environmentally relevant concentrations. No differences were found in post-fledging survival probability of Forster's terns (Ackerman et al. 2008a) or snowy egrets (Henny et al. 2017), resight probability of dosed and released white ibises (Frederick et al. 2011: trace in diet), free-living common loons (Mitro et al. 2008), or common eiders (Provencher et al. 2017), annual adult return rate of common loons, great skuas, or Leach's storm-petrels (Meyer et al. 1998; Thompson et al. 1991; Pollet et al. 2017), or probability of survival in great egrets (Sepúlveda et al. 1999: fed capsules for total of 3 mg methylmercury) or wandering albatross (Goutte et al. 2014a; Bustamante et al. 2016). Among yearling female tree swallows that nested in a contaminated floodplain, blood mercury level in 1 year was not a good predictor of probability of returning to breed the next year, a proxy for survivorship in this highly site-faithful species (Taylor and Cristol 2015). Survival probability of free-living American avocet and black-necked stilt chicks at more contaminated sites dropped 1.4% and 3.0%, respectively, but explanatory models specifically including mercury had low predictive power (Ackerman et al. 2008b). Similarly, predicted annual survival of tree swallows at mercury-contaminated sites dropped 1–2%, but individual mercury exposure had weak explanatory power (Hallinger et al. 2011). Mercury concentration in tissues was related to lower recapture probabilities for white-winged scoters, but not king eiders (Wayland et al. 2008). Further studies of long-lived birds observed over many years of mercury exposure may yet reveal a significant effect on survivorship, but thus far there is no evidence to this effect.

5 Behavior

5.1 Parental Behaviors

Parental behavior may be altered in a variety of ways after exposure to mercury. White ibises dosed in aviaries made fewer nesting attempts and exhibited more same-sex pairing among males than was observed in the control aviary (Frederick and Jayasena 2010: trace in diet). Both free-living common loons (Evers et al. 2008) and dosed American kestrels (Albers et al. 2007: trace, low, medium, and high in diet) spent less time incubating when exposed to dietary mercury, while mercury was also related to decreased provisioning effort in loons (Merrill et al. 2005; low, medium, and high in prey (dw)). Male snow petrels with higher mercury were more likely to neglect their egg (Tartu et al. 2015) and Carolina wrens were more likely to abandon nests when on contaminated than reference sites (Jackson et al. 2011). Male American kestrels dosed with mercury were observed cannibalizing their offspring (Fallacara et al. 2011b: trace, medium in diet). No impact on mating behavior of zebra finches that were dosed in ovo was observed (Yu et al. 2016: trace, high injected in egg; Yu et al. 2017: trace, high injected in egg).

5.2 Behavior of Dependent Young

A number of abnormal chick behaviors have also been reported. Common loon chicks with higher mercury exposure spent more time preening and less time backriding, although they did not change their swimming or diving habits in lakes with higher mercury (Nocera and Taylor 1998). Loon chicks in lakes with low pH and higher mercury were also less capable of righting themselves after dietary exposure, and experimental in ovo mercury exposure resulted in other behavioral changes in captivity, including crossing a platform faster, spending more time on platforms and in sunlight, and exhibiting decreased responses to parental wails and frightening stimuli (Kenow et al. 2010: trace, medium in diet; Kenow et al. 2011: trace, medium, high injected in eggs already containing low maternally deposited mercury). Dosed mallard ducklings did not alter their response to maternal calls (Heinz 1975: trace, high in diet; Heinz 1976a: trace, high in diet; Heinz 1976b: trace in diet) until the third generation of exposure, when they exhibited a reduced response (Heinz 1979: trace in diet). Ducklings also ran further from frightening stimuli (Heinz 1975: trace, high in diet; Heinz 1976a: trace, high in diet; Heinz 1979: trace in diet), except in one experiment in which their response to a frightening stimulus did not change (Heinz 1976b: trace in diet). When mercury was injected into white leghorn chicken eggs, the surviving chicks did not differ in their response to frightening stimuli, but they did take longer to right themselves (Rutkiewicz et al. 2013: trace, low, medium, and high injected in egg).

5.3 Coordination and High-Energy Behaviors

Mercury appears to impact behaviors requiring a large energy input. Carolina wrens, house wrens, and song sparrows at sites with mercury contamination sang less complex, lower-frequency songs (Hallinger et al. 2010), whereas Nelson's sparrows at marshes with higher mercury sang faster songs with higher maximum tonal frequency and shorter gaps between bouts (McKay and Maher 2012). Injection of mercury in ovo did not impact the quality of zebra finch songs (Yu et al. 2017: trace, high injected in egg). Free-living common loons with greater mercury exposure spent less time preening and swimming (Evers et al. 2008). In dosing studies that included both lethal concentrations and lowest doses of 5 μg/g, great egrets were less active (Bouton et al. 1999: trace, high force fed capsules) and were ataxic (Spalding et al. 2000a: trace, high force fed capsules), while zebra finches became lethargic and had difficulty balancing or landing on perches (Scheuhammer 1988: low, high in diet (dw)). Domestic rock pigeons dosed with mercury also were ataxic, pecked at food less accurately and at a slower rate (Evans et al. 1982: probably low, medium ingested by intubation), and made fewer and slower responses in operant conditioning tests (Laties and Evans 1980: probably medium, high ingested by intubation). Mercury also impacted American kestrel motor skills, but only when fed at concentrations above 5 μg/g (Bennett et al. 2009: medium, high in diet). Evidence of impaired cognition in dosed zebra finches included impaired spatial memory, but not inhibitory control or ability to associate color with food (Swaddle et al. 2017: medium in diet). The same colony of mercury-dosed zebra finches exhibited behavioral changes including hyperactivity and subordination to undosed finches but were not more or less neophobic. The timing of snowy egret migration (Henny et al. 2017) and the arrival date of common eiders on breeding grounds (Provencher et al. 2016) were not related to mercury.

The relationship between foraging behaviors and mercury concentration is unclear. Common loons with higher mercury exposure spent less time foraging for themselves and their chicks (Evers et al. 2008) and exhibited an increased diving frequency (Olsen et al. 2000), which may indicate that they were having difficulty foraging. Dosed zebra finches reacted more strongly to the presence of predators, waiting longer to forage after seeing a model hawk, and thus losing more mass than control birds (Kobiela et al. 2015: medium in diet). However, dosed white ibises foraged more efficiently (Adams and Frederick 2008: trace in diet) and great egrets performed as well as birds on control diets, although they had a reduced appetite (Bouton et al. 1999: trace, high force fed capsules). Food consumption of common loons dosed in captivity was unrelated to mercury concentration (Kenow et al. 2003: trace, medium in diet).

6 Neurological Function

Although fewer studies of mercury neurotoxicity in avian models have been done in recent years, there exists a solid body of evidence indicating that mercury exposure results in axonal degeneration and other neurological problems. An opportunistically collected juvenile saltmarsh sparrow from a population with high blood mercury concentrations exhibited disrupted neuronal migration, with Purkinje cells scattered through all three layers of the cerebellum and an external granule cell layer (Scoville and Lane 2013). In mallards dosed with mercury, adult axons degenerated (Pass et al. 1975: medium, high in diet), and ducklings exhibited demyelination and neuronal shrinkage (Heinz and Locke 1976: high in diet). Rock pigeons also exhibited demyelination when dosed but, in contrast to mallards, had neuronal swelling (Evans et al. 1982: low, medium ingested by intubation). Dosed American kestrels exhibited axonal degeneration but did not develop brain lesions unless fed very high concentrations above 5 μg/g (Bennett et al. 2009: medium, high in diet). Double-crested cormorants had axonal degeneration and swollen myelin sheaths when dosed (Loerzel et al. 1999: trace, high in diet). Dosed zebra finches suffered hearing impairment, with elevated auditory brainstem response thresholds, decreased amplitudes, and longer latencies for neuronal response to tones (Wolf et al. 2017: medium in diet). Dosed male zebra finches had increased telencephalon volume, but mercury had no impact on brain mass, area X, robust nucleus of the arcopallium song nuclei, or HVC (Yu et al. 2017: trace, high injected in egg). Red-tailed hawks did not show axonal degeneration unless they were fed very high concentrations (5.2 μg/g) of mercury (Fimreite and Karstad 1971: high in diet).

Several researchers have examined neurotransmitter function. Decreased binding to NMDA receptors was related to mercury concentration in free-living bald eagles and common loons (Scheuhammer et al. 2008; Rutkiewicz et al. 2011). However, no change in binding to NMDA receptors was observed for thick-billed murres or arctic terns (Braune et al. 2012: trace, low, medium, and high injected in egg), or herring gulls (Rutkiewicz et al. 2010). Domestic quail and chickens dosed in ovo did not show changes in binding to NMDA receptors in one experiment using methylmercury-chloride, but increased binding to NMDA in chickens was observed in another using methylmercury-cysteine (Rutkiewicz et al. 2013: trace, low, medium, and high injected in egg). Glutamine synthetase (GS) did not increase in dosed hatchling chickens until they were exposed to a very high dietary concentration of 6.4 μg/g, while no change in GS was found in older chicks at any concentration (Rutkiewicz et al. 2013: trace, low, medium, and high injected in egg). In free-living bald eagles, there was a positive correlation between mercury and GS (Rutkiewicz et al. 2011). Glutamic acid decarboxylase has been found to either increase or remain the same in chickens and decrease in quail with administration of mercury (Rutkiewicz et al. 2013: trace, low, medium, and high injected in egg) and was negatively correlated with inorganic mercury in bald eagles (Rutkiewicz et al. 2011). Gamma-aminobutyric acid either showed no change, for

chickens or quail, increased in chickens exposed to 6.4 μg/g mercury injected in egg, or decreased in chickens exposed to 3.2 or 6.4 μg/g methylmercury-cysteine (Rutkiewicz et al. 2013: trace, low, medium, and high injected in egg). Muscarinic cholinergic (mACh) receptor density was unchanged in thick-billed murres and arctic terns (Braune et al. 2012: trace, low, medium, and high injected in egg) and herring gulls (Rutkiewicz et al. 2010), but mACh activity was related to mercury in free-living bald eagles and common loons (Scheuhammer et al. 2008). No differences were found for cholinesterase (ChE), or MAO in bald eagles or common loons. Similarly, no impacts on nicotinic cholinergic receptor density or nicotinic receptor alpha-7 mRNA expression were observed in herring gulls (Rutkiewicz et al. 2010). In another sample of common loons that died of botulism, no differences were observed for binding to NMDA receptors, mACh receptor density, MAO, or ChE, although it must be noted that these loons had relatively low mercury tissue concentrations and a molar excess of selenium in their brain tissue, which is known for mitigating the impact of mercury (Hamilton et al. 2011). Clearly, more work is necessary to sort out the potential effects of mercury on various neurochemicals, as well as the dose–response curves. Because of the well-known neurological effects of mercury, this sort of research is a priority.

7 Endocrine Function

7.1 Overview

While there is no evidence that mercury is a classic endocrine disrupting chemical that mimics or competes with specific hormones, there are data suggesting that mercury exposure is associated with alterations in profiles of several hormones. Much more work is needed in this area because the results are equivocal and no studies have been replicated with the same mercury doses, hormones, or species.

7.2 Corticosterone

Despite a considerable body of literature, the impact of mercury exposure on corticosterone (CORT) is still unclear. The expected stress-induced increase in CORT was weaker for nestling tree swallows living at contaminated sites (Wada et al. 2009) and dosed adult zebra finches (Moore et al. 2014: trace, low, medium, and high in diet) but did not relate to mercury level in free-living common eiders (Wayland et al. 2002) or snow petrels (Tartu et al. 2015). In captive juvenile common loons, stress-induced CORT was depressed, but free-living adult male loons with higher mercury had elevated stress-induced CORT and no relationship was found in females (Franceschini et al. 2017: trace, medium in diet). Baseline

CORT was also elevated in free-living tree swallow nestlings exposed to environmental mercury (Wada et al. 2009) as well as in dosed juvenile white ibises, although this latter response exhibited a nonlinear relationship with dose (Adams et al. 2009: trace in diet). In adult lesser scaup ducks, baseline CORT was only related positively to mercury in individuals with larger body size, while the relationship was reversed in smaller individuals (Pollock and Machin 2009). For nestling and adult tree swallows, a nonsignificant positive relationship was reported between feather mercury concentration and baseline CORT ($n = 23$), but a negative relationship was found between baseline CORT and both blood (significant) and egg (nonsignificant, $n = 21$) mercury in the same birds (Franceschini et al. 2009). Baseline CORT was also depressed in free-living nestling Forster's terns with higher mercury exposure (Herring et al. 2012). A nonsignificant trend of depressed baseline CORT was found in female common eiders with low blood mercury concentrations ($n = 190$) (Provencher et al. 2016). Finally, no significant relationship was found between mercury and baseline CORT in free-living nestling great egrets or white ibises (Herring et al. 2009, Herring et al. 2014), adult or nestling white ibises (Heath and Frederick 2005), adult snow petrels (Tartu et al. 2015), or dosed zebra finches (Moore et al. 2014: trace, low, medium, and high in diet), although the change in baseline CORT between pre- and postbreeding periods in zebra finches revealed a statistically significant interaction between sex and mercury (Maddux et al. 2014: trace, low in diet). Endocrine responses to environmental stressors are notoriously difficult to understand, given the possibility of both activational and organizational effects of stressors, and the many simultaneous confounding influences. Careful work on captive birds is needed to make progress in understanding the relationship between mercury and avian CORT responses.

7.3 Testosterone (T)

No clear patterns have yet emerged about the relationship between mercury and baseline T levels. In dosed adult white ibises, Jayasena et al. (2011: trace in diet) found no change in the baseline T of breeding males paired to females. In contrast, males paired to other males had depressed T levels while eggs were being laid in the captive colony and elevated T levels while the colony was incubating eggs. Heath and Frederick (2005) found elevated T levels associated with mercury in male white ibises incubating nests in the wild. In adult black-legged kittiwakes, baseline T was negatively related to mercury in males that skipped breeding, but not in breeding males. Gonadotropin-releasing hormone (GnRH)-induced T was not related to mercury level in breeding males or males that skipped breeding (Tartu et al. 2013). In dosed juvenile white ibises (Adams et al. 2009: trace in diet) and common loons (Franceschini et al. 2017: trace, medium in diet), no effects of mercury on T were observed. It appears that there is not a predictable relationship between mercury

exposure and T, and cases with apparent relationships may be the indirect result of perturbations by mercury of other hormones (e.g., CORT) or behavior (e.g., lack of stimulus).

7.4 Other Hormones

With respect to mercury exposure, no other hormones have been studied as extensively as CORT or T. Other hormones related to reproduction have been the most studied, but like CORT and T, their levels are highly dependent on an individual's breeding stage and thus a relationship with mercury concentration is hard to detect. The emerging relationships between mercury exposure and hormone level are correspondingly complex. A significant relationship between mercury and luteinizing hormone (LH) was found in black-legged kittiwakes that skipped breeding, but not in birds that bred. Baseline LH levels were negatively associated with mercury in skipping males but positively associated in skipping females, while LH induced by GnRH injection increased with increasing mercury levels (Tartu et al. 2013). However, both baseline and GnRH-induced LH were suppressed in male and female snow petrels with higher environmental mercury exposure (Tartu et al. 2014).

Prostaglandin synthesis declined after exposure to a high dose (5 μg/g) in a homogenate eggshell mucosa from chickens (Lundholm 1995; 1 mg methylmercury/day over 50 days in diet). White ibises had a nonsignificant increase in progesterone during incubation ($n = 6$) (Heath and Frederick 2005). Thyroid hormones, T3 and T4, were lower in nestling tree swallows exposed to mercury at contaminated sites (Wada et al. 2009), but T4 had no relationship to mercury in lesser scaup ducks (Pollock and Machin 2009). In great blue herons with relatively low mercury burdens, no relationship was found between mercury and total or free T3 or T4, and the hormone precursor dehydroretinol decreased with increased mercury levels in these herons, but there was no relationship to retinol (Champoux et al. 2017). Male snow petrels had depressed levels of stress-induced prolactin, but no association with mercury was found in baseline prolactin in either sex or stress-induced prolactin in female snow petrels (Tartu et al. 2015).

More information is available regarding estradiol. In female white ibises, estradiol levels were negatively related to mercury, significantly so prior to breeding, nonsignificantly during the courtship display period ($n = 13$) (Heath and Frederick 2005). Dosed female white ibises showed a significant decrease in estradiol in 1 year and exhibited a nonsignificant trend in the same direction the following year ($n = 20$). In male white ibises, estradiol levels were higher in dosed birds than controls during courtship but lower during other stages. Differences between dosed and control birds were amplified in males that paired, abnormally, with other males (Jayasena et al. 2011: trace in diet). Estradiol levels in juvenile white ibises increased in a dose-dependent manner with mercury dose (Adams et al. 2009: trace in diet). Estradiol levels were not related to mercury in dosed juvenile

common loons (Franceschini et al. 2017: trace, medium in diet). Given the number of studies, it is perhaps surprising that a clearer pattern is not apparent in the relationship between mercury exposure and various hormones. There seems to be a predictable depression of the CORT response in mercury-exposed birds, but effects on the sex hormones have proven to be complex, indirect, or fleeting and cannot be generalized at this point.

8 Immunocompetence

8.1 Overview

The impact of mercury on immune function is relatively understudied. There has been little replication for most endpoints, and field investigations have been limited to nonspecific measures of immune response, such as the phytohemagglutinin (PHA) skin-swelling assay, which leave considerable room for interpretation. However, a general picture is emerging that mercury negatively affects the immune systems of birds.

8.2 Blood Cells

The most widely reported white blood cell endpoints relate to heterophils and lymphocytes. The number of heterophils increased with mercury in dosed great egrets (Spalding et al. 2000a: trace, high force fed capsules) and dosed American kestrels (Fallacara et al. 2011a: trace, medium in diet), while the percentage of heterophils increased with mercury in free-living western grebes (Elbert and Anderson 1998). Two studies of free-living egrets reported a different trend in response to higher mercury; a decrease in heterophils that was significant in two out of three years for snowy egrets (Hoffman et al. 2009), and a nonsignificant decrease in the number of heterophils in great egrets ($n = 11$) (Sepúlveda et al. 1999: fed capsules for total of 3 mg methylmercury). The number of lymphocytes also exhibited a nonsignificant decrease associated with mercury in that study ($n = 11$) (Sepúlveda et al. 1999: fed capsules for total of 3 mg methylmercury). This result corroborates other results, including a significant decrease with higher mercury in the number of lymphocytes in dosed American kestrels (Fallacara et al. 2011a: trace, medium in diet) and decreased B-cell proliferation in dosed zebra finches (Lewis et al. 2013: trace, low in diet). Dosed great egrets, however, have also exhibited an increase in the number of lymphocytes (Spalding et al. 2000a: trace, high force fed capsules), as have free-living snowy egrets (Hoffman et al. 2009). In accordance with these findings about heterophils and lymphocytes, the heterophil-to-lymphocyte ratio increased for dosed American kestrels (Fallacara

et al. 2011a: trace, medium in diet) and dosed common loons (Kenow et al. 2007: trace, medium in diet). Thus, mercury exposure can increase heterophils and decrease lymphocytes, but this is not always found.

Fewer results have been published regarding other white blood cells. Eosinophils exhibited a nonsignificant decrease in number with mercury level in great egrets ($n = 11$) (Sepúlveda et al. 1999: fed capsules for total of 3 mg methylmercury), and a significant decrease in proportion to other blood cells in environmentally exposed western grebes (Elbert and Anderson 1998). Macrophage activity decreased with mercury level in free-living black-footed albatross (Finkelstein et al. 2007), and macrophage suppression was also observed in dosed American kestrels (Fallacara et al. 2011a: trace, medium in diet). Abundance of monocytes increased with mercury in dosed great egrets (Spalding et al. 2000a: trace, high force fed capsules) but did not change in dosed American kestrels (Fallacara et al. 2011a: trace, medium in diet).

A small amount of information is available on how mercury impacts other aspects of blood. Hematocrit decreased in response to mercury in black-crowned night herons (Hoffman et al. 2009), snowy egrets (Henny et al. 2002: trace, low, medium, and high in prey), and dosed great egrets (Spalding et al. 2000a: trace, high force fed capsules). Sepúlveda et al. (1999: fed capsules for total of 3 mg methylmercury) observed a significant increase in hematocrit with mercury exposure in great egrets during 1 year, but a nonsignificant decrease in another year ($n = 11$). Packed cell volume and hemoglobin were not impacted in dosed zebra finches (Yu et al. 2016: trace, high injected in egg). Plasma proteins in general may decrease, as observed in both dosed and environmentally exposed great egrets (Hoffman et al. 2005: trace, high in diet; Sepúlveda et al. 1999: fed capsules for total of 3 mg methylmercury; Spalding et al. 2000a: trace, high force fed capsules). However, the response is likely more complicated, as common loons displayed an increase in globulin and a decrease in albumin (Kenow et al. 2007: trace, medium in diet).

8.3 Immune Responsiveness

A considerable body of literature shows that mercury decreases general immune response in birds, although there are variable results from different assays. PHA-induced swelling was lower for dosed great egrets (Spalding et al. 2000a: trace, high force fed capsules), and dosed American kestrels (Fallacara et al. 2011a, b: trace, medium in diet), and environmentally exposed tree swallows (Hawley et al. 2009). Antibody response to sheep red blood cells (SRBCs) was lower in dosed American kestrels (Fallacara et al. 2011a: trace, medium in diet) and dosed common loons (Kenow et al. 2007: trace, medium in diet). However, Kenow et al. (2007: trace, medium in diet) reported no change in PHA-induced swelling in dosed

common loons. In common eiders, no relationship was found between mercury and PHA-induced swelling (Wayland et al. 2002), and no difference in skin-swelling response to PHA injection was detected between dosed and control zebra finches (Caudill et al. 2015: trace, low, medium, and high in diet). Negative results were also reported for the relationship between mercury and antibody response to SRBC in a dosing study (American kestrel, Fallacara et al. 2011a: trace, medium in diet) and a field study (tree swallow, Hawley et al. 2009).

Other evidence for a generally compromised immune response includes a greater rate of bacterial infections in dosed common loons (Kenow et al. 2007: trace, medium in diet). Concentrations of heat shock protein 70 increased with mercury in great egrets, but not in white ibises (Herring et al. 2014). Finally, great white herons found dying of chronic disease (e.g., gout) had higher body burdens of mercury than birds dying of acute causes, e.g., injuries (Spalding et al. 1994). In common eiders with near-baseline mercury burdens, no correlation with immunoglobulin Y was found (Provencher et al. 2016). A concerted effort to measure the same endpoints across different mercury exposures and species might quickly resolve why results have been inconsistent across multiple studies. Specifically, more studies are needed that measure response to challenge from parasites or diseases, rather than baseline levels of various immune system components, to evaluate the effect size and potential cost of the deleterious effects of mercury on the immune system.

9 Other Physiological Endpoints

9.1 Oxidative Stress

A growing body of evidence indicates that mercury exposure induces oxidative stress. Although one study of glutathione in dosed laughing gulls failed to find evidence for changes in reduced glutathione (GSH), oxidized glutathione (GSSG), or the ratio of oxidized GSSG to reduced GSH (Jenko et al. 2012: trace, low, medium, and high injected in egg), evidence of mercury-related oxidative stress has been observed in a number of other species. GSH was negatively related to mercury level in the livers of greater scaup, surf scoters, and ruddy ducks (Hoffman et al. 1998), Forster's terns (Hoffman et al. 2011), and great blue herons (Custer et al. 1997), and in the kidney and brain of snowy egrets (Hoffman et al. 2009), although it was not affected in livers of dosed zebra finches (Henry et al. 2014: trace, low, medium, and high in diet). One study observed the opposite relationship with mercury, elevated GSH in domestic duck brains and livers (Ji et al. 2006: trace in prey). GSSG increased in the liver, brain, and kidney of dosed common loons (Kenow et al. 2008: trace, medium in diet) and was also positively related to mercury in the livers of surf scoters and ruddy ducks (Hoffman et al. 1998), great egrets (Hoffman et al. 2005: trace, high in diet), and dosed zebra finches (Henry

et al. 2014: trace, low, medium, and high in diet), and in the kidneys of snowy egrets and of Forster's terns (Hoffman et al. 2009, 2011). Interestingly, the opposite trend was observed in the brains and livers of snowy egrets and brains of Forster's terns (Hoffman et al. 2009, 2011).

The ratio of GSSG to GSH, which represents the ratio of unavailable to available antioxidant and may be the most relevant marker for disruption of glutathione function, increased with mercury exposure in loon brains (Kenow et al. 2008: trace, medium in diet), indicating oxidative stress. Increased GSSG:GSH was also associated with mercury in the livers of greater scaup (Hoffman et al. 1998), Forster's tern (Hoffman et al. 2011), double-crested cormorant (Henny et al. 2002: low, medium, and high in prey), and dosed zebra finch (Henry et al. 2014: trace, low, medium, and high in diet), as well as the kidneys of free-living snowy egrets (Hoffman et al. 2009). Reports of decreased GSSG:GSH in brains and livers of snowy egrets (Hoffman et al. 2009), kidneys of great egrets (Hoffman et al. 2005: trace, high in diet), and livers of common loon (Kenow et al. 2008: trace, medium in diet) might be interpretable as compensatory responses. GSH peroxidase, which converts oxidized GSSH to reduced GSH, declined with increased mercury in great egret livers, kidneys, plasma, and brains (Hoffman et al. 2005: trace, high in diet), snowy egret blood and kidneys (Hoffman et al. 2009), cormorant livers (Henny et al. 2002: low, medium, and high in prey), and common loon brains, consistent with a link between mercury and oxidative stress. But this same bioindicator increased in loon kidney and liver (Kenow et al. 2008: trace, medium in diet), as well as in surf scoter liver (Hoffman et al. 1998) and domestic duck brain and liver (Ji et al. 2006: trace in prey). Evidence of oxidative stress was deduced from increased total thiol levels in lesser scaup (Custer et al. 2000), and wandering albatross plasma also showed evidence of oxidative damage, although no impact was observed on the inflammatory protein haptoglobin (Costantini et al. 2014). In addition to these biochemical changes, mercury exposure increased the expression of two cellular stress-related genes, glutathione peroxidase 3 and glutathione *S*-transferase μ3, in female double-crested cormorants (Gibson et al. 2014). In two populations of tree swallows with very low tissue mercury concentrations, a number of conflicting results were obtained. For one, protein-bound thiol (PBSH) increased with mercury and no correlation was found between mercury and GSH, thiobarbituric acid reactive substances (TBARS), GSSG, or total sulfhydryl (TSH) (Custer et al. 2006). In the other, PBSH, GSSG, and TSH decreased, GSH increased, and no correlation was observed between mercury concentration and TBARS or the ratio of GSSG:GSH (Custer et al. 2008: trace in prey).

Oxidative stress may be responsible for reports of damage to livers and other internal organs in birds with high mercury levels. Snowy egrets had liver and kidney damage (Hoffman et al. 2009), European starlings showed extensive nephritic lesions after being dosed unintentionally in captivity with an unidentified form of methylmercury in their food (Nicholson and Osborn 1984: medium in diet), black-crowned night herons, snowy egrets, and double-crested cormorants experienced hepatotoxicity and nephrotoxicity with higher exposure to mercury (Henny et al. 2002: trace, low, medium, and high in prey), and domestic ducks exhibited

minor kidney damage and degeneration (Snelgrove-Hobson et al. 1988: trace, high in diet). Henny et al. (2002: trace, low, medium, and high in prey) also found that young snowy egrets had enlarged livers and kidneys (and smaller brains), and double-crested cormorants had enlarged spleens, which may have been the result of organ damage rather than growth.

9.2 Chromosomal Damage

Whether or not mercury causes chromosomal damage in birds has not been thoroughly investigated, and the issue would benefit from future research. A handful of studies have used the half-peak coefficient of variation (HPCV) of the G1 cell population as an indicator of chromosomal damage. No difference was found between the HPCV of experimentally dosed and control common loons (Kenow et al. 2008: trace, medium in diet). In free-living lesser scaup (Custer et al. 2000) and tree swallows (Custer et al. 2006: trace in prey (dw)), no evidence of chromosomal damage was found, but the mercury levels of these birds were not elevated above background concentrations and so the interpretation is difficult.

9.3 Metabolism

Very few studies have investigated changes in metabolism in response to environmentally relevant mercury contamination, and none of these have been replicated. In western grebes, blood potassium and phosphorus decreased with increasing tissue mercury concentration (Elbert and Anderson 1998), and plasma phosphate also decreased in great egrets (Hoffman et al. 2005: trace, high in diet), although plasma potassium did not change in Japanese quail fed methylmercury (Hill and Soares 1984: trace, medium, and high in diet). After dietary mercury exposure at the upper limit of what we defined as sublethal concentrations (5 μg/g), white leghorn chickens exhibited decreased calcium content in their blood plasma (Lundholm 1995: 1 mg methylmercury/day for 50 days in diet). Blood calcium and glucose levels of free-living snowy egrets also decreased with elevated mercury, as did glucose levels of black-crowned night herons (Hoffman et al. 2009). No relationship with mercury was observed in plasma triglyceride levels, an indicator of migration stopover refueling rate, in northern waterthrushes (Seewagen 2013), nor with blood glucose levels or blood reserves of lipids, protein, or minerals of lesser scaup (Anteau et al. 2007; Pollock and Machin 2009).

9.4 Growth and Condition

Mercury exposure does not appear to strongly impede overall growth but may result in some biologically significant changes in size of body components. No changes were observed in overall body mass of dosed American kestrels (Fallacara et al. 2011b: trace, medium in diet), or common loons (Kenow et al. 2003: trace, medium in diet), tarsus length of dosed American kestrels or tarsus or primary feather length of free-living tree swallows (Wada et al. 2009). A study of three species of arctic-breeding shorebirds found no association between mercury level and body condition (Hargreaves et al. 2010). Mercury-related effects were not seen in body length or asymptotic mass of common loons (Kenow et al. 2003: trace, medium in diet), nor body mass, tarsus length, or wing chord of urban red-winged blackbird nestlings (Gillet and Seewagen 2014). However, common loons from lakes with low pH, which are more susceptible to mercury bioaccumulation, did have lower asymptotic mass (Kenow et al. 2003: trace, medium in diet). Dosed great egrets reduced their food intake and had lower weight index scores (Spalding et al. 2000b: trace, high force fed capsules). Similarly, young nestling tree swallows at sites with higher mercury also had a decreased linear growth rate in grams per day, although wing and tail feather growth were not affected (Longcore et al. 2007). In contrast, female common eiders with higher blood mercury arrived at breeding grounds in better condition, as defined by mass divided by head length, although mercury levels were generally low (Provencher et al. 2016). The growth of nestling Leach's storm-petrels, however, was not correlated with mercury burden (Pollet et al. 2017).

A multitude of other indices have been used to assess body condition after mercury exposure, ranging from size-corrected body mass to feather growth rate. These varied assays make categorizing the effect of mercury on condition difficult. Body weight, as well as liver and heart weight, decreased in surf scoters, and the liver-to-body weight ratio increased in ruddy ducks (Hoffman et al. 1998). Male American kestrels dosed with mercury also had lower body weight, but only in one treatment group (Albers et al. 2007: trace, low, medium, and high in diet). Meanwhile, no change in body or organ weight was detected in greater scaup (Hoffman et al. 1998), or in the body weight of bald eagles (Weech et al. 2006), or in body mass, body size, or organ mass of common eiders (Wayland et al. 2002). Great white herons dying of chronic disease, and with elevated mercury in tissues, had less body fat, although there was a statistical interaction with age (Spalding et al. 1994).

Studies with more complex measures of body condition provide an even more ambiguous picture. Atlantic puffins, common guillemots, razorbills, and black-legged kittiwakes with higher mercury had decreased body conditions in terms of liver-to-kidney mass (Fort et al. 2015). When defined as a ratio of mass to structural size, California clapper rails with higher mercury had lower body condition (Ackerman et al. 2012), but using the same metric, white ibises showed a nonsignificant trend of improved body condition with mercury level ($n = 19$) (Heath and Frederick 2005). Also, neither white ibis nor great egret chicks exhibited changes in

body condition as measured by the residuals obtained from regressing mass on tarsus length (Herring et al. 2014), and similarly, using residuals of mass regressed on skull length, snow petrels did not exhibit differences in body condition that related to mercury (Tartu et al. 2015). Acadian flycatcher "frame size," calculated using a PCA including wing chord and tarsus length regressed on mass, was not related to low level environmental mercury exposure (Rowse et al. 2014). Using body mass-to-body length and body mass-to-keel length as a measure of body condition resulted in a positive relationship between body condition and mercury in common mergansers (Kalisińska et al. 2010), but the interpretation of this result may not be straightforward given that birds acquiring more or better food might also acquire more mercury.

In terms of feather growth, common loons had increased flight feather asymmetry, but this was only the few birds with the highest environmental exposures, resulting in 40 μg/g mercury in feathers (Evers et al. 2008). Neither these loons, nor glossy ibises or double-crested cormorants, exhibited increased feather asymmetry when exposed to more moderate mercury levels (Clarkson et al. 2012). Composite fluctuating asymmetry, based on wing chord, tarsus, primary feather 10, rectrix feather 6, and, with the strongest correlation, rectrix feather 1 was related to mercury in Forster's terns, but not Caspian terns, American avocets, or black-necked stilts (Herring et al. 2017). However, daily feather growth as a nutritional condition index, measured through ptilochronology, had a negative relationship with mercury exposure in glossy ibises (Clarkson et al. 2012). In contrast, dosed European starlings exhibited increased molt rate (Carlson et al. 2014: low, medium in diet). These starlings also exerted less energy during takeoff than birds fed control diets. Belted kingfishers with higher mercury had brighter blue feathers, indicating decreased melanin content (White and Cristol 2014), and a consistent result was found in eastern bluebirds (McCullagh et al. 2015).

10 Conclusion

Our comprehensive review of existing studies shows that mercury can negatively impact nearly every aspect of avian physiology (Fig. 1a, b). Reproduction is by far the best-studied category of endpoints because of its immediate relation to fitness, and mercury exposure clearly reduces the number of surviving offspring in wild or captive birds. Reproductive phenology does not appear strongly altered by mercury, so the reduction in number of offspring may be a result of eggshell malformation, teratogenicity, or nestling and fledgling mortality. Meanwhile, chick behavior and parenting can be abnormal as the result of mercury exposure.

While offspring survival appears to be affected in the nest, longevity after leaving the nest does not decline detectably due to mercury exposure. Rather, exposed individuals face behavioral shifts away from higher energy activities. Hunting and foraging efficiency may be relatively resistant to the negative effects of mercury, with little consensus among published results, and similarly there is no clear pattern

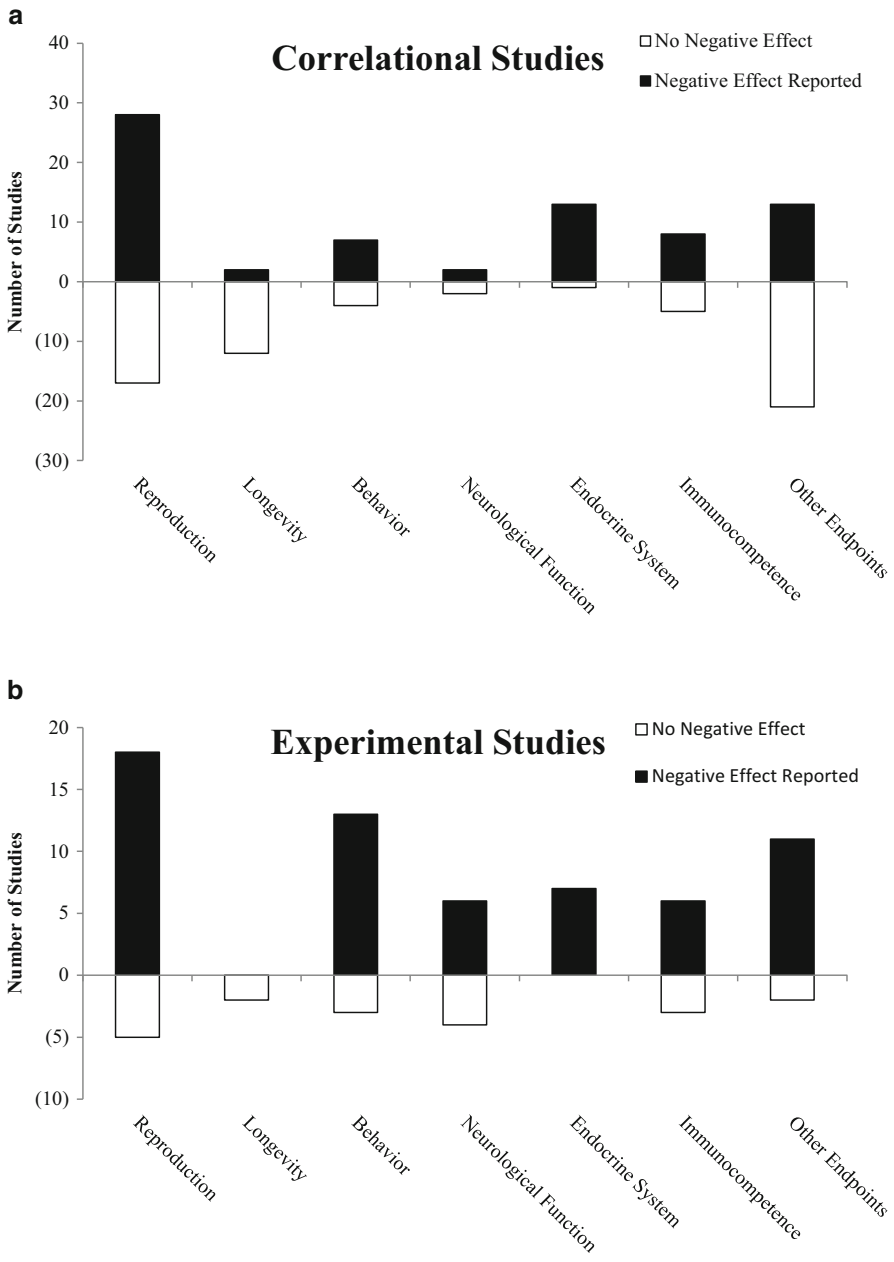

Fig. 1 Number of published reports of negative effects of mercury exposure (*black bars*) and number reporting no effects or positive effects (*white bars*) for (**a**) correlational field studies and (**b**) experimental dosing studies

regarding growth and body condition. However, immune function has frequently been found to be compromised, in addition to a number of changes in white blood cell counts.

Additional endpoints that consistently reveal the deleterious effects of mercury are oxidative stress and some aspects of neurological function, including axonal degeneration. But many important endpoints remain understudied. There is currently too little information to make conclusions regarding neurotransmitter function or metabolism. Many researchers have investigated various hormones, especially CORT and T, but together the results do not provide a coherent explanation for how mercury is impacting either organizational or activational aspects of the endocrine system. For most hormones, there has been little to no investigation, particularly with respect to different stages of the reproductive cycle.

A majority of studies have detected effects of mercury exposure on myriad avian endpoints. In fact, survivorship is the only endpoint for which we can conclude that mercury has no detectable effect, and even this conclusion must be tempered by logistical issues of statistical power to detect small differences. However, it is noteworthy that for many endpoints, even those for which there is much evidence for deleterious effects of mercury, there is disagreement between studies, with some studies showing no effects. By lumping studies into categories defined by endpoint, we are necessarily glossing over other explanatory factors, such as whether exposure was experimental dosing or correlational fieldwork, or the statistical power of each study, the variable sensitivity of different species of birds to mercury, or the magnitude of the mercury exposure. Each of these factors may have influenced the findings of a particular study, but our qualitative review does not facilitate the weighing of these other explanatory variables.

Field studies, in which environmentally exposed birds were sampled and compared by site or tissue mercury concentration, may be inherently biased towards negative results because of the possibility of resistance evolving in a population that has been historically exposed to a contaminant. Strong selection by a contaminant will leave only the resistant individuals in a population. Further, sampling methods that rely on competition among individuals, such as for nest sites where eggs or tissues are sampled, will further bias results towards the strongest competitors, which may also be the most resistant individuals in the population. Thus, one could argue that field studies will underestimate the effects of a contaminant such as mercury, because only the most robust populations and individuals are present to be sampled. Experimental dosing studies, in which individuals with no history of prior exposure are assigned randomly to treatment groups, should avoid this problem and might therefore be predicted to be more likely to detect effects of contaminants. However, there is a strong argument to be made that dosing studies performed in captivity will also underestimate effects of contaminants. This is based on the observation that challenges present in the lives of wild animals, such as learning and remembering the locations of food, avoiding predators, competing for scarce resources, migrating, or choosing an appropriate mate, are generally eliminated in laboratory studies. Thus, a contaminant like mercury, with well-established neurological and cognitive effects, may still have little detectable effect on endpoints

such as survival or reproduction in captive dosing studies, because most barriers to survival or reproduction that require memory and learning have been removed. In the absence of a strong basis for predicting whether field or captive studies will have greater likelihood of detecting effects of mercury, we simply note that a majority of studies detected effects of mercury on some endpoint, but laboratory studies were even more likely to detect effects of mercury than field studies (laboratory 91%, field: 72%, Fig. 1)

Another obvious difference between studies that could affect outcomes is that some had low statistical power due to small sample sizes. It is possible that endpoints with negative results in our review tended to come from the studies with smaller sample sizes. To examine this possibility, we plotted the sample sizes of each experimental dosing study to visualize the distribution of studies that detected or failed to detect effects of mercury, across all endpoints (Fig. 2). We excluded field studies because most included multiple years and study sites, complicating efforts to link sample sizes with significant results. Arbitrarily defining studies with small sample sizes as those with fewer than 20 individuals sampled in the smallest treatment group, we find that the probability of detecting some effect of mercury was similarly high across studies with small and larger sample sizes (small: 92% and larger: 80%). This suggests that the studies we reviewed generally exceeded the sample size necessary for reasonable statistical power to detect effects and thus sample size was not a determining factor in whether an effect of mercury was reported.

It is not surprising that different species, with their unique life histories and separate evolutionary paths, would differ in sensitivity to particular contaminants. To address this, we took advantage of the monumental study involving injections of methylmercury into eggs followed by artificial incubation, in which Heinz et al. (2009) categorized 23 species as having low, medium, or high sensitivity to mercury.

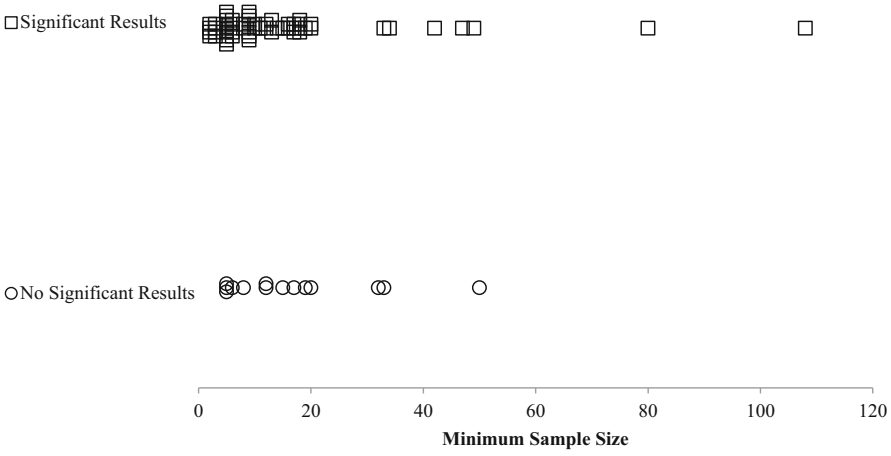

Fig. 2 Minimum sample size included in experimental reports finding significant impacts of mercury exposure (*squares*) or finding no impact from mercury exposure (*circles*)

Using our best guess, based on taxonomic similarity, we classified all species included in this review into the low, medium, and high sensitivity categories (Table 1). We then looked at all endpoints measured, whether in the same or different studies, for species in these three categories. If species sensitivity has an important effect on whether studies detected effects of mercury, there should be greater odds that a particular endpoint measured in a species with high sensitivity will show an effect of mercury exposure. Across all categories of sensitivity, approximately twice as many studied endpoints exhibited effects of mercury as were unaffected. This preponderance of results showing effects of mercury may be an effect of publication bias, or the intuition of researchers as to which endpoints are likely to be vulnerable to perturbation by mercury. But, a small effect of species sensitivity may be detectable here as well. Among 17 species with low sensitivity to mercury, the ratio of endpoints exhibiting effects of mercury to those failing to find effects was 1.80:1 (across 56 tested endpoints). For the 40 species in the medium sensitivity category, the ratio was 1.98:1 (across 61 tested endpoints), and for the 11 species with high sensitivity that increased to 2.07:1 (across 46 tested endpoints). The highest and lowest categories of species sensitivity differed by only 4% in the relative odds of detecting an effect of mercury, suggesting that species sensitivity is not a major factor in determining whether a studied endpoint will exhibit a detectable effect of mercury. However, because assignment of species sensitivity is a field still in its infancy, when considering the response to mercury of various endpoints discussed in this review, such as survival or endocrine function, the overall sensitivity of the species studied is a factor worth noting.

Finally, it seems intuitive that the intensity of exposure should be a good predictor of whether a particular study of mercury leads to a finding of deleterious effect. Unless most studies utilized exposures above the threshold for effects, or nonlinear responses are common, then studies including high exposures (dosing concentrations >2.0 μg/g) would be predicted to be more likely to produce evidence of deleterious effects of mercury than those with only trace (<0.5 μg/g), low (0.5–1.0 μg/g), or medium (1.0–2.0 μg/g) doses. In fact, 95% of the 21 studies without a high dosage produced evidence of effects of mercury, whereas only 86% of the 36 studies that included a high dose produced such results. Because there was little evidence of nonlinear effects of mercury (e.g., only 2 reports of hormesis) in the studies reviewed here, our conclusion is that in experimental studies, dosages selected were adequate to test the chosen endpoint, and thus variation in exposure is not likely to explain contrasting results for a particular endpoint.

Researchers should try to build on existing knowledge by employing previously studied biomarkers in new situations or species, or replicating previous studies with lower levels of mercury exposure. Very few studies have examined the effects of low mercury concentrations using experimental dosing, but these are likely the most relevant for understanding environmental exposures. There is a persistent gap in understanding between studies employing egg injection and those using maternal transfer. A few studies that calibrate the difference in embryotoxicity of these two means of exposure would open up vast opportunity for egg injection studies with more direct applicability in risk assessment and conservation. The most fertile

frontier for research on sublethal effects of mercury will be the careful study of disruption of hormonal pathways regulating reproduction. This will be important because it relates directly to the biggest fitness effect of mercury, reduction in breeding success, but it may also provide valuable crossover knowledge for understanding human health effects of mercury. The mechanisms for many of the results reported in this review remain nearly a complete mystery, and similarly, some important traits, such as molt and migration behavior, have received disproportionately little attention. To collect meaningful data on most of the endpoints that remain inconclusive, especially neurological and endocrine function, great care must be taken to design appropriate experiments that take into account stage of the life cycle. Studies done during molt, for example, may fail to produce the same effects as those outside of molt. Disruption of endocrine pathways may occur over just a few days of the breeding season or may be apparent in one sex but not the other. Studies that provide just a snapshot of the life cycle will be less valuable and possibly misleading. Above all, researchers must remember that dosing birds in captivity may underestimate effects because of the lack of relevant challenges faced by captives. Studies on long-exposed populations in the field will also underestimate the effects of mercury if tolerance or resistance has evolved due to selection. The most effective studies will be those that examine free-living birds which have been exposed to mercury experimentally—a daunting logistical challenge but not beyond the creative abilities of the many excellent researchers featured in this review.

11 Summary

We reviewed over 150 published articles in which researchers tested the effect of methylmercury exposure (<5 μg/g) on various avian endpoints. The vast majority of both field (72%) and laboratory (91%) studies found effects of mercury, across hundreds of physiological and behavioral endpoints and almost 70 different bird species. The majority of sublethal effects were subtle and some studies of similar endpoints have reached differing conclusions. Generally, though, there was little evidence that opposing conclusions were the result of differences in sample size, species sensitivity to mercury, or intensity of methylmercury exposure. Strong support exists in the literature for the conclusion that mercury exposure reduces reproductive output, compromises immune function, and causes avoidance of high-energy behaviors. For other endpoints, notably some measures of reproductive success, endocrine function, and body condition, there is weak or contradictory evidence of adverse effects and further study is required. There was no evidence that environmentally relevant mercury exposure affects longevity, but several of the sublethal effects identified likely do result in fitness reductions that could adversely impact populations. The most definitive conclusion to be drawn from this review is that to understand how mercury is affecting birds, more experiments are required that focus on a consistent set of physiological endpoints. Despite some knowledge

gaps, research on the sublethal effects of mercury has produced an overwhelming case that mercury harms individual birds in many ways, with effects on reproduction that could be responsible for population declines.

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Index

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