Public Health Risk Assessment and Risk Management for Safe Drinking Water

Steve E. Hrudey

THE GROUNDWATER PROJECT

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Dedication

This book is dedicated to my parents, Kay and Steve Hrudey, both first-generation Ukrainian Canadians raised during the depression in northeastern, rural Alberta, who imbued me with a commitment to hard work, learning, and public service. I also acknowledge my Imperial College mentor, Dr. Roger Perry for opening my eyes to the enormous scope and challenge of environmental health risk assessment and management. Finally, importantly, it is dedicated to my own family: my wife, Elizabeth, sons Steve and Peter, and daughter Jessica.

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The Groundwater Project Foreword

The United Nations (UN) - Water Summit on Groundwater held from 7 to 8 December 2022 at the UNESCO headquarters in Paris, France, concluded with a call for governments and other stakeholders to scale up their efforts to better manage groundwater. The intent of the call to action was to inform relevant discussions at the UN 2023 Water Conference held from 22 to 24 March 2023 at the UN headquarters in New York City. One of the required actions is *strengthening human and institutional capacity*, for which groundwater education is fundamental.

The 2024 World Water Day theme is *Water for Peace*, which focuses on the critical role water plays in the stability and prosperity of the world. The UN-Water website↗ states that *more than three billion people worldwide depend on water that crosses national borders*. There are 592 transboundary aquifers, yet most countries do not have an intergovernmental cooperation agreement in place for sharing and managing the aquifer. Moreover, while groundwater plays a key role in global stability and prosperity, it also makes up 99 percent of all liquid freshwater—accordingly, groundwater is at the heart of the freshwater crisis. *Groundwater is an invaluable resource*.

The Groundwater Project (GW-Project), a registered Canadian charity founded in 2018, is committed to advancement of groundwater education as a means to accelerate action related to our essential groundwater resources. We are dedicated to *making groundwater understandable* and, thus, enable *building the human capacity for sustainable development and management of groundwater.* To that end, the GW-Project creates and publishes high-quality books about *all-things-groundwater*, for all who want to learn about groundwater. Our books are unique. They synthesize knowledge, are rigorously peer reviewed and translated into many languages, and are free of charge. An important tenet of GW-Project books is a strong emphasis on visualization: Clear illustrations stimulate spatial and critical thinking. The GW-Project started publishing books in August 2020; by the end of 2023, we had published 44 original books and 58 translations. The books can be downloaded at gw-project.org↗.

The GW-Project embodies a new type of global educational endeavor made possible by the contributions of a dedicated international group of volunteer professionals from a broad range of disciplines. Academics, practitioners, and retirees contribute by writing and/or reviewing books aimed at diverse levels of readers including children, teenagers, undergraduate and graduate students, professionals in groundwater fields, and the general public. More than 1,000 dedicated volunteers from 70 countries and six continents are involved—and participation is growing. Revised editions of the books are published from time to time. Readers are invited to propose revisions.

We thank our sponsors for their ongoing financial support. Please consider donating to the GW-Project so we can continue to publish books free of charge.

The GW-Project Board of Directors, January 2024

Foreword

Many groundwater investigations around the world are conducted in response to known or feared contaminants in the subsurface. In fact, huge financial resources are allocated to groundwater contamination assessments in affluent countries; most of these assessments pertain in one way or another to issues addressed by this book, *Public Health Risk Assessment and Risk Management to Ensure Safe Drinking Water*↗.

Assessment of groundwater contamination is fraught with peril for water managers—more so than for surface waters because groundwater cannot be seen. Further, the origins and travel paths of the water consumed from any specific well are, commonly, unknown, or subject to speculation. For example, when pollutants are dumped onto or disposed of in the ground in the vicinity of a water well at any time in the past, there is concern that the well is polluted. Laboratory reports indicating contaminated well water, typically raise fears that the health of those drinking the water has been compromised. This book explains how can we determine whether there is a scientific basis for such fear.

Studies conducted over more than a century have led to standards or guidelines to judge the safety of water for human consumption. These judgments about safety derive from the results of risk assessment for which knowledge is framed as mathematical formulations drawn from the scientific disciplines of toxicology and epidemiology. However, judgments about drinking water risks are also embedded in a web of ideas about safety and harm. With exceptional clarity, the author explains drinking water risks in this context. For those whose work concerns groundwater quality and contamination, this book is the place to start to develop insight into how decisions are made by those responsible for water safety.

This book is the second Groundwater Project publication about risk and is complementary to the first, which was written by Edward McBean (2023): *Groundwater Quality and Examples of Risk Interpretation Procedures*↗. McBean's book is a general introduction of risk. It is not specific to drinking water standards/guidelines and how they are determined, in the context of risk exposure, management, and communication.

The author of this book, Dr. Steve Hrudey, was educated in public health engineering and spent most of his career as a professor in the Faculty of Medicine and Dentistry at the University of Alberta where he is now an emeritus faculty member. He is among the pioneers internationally in the establishment of the subject matter of this book as an advanced realm of study and practice.

John Cherry, The Groundwater Project Leader

Guelph, Ontario, Canada, November 2024

Preface

Groundwater professionals engaged in providing drinking water know that water-quality criteria are central to judging the suitability of a groundwater source for drinking water. While aesthetic characteristics (odor, color) are important, ensuring that the drinking-water source can be relied upon to be safe is the paramount concern.

However, determining what constitutes safe for human consumption turns out to be more challenging than might be assumed. The challenge of determining whether water is safe to drink is typically addressed by relying upon drinking-water guidelines and standards to judge the quality of the groundwater source. Those criteria are based upon human health-risk assessments to ensure that chemicals and microbial pathogens do not exceed intentionally cautious levels.

Although this book was solicited for a collection of books aimed at groundwater-relevant topics, the content is not limited to public health risk assessment of groundwater; the content addresses the quality and safety of all drinking water supplies.

Ultimately, health-risk assessments rely upon evidence generated by the public health sciences of epidemiology and toxicology. Those disciplines may not be included in the basic training of groundwater professionals. This book seeks to provide an overview of the strengths and limitations of the basic, public-health, scientific foundations along with an introductory-level explanation of how public health evidence is used in risk assessment to ultimately inform health-risk management to ensure safe drinking water.

To be clear, this book is not intended to be a primer for actually doing health risk assessments. Numerous guidance documents have been prepared by various regulatory and health agencies, some of which have been cited in Table 10 for the benefit of readers. Rather, this book seeks to provide a basis for groundwater professionals to be able to review, understand, and potentially critique health-risk assessments that may bear on a groundwater supply that the professional is engaged with. This approach is perhaps best reflected in the coverage of toxicology that is limited to an overview of relevant interpretive issues.

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- Dr. Ray Copes, Occupational and Environmental Health Division, Public Health Ontario, Toronto, Ontario; Adjunct Professor, Dalla Lana School of Public Health, University of Toronto;
- Dr. Steve Craik, Adjunct Associate Professor, Department of Civil and Environmental Engineering, University of Alberta;
- Dr. Steve McColl, Associate Professor Emeritus, School of Public Health Sciences, University of Waterloo, Waterloo, Ontario.

I appreciate the contributions of Elizabeth Hrudey for copyediting and Katerina Carastathis for document support. I am grateful to Amanda Sills and the formatting team of The Groundwater Project for their oversight and copyediting of this book. I thank Dr. Eileen Poeter (Professor Emeritus, Colorado School of Mines, Golden, Colorado, USA) for reviewing, editing, and producing of this book.

The sources of materials presented in figures and tables are acknowledged in the captions. Figures and tables without a citation to source are original to this book.

1 Introduction

1.1 What is Safe Drinking Water?

Readers may be surprised to learn that a regulatory definition of safe drinking water is neither commonly agreed upon nor explicitly stated. None of the US Safe Drinking Water Act (SDWA) from the US Environmental Protection Agency (US EPA, 2023a), the Canadian Guidelines for Drinking Water Quality (Government of Canada, 2023) nor the Ontario Safe Drinking Water Act (Government of Ontario, 2002) provide a definition of safe drinking water. The US EPA has shown a reluctance to define what is safe for environmental exposures, going as far as proposing a rule on April 4, 2023, under the US SDWA to prohibit water utilities from claiming their drinking water is safe in their obligatory consumer confidence reporting under the SDWA—despite the absence of any definition of "safe" in the Act, (US EPA, 2023b; Hrudey, 2024).

In contrast, the World Health Organization (WHO, 2022a, pp. 1–2) has attempted to define safe drinking water as:

> *"Safe drinking-water, as defined by the Guidelines, does not represent any significant risk to health over a lifetime of consumption, including different sensitivities that may occur between life stages. Those at greatest risk of waterborne disease are infants and young children, people who are debilitated and the elderly, especially when living under unsanitary conditions."*

There is merit in the WHO definition because the WHO Drinking Water Guidelines (WHO DWG) consist of more than a table of numerical contamination limits; the definition encompasses a comprehensive and well-documented risk-management approach in the form of drinking-water safety plans (WHO DWG Section 5.5; Hrudey et al., 2024a) that address the entire water system from raw water source to the consumer's tap and the operations and management of the entire system.

In a similar manner, the Australian Drinking Water Guidelines (ADWG), developed by the National Health and Medical Research Resource Council (NHMRC, 2023)—while not explicitly defined—describe safe drinking water as satisfying the quantitative criteria for contaminant levels and explain how this can be achieved by an operational, quality-management framework similar to the WHO water safety plan system. Finally, although the Ontario Safe Drinking Water Act—that was adopted to implement the recommendations of the Walkerton Inquiry (O'Connor, 2002a, 2002b) into the fatal drinking-water outbreak in Walkerton, Ontario, Canada—did not define safe drinking water, it mandated a Drinking Water Quality Management Standard that provides an operational, quality-management framework (Fuller et al., 2023).

The reasons for a reluctance to define safe drinking water, particularly in the US, are not explicitly documented but can be inferred from decades-long development of

quantitative, cancer-risk assessments beginning soon after the creation of the US EPA in 1972.

The most recent (October 2024) Guidelines for Canadian Drinking Water Quality (GCDWQ) do not provide a definition, and I could not find one in any provincial or territorial legislation. This is an important point because it touches on two of the central questions asked during the engagement process: What should be regulated, and to what standards? These questions required consideration of the threats to safe drinking water. In other words, what contaminants, and how much of them, might take water from safe to unsafe? Answering those questions effectively, however, calls for at least a conceptual definition of safe drinking water.

Within Canada, the second report of the Walkerton Inquiry (O'Connor, 2002b) provides an insightful perspective. The Walkerton tragedy occurred because drinking water was clearly unsafe. Defining unsafe water is clear enough. O'Connor (2002b, p. 5) stated that the goal of the recommendations was "*to ensure that Ontario's drinking water systems deliver water with a level of risk so negligible that a reasonable and informed person would feel safe drinking the water*."

This approach implies two obligations (Swain et al., 2006): first, to assure that risks are negligible; and second, to provide consumers with information about drinking-water risks. Having consumers justifiably feel safe about drinking water is not sufficient. Consumers need to be well and accurately informed about the residual nonzero risks.

For me, the notion that safety is defined by a risk being so small that one need not worry about it originated with a Yukon First Nations' councillor, Malcolm Dawson (as cited in Hrudey & Krewski, 1995). The goal of reducing drinking-water risks to a level that a reasonable and informed person would not worry about is a thoughtful and achievable objective for drinking water.

"Safe" does not mean zero risk. Such a simplistic concept cannot withstand serious scrutiny. The WHO (2022a, p. 1) definition refers to water that "*does not represent any significant risk to health over a lifetime of consumption*." This definition raises questions about what is "*significant*," but it is more realistic tan the untenable idea of zero risk. Swain and others (2006, p. 8) drew an analogy with an activity we all likely agree carries tangible risk—namely, driving.

> *"Most people would agree that going through a red light is unsafe—done often enough, it will result in a crash. On the other hand, we generally regard driving through a green light as safe, but it is not entirely free of risk. Accidents do happen to drivers obeying the lights: the goal of traffic planners, lawmakers and police is to minimize the risks of this happening."*

Another reality is that there is no sharp dividing line between safe and unsafe. Returning to the driving analogy, *"driving through a yellow light is not as safe as driving*

through a green, but it is much safer than running a red. The yellow represents a transition from a low-risk situation to one that is clearly unsafe" (Swain et al., 2006, p. 8).

1.2 The Nature of Contamination of Water

Ensuring safe drinking water is challenging because water comes as close to being a universal solvent as any substance we know. Even substances that are described as insoluble in water generally have some detectable level of solubility in water. The enormous range of concentrations of substances present in water is discussed in Section 2. Here we first look at how substances in water can be classified. This is depicted in Figure 1.

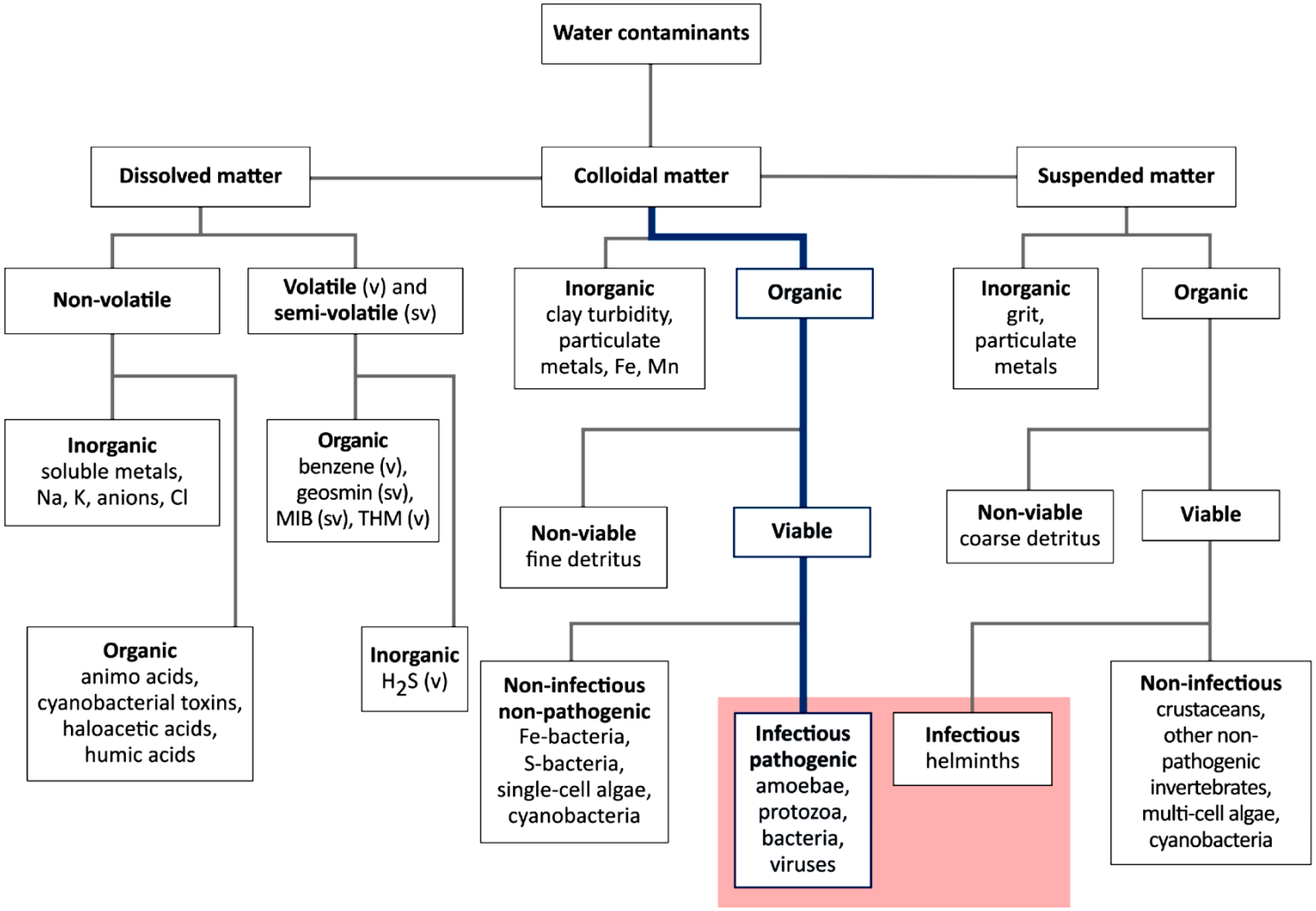

Figure 1 - Categorization and examples of substances (contaminants) as found in water with the blue line and pink box highlighting infectious organisms. (v = volatile, sv = semi-volatile; adapted from Hrudey, 2002).

1.3 How can Safe Drinking Water be Ensured?

The discussion in this book provides examples of some measures to achieve safe drinking water that are neither effective nor reliable. Experience has shown that the greatest threat to safe drinking water arise from microbial pathogens that pose a pervasive risk to any water supply. Measures for ensuring safe drinking water need to be effective and consistent for all situations, and that presents a difficult challenge. Recognizing this reality has led to the adoption of quality management systems, commonly recognized as drinking water safety plans, that are elaborated on in Section 5.5 (Hrudey et al., 2024b).

1.4 Do Aspects of Groundwater Affect Drinking Water Safety?

As noted in the Preface, this book's discussion of public health risk assessment is not unique to groundwater; it addresses the safety of all drinking water supplies. An excellent, comprehensive book that is freely available online and that is specific to ensuring the safety of groundwater supplies for drinking water was provided by Schmoll and others (2006). Its content is as valid today as when it was published and is recommended reading for groundwater professionals.

Reviews of drinking water outbreaks of infectious disease have been published (Hrudey & Hrudey, 2004, 2014, 2019, 2021). These reviews reveal that many of the most severe outbreaks, in terms of number and severity of cases of illness, have occurred with groundwater supplies, most notably with the fatal outbreaks in Walkerton, Ontario, Canada, in May 2000 (Hrudey & Hrudey, 2004, 2014) and Havelock North, New Zealand, in August 2016 (Graham et al., 2023). The details of the many factors contributing to these severe outbreaks reveal considerable complacency about the inherent safety of groundwater supplies. The contribution of complacency is apparent in the disproportionate fraction for more recent outbreaks that occur in ground water systems-18 of 23 outbreaks reported since 2010 (Hrudey & Hrudey, 2021). This may also reflect the reality that many smaller and potentially vulnerable water supplies are sourced from groundwater. Over-confidence in the safety of groundwater has led to some groundwater supplies being delivered without disinfection. There is also a body of evidence indicating that groundwater supplies may be particularly vulnerable to contamination by viruses because the absence of easily-used bacterial indicators (e.g., *E. coli*) does not ensure the absence of viruses (Abbaszadegan et al., 2003; Borchardt et al., 2007, 2012; Locas et al., 2008). Regarding chemical contaminants, those which are frequently associated with groundwater sources include organic solvents (e.g., trichloroethylene, tetrachlorethylene) and the inorganic agents such as: arsenic, fluoride, manganese, nitrate-nitrite, and uranium. These are addressed in Section 2.4.

2 Experience with Drinking-Water Contamination Affecting Human Health

2.1 History and Understanding of Safe Drinking Water

Drinking water has always been essential to human survival, but awareness that contamination of drinking water is a direct cause of human illness has been recognized and understood only since the mid-1800s. The history of how that recognition emerged has been documented by Hrudey and Hrudey (2004).

Interestingly, for the topic of this book, an early circumstance that provided a major contribution to this line of inquiry was a case of contaminated groundwater in the Soho district of London, England. At that time, drinking water was provided to households by local pumps or by a variety of water companies drawing from surface-water sources. Urban areas, like London, often experienced epidemics of infectious disease, most commonly typhoid or cholera. Two British physicians, John Snow (cholera) and William Budd (cholera and typhoid), developed theories about these diseases being communicable—in particular, via consumption of drinking water contaminated by human feces. Their pioneering efforts were remarkable developments. Bacteria, specifically microbial pathogens, had just been discovered but were not widely recognized for another 30 years. Likewise, most public health authorities favored inaccurate theories about these gastrointestinal diseases being transmitted by an airborne route, the so-called miasma theory.

Snow had been developing theories about waterborne transmission of cholera for decades. He published his theory in 1849, which was acknowledged by Budd in his own publication only a few months later, wherein Snow concluded (cited in Budd, 1849⁄2013; Smith, 2002, pp. 1567–1568; Hrudey & Hrudey, 2004):

> *"1. That the cause of malignant cholera is a living organism of distinct species.*
>
> *2. That this organism—in shapes hereafter to be described—is taken by the act of swallowing into the intestinal canal, and there becomes infinitely multiplied by the self-propagation, which is characteristic of living beings.*
>
> *3. That the presence and propagation of these organisms in the intestinal canal, and the action they exert, are the cause of the peculiar flux which is characteristic of malignant cholera; and which, taken with its consequences, immediate and remote, constitutes the disease.*
>
> *4. That the new organisms are developed only in the human intestine.*
>
> *5. That these organisms are disseminated through society, (1) in the air, in the form of impalpable particles; (2) in contact with articles of food; and (3) and principally, in the drinking-water of infected places."*

The case for proving the role of contaminated drinking water in causing cholera was greatly enhanced by an explosive 1854 cholera outbreak in Soho, London, that saw over 500

deaths in only ten days. Snow collected evidence about who suffered from cholera and where they obtained their drinking water to argue that the Broad Street pump was the source of the cholera outbreak. Snow famously convinced local officials to remove the handle from the pump and he has been historically credited, somewhat erroneously, with bringing that epidemic to an end. The pump handle was removed nine days after the initial onset of fatal cholera cases, but Snow's own evidence shows (Hrudey & Hrudey, 2004; Snow, 1855) the epidemic was largely over, likely because many fearful residents had vacated the afflicted neighborhood. This event is recognized by a model pump monument on the sidewalk outside the John Snow pub in Soho. A subsequent sanitary investigation found that the Broad Street well was subject to seepage from a nearby cesspool that had received a diaper from an infant who died from cholera (Cosgrove, 1909).

Although not as legendary for receiving public attention, follow-up by Snow in his study of cholera incidence among London residents receiving water drawn from the River Thames is widely acknowledged as demonstrating the potential of epidemiology in investigating causes of human disease. Snow was credited as becoming the father of epidemiology. He employed what is colloquially termed shoe leather epidemiology by interviewing residents and determining which utility company provided their water and whether any residents were infected by cholera. This effort was interesting (Table 1) because one company, Lambeth, drew Thames water upstream of the city (i.e., less faecally polluted), while the other—Southwark and Vauxhall—drew Thames water from central London, where it was faecally polluted.

Table 1 - London cholera deaths in 1854 in John Snow's grand natural experiment (Snow, 1855).

	Number of houses	Deaths from cholera	Deaths in each 10,000 houses
Southwark and Vauxhall Company	40,046	1,263	315
Lambeth Company	26,107	98	37
Rest of London	256,423	1,422	59

The cholera death rate per 10,000 houses reveals an 8.5 times higher cholera death rate among residents being served by polluted Thames River source water versus those served by less-polluted, upstream Thames River source water and 5.3 times higher than among residents in the rest of London. This pioneering example of comparing disease rates for humans with different environmental exposures is at the heart of epidemiology, the primary basis for obtaining human evidence about disease. Epidemiology as a means of gathering evidence is discussed in greater detail in Section 3.

Implementation of chlorination and filtration over succeeding decades has virtually eliminated typhoid and cholera in affluent nations (Hrudey & Hrudey, 2004). The US Centers for Disease Control and Prevention (CDC) reported that typhoid fever numbered approximately 100 cases per 100,000 people in 1900 but had decreased to 33.8 cases per 100,000 people by 1920 and 0.1 cases per 100,000 people by 2006, corresponding to 353 total cases, mostly among international travelers (CDC, 2023a). Cholera was common

domestically in the 1800s, but water-related spread of this disease has been eliminated by modern water- and sewage-treatment systems (CDC, 2023b).

Despite the foregoing achievements, major drinking-water disease outbreaks have continued to an unacceptable extent (Hrudey & Hrudey, 2004, 2014, 2019, 2021). The role of applying risk management to prevent unsafe drinking water outbreaks has been summarized (Hrudey et al., 2006). In 1993, Milwaukee, Wisconsin, USA, experienced a huge drinking-water outbreak of cryptosporidiosis, estimated to have caused over 400,000 cases (MacKenzie et al., 1994) and contributing to the deaths of more than 50 HIV patients over the following two years (Hoxie et al., 1997). This experience led to major rethinking of the requirements for water filtration for pathogen removal, because *Cryptosporidium* is chlorine-resistant (Hrudey & Hrudey, 2014).

In May 2000, the drinking-water outbreak in Walkerton, Ontario, Canada, contributed to more than seven deaths, 65 hospitalizations, and more than 2,000 cases of gastrointestinal illness (O'Connor, 2002a). This public health disaster led to a total restructuring of Ontario's drinking-water regulatory system to require a comprehensive quality-management system (O'Connor, 2002b, Fuller et al., 2023). A noteworthy feature of this outbreak with regard to the topic of this book is that the shallow well that was responsible for causing this outbreak had been thoroughly vulnerable to contamination for 22 years before the outbreak (Hrudey & Hrudey, 2014).

New Zealand experienced its own version of Walkerton in 2016 when a shallow-well drinking-water outbreak contributed to four deaths, 45 hospitalizations, and an estimated 5,500 cases of gastrointestinal illness (Gilpin et al., 2020; Graham et al., 2023; Hrudey, 2017). Even more recently, Askøy, Norway, experienced a fatal drinking-water outbreak in 2019 from an untreated spring source, contributing to two deaths, 76 hospitalizations, and more than 2,000 cases of gastrointestinal illness (Hyllestad et al., 2020; Mortensen et al., 2021; Paruch et al., 2020).

The foregoing discussion has mentioned only drinking water made unsafe by microbial pathogens, not by chemical contaminants. As further discussed in this book, pathogens are overwhelmingly responsible for drinking-water contamination that causes human illness. This is a result of the pervasive presence of pathogens that occur wherever humans, pets, livestock, or wildlife are found—that is, everywhere. Likewise, the capability of microbial pathogens to cause human illness via drinking-water exposure is certain, because there is consistent, reliable evidence about microbial pathogens causing human disease. By comparison, the incidence of chemical contaminants causing human illness through drinking-water exposure is far more site-specific and in most cases is uncertain with regard to causal evidence. Chemical contaminants with a high level of certainty of being able to cause human illness via drinking-water exposure are largely limited to arsenic, fluoride, selenium, nitrate-nitrite, and lead (Thompson et al., 2007).

The foregoing reality does not mean that human exposure to chemical contaminants cannot cause adverse health effects; they most certainly can, but the likelihood of such adverse health effects is entirely a function of the level of human exposure for each specific contaminant. The qualifier above, '*causing human illness via drinking-water exposure*' is a critical, key distinction that should not be overlooked. Although chemical contaminants covered by drinking water standards can be detected in drinking water in some cases, the levels at which they typically might be detected are normally insufficient to cause adverse human health effects with short-term exposures. Very low levels of some chemical contaminants can cause an aesthetic nuisance, such as odor.

Drinking-water limits for chemical contaminants are generally set based on precautionary limits for long-term (chronic) exposure. The evidence for such chronic health effects is very difficult to obtain and is, inevitably, highly uncertain; it can normally be estimated only through observational epidemiology, which is described in Section 3. Critical limitations to this approach to gathering evidence include: 1) the inability to obtain evidence about the actual level of individual exposure via drinking water for the entire period of chronic exposure; and 2) many of the outcomes hypothesized to be caused by chemical contaminants—such as various cancers—are common in society in comparison to the occurrence of waterborne disease. For example, 45 percent of Canadians experience some form of cancer in their lifetime based on thoroughly documented evidence (Canadian Cancer Society, 2023) while extremely inferential estimates suggest that only 0.012 percent of Ontario residents are hospitalized per year (less than 1% per lifetime) from waterborne illness (Greco et al., 2020).

Human epidemiological evidence is challenging to obtain because generally it must rely on historical, retrospective, exposure studies on specific, generally limited-sized population samples over long periods. This is particularly true for health outcomes such as cancer. Consequently, most chemical contaminant limits for drinking water are based on toxicological evidence obtained from experiments with laboratory animals (typically genetically defined species of rats, mice, or hamsters). The limitations of this approach to estimate adverse human health outcomes are manyfold and are discussed in Section 3.

2.2 Chemical Contaminants

Quantitative drinking-water quality criteria are dominated by chemical contaminants. The scope of that domination is illustrated for five major advanced jurisdictions in Box 1↴.

Box 1 illustrates how divergent the drinking-water limits are among these five major advanced jurisdictions. There are only 13 contaminants or contaminant groups that have limits among all five jurisdictions (antimony, arsenic, benzene, bromate, cadmium, chromium, copper, 1,2-dichloroethane, fluoride, lead, mercury, nitrate-nitrite, and selenium) of the 201 listed in Box 1. Likewise, there are 142 contaminants or contaminant

groups that have a limit in only one jurisdiction. In those cases where more than one jurisdiction has specified a quantitative value, these are seen to differ by a range of two-fold to 857-fold (hexachlorobutadiene); in several cases some jurisdictions found no need to propose a quantitative limit, while others did. For example, the WHO Drinking Water Guidelines (WHO, 2022a, p. 196–197 has evaluated another 19 agricultural chemicals that were not included among the guidelines values because they were judged to be "*unlikely to occur in drinking water*" or "*at concentrations well below concentrations of health concern*":

ammonia
chlorobenzilate
1,3-dichloropropane
dinoseb
formothion
hexachlorocyclohexanes
MCPB {4-(4-chloro-o-tolyloxy) butyric acid}
methanmidophos
methyl parathion
mirex
monocrotophos
2-phenylphenol
phorate
propoxur
pyridate
pyriproxyfen
quintozene
toxaphene
triazophos

Of these contaminants that WHO discounted a need for a quantitative limit, dinoseb and methyl parathion (parathion-methyl) has limits set by the ADWG (NHMRC, 2023) and toxaphene has a maximum contaminant level set under the US SDWA (US EPA, 2023).

A practical, statistical reality poses a serious problem for reliably detecting trace levels of chemical contaminants in drinking water (Hrudey & Leiss, 2003)—namely, the more infrequent the authentic occurrence of a given contaminant, the much greater the likelihood an intermittent apparent detection of that contaminant is a false positive for any number of reasons (including analytical error or contamination of the sample). This reality is demonstrated and explained in Sections 3 and 5.

The large numbers of chemical contaminants listed, and the diversity of listings and quantitative values set among the five advanced jurisdictions may become more understandable when the methods and assumptions used to set these values are explained in Sections 3, 4, and 5.

2.3 Microbial Pathogens

Microbial pathogens that are primarily relevant to drinking-water outbreaks in developed countries can be classified as bacteria, viruses, or protozoa. Documenting details about the characteristics of these pathogens is beyond the scope of this book, but several excellent literature resources collectively cover the details of all microbial pathogens that are relevant to drinking-water disease outbreaks and certainly those that are relevant to groundwater and public health (American Water Works Association, 2025; Cloete et al., 2004; Hrudey & Hrudey, 2004).

A key distinction between these microbial pathogens and the chemical contaminants described in Box 1 is that unlike most of those chemical contaminants, there is no uncertainty about the ability of specific microbial pathogens to cause human illness via drinking-water exposure. This is true because the microbial pathogens described have all been documented to have caused drinking-water disease outbreaks. By comparison, only a comparatively short list of chemical contaminants discussed in Box 1 have been found to have reasonably certain credible evidence of having caused human illness via drinking-water exposure (Thompson et al., 2007). Information about the significance of waterborne pathogens is provided in Tables 2, 3, and 4. Table 2 provides information on waterborne pathogens and their significance in water supplies. Table 3 provides the probability that a human will become infected by ingesting a single microbial pathogen. Table 4 provides data on drinking-water borne outbreaks in affluent countries between 1975 and 2019) that have been reported in the open literature.

Table 2 - Waterborne pathogens and their significance in water supplies (adapted from WHO, 2004).

Pathogen	Health significance	Persistence in water supplies	Resistance to chlorine	Relative infectivity[a]	Important animal source
Bacteria					
Campylobacter jejuni— C. coli	High	Moderate	Low	Moderate	Yes
Escherichia coli— pathogenic	High	Moderate	Low	Low	Yes
E. coli— enterohemorrhagic	High	Moderate	Low	High	Yes
Legionella spp.	High	Multiply	Low	Moderate	No
Salmonella typhi	High	Moderate	Low	Low	No
Other salmonellae	High	May multiply	Low	Low	Yes
Shigella spp.	High	Short	Low	Moderate	No
Vibrio cholerae	High	Short	Low	Low	No
Viruses					
Enteroviruses	High	Long	Moderate	High	No
Hepatitis A	High	Long	Moderate	High	No
Noroviruses and sapoviruses	High	Long	Moderate	High	Potentially
Rotavirus	High	Long	Moderate	High	No
Protozoa					
Cryptosporidium parvum	High	Long	High	High	Yes
Giardia lamblia	High	Moderate	High	High	Yes
Naegleria fowleri	High	May multiply	High	High	No
Toxoplasma gondii	High	Long	High	High	Yes

[a] Infectivity presumes that the microorganism is viable.

Table 3 - Probability that a human will become infected by ingesting a single microbial pathogen[a] (Hrudey & Hrudey, 2004; adapted from Hurst, 2002).

Type of microorganism	**Probability of infection per ingested microorganism[e]**
Bacteria[b]	
Enteric pathogenic bacteria (overall estimate)	0.00001
Viruses[c]	
Enteric pathogenic viruses (overall estimate)	0.5
Rotavirus	~1[f]
Protozoa[d]	
Cryptosporidium parvum	0.033
Giardia lamblia	0.1

[a] Probabilities were determined by volunteer feeding studies. The success of infection was determined by testing the sera of the volunteers before and after those individuals were dosed with viable microorganisms. The values listed in this table are medians based on data published by Hurst and others (1996). When values for the same genus or species of microorganism were available from more than a single study, an overall estimate was derived to represent that genus or species by calculating the median of the pertinent values. Likewise, overall estimates for any particular group (e.g., enteric pathogenic bacteria) of microorganisms were derived by calculating the median of the values available from studies in which members of that group had been examined.

[b] The number of bacterial organisms was determined by culture.

[c] The number of viruses was determined by an infectivity assay in cultured cells.

[d] The number of protozoa was determined as either cysts (for Giardia) or oocysts (for *Cryptosporidium*) by direct microscopic enumeration, assuming viability.

[e] Probability of infection associated with each microorganism ingested. This calculation is performed as 1/minimum infectious dose.

[f] For this virus type, the number of virus particles required to cause an infection of cultured cells is greater than the number of virus particles required to cause infection of a human. Thus, the value of the probability of a human developing an infection of cultured cells is greater than the number of virus particles required to cause infection of a human. Thus, the value of the probability of a human developing an infection from this virus type is higher than the measurement obtained by cell culture assay of the virus.

Table 4 - Drinking-water–borne outbreaks in affluent countries from 1975 to 2019 as reported in the open literature (Hrudey & Hrudey, 2004, 2019; Hrudey, 2021).

Pathogen	Number of outbreaks documented[a]	Year of latest reported outbreak	Laboratory confirmed cases[b]	Estimated cases—median[c]	Hospital admissions	Deaths[d]
Campylobacter and/or pathogenic *Escherichia coli*	29	2019	1,881	>47,000	266[e]	~29
Norovirus	28	2017	1,757	>43,000	11	NR[f]
Cryptosporidium	24	2013	3,683	>496,000	496	>50[g]
Giardia	15	2004	6,370	>57,000	NR[f]	NR[f]
Salmonella	2	2008	155	>1,950	35	8
Rotavirus	2	2012	394	>14,600	NR[f]	NR[f]
Shigella	2	2002	191	>1,900	NR[f]	NR[f]
Toxoplasma	1	1995	100	>5,300	NR[f]	NR[f]
HepatitisA	1	1980	36	>7,900	NR[f]	NR[f]
Pathogen—not identified	7	2012	1,326	>16,000	NR[f]	NR[f]

[a] Most likely underestimates of actual number of cases because of chronic underreporting of outbreaks and waterborne illness.

[b] Laboratory confirmed cases are typically a small fraction of total cases, because these typically require analysis of a faecal sample, something that is difficult for public health authorities to obtain voluntarily and often limited to hospitalized patients or those seeking medical attention; pathogen identification in faecal samples typically have a high false-negative rate.

[c] Most likely underestimates of actual number of cases because of underreporting and limitations of epidemiological investigation.

[d] Deaths are often caused in a contributory manner in vulnerable individuals.

[e] Includes at least 61 cases of haemolytic uremic syndrome, a serious kidney ailment that can cause kidney failure and/or chronic, lifelong illness.

[f] NR = not reported.

[g] Estimated number of fatalities among HIV-infected patients who were chronically infected by *Cryptosporidium* during the Milwaukee outbreak and died within two years of contracting cryptosporidiosis (Hoxie et al., 1997).

Ashbolt (2015) reports there are over 500 waterborne pathogens of potential health concern in drinking waters, as identified by the US EPA, but a much smaller list of pathogens is recognized as confirmed causes of drinking-water outbreaks in developed nations over the past 50 years as shown in Table 5.

Table 5 - Estimated health effects of foodborne pathogens in the United States for those that are also waterborne (Hrudey & Hrudey, 2004; Mead et al., 1999; Chin, 2000; Haas et al., 1999; Marshall et al., 1999; Hurst, 2002; Moe, 2002).

Pathogen	Faecal source	Incubation period (d)	Illness duration (d)	Total annual US cases (est.)	Fraction of foodborne cases[a] (%)	Hospitalization rate (%) (Mead et al., 1999)	Chronic conditions that may follow acute infection	Fatality rate (%)
Bacteria								
Campylobacter jejuni	Human or animal	1 to 10	2 to 5	2.4 million	80	3[b]–10	Reactive arthritis, Guillain-Barré syndrome	0.1
Escherichia coli O157:H7	Human or animal	3 to 8	1 to 12	73,000	85	13[b]–30	Haemolytic uremic syndrome (HUS), kidney damage	0.8
Escherichia coli enterotoxigenic	Human	0.5 to 5	3 to 5	79,000	70	0.5		0.01
Salmonella non-typhoidal	Human or animal	0.3 to 3	2 to 5	1.4 million	95	4[b]–22	Reactive arthritis, meningitis, endocarditis, pneumonia, osteomyelitis	0.8
Shigellae	Human	0.5 to 7	4 to 14	450,000	20	6[b]–14	Reactive arthritis, HUS kidney damage	0.2
Viruses								
Norovirus	Human	1 to 3	0.5 to 4	23 million	40	n.e.[c]		n.e.[c]
Rotavirus	Human	1 to 3	3 to 7	3.9 million	1	n.e.[c]		0.55[d]
Hepatitis A	Human	15 to 50	7 to months	83,000	5	13–28[d]	Reversible liver damage	0.1 to 0.3
Protozoa								
Cryptosporidium parvum	Human or animal	4 to 28	4 to 30	300,000	10	1[d]–15		0.5
Giardia lamblia	Human or animal	5 to 25	7 to >100	2 million	10	0.5[b]	Lactose intolerance, chronic joint pain	n.e.[c]
Toxoplasma gondii	Animal or meat	5 to 23	n.a.[e]	225,000	50	n.e.[c]	Intellectual disability, loss of vision, hearing impairment	n.e.[c]

[a] Waterborne disease fraction would be some small portion of 100 percent minus the estimated foodborne fraction. [b] Estimates from (Haas et al., 1999). [c] n.e. = not estimated; the methodology used by Mead and others (1999) did not allow estimates of hospitalization rate and case fatality rate to be estimated for these pathogens and no other estimates were found. [d] Estimates from (Hurst, 2002). [e] n.a. = not applicable; toxoplasmosis has an ill-defined duration because cysts of *T. gondii* can remain dormant in tissue for an entire lifetime.

Monitoring of individual, specific microbial pathogens is generally neither feasible nor informative because specific methods to detect pathogens are difficult to employ and actual pathogen numbers are typically low unless there is gross faecal contamination. This has created a need for so-called indicator organisms. Ashbolt and others (2001) discussed indicators of microbial water quality in detail, classifying them as:

- process indicators (a group of organisms for monitoring the effectiveness of a treatment process such as disinfection);
- faecal indicators (a group of organisms to indicate the presence of faecal contamination of water); or
- index/model organisms (groups of organisms indicative of pathogenic organisms, *E. coli* for bacterial enteric pathogens, and coliphages for human enteric viral pathogens).

Characteristics of an effective indicator organism are discussed by Hrudey and Hrudey (2004). Indicator organisms should show the following characteristics (Olivieri, 1982; Pipes, 1982; Payment et al., 2003):

- be detectable when the pathogenic microorganisms of concern are present but absent in uncontaminated water;
- be present in detectable numbers much greater than the pathogen(s) they are intended to indicate;
- survive in environmental conditions or water and wastewater treatment processes similar to the pathogens they are intended to indicate; and
- be feasible to isolate, identify, and enumerate.

Historically, coliform bacteria (total coliforms and faecal [thermotolerant] coliforms) have been used as faecal indicator bacteria. *Total coliforms* are now generally recognized as including free-living bacteria that substantially lowers their utility for being specific to faecal bacteria (Allen, M. J. et al., 2015). *Thermotolerant coliforms* (previously inaccurately named *faecal coliforms*) had emerged as a better choice, but in recent decades *E. coli* has become recognized as a much more specific indicator organism for faecal contamination (Edberg et al., 2000).

Several problems and misunderstandings that are associated with the use and meaning of common microbial indicators such as *E. coli* include:

- Failure to recognize that such indicators provide a precautionary warning about possible pathogen presence; however, a valid indication of faecal contamination does not guarantee that infective doses of pathogens are present.
- Such faecal microbial indicators have not been detected in some documented cases of drinking-water outbreaks involving protozoan pathogens such as *Cryptosporidium* and *Giardia* as well as viral pathogens such as norovirus.

- *E. coli* can be totally inactivated in chlorinated drinking water, while chlorine-resistant pathogens such as *Cryptosporidium* will not be affected and can remain infective.

Because of these limitations, research has continued toward identifying better indicator microorganisms including faecal streptococci, enterococci, various bacteriophages, and Bacterioides spp., as well as rapid advances in detection of pathogen-specific RNA or DNA (Motlagh & Yang, 2019). The latter methods have proven useful for microbial source tracking because they are very specific and highly sensitive. However, because they respond to genetic signals, they do not provide insight about whether the source of those genetic signals is from viable organisms.

Techniques have been developed that allow private well owners to test their water for indicator organisms, such as *E. coli*. Private well owners would be wise to check their well water annually as long as they are accurately informed that a positive detection indicates the likelihood that their well water has been contaminated with faecal matter and needs, at minimum to be disinfected. However, negative *E. coli* results do not ensure that the well water has not been contaminated by viral or protozoan pathogens.

As noted in the previous section, rare detection of indicator organisms in treated drinking water will be subject to a high proportion of false positives, a feature that is demonstrated and resulting problems explained in Section 5 (Hrudey & Leiss, 2003).

2.4 Chemical versus Microbial Risk in Drinking Water

Given the sheer number (a tiny fraction of the almost limitless number of possible chemicals) of chemical contaminants listed in drinking-water standards and guidelines, one may conclude that chemical contaminants in drinking water are more important than microbial pathogens. Chemical substances are found over an enormous numerical range in water. Discussions about contaminants and possible health effects are typically presented with concentrations of the contaminants in mass per unit volume of water. The impression of magnitude that such reporting can provide is elastic because reporting a concentration in pg/L will show a number that is 1,000 times larger than a concentration reported in mg/L. Figure 2 shows the comparative quantitative relationship of various concentrations of ethanol, a substance that is totally miscible in water, is commonly consumed by humans that can cause adverse health outcomes and can be lethal to humans. It illustrates the remarkably small concentration range from legal impairment to lethality for molecules of the common toxic substance ethanol in blood. In comparison, the number of ethanol molecules per liter of water needed to be detectable is 10^5-fold (100,000-fold) lower than the amount needed to legally impair a human. This example illustrates how our analytical capability to detect chemicals greatly exceeds our capability to judge health impacts at low levels.

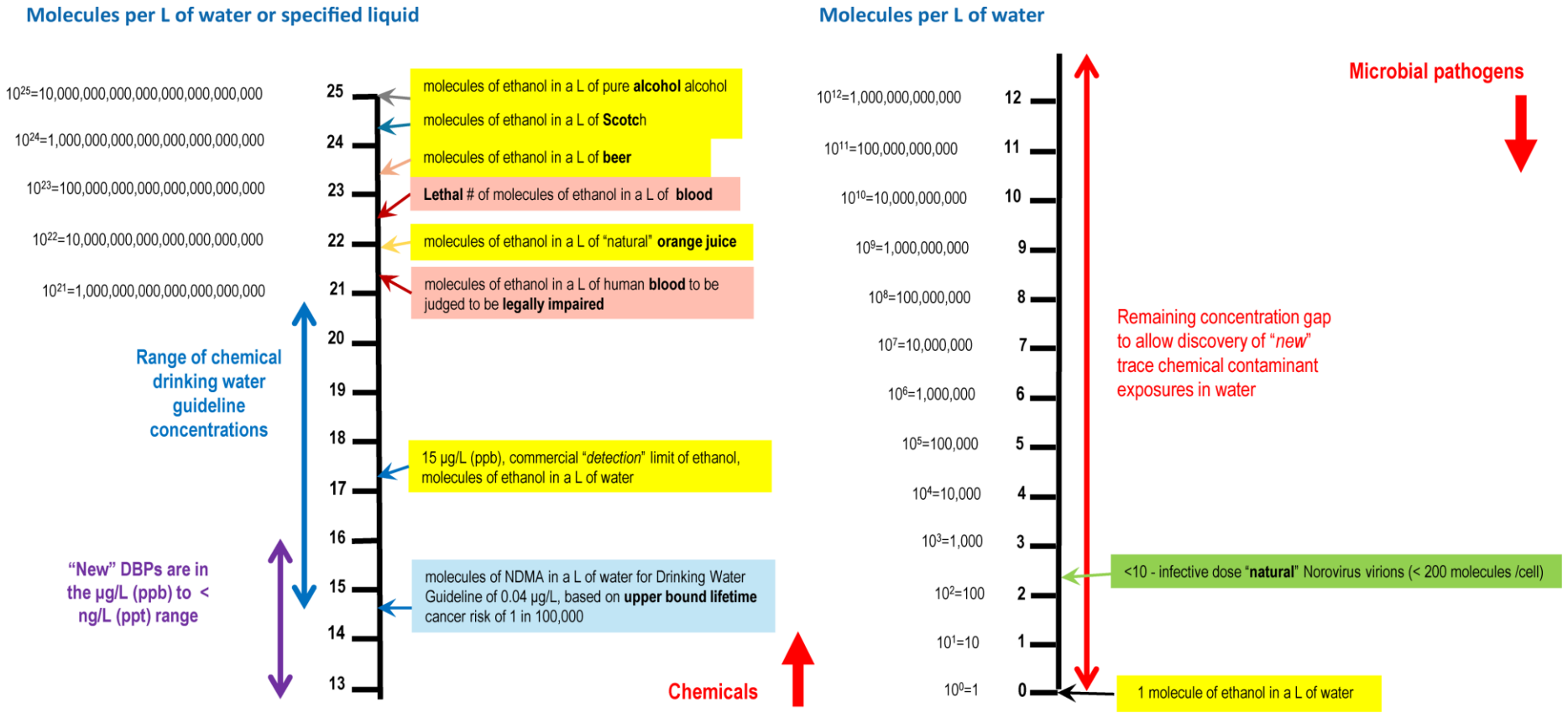

Figure 2 - The numerical range over which chemical substances are found in water, using a different perspective than is typically considered in discussions about water quality. Chemicals are presented as molecules per L, while the pathogen norovirus has <200 molecules per virion (individual virus)↗. Avogadro's Number (6.022×10^{23} molecules per g-mole) is used to convert toxic substance concentrations in water to numbers of molecules (using ethanol as a reference for toxic chemicals). Of course, the absolute quantity of toxic substances is not the primary determinant of a health outcome. What matters is how much exposure occurs in comparison with how much is necessary to cause the health outcome. The science that addresses toxic substances, toxicology, is discussed in Section 3, where an axiom of toxicology—the dose makes the poison—is explained. With the complexity of the content addressed in this figure, the descriptions provided are necessarily simplified and do not claim to describe all of the subtleties involved. DWG=drinking water guideline; DBP=disinfectant by-product; NDMA= N-nitrosodimethylamine.

Figure 2 also shows that the concentration of a drinking water contaminant (NDMA) deemed to pose less than a 1 in 100,000 lifetime risk of causing cancer is more than 1,000,000,000,000 times higher than the infective dose of the viral pathogen, Norovirus. Finally, there is a range of over 10,000,000,000 down to a single molecule of ethanol that represents the range for future detection of chemical water contaminants with improved water analysis.

Another noteworthy feature of microbial pathogens compared with chemical contaminants is that pathogens can reproduce, given favorable environmental conditions, to facilitate their delivery of adverse health impacts. The closest similar capability for chemical contaminants, which cannot reproduce themselves, might be initiator (DNA-reactive) chemical carcinogens that are able to initiate genetic changes in a normal human host cell to transform it into a tumorigenic cell that can ultimately reproduce into a malignant tumor (as outlined below).

A key feature of determining health effects at low level exposures, is whether there are thresholds in the dose-response relationship. This is elaborated on in Section 4. Although Albert (1994) noted that every statistician had their own model for low-dose risk assessment, the one-hit (i.e., single-hit) theory with linear, no-threshold extrapolation to zero dose came to dominate the early applications (1976 onwards) of quantitative carcinogen risk assessment. This approach arose from studies on the ability of X-ray radiation to induce mutations in fruit flies. Calabrese (2013, 2017) describes in detail how this concept—that was not demonstrated by evidence—was translated into a theoretical foundation for low-dose cancer risk assessment.

In its simplest terms, the premise that a chemical carcinogen could initiate a genetic mutation in a cell by a single molecular interaction was relevant because that cell could replicate and multiply that infinitesimal reaction into a cloned mass of damaged daughter cells, which could become a tumor. However, that development was not certain, because numerous events would need to occur. These events include that a single molecule of a DNA-reactive (genotoxic) carcinogen would need to reach a target tissue (i.e., not be excreted, metabolized, or otherwise inactivated), then it would need to cause a mutation in a gene that could lead to cancerous cell progeny, and finally it would need to avoid the damage being repaired by the phenomenal capacity of DNA repair enzymes (Koshland, 1994).

For comparison, a single microbial pathogen—although admittedly a more complex entity than a single molecule of a chemical carcinogen—also has the intrinsic capacity to replicate under the right circumstances and produce multiple infective clones. Table 3 lists the estimated probability that ingestion of a single microbial pathogen of a given type results in human illness. The experimental evidence for these estimates is superior to that adopted for the risk from chemical carcinogens.

2.4.1 Contaminants in Groundwater

Any of the contaminants delineated in Box 1, Figure 2, and in Sections 2.2 and 2.3 can occur in groundwater. However, some problem contaminants are more commonly encountered in groundwater. These are addressed in sections 2.4.2 and 2.4.3.

2.4.2 Chemical Contaminants in Groundwater

Several chemical contaminants recognized for occurrence in groundwater—arsenic, fluoride, selenium, nitrate-nitrite—have been identified as priority contaminants for their capability to cause adverse human health effects by means of drinking water exposure (Thompson et al., 2007). Others—manganese, trichloroethylene, tetrachloroethylene, and uranium—have been commonly identified as being problem groundwater contaminants. A brief summary of each of these contaminants is provided in this section.

Arsenic

Arsenic is a naturally occurring trace element (0.00021 percent of the Earth's crust)[1] in minerals that can release the element into groundwater by natural geological processes and cause locally elevated concentrations. All of the health-based guidelines listed in Box 1 for arsenic are consistent at 0.01 mg/L (Health Canada, 2006).

The basis for these criteria is that arsenic is generally accepted as a human carcinogen even though the specific mechanism of its carcinogenesis remains unknown. That ambiguity creates uncertainty about the most reliable way to predict cancer risk at low doses even though evidence of cancer causation via drinking water exposure at higher natural arsenic concentrations has been documented in locations such as Bangladesh and Taiwan.

Conventional municipal water treatment is not effective in removing arsenic to levels below 0.01 mg/L, meaning that water supply sources with higher concentrations require specialized treatment for arsenic removal.

Fluoride

Fluoride is a naturally occurring element (0.054 percent of the Earth's crust)[1] in minerals that can release the element into groundwater by natural geological processes and cause locally elevated concentrations. Fluoride is added intentionally to many drinking water supplies because of evidence indicating that it reduces dental cavities if present in controlled amounts (an optimal level is 0.7 mg/L).[2]

Health-based guidelines and standards listed in Box 1 for fluoride are mostly consistent at a maximum concentration of 1.5 mg/L, except for in the US SDWA at 4 mg/L. In 2022, an estimated 14.4 million Canadians (38.8 percent) were provided with fluoridated

[1] https://periodictable.com/Properties/A/CrustAbundance.an.html↗.
[2] http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/2008-fluoride-fluorure/index-eng.php↗.

public water supplies.[3] The basis for limiting fluoride in drinking water is the cosmetic effect of mild dental fluorosis, a staining of teeth that is judged to not be adverse to health at mild or very mild levels (Health Canada, 2010a). A severe adverse effect, occurring at higher levels of fluoride exposure, is skeletal fluorosis. Water treatment technologies, such as activated alumina, reverse osmosis, lime softening, and ion exchange can be used by public water suppliers to satisfy the health-based limit.

Manganese

Manganese is a naturally occurring element (0.11 percent of the Earth's crust)[4] in minerals that can release the element into groundwater by natural geological processes and cause locally elevated concentrations.

A health-based guideline of 0.12 mg/L and an aesthetic objective of 0.02 mg/L has been set in Canada (Health Canada, 2019a), as well as health-based guidelines of 0.08 mg/L (WHO, 2022a) and 0.5 mg/L (NHMRC, 2023) and aesthetic objectives of 0.02 mg/L (WHO, 2022a) and 0.1 mg/L (NHMRC, 2023). The latter are based on the propensity of soluble manganese being oxidized and precipitated to produce dark staining of laundry and plumbing fixtures.

The health-based limits are derived from experimental animal evidence suggestive of neurological effects in infants that is intended to be precautionary for human infants as a sensitive human receptor. Well-operated and optimized water treatment plants can achieve manganese concentrations of 0.015 mg/L (Health Canada, 2019a).

Nitrate-Nitrite

Nitrate and nitrite are naturally occurring products of microbial oxidation of nitrogen-containing compounds including proteins and ammonia found in organic matter and domestic wastewater. They are also soluble products of nitrogen-containing fertilizers, making these contaminants a concern for groundwater contamination in areas of intensive agriculture (Health Canada, 2013).

Health-based guidelines and standards delineated in Box 1 for nitrate in drinking water are consistent with some expressed as 50 mg/L nitrate, which is roughly equivalent to 10 mg/L (expressed as nitrate-nitrogen); and 3 mg/L for nitrite, which is roughly equivalent to 1 mg/L (expressed as nitrite-nitrogen). Historically, methaemoglobinemia (interference with the oxygen-carrying capability of haemoglobin) in bottle-fed infants has provided the quantitative basis for limiting human exposure to nitrate and nitrite in drinking water (Health Canada, 2013). Concerns also exist for thyroid gland function. Conventional municipal water treatment processes are not effective in removing these very soluble contaminants making specialized treatments (e.g., ion exchange, biological

[3] https://www.canada.ca/en/public-health/services/publications/healthy-living/community-water-fluoridation-across-canada.html#↗.
[4] https://periodictable.com/Properties/A/CrustAbundance.an.html↗.

denitrification, reverse osmosis, or electrodialysis) necessary for nitrate–nitrite removal (Health Canada, 2013).

Selenium

Selenium is a relatively rare, naturally occurring element (0.000005 percent in the Earth's crust)[5] that is widely distributed. Selenium can release into groundwater by natural geological processes and cause locally elevated concentrations.

A health-based guideline of 0.05 mg/L has been set in Canada (Health Canada, 2014) while in Australia it is set at 0.01 mg/L (NHMRC, 2023). Selenium is an essential nutrient because it is involved in several proteins and enzymes. A recommended minimum daily intake for selenium varies between 15 and 55 μg per day, depending on age. Selenium is not classifiable as to its carcinogenicity, but chronic exposure has been reported to include hair loss, nail and skin anomalies, tooth decay, and—in severe cases—disturbances of the nervous system.

Removal of selenium at the municipal level has not been studied, but some residential treatment devices have been certified for selenium removal.

Tetrachloroethylene

Tetrachloroethylene (also known as perchloroethylene and tetrachloroethene) is a volatile organic solvent widely used in dry cleaning, a variety of industrial cleaning operations, and as an organic synthesis intermediate (Health Canada, 2015). Tetrachloroethylene has posed a groundwater contaminant risk primarily as a result of spills and leaking storage tanks.

Health-based guidelines and standards listed in Box 1 for tetrachloroethylene in drinking water range from 0.005 to 0.1 mg/L. Health-based concerns have reflected observation of a variety of cancers in experimental animals, but human studies—including long-term occupational exposures—have been sufficiently inconsistent to cause health-based criteria to be set at 0.01 mg/L based on non-cancer adverse effects (Health Canada, 2015).

Conventional municipal water treatment technologies are not effective for removing tetrachloroethylene, meaning that specialized treatment such as packed tower aeration or granular-activated carbon adsorption are required to bring contaminated groundwater into compliance with health-based limits.

Trichloroethylene

Trichloroethylene (also known as TCE and trichloroethene) is a volatile organic solvent widely used in a variety of industrial cleaning and degreasing operations (Health

[5] Ibid.

Canada, (2005). TCE has posed a groundwater contaminant risk primarily as a result of spills and leaking storage tanks.

Health-based guidelines and standards listed in Box 1 for trichloroethylene in drinking water range from 0.005 to 0.008 mg/L. Health-based concerns have reflected observation of a variety of cancers in experimental animals including kidney and testicular tumors in rats and liver tumors in mice, but human cancer studies have been ambiguous leading to TCE being classified as "probably carcinogenic to humans." Drinking-water exposure, in addition to ingestion, includes inhalation and dermal absorption from showering and bathing.

Conventional municipal water treatment technologies are not effective for removing TCE, meaning that specialized treatment such as air stripping (i.e., packed tower aeration) or granular-activated carbon adsorption are required to bring contaminated groundwater into compliance with health-based limits.

Uranium

Uranium is widespread in natural minerals and has been identified as comprising 0.00018 percent of the Earth's crust.[6] Natural uranium is weakly radioactive and must be enriched to be used in nuclear applications.

Uranium is included in this discussion about contamination of groundwater because of its chemical toxicity (Health Canada, 2019b). Uranium has been assigned a health-based value of 0.02 to 0.03 mg/L for the guidelines and standards listed in Box 1. There is insufficient evidence to assign a cancer risk related to oral exposure to natural uranium in drinking water, but chronic exposure may cause an adverse effect in kidneys (Health Canada, 2019b).

Conventional municipal water treatment with coagulation/filtration, lime softening, or specialized treatment with ion exchange or reverse osmosis can achieve concentrations in treated water that comply with the health-based limits.

2.4.3 Microbial Contaminants in Groundwater

All classes of microbial contaminants (viruses, bacteria, and protozoa) have caused drinking water outbreaks in groundwater systems (Hrudey & Hrudey, 2004, 2014, 2019, 2021). However, given natural filtration that occurs to varying degrees and vulnerability to surface contamination, smaller pathogens (viruses) have a physical advantage to cause groundwater contamination compared with larger pathogens (protozoa).

Given the potential for microbial contamination to cause serious disease among drinking water consumers and the difficulty in routinely monitoring for pathogens, quantitative health-based criteria for pathogen concentrations are not set generically. Preventive measures can be achieved by setting a generic treatment-based standard (e.g., a

[6] Ibid.

generic disinfection requirement) or a site-specific standard based on quantitative microbial risk assessment: QMRA which is described in Section 4.3.6.

Because of the experience with enteric microorganism-contamination of drinking water causing serious illness in consumers, the preventive approach has been to specify that any detection of an enteric microorganism indicator (e.g., *E. coli*) in a 100-mL sample of treated water is judged to be unacceptable and requires immediate investigation and re-sampling. Detection of *E. coli* in a groundwater supply suggests that the source has been subject to faecal contamination (Health Canada, 2020). An unavoidable conclusion of a validated *E. coli* detection is that either 1) disinfection is not functioning for technical reasons because *E. coli* is so easily inactivated, or 2) the disinfection system has been overwhelmed by contamination that makes normal disinfectant dosing inadequate. The latter happened in the Walkerton contaminated-groundwater outbreak (Hrudey & Hrudey, 2014).

Treatment-based criterion based on application of QMRA to pursue population health-based targets have been developed for enteric pathogenic viruses to achieve a 4 $\log_{10}$ removal (i.e., 99.99 percent removal; Health Canada, 2019c) and for pathogenic protozoa to achieve a 3 $\log_{10}$ removal (i.e., 99.9 percent removal; Health Canada, 2019d).

3 The Basic Sciences for Assessing Public Health Risks

3.1 How We Learn What We Believe about Public Health

As scientific information has grown supra-exponentially over the past century, scientists are challenged to stay current with that growing body of information. This makes it more difficult to direct attention to the question of what techniques have been used to generate that information.

Comprehensive understanding of the techniques employed to understand environmental health risks is strikingly deficient in the education of environmental scientists. Public health specialists are generally better informed on some of the basic methodologies—mostly epidemiology, less so on toxicology—but public health specialists focusing on environmental health sciences are generally not well informed about the realities and limitations of evidence gathering in environmental science.

Thomas and Hrudey (1997) attempted to address the perceived deficiencies by analyzing the most tangible form of environmental health risk: risk of death. This book was based on a detailed analysis of Statistics Canada↗ vital statistics databases that document the reported causes of death for all Canadians for whom a death certificate was filed. This biostatistical information—termed *direct evidence* of the formally reported cause of death—is collected and summarized on an annual basis. In the case of Thomas and Hrudey (1997), this was done primarily for 1994 data (with summary evidence for 1991, 1992, 1993, and 1994 for comparison—the latest evidence available at the time of writing of their 1997 book).

As illustrated in Figure 3, two methodologies are used to address causality for an agent or hazard. They are explained in the toxicology section (3.2) and the epidemiology section (3.3). In both cases, the methodologies seek to establish the relationship, if any, between exposure to an agent or hazard and an adverse health outcome.

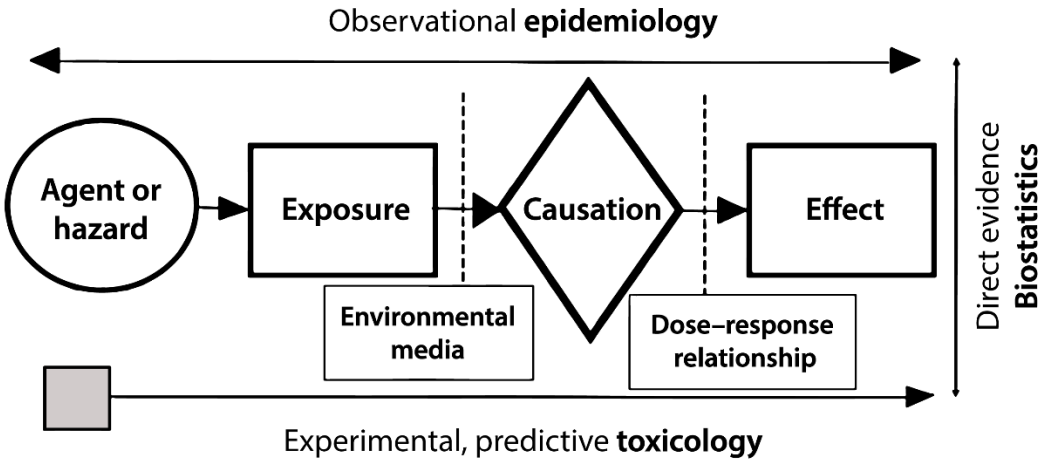

Figure 3 - Comparison of toxicology and epidemiology in assessing causation of environmental health risks (adapted from Thomas and Hrudey, 1997). Epidemiology is based on statistical correlation of the agent or hazard with an effect in humans, while toxicology is based on evidence of a connection between dosing of subjects with an effect observed in the dosed subjects.

Figure 3 is extremely simplified because causation of disease is invariably extremely complex. There is rarely a clear single cause for any specific adverse health outcome (Bonita et al., 2006). Causes are categorized as either sufficient or necessary. When an apparent cause inevitably initiates or ultimately yields the health outcome, it is categorized as *sufficient*. If the health outcome cannot occur in the absence of something, that something is considered a *necessary* cause. Exercise 1 is concerned with the causal chain for environmental health effects (adapted from Thomas & Hrudey, 1997).

For the purposes of risk assessment and judging causation, toxicology is normally prospective in nature—that is, agents suspected of causing adverse health effects are experimentally dosed in "appropriate" animal models. Determining health effects for humans based on animal models introduces inevitable uncertainty, as is elaborated on in Section 3.2. Also, there are uncertainty issues related to the nature of the exposure (experimental dosing), magnitude of exposure, and duration of exposure. Despite its limitations, the toxicology approach has the substantial advantage of allowing forward-looking research that might prevent adverse health effects without waiting for significant human health outcomes to occur. Such research also provides tangible insights about causal mechanisms because of the ability to perform autopsies on experimental animals.

Epidemiology normally involves the observation of human subjects to infer whether there is a statistically relevant relationship between an exposure to an agent or hazard and an adverse health outcome. This type of epidemiology is necessarily observational because bioethics preclude the possibility of performing an experiment with potentially harmful agents on human subjects. The time course of such studies can be retrospective, studying individuals who have experienced adverse health outcomes based on prior exposures to the agent under study by gathering evidence on those past exposures

for affected individuals along with "appropriate" control individuals who have not experienced the adverse effect. Ensuring that control individuals are appropriate is a major issue and source of uncertainty, as discussed in Section 3.3.

Likewise, such studies can be prospective—studying into the future—with a cohort of individuals who do not currently have the adverse outcome. During this forward-looking period, exposure to the agent(s) under study is monitored. When a sufficiently large number of individuals have experienced the adverse outcome, analysis is done to compare them to those who have not experienced the adverse outcome in relation to whether study individuals experienced exposures to the agents under study.

The time required for either retrospective or prospective epidemiologic studies depends on the nature of the agent causing the adverse effect(s), with acute effects involving a comparatively short period and chronic effects involving a longer period. Agents that involve outcomes such as cancer, typically require decades to emerge.

Uncertainty is a dominant feature of any investigation of environmental-health-risk issues. An adverse health effect caused by an environmental contaminant exposure can generally not be established with absolute certainty. Microbial disease infections are somewhat of an exception, because causation can be more confidently assigned according to Koch's postulates (Segre, 2013) published in 1890, which specified:

1) the microorganism must be found in diseased but not healthy individuals,
2) the microorganism must be cultured from the diseased individual,
3) inoculation of a healthy individual with the cultured microorganism must recapitulate the disease, and
4) the microorganism must be re-isolated from the inoculated, diseased individual and matched to the original microorganism.

These were originally established in the context of specifying whether a given microorganism is capable of causing human disease, a key consideration at that time, shortly after bacteria were first identified. This consideration is particularly relevant for postulates 3 and 4, which are not applicable to infections for microorganisms that are already known to be capable of causing human disease.

Advances in molecular biology have allowed for substantial verification of causation by demonstrating that infected individuals have been infected by specific genetic strains of a microorganism. In contrast, chemical contaminants can generally be detected at trace levels in most members of a population, so the mere presence of a chemical contaminant within the human body cannot establish causation.

The following discussion about Figure 4 applies primarily in reference to chemical contaminants. Key to the interpretation of this figure is the notation below the figure that indicates certain knowledge is depicted by gray shading while uncertainty is depicted by the white space surrounding the central gray region.

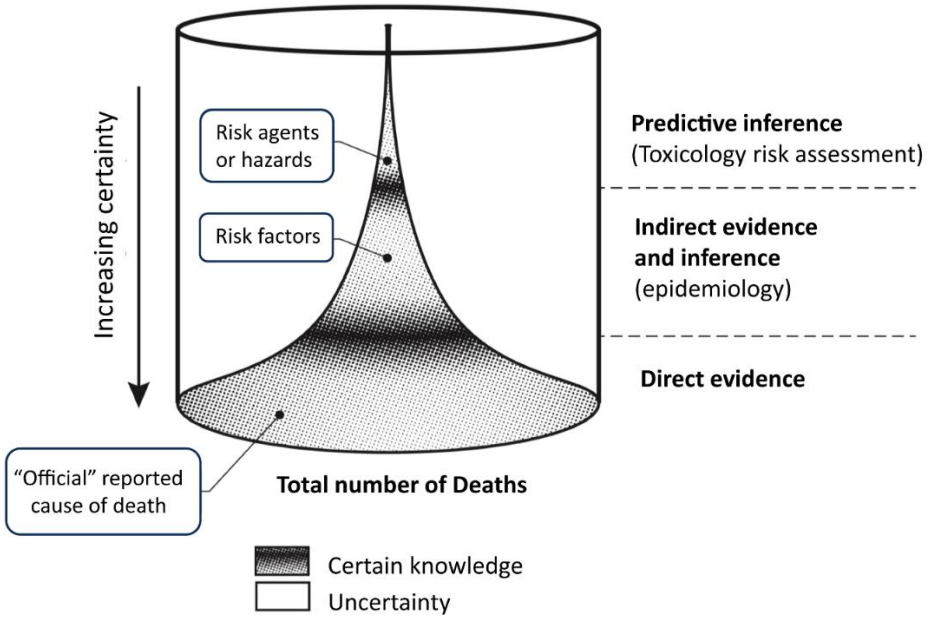

Figure 4 - Taxonomy of knowledge about externally-mediated, fatal, human-health outcomes (adapted from Thomas and Hrudey, 1997). Exercise 2 is concerned with the relationship between methods of gaining evidence about human-health risks and the comparative degree of uncertainty.

This figure is best interpreted by working from the bottom up. The base of the figure is the total number of deaths in a specified jurisdiction (province/state or nation) for a specified period (typically a year). The figure implies there is no uncertainty in these numbers, but—even though developed nations maintain a system of requiring death certificates to be filed by a medical practitioner for every death that is reported—there is always some small level of uncertainty. Deaths may rarely go unreported or be delayed in reporting, and residents of a given jurisdiction may die while away from their normal residence. These sources of uncertainty about the total number of deaths are trivial in relation to the inevitable uncertainty associated with information about cause of death found higher up in Figure 4. Unfortunately, although the total number of deaths has the least uncertainty, this statistic alone provides little useful insight for informing risk management because it provides no insights about cause of death.

Death certificates are required to specify a cause of death, so (in theory) direct information about cause is provided. In many jurisdictions, death-registration forms ask for an immediate cause of death, as well as antecedent causes, giving rise to the immediate cause with the underlying cause[7] listed last. There is also space to report other significant conditions contributing to death.

However, the evidence about cause of death available to the physician or the coroner completing the death certificate is highly variable regarding accuracy. For example, Harteloh and others (2010) studied the reliability of cause of death certification in the

[7] World Health Organization definition of underlying cause of death: "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." www.who.int/standards/classifications/classification-of-diseases/cause-of-death.

Netherlands and found with a study of 10,833 death certificates that overall agreement among four certificate coders on the underlying cause of death was 78 percent. Agreement was highest (> 90 percent) for major diseases like cancer and cardiac disease but was much lower (< 70 percent) for chronic diseases such as diabetes. If someone dies in a vehicle crash, suffering massive physical trauma, the possibility that the individual may have suffered a fatal stroke or cardiac arrest before impact could be determined only by an autopsy and, even then, not necessarily with confidence. In Canada from 2017 to 2021, only from 6.2 to 6.4 percent of total deaths (278,298 to 311,640) were subjected to autopsy.[8] Regardless, at higher levels in Figure 4, uncertainty in reported cause of death becomes substantial.

A massive database is assembled by government, vital-statistics agencies providing the compiled data on the underlying causes of death according to internationally defined categories. Currently, available data from Statistics Canada are based on the 10th revision of the International Classification of Disease (ICD-10).[9] The 11th revision (ICD-11)[10] was adopted by WHO in January 2022. The value of these data for pursuing environmental health risks is limited because data such as the number of various types of cancer deaths does not identify what factors caused any case of cancer. The fact that an estimated 45 percent of Canadians experience cancer in their lifetime and about 1 in 4—that is, 26 percent of males and 22 percent of females—die of cancer (Canadian Cancer Society, 2023) tells us almost nothing about the role of any environmental factors in causing those cancers.

Although epidemiology is discussed in more detail in Section 3.3, discussion of Figure 4 is needed here. For evidence about factors or agents that cause a specific disease leading to death, it is necessary to move further up in Figure 4 to evidence and inference arising from epidemiological estimates. The essence of epidemiological studies is the search for evidence of correlation between an exposure or risk factor and a disease outcome (Angell, 1996) for a sample population.

First, correlation can be evidence in support of causation, but correlation alone is not proof of causation. Likewise, findings for a sample population cannot necessarily be translated to the entire population. Because there is a wide range of study designs, quality of study implementation, and the size and representativeness of the study population, Figure 4 necessarily shows a wide and growing range of uncertainty as we move upwards. The strongest feature of epidemiologic studies is that they involve the study of humans, but this feature ethically limits environmental epidemiologic studies to being observational

[8] Statistics Canada - Deaths subject to autopsy. www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310071601↗.

[9] Statistics Canada - Deaths and age-specific mortality rates, by selected grouped causes. www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039201↗.

[10] WHO International Classification of Diseases 11th Revision - The global standard for diagnostic health information. https://icd.who.int/en↗.

rather than experimental—that is, human populations cannot be experimentally exposed to environmental risk factors.

At the top of Figure 4 is predictive inference—toxicological risk assessment (covered in Section 4)—where confident/certain knowledge can shrink to an almost-negligible amount and uncertainty dominates. This relationship arises because evidence about specific agents is obtained using toxicology experiments with animal models. While the ability of animal experiments to provide insights into causation (e.g., control over the agent dosing administered, exposure conditions, ability to perform autopsies on all subjects) is substantial, the uncertainties associated with using practical-sized experimental populations are challenging, such as extrapolating from high experimental doses to low environmental exposures for humans, and extrapolating from animal physiology to human physiology.

These factors invariably introduce enormous uncertainty, at least as much as depicted in Figure 4, despite the advantages associated with using controlled experiments. At its most basic level, humans are not rats, mice, or hamsters, so the animal-to-human extrapolation is a serious limitation. Likewise, biological mechanisms of toxic substances are inevitably dose specific, meaning that toxic outcomes observed at experimental high doses do not necessarily operate in the same manner at low dose—or even at all. There is a growing trend toward reducing the use of animal toxicology experiments that result in even greater reliance on inference.

Despite all these factors, the anticipatory ability of toxicological risk assessment to attempt to predict harm—without reliance on allowing that harm to occur in a human population, so that it can be studied by epidemiology—is a major advantage of the predictive toxicology approach. That said, when it comes to environmental health-risk assessment, evidence from this inevitably uncertain approach is far more rapidly accessible and available than epidemiologic evidence.

A useful concept in considering studies in toxicology and epidemiology is the broad categorization into hypothesis-generating studies versus hypothesis-testing studies. Given the complexity of environmental health risks, there is a need to explore possible, subtle, and diverse adverse outcomes from environmental exposures. Hypothesis-generating studies are necessary to be able to explore the possibility of toxic effects from the myriad possible environmental exposures. Such studies seek evidence that supports the possibility of a causal relationship between an exposure and an adverse outcome; however, because of their exploratory nature they should not be treated as definitive nor even likely proof of a causal relationship.

Hypothesis-testing studies are much more demanding in scope and design. They seek to test, rigorously, the evidence for causation to eliminate, as far as possible, simple correlation of exposure and adverse outcome as opposed to coherent and consistent evidence of a causal relationship. The latter inevitably requires multiple lines of evidence

and consistent replication in different populations and exposure scenarios. As might be expected, there are results from many more hypothesis-generating studies than there are from hypothesis-testing studies.

3.2 Toxicology for Risk Assessment

Toxicology is regarded as the basic science of poisons. It involves a wide range of activities and research related to the adverse health effects of substances on humans and animals. The Society of Toxicology (2024)[11] defines this field as *"the study of the adverse effects of chemical, physical, or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects."* However, bioethics do not condone experimental toxicology research on humans, so the aspects of environmentally relevant toxicology involving humans are inherently limited to retrospective studies of unintended contaminant exposures.

Risk assessment seeks to be forward-looking for predicting adverse outcomes, but, as noted, toxicology evidence from human contaminant exposures is necessarily retrospective (i.e., studying contaminant exposures that have happened) and, to be statistically meaningful, human health risk assessment preferably relies on epidemiological studies that are discussed in Section 3.3. The discussion in this section focuses on applications of toxicology that are directly useful for risk assessment, which for environmental health risks generally means toxicology applied to animal experimental research.

A fundamental tenet of toxicology is attributed to Paracelsus[12] (Klaassen, 2019): *"What is there that is not poison? All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison."* Reality establishes the critical role of dose–response assessment, a process that is discussed in more detail in Sections 3.2.1 and 4.3.4 along with other key elements involved with toxicological risk assessment discussed in additional sections of this book (i.e., Section 4.3.1, *Issue/Problem Definition*; Section 4.3.2, *Hazard Identification*; Section 4.3.3, *Dose–Response Assessment*; Section 4.3.4, *Exposure Assessment*; and Section 4.3.5, *Risk Characterization)*.

A key meaning of this tenet is that the term toxic substance is essentially an oxymoron despite its ubiquitous and even legislative[13] usage. All substances—including essential ones such as oxygen, carbon dioxide, and water—are harmful to human health if the exposure (dose) is high enough. Normally in environmental health risk scenarios (i.e.,

[11] www.toxicology.org/about/relevance.asp↗.

[12] Paracelsus (1493–1541) was a Swiss physician who challenged conventional thinking among medical practitioners.

[13] "*The Toxic Substances Control Act of 1976 provides [the US] EPA with authority to require reporting, record-keeping and testing requirements, and restrictions relating to chemical substances and/or mixtures. Certain substances are generally excluded from TSCA, including, among others, food, drugs, cosmetics and pesticides*." https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act↗.

other than accidental exposures from spills or other high-level chemical releases), exposures are very low, making it possible (if not likely), that effective doses are too small to exert an observable toxic effect. As exposures trend progressively lower, uncertainty about the resulting nature and degree of adverse effects necessarily increases. This inevitable trend leads to the depiction shown in Figure 4, even before considering the enormous increase in uncertainty that arises with evidence from animal experiments needing to be interpreted for human health risk.

Toxicology relies on both science and art. The science involves controlled experiments and observation. The art involves interpretation of evidence, inference, and prediction. The science of toxicology is critically important—the usefulness of toxicological art depends upon the quality of the scientific evidence. The inference and prediction, despite being fundamentally reliant upon the scientific/biomedical evidence, are judgmental and are not equivalent to direct experimental validation.

3.2.1 Understanding Some Fundamental Aspects of Toxicology

Toxicology is a wide-ranging, very complex field of study—much too complex to review in detail for the purposes of this overview of public health risk assessment. This discussion focuses on a few concepts that need to be understood to ensure that risk assessment predictions are sensible and realistic.

There are many possible toxic effects in humans including cancer, reproductive effects (fertility, birth defects), neurotoxic effects, and immune system effects. These adverse effects can be reflected as damage to specific organs like the liver, lungs, kidney, heart, or circulatory system. Such effects can be generally categorized as a) immediate or delayed, b) reversible or irreversible, and c) local or systemic.

Immediate (acute) toxic effects are revealed a short time after exposure, which may be limited to a single exposure in contrast to *delayed* effects that are not evident for some period of time after exposure (chronic) and may be the result of repeated, lower-level, toxic exposures. Cancer is a very complex toxic outcome that is generally considered to be a multiple-stage process that typically occurs over many years to decades.

Toxic effects in an organism occur via molecular level chemical reactions or physical processes, and are considered adverse if these result in an adverse outcome for the organism: otherwise, these processes are not fundamentally different from the myriad other molecular processes that occur in a living organism.

Living organisms have varying degrees of reserve capacity to tolerate or repair molecular level damage caused by a toxic agent. Consequently, exposure and molecular level damage does not necessarily translate to adverse effects at the organism level.

The Paracelsus quote noted in Section 3.2 can be paraphrased as, "*the dose makes the poison.*" What needs to be adequately understood is the enormous range over which different substances can exert a toxic effect (e.g., Figure 2). Toxic doses are typically

quantified in terms of the mass quantity administered per kg of body mass. The median toxic dose is the dose sufficient to cause the toxic effect in half of an exposed population. For lethality, this is termed the "*median lethal dose*" or the LD_{50}. The enormous range of toxicity is illustrated by noting examples such as the LD_{50} of ethyl alcohol which is ≈10,000 mg/kg and contrasting it with botulinum toxin that has an LD_{50} of 0.00001 mg/kg. This is a billion-fold (1,000,000,000x) range of lethal toxic potency.

The premise that a toxic substance can exert its toxic effect independent of the route of exposure (e.g., ingestion, inhalation, dermal absorption, subcutaneous, intravenous) is not accurate. A simple illustration that the route of dosage is critical to the outcome is the fact that the highly lethal botulinum toxin is marketed as Botox® Cosmetic for reducing facial wrinkles by subcutaneous injection whereby it paralyzes facial muscles that cause wrinkles to form.

The premise that a substance that is toxic by one mechanism will necessarily be toxic by any other mechanism is also inaccurate. Toxic effects occur at the molecular level by interfering with vital biological functions. Such toxic effects are specific and cannot be generalized to other mechanisms. Perhaps the only toxic substance exposure that can be considered to have more generalized toxicity are those that emit forms of ionizing radiation. This type of toxicity has been described as being like microscopic bullets because ionizing radiation provides a stream of high-energy particles that cause indiscriminate damage to molecules in the pathway of that stream.

Because ethics preclude conducting toxicity experiments in humans, toxicology in support of health risk assessment largely relies on experiments with laboratory animals that must be interpreted for their relevance and applicability to humans. On one level, humans are animals, but there are many important anatomical and physiological differences between laboratory animals (typically rodents) and humans that make direct translation of toxic outcomes challenging. Additionally, a societal trend questions the ethics of animal experimentation and recognizes the many limitations of past testing practices (Aktar, 2015). Krewski and others (2009) summarize a major report on a strategy and visions for future toxicology studies that was prepared for the US Environmental Protection Agency and National Research Council (NRC, 2007).

3.2.2 Types of Toxicology Studies

As noted earlier, toxicology studies for human health risk assessment are generally performed on laboratory animals. The many different types of study are classified according to the objectives being pursued (enHealth, 2012a) as follows.

1) Short-term toxicity is addressed by *acute toxicity studies* including oral, dermal, inhalation, eye irritation, and skin irritation. A typical outcome for individual substances is determination of the LD_{50}.

2) *Sub-chronic studies* are longer but still relatively short-term, with repeated doses—typically for 90 days in rodents.
3) *Chronic studies* are long-term to represent most of the animal's life span: 1.5 years in mice and 2 years in rats. For example, cancer bioassays are generally required to be full chronic studies. These animal bioassays have been the primary basis for classifying substances as carcinogenic, but the limitations of these bioassays have been increasingly recognized (i.e., reliance on small numbers of animals—typically 50 animals per dose level—and limited range of dosage—typically less than 3 dose levels including the maximum tolerated dose, MTD). These are considered in more detail in Section 4.3.5, *Risk Characterization*.
4) *Reproductive toxicity testing* is very challenging as it seeks to characterize adverse effects on the reproductive performance of a species for both female and male reproductive systems. These may include multi-generatational studies.
5) *Developmental toxicity studies* address one or more of the range of possible adverse *in utero* outcomes including death, malformations, functional deficits, and developmental delays.
6) *Genotoxic studies* address the capability of a toxic agent to cause gene or chromosomal mutations. A wide and growing array of study types address this capability to cause mutations. There is a consensus that conclusions about this capability requires a data set comprising multiple tests to reach conclusions about whether a given agent is classified as a mutagen.

As the science of toxicology advances, additional endpoints and test procedures continue to be developed and implemented.

3.2.3 Absorption, Distribution, Metabolism and Excretion (ADME)

Generally, health risk assessments address human exposure by estimating concentrations of toxic agents in air, food, or water, then adopting representative consumptions rates for breathing, food consumption, or drinking water consumption. This approach is a major simplification of human exposure because adverse outcomes vary widely as a result of differences in the physical/chemical properties of the agent, the exposure scenario, animal species, and—for humans—inter-individual variability.

The fate, behavior, and consequences of exposure to a toxic agent depends on a sequence of processes: absorption, distribution, metabolism, and excretion. These processes determine an overall behavioral characteristic of a toxic agent termed *bioavailability* (Hrudey et al., 1996) that has been defined many different ways. For our purposes, bioavailability can be defined for a toxic agent as the extent and rate at which it absorbs into the systemic circulation (blood stream) in its unaltered (parent) form at the point of external exposure. A toxic agent with no bioavailability will not reach any internal organ, thus cannot exert an adverse effect.

Absorption is the critical first stage necessary for any internal effect to occur. This entails crossing one of the barriers to internal uptake: the skin, the lining of the gut, or membranes of the respiratory tract. Absorption depends upon the physical/chemical characteristics of the toxic agent as well as the nature of the exposed species or variability in an exposed individual human.

Distribution is the extent to which a toxic agent reaches target sites within the body. This is primarily a function of the circulatory system and the distribution of blood flow to various internal organs. There are two important barriers to the distribution of substances in the blood stream: the placenta, which controls the passage of substances in the maternal circulation to the developing fetus, and the blood-brain barrier, which controls the passage of substances from human circulation to the brain.

Metabolism is the bio-transformation of parent agents into modified chemicals by various biochemical reactions within the body. The blood stream carries absorbed substances to the liver, which is the major site for metabolism of foreign substances; however, the skin, lungs, intestines, kidneys, and other internal sites also metabolize foreign substances. Metabolism may detoxify substances or make them more amenable to the final element of ADME: excretion. However, metabolism may also make substances more toxic by making them more reactive.

Excretion is a vital process for eliminating parent or metabolized toxic agents from the body, primarily through urine, faeces, or exhaled air. Metabolism that renders agents more water soluble increases the ability to excrete agents via urine. Once agents are excreted, they can no longer exert toxic effects on the organism from which they are excreted.

3.2.4 Threshold and Non-threshold Toxic Agents

One of the most controversial, and often misunderstood, concept in toxicological risk assessment concerns whether an agent is believed to exhibit a threshold below which no adverse effect is believed to occur. This topic is controversial because of the need to adopt a precautionary approach for controlling environmental exposures to toxic agents to minimal levels when there is considerable uncertainty about many aspects of the risk posed by a toxic agent. The difficulty arises because of the enormous range of potential exposures (Figure 2) to toxic agents, often orders of magnitude below detectable concentrations, making it impossible to obtain experimental evidence to confirm or refute whether a meaningful threshold exists.

The major use of a non-threshold assumption in risk assessment has been for agents considered to be carcinogens. This topic is considered in more detail in Section 4.3.5, *Risk Characterization*. In the earliest days of evaluating carcinogens in environmental risk assessment in the 1970s, anything classified as a carcinogen was assumed to exhibit no threshold. However, decades of research have demonstrated that many substances classified as carcinogens have been shown to cause tumors by a mechanism that has a

demonstrable threshold. The most relevant for drinking water is the case of chloroform, which is the dominant trihalomethane (THM) disinfection by-product (DBP). The chloroform story is elaborated in Box 2 which was originally prepared for enHealth (2002) and has been expanded for this book. A consequence of the misunderstanding about chloroform's status as a carcinogen in drinking water is discussed by Bull and others (2012).

Arsenic in drinking water, while accepted by consensus as a cancer risk, remains controversial about whether or not it exhibits a threshold (Lamm et al., 2021; Schmidt, 2014; Tsuji et al., 2021).

The inability to demonstrate a threshold experimentally has led to claims that no level of exposure is safe—that is, there is no threshold (Hrudey 2024). This case was illustrated by considering the case of lead exposure in children, which is certainly a valid concern for drinking water that can be contaminated by lead from the past practice of using lead pipes for residential water service connections and from corrosion of plumbing fixtures made of lead-containing alloys. Hrudey (2024, p. 52) illustrated the problem by noting that the US Centers for Disease Control and Prevention (CDC) correctly stated that "*No safe blood level in children has been identified*" as distinct from the US Environmental Protection Agency claim that "*There is no safe level of lead*." The distinction is explained by noting that the current CDC detection limit for lead in blood is 0.07 μg/dL, which corresponds to 3,500,000,000,000 atoms of lead per dL—more than sufficiently removed from zero to allow for a non-detectable threshold concentration of lead to exist.

3.2.5 Interpreting Toxicology Studies - Weight of Evidence

Interpreting the ultimate meaning of a set of toxicological data is inevitably a challenging exercise in judgement (enHealth, 2012). The body of toxicological evidence for a given agent will inevitably come from a diverse range of sources that will not be consistent in substantive details (e.g., species tested, dose range, means of dose delivery, timing, and so on). Toxicological evidence can be judged for various specific elements to allow conclusions about those elements of the evidence, with conclusions ranging from clear evidence, some evidence, equivocal evidence, to no evidence. The weight of evidence seeks a more comprehensive assessment integrating all available data.

A meaningful assessment of the weight of evidence for a body of toxicological data must address the state of knowledge about the mode or mechanism of action (MOA), even if only to conclude there is inadequate or no evidence about the MOA. A body of evidence that provides no useful insight about the MOA is inherently limited for drawing meaningful conclusions about the risk that is posed by that contaminant.

3.3 Epidemiology for Risk Assessment

Elaborating on the introduction provided in Section 2.1, Snow's innovations led to him being widely regarded as the father of epidemiology (Vinten-Johansen et al., 2003). Snow, along with William Budd, revealed the relationship of cholera to drinking water during periodic outbreaks in the mid-1800s. Snow earned the title of father of epidemiology by performing detailed studies about the location of residences and the sources of their drinking water being associated with contamination by human sewage leading to infection by pathogenic bacteria causing cholera.

Despite many practical limitations, epidemiology has grown to be regarded as the basic science of public health. This is somewhat ironic, because Snow's use of epidemiologic methods was able to prove that the prevailing views about the causes of cholera among public health authorities of that time were largely incorrect. Epidemiology can be credited as the primary, gold standard for evaluating the ability of medicines and medical interventions to control or resolve adverse health conditions in humans, primarily by means of randomized, double-blind clinical trials. Likewise, the ability of various microbial pathogens to cause human disease has been shown with epidemiologic evidence and confirmed by biomedical evidence.

Because epidemiology is obtained from studies on humans, it is potentially the most relevant and influential means of obtaining evidence about human health risks. However, it is likely the technique least well understood by natural scientists. Consequently, epidemiology is discussed here in greater detail than toxicology was discussed in Section 3.2.

A particularly controversial issue with groundwater contamination has been cancer clusters – situations where an apparent excess of cancer cases occurs in a geographic location that is near a potential source of contamination. Such occurrences can be very influential with affected populations and such stories have been popularized with major movies - A Civil Action (1998, John Travolta), Erin Brockovich (2000, Julia Roberts), Dark Waters (2019, Mark Ruffalo). Cancer cluster is not defined in the exhaustive Dictionary of Epidemiology – 6th ed. (Porta, 2016) but cancer clusters would be considered descriptive, hypothesis-generating studies, at best, in the hierarchy of epidemiology capable of supporting causation (Section 3.3.5).

A cancer cluster, which can be documented to varying degrees of rigor, will normally be limited in the total number of cancer cases involved. This factor alone will limit the ability of epidemiologic methods to establish meaningful statistical analysis. Far more relevant is the normally limited to non-existent evidence of exposure (amount and duration) to plausible levels of contaminants that might explain cancer causation (Saunders et al., 1997). Although such clusters often drive health concerns among potentially exposed residents, cancer clusters provide comparatively weak to non-existent epidemiological evidence to support causation. Hole & Lamont (1992), public health cancer researchers,

studied 26 local government districts in western Scotland for occurrence of 34 types of cancer and concluded: "*In the absence of a prior hypothesis, small area analysis of epidemiological data for periods of less than 10 years will almost always give misleading results for all but the most common diseases*." Goodman and others (2012) "*reviewed 428 investigations evaluating 567 cancers of concern. An increase in incidence was confirmed for 72 (13%) cancer categories (including the category "all sites"). Three of those were linked (with variable degree of certainty) to hypothesized exposures, but only one investigation revealed a clear cause. Conclusions: It is fair to state that extensive efforts to find causes of community cancer clusters have not been successful. There are fundamental shortcomings to our current methods of investigating community cancer clusters*."

Provided that cancer clusters are correctly recognized as hypothesis-generating evidence at best, they can be helpful, but they do not provide plausible evidence of environmental disease causation without major additional study to obtain credible evidence of plausible exposure levels and duration to recognized carcinogenic agents.

The ability of epidemiologic methods to identify and confirm adverse human health effects from low level environmental exposures to chemicals is far less certain than has been achieved for microbial pathogens. Taubes (1995) summarized the challenges in a special news feature in the journal *Science* titled *Epidemiology Faces Its Limits*. This article was motivated by the frequency of conflicting accounts based on news reports citing epidemiologic studies on numerous environmental, pharmaceutical, lifestyle, and other low-level health risks. Taubes interviewed several leading US epidemiologists and quoted them extensively. His article provoked six letters, but only one of them—signed by eight epidemiologists (Willett et al., 1995)—was specifically critical of the article, mostly for failing to emphasize the merits and value of epidemiology for revealing risk factors for human illness. Notably, the Taubes article has been cited 634 times (according to Web of Science, as of October 13, 2024), which indicates a high level of interest in the topic and issues raised. A sample of papers that have cited Taubes (1995) is provided in Table 6 to illustrate the diversity of commentary about the limitations and strengths of epidemiology.

Table 6 - A sample of publications since January 2000 that have cited Taubes (1995) about the limits of epidemiology.

Citation	Title
Adami et al., 2011	Toxicology and epidemiology: Improving science with a framework for combining toxicological and epidemiological evidence to establish causal inference
Allen, R. W., et al., 2015	Randomized controlled trials in environmental health research: Unethical or underutilized
Aschner et al., 2016	Upholding science in health, safety and environmental risk assessments and regulations
Berry, 2016	The dangers of hazards
Boffetta et al., 2008	False-positive results in cancer epidemiology: A plea for epistemological modesty
Bracken, 2009	Why are so many epidemiology associations inflated or wrong? Does poorly conducted animal research suggest implausible hypotheses?
Bracken, 2001	Commentary: Toward systematic reviews in epidemiology
Calabrese et al., 2015	Cancer risk assessment: Optimizing human health through linear dose–response models
Demetriou et al., 2012	From testing to estimation: The problem of false positives in the context of carcinogen evaluation in the IARC monographs
Gori, 2001	The costly illusion of regulating unknowable risks
Grimes, 2015	Epidemiologic research with administrative databases: Red herrings, false alarms and pseudo-epidemics
Guzelian et al., 2005	Evidence-based toxicology: A framework for causation
Hrudey, 2012	Epidemiological inference and evidence on disinfection by-products and human health
Ioannidis, 2005	Why most published research findings are false
Lagiou et al., 2005	Causality in cancer epidemiology
Lesko et al., 2020	The epidemiologic toolbox: Identifying, honing, and using the right tools for the job
McLellan, 2012	Role of science and judgment in setting national ambient air quality standards: How low is low enough?
Nachman et al., 2011	Leveraging epidemiology to improve risk assessment
Niederdeppe et al., 2008	Cancer news coverage and information seeking
Niederdeppe et al., 2010	Does local television news cultivate fatalistic beliefs about cancer prevention?
Peng et al., 2006	Reproducible epidemiologic research
Rier, 2004	Audience, consequence, and journal selection in toxic-exposure epidemiology
Ruden & Hanssson, 2008	Evidence-based toxicology: “Sound science” in new disguise
Shrader-Frechette, 2007	Relative risk and methodological rules for causal inferences
Shrenk, 2018	What is the meaning of ‘A compound is carcinogenic’?
Sinclair & Fairley, 2000	Drinking water and endemic gastrointestinal illness
Smith & Ebrahim, 2001	Epidemiology—Is it time to call it a day?
Swaen et al., 2001	False positive outcomes and design characteristics in occupational cancer epidemiology studies
Vandenbroucke et al., 2007	Strengthening the reporting of observational studies in epidemiology (STROBE) – Explanation and elaboration
Vanderweele & Ding, 2017	Sensitivity analysis in observational research: Introducing the E-value
Wakeford, 2015	Association and causation in epidemiology: Half a century since the publication of Bradford Hill’s interpretational guidance
Weed, 2006	Commentary: Rethinking epidemiology
Weed & McKeown, 2003	Science and social responsibility in public health
Wilson, 2012	The development of risk analysis: A personal perspective
Young, 2017	Air quality environmental epidemiology studies are unreliable

The titles in Table 6 alone demonstrate the range of views about the ability of epidemiology to establish causation. There is no serious question that epidemiology has

been vital in establishing the causes of a wide range of human disease, and nothing in this book should be interpreted to be claiming otherwise. That said, there is a valid question about whether observational epidemiology (the only viable approach for virtually all environmental exposure scenarios) is constrained as an approach for accurately establishing causation at comparatively low exposure levels.

These are three of the major points about epidemiology that most likely provide grounds for consensus among those who have critically considered the issues.

1) Results of single or even a small number of studies should not be accepted as reliable proof of an association between an exposure and a health outcome.
2) Epidemiology fundamentally can reveal a statistical association, but establishing causation requires additional lines of evidence such as toxicological evidence of applicable physiological mode(s) of action.
3) The strength (relative risk [RR] or odds ratio [OR], elaborated on in Section 3.3.6) of an association is critical, such that lower levels of strength of association—for example, RR < 2 to 4—should not be regarded as credible on their own.

Finally, an overriding, fundamental reality that limits the capability of epidemiological investigation of any kind to reveal evidence for very low exposure scenarios is explained in Section 5.2 (Hrudey & Leiss, 2003).

The major controversies about epidemiologic evidence for low (such as environmental) health-risk exposures have been introduced here to stimulate the interest of readers who may not be familiar with epidemiology. A more thorough examination of epidemiology as a foundation to understanding these complex issues associated with drinking water has been provided in Hrudey (2012). This section is included herein to explain the background for challenging health-risk issues concerning disinfection by-products (DBPs) in drinking water, an issue that in 2024 has been present for 50 years, having first been raised in 1974, but which remains a controversy for some in public health (Hrudey & Fawell, 2015; Hrudey et al., 2015a; Cotruvo et al., 2020).

A summary of the key issues relating to uncertainty with respect to epidemiological evidence is drawn from the more detailed discussion by Hrudey (2012) and provided in the following subsections.

Exercise 3 explores the difference between statistical inference and causal inference. Exercise 4 is concerned with inferring the consequences of specific human health risks.

3.3.1 Correlation of Outcome with Exposure

As noted in the introduction to Section 3.3, epidemiology is capable of demonstrating correlation between an exposure and an outcome (e.g., a disease or adverse effect) on its own, but the goal of demonstrating causation requires additional coincidental evidence. This is discussed further in subsections 3.3.5 and 3.3.6. The simplest depiction of the epidemiology approach is illustrated in Figure 5, where data are dichotomized into exposure or no exposure (to the hypothesized cause) and outcome (disease or no outcome). Realistically, exposure is not an all-or-nothing variable such that simplified applications of this approach require the data to be dichotomized by the data analysts. Although continuous statistical models can also be, and often are used, the premises for understanding epidemiologic data are most easily appreciated by considering the simplified 2×2, dichotomous model.

Figure 5 - Basic rationale for epidemiologic investigation - the 2×2 table (letters a, b, c, and d represent the number of study subjects reporting in that outcome quadrant). A harmful association implies that exposure causes disease. Preventive association implies exposure prevents disease.

If the data for this simplified model show that subjects who are exposed and experience the disease plus those who are unexposed and do not experience the disease exceed the sum of those who are not exposed but experience the disease plus those who are exposed but do not experience the disease, the result suggests a potentially harmful association (correlation) between exposure and disease.

Two important features should be apparent from the rationale employed to analyze epidemiologic data.

First, if the data characterizing the exposure are weak, no matter the quality of everything else that is done, the reliability (causal meaning) of the determined association is weak.

Second, for this rationale to be meaningful, the status of each individual with respect to exposure and disease must be known with confidence. This is critical, because some designs for epidemiologic studies have their exposure assessment done only at the population, rather than the individual level, making it impossible to know whether the individuals in the studied population who provide the data for those with disease were in fact exposed to the causal factor under study.

This latter reality is a fundamental weakness of population rather than individualized exposure assessment studies. Very few individualized exposure assessment

studies have been completed on drinking water health risks and that consideration is elaborated on in Section 3.3.5, *Experimental Studies*, where study designs are described.

3.3.2 Confounding

Confound, the verb, has been defined as "*to confuse and very much surprise someone, so that they are unable to explain or deal with a situation*."[14] Although "confounding" has a more detailed and explicit definition for epidemiology, the element of creating confusion in this more generic definition is certainly relevant to our discussion (e.g., as suggested in Figure 5). A more formal definition specific to epidemiology is "*Loosely, the distortion of a measure of the effect of an exposure*" (Porta, 2016, p. 12).

The issue for epidemiologic studies seeking a causal association is that many factors inevitably contribute to health outcomes. These will always include age and gender, but countless other factors may influence individual outcomes from exposures to environmental health risks. The classic, dominant confounding factor for contaminant exposures is smoking status, given the epidemiologically proven causal relationship between smoking status and numerous types of cancer as well as a variety of other adverse health outcomes. If the exercise of classifying and analyzing data on exposures and outcomes takes no account of such dominant confounding factors, such as smoking status, it is entirely possible that observed associations are caused by an uneven distribution of the confounding factors among the populations, exposed and unexposed to the cause under study.

An example that has been problematic is that studies of alcohol consumption have been confounded by the reality that smokers tend to be higher consumers of alcohol. As well, any epidemiologic study that fails to consider the age and gender of subjects is not credible. Yet, there are published environmental epidemiology studies that have not been able to account for a critically important confounder such as smoking status for a variety of reasons.

The best epidemiologic studies will seek to identify as many possible confounding factors as possible to avoid the seriously misleading outcomes that can arise if major confounding variables are overlooked. If confounders are identified, the normal practice is to try to account for them by adjusting the observed associations using mathematical adjustments to the data to account for the confounding factor(s).

While this is a reasonable approach, when dealing with a strong confounder such as smoking status, mathematical adjustment can only be as good as the validity of the formula adopted for making the adjustment. Such formulas are themselves not necessarily known to be accurate and fully applicable to the study population. This means there may well be residual, but unknown, confounding factors in the results reported. Despite the best efforts of researchers, all possible confounding variables cannot be known for any

[14] https://dictionary.cambridge.org/dictionary/english/confound↗.

particular study. In the most powerful experimental study designs (Section 3.3.5) sample populations are randomized to reduce the impact of unknown confounders.

3.3.3 Bias

Bias is a broader concept that can include confounding. A formal definition of bias (Porta, 2016, p. 9) is:

> *"Systematic deviation of results or inferences from truth. Processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from truth."*

Ways in which deviation from the truth can occur include the following:

1) Systematic variation of measurements or estimates from the true values.
2) Variation of statistical estimates (means, rates, measures of association, and so on) from their true values as a result of statistical artifacts or flaws in study design, conduct, or analysis.
3) Deviation of inferences from truth as a result of conceptual or methodological flaws in study conception or design, data collection, or the analysis or interpretation of results.
4) A tendency of procedures (in study design, data collection, analysis, interpretation, review, or publication) to yield results or conclusions that depart from the truth.
5) Prejudice leading to the conscious or unconscious selection of research hypotheses or procedures that depart from the truth in a particular direction or to one-sidedness in the interpretation of results.
6) Bias is also the result of imperfect study design and/or inaccurate data collection or reporting rather than just a failure to correct for confounding variables.

Bias can be minimized only through careful study design and implementation, aided by performance of pilot studies seeking to identify possible sources of inaccuracy in data collection. Inevitably, because epidemiologic studies are necessarily performed on a select sample of a population, there will always be sampling errors and other random errors. These sources of random (not systematic) error are addressed, at least to some degree, by determining a confidence interval for the calculated measure of association.

As a rule of thumb, the 95 percent confidence interval of that measure of association should exclude the null (no-effect) value to justify interpreting an observed association as being plausibly demonstrated. Likewise, the wider the confidence interval determined for the measure of association, the less confidence is warranted in the median value reported. Wide confidence intervals typically arise with smaller sample populations, as might be expected. Therefore, a larger sample population size should always be a consideration in how much confidence can be placed in any study result. Of course, the larger a study population, the more expensive the study—a reality that leads to many smaller sample-size

studies appearing in the literature. Sample size is always a concern with so-called *cancer clusters* that are often the underlying environmental health risk scenario.

3.3.4 Validity and Reliability

One of the challenges facing interdisciplinary studies involving natural and applied scientists (e.g., engineers, chemists, geologists, lab-based health scientists) versus health and social scientists such as epidemiologists is that common terminology used by different disciplines have different meanings for the same words.

Reliability as used in epidemiology means the repeatability of results and is similar to the meaning of precision in the natural sciences. Natural scientists, particularly analytical chemists, must know that accuracy and precision are not the same, the difference being illustrated in Figure 6.

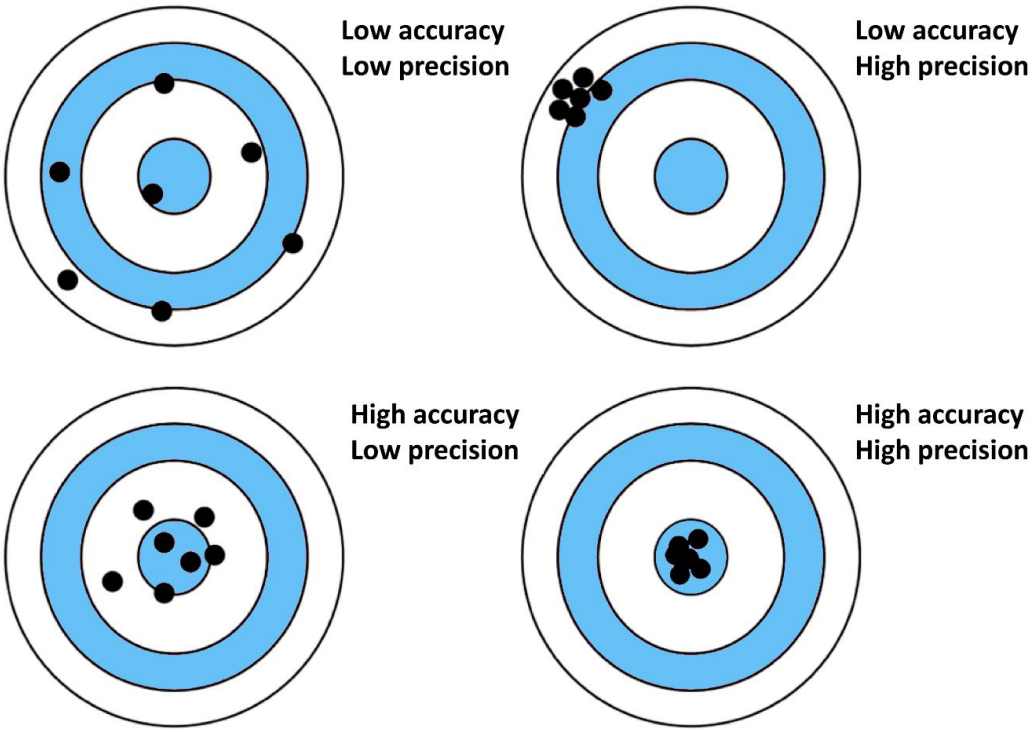

Figure 6 - Difference between precision and accuracy. *Precision* describes the repeatability of results while *accuracy* describes how well results represent the true value: the bull's eye.

Validity as used by epidemiologists is similar to what natural scientists describe as accuracy. Natural scientists who understand the distinction between accuracy and precision can be forgiven for finding the epidemiologist's use of reliability to be confusing, if not misleading. A natural scientist may reasonably view something presented as reliable as being something that can be relied upon. But a precise value that is inaccurate is not something to be relied upon. Validity presents less of a potential source for interdisciplinary confusion, as natural scientists would see some correspondence between an accurate result and a valid result.

Epidemiologists draw an important distinction between *external* versus *internal* validity. Internal validity addresses whether the results obtained accurately represent the sample group that was studied. External validity addresses whether the results obtained for a study population can be generalized (externalized) to the general population. This depends on how well the sample population is representative of the general population, but verifying this feature is easier said than done. As important as external validity must be for applying study findings for policies applicable to the general population, external validity receives less attention than it deserves when judging epidemiologic evidence for developing environmental policies.

3.3.5 Study Design for Supporting Causation

Bonita and others (2006), commissioned by WHO, provided an excellent overview of epidemiology that explains basic concepts in easy-to-understand terms. There is not universal agreement about terminology concerning study designs, but such details are not as critical as the basic concepts that relate to the ability of a given study design to support causal inference.

Epidemiological study designs can be categorized as *experimental* or *observational*, the latter being further categorized as *descriptive* or *analytical*. Experimental studies are the most capable of supporting causal inference, but their application to environmental health risks is limited by ethical constraints (e.g., intentional exposure of human subjects to potential environmental health risks will not receive research ethics approval) and practical/logistical limitations. Observational studies are by far the most common for drinking water health risks, but, as discussed later in this section, they are fundamentally limited in their ability to support causal inference. An overview of the types of studies is provided in Table 7. Observational studies are far more common for environmental health risk studies so they are discussed first.

Table 7 - Types of epidemiological study (Adapted from Bonita et al., 2006).

Type of study	Alternative name	Description or Unit of Study
Observational studies		
Descriptive studies	Aggregated studies	Description of disease occurrence in Populations
Analytical studies		
Ecological	Correlational, Aggregated	Populations
Cross-sectional	Prevalence	Individuals
Case-control	Case-reference	Individuals
Cohort	Follow-up	Individuals
Experimental studies	***Intervention studies***	
Randomized controlled trials	Clinical trials	Individuals
Cluster randomized controlled trials		Groups
Field trials		
Community trials	Community intervention studies	Healthy people Communities

Observational Descriptive Studies

Observational descriptive studies are also called *aggregated studies* because they operate at the population rather than the individual level. For example, they may compare disease patterns as a function of differences among defined groups or over time for a single defined group. The critical distinction for observational descriptive studies is that they are based on a group of people as a population and lack details on individual exposure and outcome, which precludes establishing causal inference.

A more analytical version of an observational aggregated study is a so-called *ecological*[15] *study*. These studies use data from populations in terms of their aggregate health outcomes in relation to aggregate measures of exposure. As such, they are susceptible to the so-called *ecological fallacy*[16] because they lack corresponding evidence for individuals that makes such studies unreliable for causal inference.

Another somewhat more capable study design is a so-called *cross-sectional or prevalence study* that simultaneously measures individual exposure and the health status of individuals. However, because they do so at a point in time, such studies cannot confirm that exposure preceded the outcome, a requirement to support causal inference.

Observational descriptive studies have been termed *hypothesis-generating* studies, as distinct from the analytical studies that are *hypothesis-testing* studies. The former are easier and less costly to perform and have a role to play in searching for new environmental health risks. However, their serious limitations for supporting causal inference means that results from such studies are at best tentative and cannot be conclusive in establishing an environmental health risk.

Observational Analytical Studies

The two main classes of analytical study designs: are *case-control* and *cohort* study designs. There are far more case-control studies than cohort studies concerning drinking water health risks. The reasons become clear when the nature and differences of these two analytical study designs are considered.

Case–control studies are necessarily retrospective in nature, a feature that contributes both advantages and disadvantages. A case-control study involves identifying individuals who have the health outcome under study (cases) and then finding a set of individuals who do not have the health outcome (controls) as depicted in Figure 7. The analysis involves obtaining, by whatever means are possible, information on whether the individuals under

[15] The term *ecological* study is often found in the literature, but it must be realized that such studies have nothing to do with ecology.

[16] "*[E]cological fallacy - An erroneous inference that may occur because an association observed between variables on an aggregate level does not necessarily represent or reflect the association that exists at an individual level; a causal relationship that exists on a group level or among groups may not exist among the group individuals.*" (Porta, 2016, p. 34)

study (both cases and controls) have been exposed to the cause(s) that is (are) under study. Case–control studies must select a specific health outcome to define the individuals who are cases. The exposure assessment is necessarily retrospective because when specific individuals who are cases are identified, it is necessary to look back in time for each case to estimate whether or not, or to what degree, each individual has been exposed to a hypothesized cause.

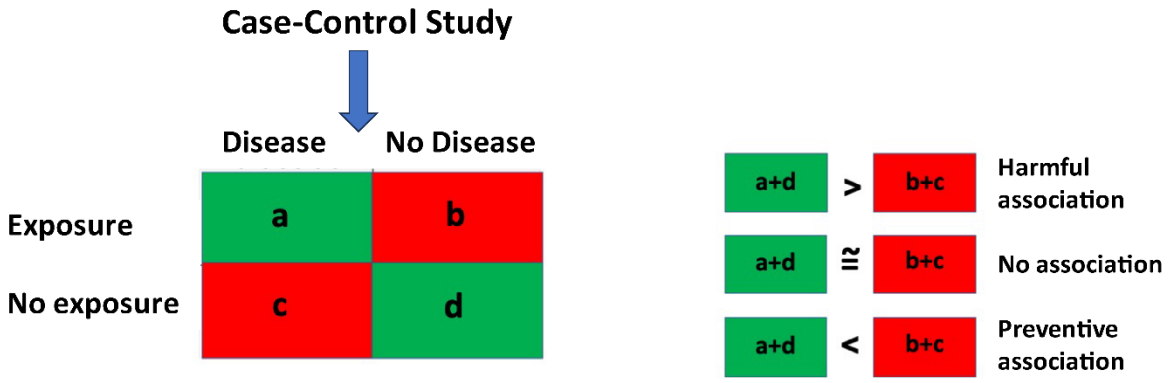

Figure 7 - Case–control study logic. A case-control study identifies a group of individuals who have the health outcome under study (cases) and a group of individuals who do not have the health outcome (controls), then estimates the exposure of each individual to the hazard being studied. The blue arrow represents the study starts by finding cases and controls (i.e., people with and without the disease. Representing exposure as all-or-nothing is a simplification of reality.

Use of a case-control study is problematic for determining drinking-water health risks because detailed, individual-level exposure assessment is not normally available and must be estimated in some inevitably imperfect manner. In many cases, exposure assessment is done for an entire group (e.g., assuming that the entire group consumes the community water supply), which may or may not (usually not) be adjusted based on individual behavior. This reality opens case–control studies to a variety of potential biases, including recall and selection bias.

Retrospective exposure assessment, when pursued on an individual basis by questionnaire, can be subject to recall bias. Individuals who have the disease under study are more likely to recall possible past exposures to potential causal agents than will control individuals. Where group assignments of exposure are relied upon, the critical classification of exposure is no longer truly performed at an individual level, calling into question the validity of the data analysis based on individuals versus aggregated populations.

Cases will be evident if the population is selected based on relevant, accessible, health records, making the case-control approach most amenable to reportable diseases. The selection of appropriate controls is far more problematic, leading to possible selection bias. If the population that controls are selected from has any characteristics (e.g., distribution of gender, age, social class) that differ from the characteristics of the cases, other risk factors associated with the differing characteristics could bias the outcomes observed. Practicality limits the number of controls to the number of cases or, in more

sophisticated studies, some multiplier (two or three times) of the number of cases. The potential for bias in selecting controls will, inevitably, always result in some degree of sampling error that is difficult to know. Error occurs because of the inability to obtain all necessary data for either the cases or the controls given that the individuals associated with incomplete data may have different relationships between exposure and outcome from those who are fully analyzed to the completion of the study. Study of diseases with a long incubation or progression time such as cancer—which can be decades long—are most amenable to the retrospective, case–control study design because the subjects already have the disease.

Cohort studies can be either prospective or retrospective in nature; the logic is shown in Figure 8. The cohort is a large sample (compared to case-control design) of individuals drawn from the population who do not have the disease as an initial condition of inclusion. The sample population is followed over time (into the future for a prospective cohort study or from a defined starting point in the past chosen before the disease is identified for any individual in a retrospective cohort study) to gather evidence about individual exposure and health outcome.

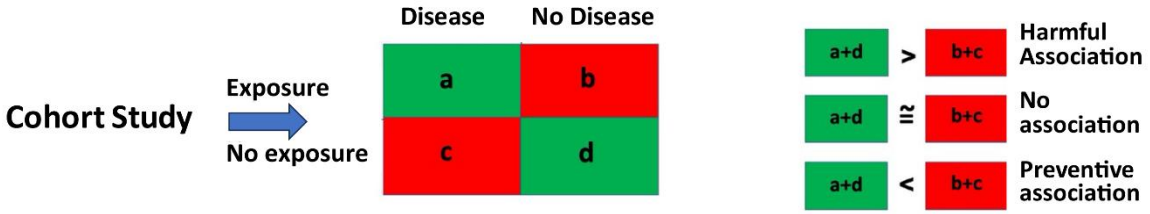

Figure 8 - Cohort study logic. A cohort study identifies a much larger group of individuals than a case-control study. None of the selected individuals have the health outcome under study when recruited. The population is studied over time to document exposure to the hazard under study and the health of each individual. The blue arrow represents the study starts by defining a population that is later separated into those who are exposed and those who are not exposed. Representing exposure as all-or-nothing is a simplification of reality.

Conceptually, cohort studies offer advantages over case–control studies by avoiding the potential for recall and sampling bias that plague case–control studies. Exposure can be measured directly and accurately into the future for individuals, and sampling bias for the individuals who do not get the disease is avoided because the individuals in the cohort define their own status with respect to disease or no disease. Cohort studies also allow multiple exposures to be followed, but they are limited to known disease categories necessary to confirm disease-free status at the study outset.

However, cohort studies are inevitably more resource intensive and expensive than case–control studies. They are also impractical for rare diseases because only a small number of an initial cohort will develop a rare disease. Likewise, prospective cohort studies that are potentially more powerful than retrospective cohort studies (because of the ability to collect better exposure evidence) are challenging in cases of diseases with long incubation or development times. In such cases—for example, cancer—studies initiated today may not obtain meaningful results for decades into the future. For these practical

reasons, there are few prospective cohort studies addressing drinking water health risks for diseases such as cancer.

Experimental Studies

Experimental studies refer to studies where exposures are provided to a human population under controlled conditions that are known and compared with a population where the exposure is absent. This approach is widely used in what are commonly called clinical trials to assess medical interventions, pharmaceuticals, and vaccines where the potential medical benefits can be used to justify the ethical basis for a trial. This approach has ethical limitations for environmental health risks and few examples are found for drinking water health risks (e.g., Payment et al., 1997, 1991; Hellard et al., 2001; Colford et al., 2005, 2006). These are essentially limited to designs where exposure is already accepted and the experimental intervention is provided to reduce an existing exposure.

The gold standard of experimental studies is the randomized, double-blind clinical trial. The randomization is provided by assigning individuals to exposed and control groups to minimize sampling bias. Double-blinding involves keeping both study participants and the study investigators blinded to the exposure status of each individual. This measure is intended to prevent participants from being influenced by the knowledge of whether or not they have been exposed and, likewise, to prevent the investigators from allowing any subtle bias to their analysis and interpretation of study results. Where feasible a cross-over (i.e., exposed and unexposed groups are reversed part way through the study) can be added to provide additional insight while eliminating sampling bias between a simple exposed – unexposed design.

Despite the use of these measures, results from such gold-standard studies frequently contradict one another (Figure 9) because a variety of the factors—differences in study design and performance, confounding, bias, sampling errors—cannot be completely eliminated from such studies.

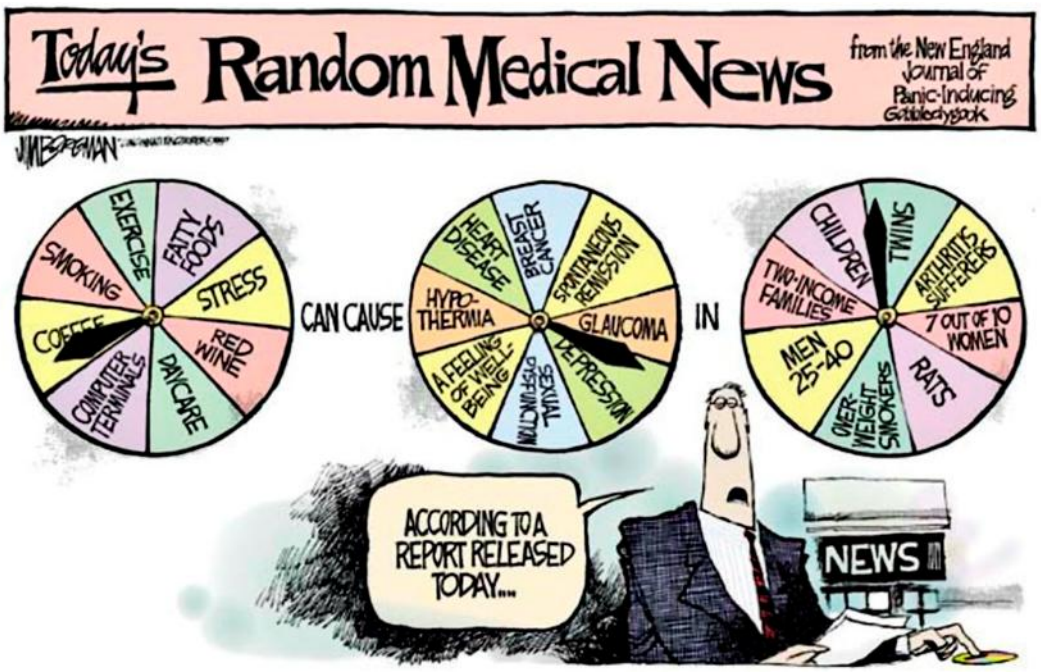

Figure 9 - Cartoon capturing the nature of news reporting of single epidemiologic studies (Borgman, 1997).

3.3.6 Weighing Epidemiological Evidence for Causation

As noted earlier—but it bears repeating—epidemiology by itself can provide only direct evidence of correlation between exposure and outcome; evidence of causation requires additional information. This matter of interpretation has attracted the attention of public health professionals for over 50 years.

The first major criteria for judging the contribution of epidemiological evidence for causal inference were offered by Bradford Hill (1965) and the US Surgeon General (US Public Health Service, 1964). Further elaboration of the complexity of causation was provided by Susser (1991) and more recently by Shimonovich and others (2021). For the purposes of this book, we will refer to the causal criteria provided by Bonita and others (2006)—while recognizing this is an extremely complex subject and that Rothman and Greenland (2005) have questioned the utility of causal criteria, in part because of the diverse nature of causal factors in multifactorial circumstances.

Temporal Relationship

Logically, exposure to the cause under study must precede the health outcome. Study design and data analysis must be able to ensure this criterion is satisfied to support the exposure being causal. To satisfy this requirement, data are required for incident (newly occurring disease) rather than prevalent (currently existing disease), a distinction that is easily missed for newcomers to the field. An inability to satisfy this requirement is the reason cross-sectional studies are not classified as analytical studies.

Plausibility

The biological plausibility of a proposed cause for a given health outcome is necessary to provide confidence in a prospective causal association. Lack of evidence from human or animal toxicology does not preclude the possibility of such evidence being generated in the future. But the absence of such evidence or evidence to the contrary necessarily reduces the confidence in the exposure under study being causal, based solely on epidemiological correlation. Evidence of a biologically plausible mode of action that is relevant (i.e., considering the degree and nature of exposure) to that in an epidemiological study can support a causal relationship.

Consistency

Among the many cautions applicable to judging the merits of epidemiological results is the rule that no conclusions leading to responsive action should be based on the results of a single epidemiological study. This rule does not preclude the evidence ultimately being shown to be valid where limited studies have been performed, but it offers an important, if not apparently typical, application of the precautionary principle[17] by avoiding actions based on evidence that may be completely wrong and lead to serious or irreversible consequences. The foregoing advice (i.e., repeatability) is a cornerstone of scientific research. However, given the diversity and nature of qualifiers that apply to the interpretation of epidemiological evidence, simple replication is generally inadequate.

Taubes (1995, p. 169) quoted a recognized pioneer of evidence-based medicine, David Sackett, on the role of consistency:

> *"It is persuasive only if the studies use different architectures, methodologies, and subject groups and still come up with the same results. If the studies have the same design and 'if there's an inherent bias,' he explains, 'it wouldn't make any difference how many times it's replicated. Bias times 12 is still bias.' What's more, the epidemiologists interviewed by Science point out that an apparently consistent body of published reports showing a positive association between a risk factor and a disease may leave out other, negative findings that never saw the light of day."*

[17] The precautionary principle: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (United Nations Conference on Environment and Development, June 1992) www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_CONF.151_26_Vol.I_Declaration.pdf↗.

Dose–Response Relationship

Existence of a dose–response relationship means that the frequency and/or severity of the study outcome increases with observation of an increasing frequency or magnitude of exposure to the causal agent under study. Bearing in mind there are agents known to have unusually shaped dose–response curves (e.g., vitamins and essential nutrients typically exhibit a U-shaped curve, indicating adverse effects both for inadequate doses and for overdoses), a general expectation is that the characteristics described in the opening sentence of this section will indicate grounds for believing that the results obtained support a causal relationship. That said, exposure assessment is commonly weak or at least problematic for studies of drinking water health risks.

Strength of the Association

Given that epidemiology is fundamentally capable of measuring statistical association (correlation) between exposure and outcome, measures of the strength of that association are an important result for any analytical epidemiological study. The primary measures of that strength are the rate ratio (RR, also called risk ratio or relative risk) and the odds ratio (OR, an approximation of RR that can be estimated from a case–control study; George et al., 2020).

The RR compares the rates of disease incidence as a ratio for the exposed over the unexposed population as shown in Equation (1).

$$\mathrm{RR} = \frac{\text{Disease incidence rate in the exposed population}}{\text{Disease incidence rate in the unexposed population}} \quad (1)$$

where:

- $\mathrm{RR} \approx 1.0$ is the null value indicating no association between exposure and outcome
- $\mathrm{RR} > 1.0$ suggests that exposure is positively associated with disease
- $\mathrm{RR} < 1.0$ suggests that exposure is negatively associated with disease (i.e., apparently preventive)

The OR compares the odds of exposure in the cases with the exposure in controls as shown by Equation (2).

$$\mathrm{OR} = \frac{\text{Odds of exposure in cases}}{\text{Odds of exposure in controls}} \quad (2)$$

where:

- $\mathrm{OR} \approx 1.0$ is the null value indicating no association between exposure and outcome
- $\mathrm{OR} > 1.0$ suggests that exposure is positively associated with disease

OR < 1.0 suggests that exposure is negatively associated with disease (i.e., apparently preventive)

Because well-conducted cohort studies are generally superior to well-conducted case–control studies for supporting causation, RR is preferred to OR. The latter is necessary because the incidence rate is not known in a case–control study because cases have been selected for the study. In general, the rarer a disease, the closer the OR will converge on the RR, so for those environmental health risks that do not cause common diseases, OR and RR can generally be assumed to be similar.

One element of general common ground between critics of epidemiological evidence in drinking water health risks and practicing epidemiologists has been that—especially where only a small number of studies has been done— the meaning of a RR less than 3 to 4 should be regarded as suspect until replicated by other studies on other populations (Taubes, 1995; Willett et al., 1995). The drinking water health risk literature is rife with examples where this simple guidance has been overlooked or ignored.

Reversibility

For health outcomes that can be reversed or recovered from, there is a possibility, in rare cases, of being able to observe reversal. This will be possible only for an experimental study that has excellent exposure assessment that will accurately characterize the magnitude of exposure and its absence or substantial reduction.

Study Design

There is a clear hierarchy in the capability of the various study designs to provide credible evidence, progressing from the weakest—observational descriptive studies (hypothesis-generating studies)—through to the more credible observational analytical studies (hypothesis-testing studies) up to experimental studies, such as the current gold standard of double-blind, randomized controlled (clinical) trials. Most environmental health-risk studies will be limited to the first two categories, which introduces inevitable uncertainties about causation for such studies. The opportunities for conducting experimental studies of drinking water health risks are limited, but there have been a few notable attempts, specifically for drinking-water studies of infectious disease (Colford et al., 2005, 2006; Hellard et al., 2001; Payment et al., 1991, 1997).

Judging the Evidence

This is not a criterion, as such. Despite the merits of all the foregoing points about evaluating epidemiologic results for evidence of causation, no overall rule ensures clarity on this critical matter. This consideration clearly demands judgment. Rothman and Greenland (2005, p. S144) take a broad view of the very concept of causation, noting the complexity of types and interactions among causes and causal factors to develop a description of disease causation as

> *"…a cause of a disease event is an event, condition, or characteristic that preceded the disease event and without which the disease event either would not have occurred at all or would not have occurred until some later time. Under this definition it may be that no specific event, condition, or characteristic is sufficient by itself to produce disease."*

This practical description highlights the critical importance of the temporal relationship as a disqualifying criterion if not satisfied. Otherwise, their description of causation presents the general complexity of causation as a multifactorial phenomenon.

Rothman and Greenland (2005, p. S144) argue against the dogmatic use of causal criteria in judging epidemiologic evidence and the naive application of such criteria by those inexperienced and unfamiliar with the discipline: "*Causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as a criterion-guided process for deciding whether an effect is present or not*."

While this guidance presumably applies in any scientific field, the reality is that the interdisciplinary nature of environmental health risk is such that users of epidemiologic data need to be able to ask challenging questions about the merits of such data. In a world of academic competition for funding and recognition, it is not wise to expect non-epidemiologists to accept and apply epidemiologic results to authentic problems simply because a study is published by epidemiologists in a recognized journal, any more than would be true for "evidence" published by any other discipline.

Criticizing epidemiology is easy for lab scientists who are used to performing controlled experiments to test their hypotheses. Trichopoulus (Willet et al., 1995, p. 1326) offered two main points in response to the Taubes article (1995) that was critical about epidemiological evidence. First, they commented, *"Taubes writes that I have expressed the view that only a fourfold risk should be taken seriously. This is correct, but only when the finding stands in a biological vacuum or has little or no biomedical credibility."* Second, they noted, "*Epidemiology should be evaluated in comparison to other disciplines that serve the same objective, that is, to identify the causes of human disease and facilitate their prevention."*

In support of his second point, Trichopoulis referred to the famous quote by Winston Churchill about forms of government: "*No one pretends that democracy is perfect or all-wise. Indeed, it has been said that democracy is the worst form of Government except for all those other forms that have been tried from time to time…"*(Willet et al., 2016, p. 1326).

Although epidemiology faces enormous challenges in uncovering valid evidence of causation, it also offers several advantages in relation to the other primary means of learning about causation: e.g., experimental toxicology. Making informed judgments about causal evidence for environmental health risks requires drawing on the best features of both approaches (Table 8).

Table 8 - Comparison of observational epidemiology with experimental toxicology for providing insights into human health risk (Hrudey, 2012).

Observational epidemiology	Value[a]	Experimental toxicology	Value[a]
Observe human subjects	+	Use animals (typically rodents)	-
Adjustment for differences in absorption, distribution, metabolism, and excretion generally not required	+	Adjustment for differences in absorption, distribution, metabolism, and excretion required for human risk assessment	-
Large sample size possible in some cases	+	Sample size limited by practicality	-
Wide genetic variability possible	+/-	Narrow genetic variability	-/+
Diverse and wide sensitivity of subjects	+/-	Narrow range of sensitivity of subjects	+/-
Low exposure range; realistic but insensitive	+/-	High exposure range; sensitive but commonly yields artifacts	-/+
Can assess combined realistic exposure	+	Combined mixtures are difficult	-
No control over exposures	-	High control over exposures	+
Individual measurement of exposure generally not feasible or limited	-	Individual measurement of exposure is feasible	+
No control over confounding factors; only imperfect mathematical adjustment	-	High control over confounding factors through experimental design	+
Randomization not possible	-	Randomization is normal	+
Time frame for chronic diseases is long (decades)	-	Time frame for chronic diseases is much shorter (typically 2 years)	+
Prospective studies are limited in feasibility	-	All experiments are prospective in nature	+
Capability to ascertain mechanism by postmortem investigation is rare	-	Postmortem examination normal to provide insights into mechanism	+
Recall bias in case-control studies	-	Recall bias plays no role	+

[a]Some characteristics may be valuable in some circumstances and disadvantageous in others (+/- or -/+).

A generic hierarchy for the value of evidence for the purposes of predicting human health risk is depicted in Figure 10, presuming the evidence is generated by quality investigations considering all of the cautions discussed. Exercise 5 explores the many different epidemiological study designs.

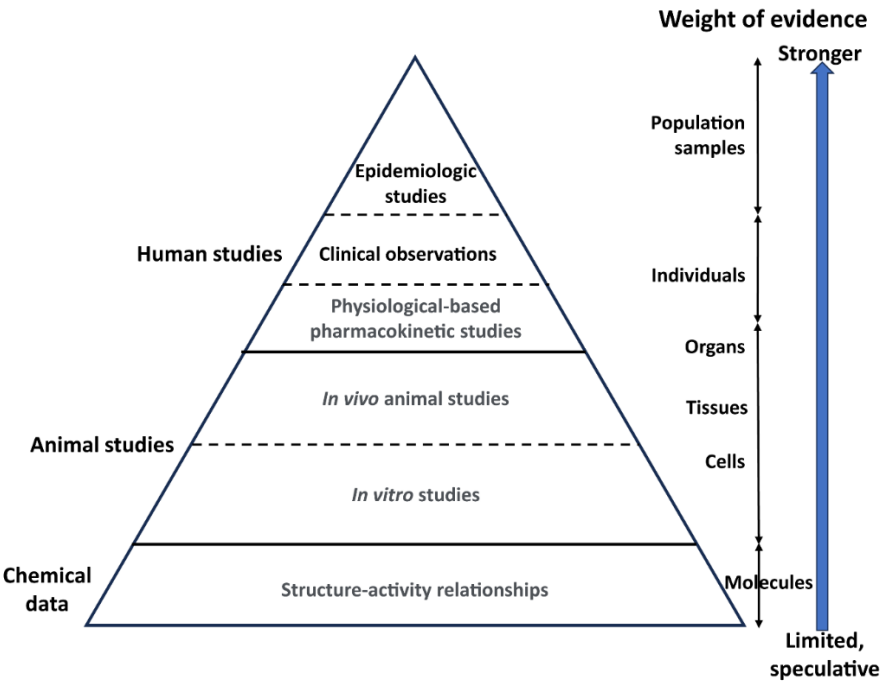

Figure 10 - Hierarchy of data strength for identifying human health hazards.

4 Health Risk Assessment

4.1 Comparative Human Health Risks and Environmental Health

Before discussing how human health risks are assessed, it is worthwhile to consider some fundamentals about human health risk. Perhaps no insight is more fundamental than the fact that for every person, their lifetime risk of death is equal to 1—that is, every person who is born will die someday. This reality means that environmental risk management can seek only to reduce or prevent premature death. Because no individual can know what their lifespan will be until they face death, premature death can be addressed only at a population level.

Even at that level of abstraction, it is a challenge to characterize health risks. However, a common view of environmental health risk that has not been seriously challenged in public discourse is the claim that environmental factors/chemical contamination have been a major, if not growing, health risk facing residents of developed economies. This has been driven largely by beliefs that cancer, a particularly dreaded disease, is primarily caused by chemical contaminants.

That belief can likely be traced back to a misunderstanding created by a WHO report (1964) that stated that three-quarters of all cancers were caused by extrinsic factors (those other than genetic predisposition). Dr. John Higginson (1969), the founding director of the WHO International Agency for Research on Cancer (IARC), extended this to as high as 90 percent of all cancers.

The misunderstanding was that extrinsic factors (nongenetic) were also expressed as *environmental factors*. Extrinsic factors were intended to mean all factors other than genetic that operated after a person was born, including (at a minimum) diet, smoking, alcohol consumption, and sexual behavior. The burgeoning environmental movement of the 1960s and 1970s equated these environmental factors with human-made chemical contamination.

Epstein (1979) popularized this interpretation, describing cancer as the plague of the twentieth century. Even environmental science journals considered credible, being publications of the American Chemical Society, joined this story line, stating without evidence, that: "*environmentally-caused diseases are definitely on the increase*" (Ember, 1975, p. 1116).

The fact that the raw (total) number of cancer cases has increased must be expected because the population has doubled since 1970, so there are twice as many people who can experience cancer. Likewise, "*Age is the most important risk factor for cancer—cancer rates peak in males and females aged 85 to 89 years*" (Canadian Cancer Statistics Advisory Committee, 2023, p. 14). As a result, total cancer cases in society will increase as the societal population ages. This reality has contributed to the inaccurate belief that cancer causation is increasing

in society. When adjusted for population size (i.e., expressed as a rate per 100,000) and age standardized (to compensate for the higher proportion of older people), cancer rates have declined in Canada by 1.2 percent for males since 2011 and 0.4 percent for females since 2012 (Canadian Cancer Statistics Advisory Committee, 2023). This topic is discussed further in Section 4.2.

However, a broader perspective can be illustrated by viewing life-expectancy statistics for Canada (Statistics Canada, 2016) from 1920 to 2011 (Figure 11). These data fail to support the existence of an epidemic of cancer since the 1960s for that period, considering that cancers are such prevalent diseases in the population. Recently 2020-2022, life expectancy in Canada has declined slightly with the impact of the Covid-19 pandemic.[18]

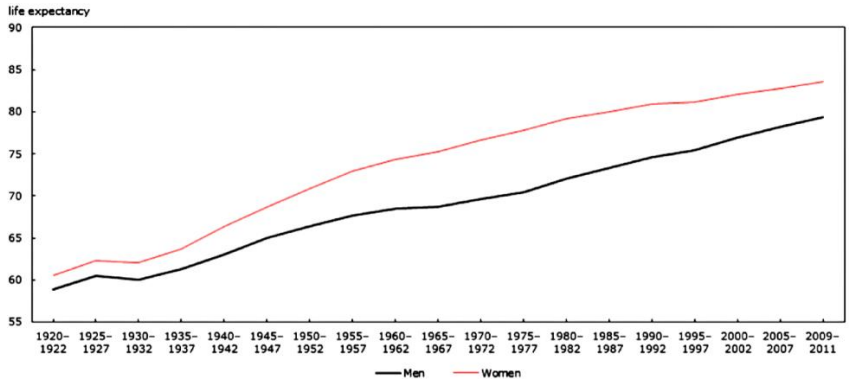

Figure 11 - Life expectancy at birth by sex, Canada, 1920–1922 to 2009–2011 (Statistics Canada, 2016).

4.2 Evolution of Environmental/Public Health Risk Assessment

The history of formal health risk assessment can be traced back to the need to assess food and drug safety before the environmental awakening of the 1960s, most notably for carcinogenic risk. Mantel and Bryan (1961, p. 458) suggested that a negligible, one-in-a-100 million lifetime risk (10^{-8}) could be considered "*virtually safe*."

The widespread appearance of environmental regulatory agencies in the 1970s created a need to formally address the human health risk from environmental contaminant exposures (Hrudey, 1998; Paustenbach, 1995). The creation of the US EPA in 1970, followed by President Nixon's declaration of a "*war on cancer*" in 1971, created a political and legal minefield for scientists seeking to pursue rational policies. In this milieu, environmental health-risk assessment was created as an apparently scientific policy response that was inevitably influenced by substantial advocacy.

The earliest risk-related efforts by the US EPA were directed at regulating pesticides, beginning with DDT, a pesticide that achieved its notoriety from the publication of the book *Silent Spring* (Carson, 1962), arguably the most influential book for raising environmental concerns in the modern era. These early regulatory efforts encountered

[18] Statistics Canada: https://www150.statcan.gc.ca/n1/daily-quotidien/231127/dq231127b-eng.htm

substantial controversy, as the US EPA found itself caught between the chemical manufacturing industry, combined with the agricultural lobby, versus the growing environmental-activist lobby (Albert, 1994). US EPA lawyers sought to have courts recognize a series of 17 cancer principles to short-circuit the interminable court battles among competing experts.

This "legal" effort earned the agency a scathing editorial from one of Britain's most prominent medical journals, *The Lancet* (Anonymous, 1976, p. 571) in which these cancer principles were described as "*ranging from the innocuous to the absurd*." *The Lancet* critique focused on three of the principles that claimed: cancer incidence was increasing in the US; animal studies showing an agent causing benign or malignant tumors was reliably accepted by scientists as sufficient evidence of carcinogenicity of the agent in humans; and there was no method for establishing a no-effect level for human exposures to carcinogens.

The first claim about cancer incidence increasingly reflects a common misunderstanding about the nature of cancer statistics. As noted in Section 4.1, any trend analysis for disease incidence must first acknowledge that populations are increasing over time. Consequently, trends in disease incidence must consider the trends on a per capita (rate) basis to separate them from population increases.

Even more important, age is known to be the largest single risk factor for cancer (Canadian Cancer Statistics Advisory Committee, 2023). Canada's population over 65 years is currently 4.2 times greater than it was in 1970, so any trend analysis of cancer incidence must be adjusted for age—what is termed to be *age standardization*.

Finally, trends over time caused by changes in diagnostic and reporting techniques affect cancer incidence data in any jurisdiction. These trends are shown for Canada from 1982 to 2021 in Figure 12. We are better able to diagnose cancer occurrences now, which increases the number of reported incidences, however when we consider the rate of cancer per unit of population, the incidence rate is about the same today as in 1984, while the death rate from cancer has declined substantially (Figure 12a). The total number of incidences and deaths have increased because of the overall increase in population and the increased age of the population—because age is the largest risk factor for cancer—but the age- and population size- adjusted numbers are fairly stable. The green line on Figure 12b,c includes adjustment for age and population size, so trends of this line reflect the combined change in risk and control practices over time. The green line on Figure 12b indicates only a slightly higher incidence rate today while the same line on Figure 12c reveals the death rate is notably lower today than in 1984. Thus, the prevailing belief that we are experiencing an epidemic of cancer because of environmental contaminant exposures, as suggested by Carson (1962), is not valid. The prevalent epidemic-of-cancer fallacy is refuted by overwhelming evidence.

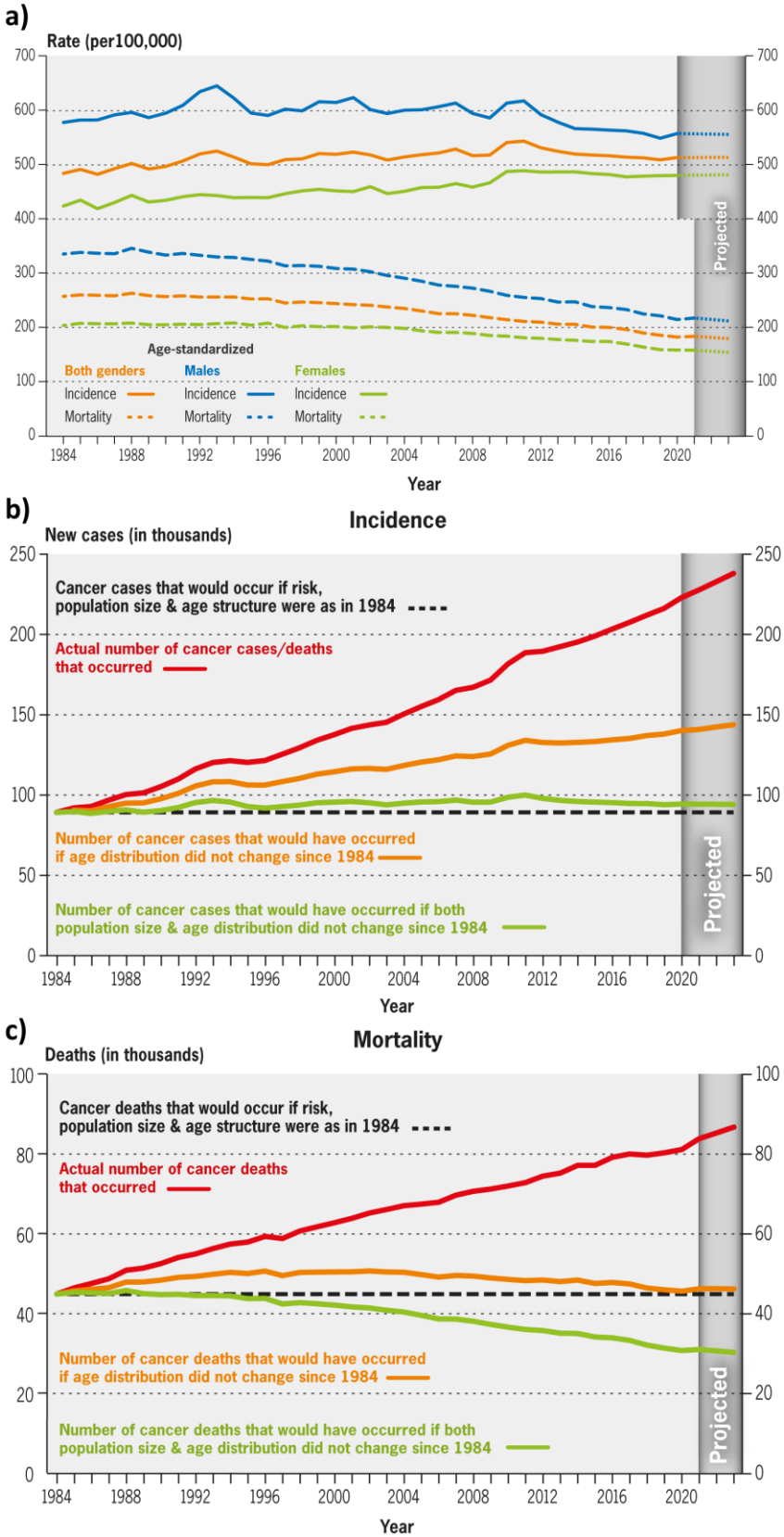

Figure 12 - Canadian trends for all cancers and ages from 1984 to 2023. a) Age-standardized rates of new cases and deaths. Then, b) and c), incidence and mortality, respectively, attributed to population growth, aging population, and changes in cancer risk and cancer control practices. New cases exclude non-melanoma skin cancer (neoplasms, NOS; epithelial neoplasms, NOS; and basal and squamous; Canadian Cancer Statistics Advisory Committee, 2023).

The second claim about the suitability of animal testing for determining whether any given agents are human carcinogens has been the subject of considerable scientific commentary and criticism over the past 50 years. As with most controversies, there are valid arguments on both sides, but the US EPA premise that evidence of benign or malignant tumors in animal studies provides reliable evidence for carcinogenicity of an agent in humans was certainly overstated. International practice for classifying agents regarding carcinogenicity has been undertaken by IARC. It has produced monographs on various agents and exposures based on expert panels that assess the evidence and classify agents into four specific categories (IARC, 2019, p. 35-36).

1) *"The agent is carcinogenic to humans (Group 1): This category applies whenever there is sufficient evidence of carcinogenicity in humans. In addition, this category may apply when there is both strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens and sufficient evidence of carcinogenicity in experimental animals."*
2) *The agent is probably carcinogenic to humans (Group 2A): This category generally applies when the IARC working group has made at least two of the following evaluations, including at least one that involves either exposed humans or human cells or tissues: limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, or strong evidence that the agent exhibits key characteristics of carcinogens."*
3) *The agent is possibly carcinogenic to humans (Group 2B): This category generally applies when only one of the following evaluations has been made by the working group: limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, strong evidence that the agent exhibits key characteristics of carcinogens."*
4) *The agent is not classifiable as to its carcinogenicity to humans (Group 3): Agents that do not fall into any other category are generally placed here."*

These categories illustrate that animal evidence alone is not accepted by IARC when establishing any agent as being carcinogenic to humans. IARC (2019) cited a valuable summary by Smith and others (2016) of the characteristics that a carcinogen should exhibit (Table 9).

Table 9 - Characteristics Indicating the capability of an agent to be a carcinogen (after Smith et al., 2016).

Characteristic of agent	Examples of relevant evidence to demonstrate the characteristic
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision, or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics, and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the ten characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which, when combined, provides stronger evidence for a cancer mechanism than would oxidative stress alone.

The third claim about there being no method to establish a no-effect level for carcinogens was presented by US EPA leaders as "*a safe level of exposure was non-existent*" (Albert et al., 1977, p. 1538). Hrudey and Krewski (1995) addressed that premise head-on by adopting the precautionary cancer-risk assessment process that the US EPA had developed and evaluating the smallest possible chronic daily dose over a lifetime for four carcinogens, including the most potent (by 100-fold over the next most potent) carcinogens rated by the US EPA. This analysis revealed that such a low, but non-zero exposure, would predict only 0.00001 cases of cancer over a 70-year lifetime even if the entire population of the world was exposed at this non-zero level. This analysis illustrates that although defining the specific low dose for any specific carcinogen that may be regarded as safe remains open to discussion, there should be no debate that there is a level of carcinogen exposure that is low enough to qualify as negligible.

Also noteworthy are the data in Figure 13 showing that the potency of carcinogens tested in animal bioassays range over 10^{10}—a huge range. Not all carcinogens are created equal in their capability to cause cancer.

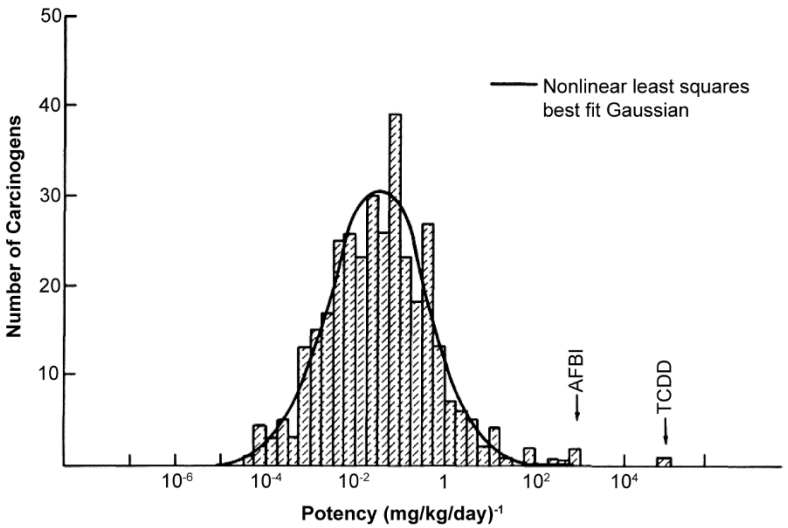

Figure 13 - Distribution of potency estimates (i.e., how little of an agent is capable of causing relevant tumors) for 343 agents/bioassays selected from the database of Gold and others (1984) with 770 compounds and 3,000 carcinogen bioassays that were selected to have (1) oral route of administration, (2) p value < 0.01 for increased incidence of animals with specific neoplasms (tumors), and (3) most sensitive species/sex/organ site combinations. AFB1 and TCDD refer to aflatoxin B1 and 2,3,7,8 tetrachlorodibenzo-p-dioxin (Flamm et al., 1987).

Regulating carcinogens has dominated the field of environmental health-risk assessment. Toxic agents came under legislative control in the US in 1976 with the Toxic Substances Control Act, which provided the US EPA with the regulatory authority to protect public health and the environment through controls on toxic chemicals. The same year also saw passage of the Resource Conservation and Recovery Act to control designated hazardous waste from generation to disposal.

In 1977, a chemical-waste treatment facility in Bridgeport, New Jersey, USA, experienced an explosion and fire that killed six and hospitalized 35 people. In 1978, public health concerns with poor hazardous waste disposal at Love Canal, near Niagara Falls, New York, USA, led to the declaration of a state of emergency by President Carter. These and other high-profile events led to the passage of Superfund, officially known as the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), which created funding for contaminated site clean-ups.

Contaminated site clean-up and hazardous waste management became major players in the development of environmental health risk assessment. Since then, many detailed guidance documents have been published to inform risk assessment practitioners and reviewers. A selection of those, emphasizing the most recent guidance documents, but also including some of the original seminal documents, are summarized in Table 10.

Table 10 - A sampling of accessible guidance documents on environmental health risk assessment.

Citation	Title
Alberta Health (2019)	Guidance on human health risk assessment for environmental impact assessment in Alberta, Canada
Agency for Toxic Substances and Disease Registry (2023)	Public health guidance manual. Online.
British Columbia Ministry of Health (2022)	BC guidance for prospective human health risk assessment - *Version 2.0*
enHealth (2012a)	Environmental health risk assessment - Guidelines for assessing human health risks from environmental hazards
Health Canada (2021a)	Overview of Health Canada guidance documents related to human health risk assessment of federal contaminated sites
Health Canada (2021b)	Guidance on human health preliminary quantitative risk assessment. Federal contaminated site risk assessment in Canada
Health Canada (2021c)	Toxicological reference values (TRVs)
Health Canada (2019e)	Human health risk assessment - Guidance for evaluating human health impacts in environmental assessment
Health Canada (2018)	Guidance on the use of quantitative microbial risk assessment in drinking water
Health Canada (2010b)	Guidance on human health detailed quantitative risk assessment for chemicals ($DQRA_{Chem}$)
Hrudey (1998)	Quantitative cancer risk assessment - Pitfalls and progress
International Programme on Chemical Safety (2021)	WHO human health risk assessment toolkit: chemical hazards, 2nd edition
International Programme on Chemical Safety (1999)	Principles for the assessment of risks to human health from exposure to chemicals
International Programme on Chemical Safety (1994)	Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits
National Research Council (2009)	Science and decisions: Advancing risk assessment
National Research Council (1996)	Understanding risk: Informing decisions in a democratic society
National Research Council (1994)	Science and judgment in risk assessment
National Research Council (1983)	Risk assessment in the federal government: Managing the process
Ontario Ministry of the Environment, Climate Change and Parks (2021)	Procedures for the use of risk assessment Part XV.1 Environmental Protection Act
Paustenbach (1995)	The practice of health risk assessment in the United States (1975–1995): How the US and other countries can benefit from that experience
US EPA (2011)	Exposure factors handbook - 2011 update
US EPA (2005)	Guidelines for carcinogenic risk assessment
US EPA (1989)	Risk assessment guidance for Superfund
US EPA (1984)	Risk assessment and management: Framework for decision making
Walker and others (2015)	Manual for the application of health-based targets for drinking water safety

Despite what risk assessments on contaminated sites might predict, Saunders and others (1997) performed a systematic review of studies assessing human health impacts from waste disposal sites. Nine hundred candidate studies were identified from extensive literature searches and were pared down to 43 potentially eligible studies that were screened in detail by two independent reviewers. This process yielded 14 studies judged to have sufficient rigor to potentially provide evidence of a causal association between contaminant exposures and human health outcomes.

For these 14 highest-rated epidemiological studies, exposure measures were poorly rated in all cases; outcome measures were generally well rated; and measurement bias, selection bias, and confounding biases were intermediately rated. Consequently, none of

these studies provided convincing evidence of causal relationships between hazardous waste site exposure and adverse human health effects, a finding that is consistent with other reviews, such as that from the National Research Council (NRC; 1991), Najem and Cappadona (1991), and Upton and others (1989). The Saunders and others (1997) finding does not mean there are no human health effects arising from the studied hazardous waste sites. Rather, the absence of comprehensive, effective individual exposure assessment precludes being able to determine a causal relationship to contaminants from these sites. This is essentially the problem explained in Section 3.3.

4.3 Overview of Guidance on Environmental Health Risk Assessment

Environmental health-risk assessment generally must be conducted without the benefit of even cursory epidemiological studies, let alone those that were deemed by Saunders and others (1997) to be the best epidemiological studies available among 900 potentially relevant studies. Naturally, this lack of reliable human health studies makes the practice of environmental health-risk assessment challenging. An overview of the generally accepted approach to performing environmental health-risk assessment follows.

The influential *Risk assessment in the federal government: Managing the process* (NRC, 1983)—often called the *Red Book*—clarified the distinction of risk assessment from risk management and set out much of the terminology that is still in use. The following discussion is organized according to that provided by enHealth (2002, 2012a), which offers guidance that is not bounded by the straitjacket imposed on many regulatory agencies. NRC (2009) describes, in some detail, the range of complexities that most "how to" guidance documents do not address. enHealth (2012a) adapted and summarized the updated approach recommended by NRC (2009) as shown in Figure 14. There is far too much detail in all the available guidance documents (Table 10) and Figure 14 to repeat here—the following discussion provides a high-level overview of the main elements of environmental health risk assessment.

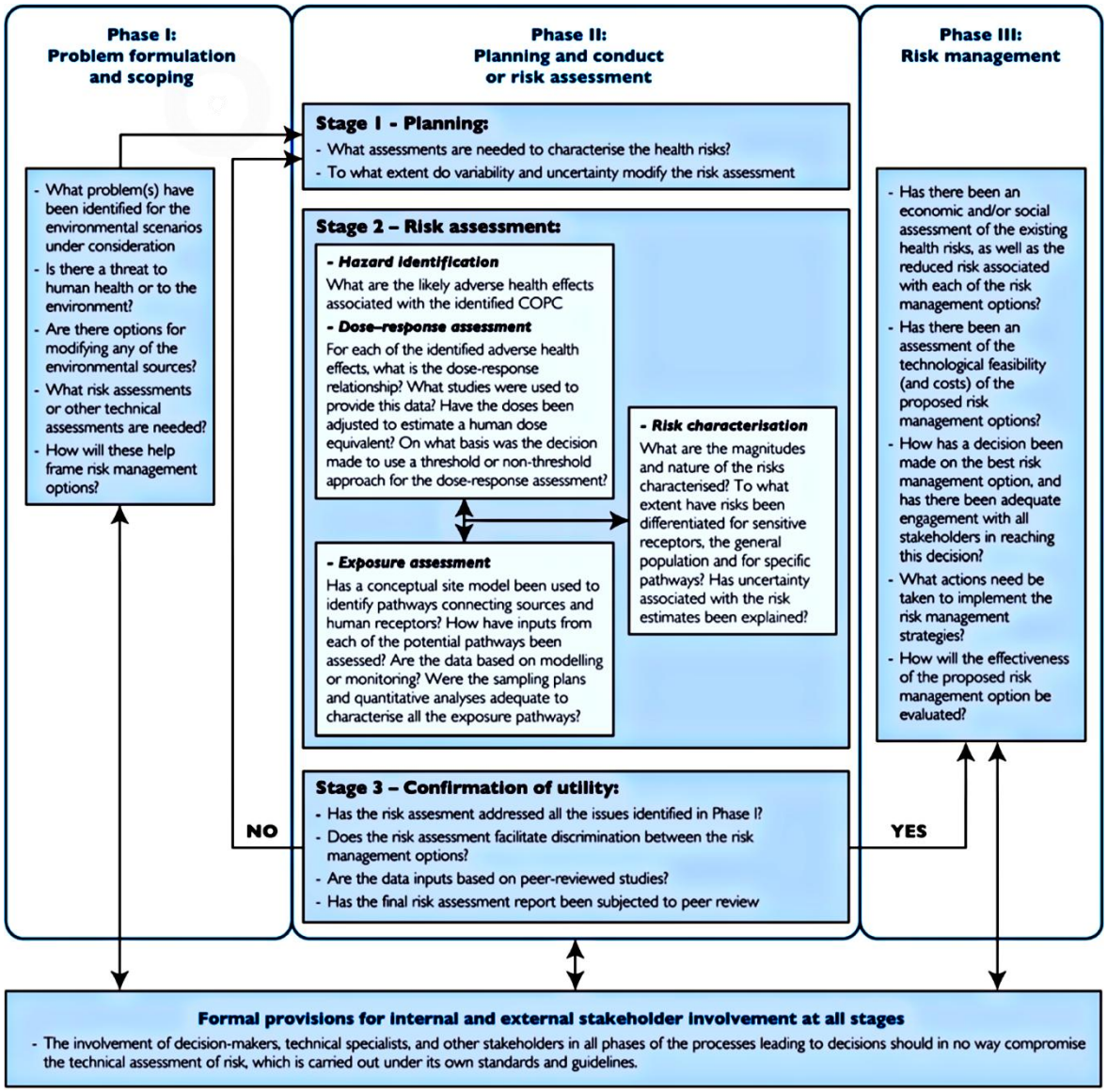

Figure 14 - A proposed, updated, phased environmental health-risk assessment approach including problem formulation and relation to risk management and stakeholder engagement (enHealth, 2012a, adapted from NRC, 2009).

4.3.1 Issue/Problem Definition

As much as it seems obvious that the first step of any major assessment of risk should be to define what is the nature and scope of the situation that is to be assessed, early guidance seemed to presume that everyone (e.g., risk assessors, regulatory risk managers, the affected public) had equal and adequate understanding of the issues of concern that needed to be assessed. Those familiar with solving difficult problems will generally acknowledge that fully and carefully defining a problem before seeking to deal with it is often the most critical step.

Questions that should be addressed at this stage include the following (enHealth, 2012a, p. 7).

- *"What are the true drivers for the issue being assessed? For example, there is no point in doing a quantitative cancer-risk assessment if the real concern is cognitive impairment of children, and if the latter cannot be addressed by risk assessment, another approach may be necessary.*
- *Are intervention strategies available to manage the outcomes of the environmental health-risk assessment (e.g., containment of contaminated soil, chlorination of water, pasteurization of food)?*
- *Have transport mechanisms been adequately considered (e.g., meteorological factors affecting air pollution, vectors for communicable diseases)?*
- *Are there factors that could affect persistence (e.g., photolysis and volatilization of chemicals, desiccation of microorganisms)?*
- *Has the risk assessment been initiated as the result of a breakdown of public health measures (e.g., flooding affecting waste control and potable water treatment)?"*

The effectiveness of a risk assessment being able to achieve relevant objectives will be enhanced by unambiguously establishing, at the outset, the problem(s) that need(s) to be addressed and what objectives will ensure that the risk assessment succeeds.

Finally, uncertainty is an unavoidable reality in all stages of risk assessment. At a minimum, uncertainty must be addressed at each of the following steps delineated in Sections 4.3.2 through 4.3.5. Common issues that should be addressed have been provided for the stages described in the following subsection (NRC, 1994). Although the points were provided for a generic risk assessment by an expert panel, many of the questions raised will often not be possible to answer. Seeking answers to the questions posed will, if nothing else, reveal how little is known.

4.3.2 Hazard Identification

Perhaps the most important step in hazard identification is to accurately and fully understand what is meant by *hazard* as opposed to *risk*. Although these terms are often used interchangeably in public discourse, they have important and distinctly different meanings as used in risk assessment. The ADWG (NHMRC, 2023, p. 28) provides the following detailed definitions for the purposes of ensuring safe drinking water.

- *"A hazard is a biological, chemical, physical or radiological agent that has the potential to cause harm."*
- *"A hazardous event is an incident or situation that can lead to the presence of a hazard (what can happen and how)."*
- *"Risk is the likelihood of identified hazards causing harm in exposed populations in a specified timeframe, including the severity of the consequences."*

The fundamental distinction drawn between hazard and risk that applies throughout this book is that hazard has the potential to cause harm, while risk is about the likelihood of that harm being realized, thereby requiring risk to include a probability

component. Also important is the realization that risk is inherently a prediction or an expectation of what will happen. The importance of this distinction about risk is elaborated in Section 6.

This can be further understood by referring to the quantitative definition of risk offered by Kaplan and Garrick (1981) in the first issue of the journal *Risk Analysis*, in which they defined risk as a multi-dimensional entity comprised of the answers to three questions.

1) What can go wrong?
2) How likely is it?
3) What are the consequences?

Further elaboration of this definition should include a specified time for the evaluation (e.g., annual risk is substantially different from lifetime risk). Perhaps more controversial is consideration of human and social factors, as discussed by Renn (1992), leading to an explanation (Hrudey, 2000) of risk as being a prediction or expectation that involves the following elements:

- a hazard (the source of danger),
- uncertainty of occurrence and outcomes (expressed by the probability or chance of occurrence),
- adverse consequences (the possible outcomes),
- a time frame for evaluation, and
- the perspectives of those affected about what is important to them.

With concepts of hazard and risk carefully distinguished, hazard identification can be pursued. The following are key issues for hazard identification within environmental health-risk assessment:

- the nature, reliability, and consistency of human and animal studies,
- the availability of information about the mechanistic basis for activity,
- the relevance of the selected animal studies to humans, and
- whether the mode of toxic action is well understood—knowledge of the mode of action is critically important in interpreting carcinogenic responses and for assessing the risk of chemical mixtures.

The last point, assessing the risk of chemical mixtures, has posed a substantial challenge to public health risk assessment because of the unlimited scope of the variables that arise with any attempt to gather evidence. The U.S. EPA launched a major decades-long research program to investigate mixtures of DBPs (Simmons et al., 2002). The issues about assessing chemical mixtures are discussed in Box 2.

Sources of evidence to be considered for hazard identification are summarized in Figure 10 and ranked according to their comparative value in terms of weight of evidence. For our purposes, I will focus on the comparative strengths and weaknesses of animal studies (experimental toxicology) versus observational human epidemiology, which are.

- Epidemiology directly assesses human health risk (on a sample of humans).
- Epidemiology requires no adjustment for differences in absorption, metabolism, detoxification, and excretion from animals to humans needs to be considered (but these do vary among humans).
- Sample sizes for human studies may be much larger than those available for animal studies (but there is much less control over confounders and bias).
- Genetic diversity in humans may be much wider than in experimental lab animal strains (which adds realism at the cost of increased variability in response).
- Epidemiological studies may include diverse groups (young, old, susceptible) that are excluded from laboratory animal toxicological studies (with an attendant increase in response variability).
- Some aspects of mental function or behavior, and more subjective effects such as nausea or headache, can be better assessed in human studies (it is impossible to ask a rat about its headache or state of mind).

Sources of uncertainty to be addressed at the hazard identification stage, according to the NRC (1994), include what is known about:

- whether a given contaminant is able to cause cancer in laboratory animals versus in humans,
- the types of studies that have been performed on laboratory animals and humans and how reliable and consistent the results are,
- the mechanisms of toxic action, and
- whether animal responses relevant to humans.

Exercise 6 is concerned with formulating a realistic concept of risk.

4.3.3 Dose–Response Assessment

Dose–response assessment is central to quantitative estimate of risk because it addresses the character and shape of the relationship(s) between exposure to the agent(s) under consideration and the adverse health outcome(s) that have been revealed. There are some issues that require scrutiny: extrapolation of dosage from high experimental range to low environmental exposure; interspecies scaling of dosage from experimental animals to humans; and translation of dosage for different routes of exposure.

Many details are involved in addressing these critical issues that are beyond the scope of this overview discussion. An overview of dose-response can be related to a generic dose–response curve depicted in Figure 15.

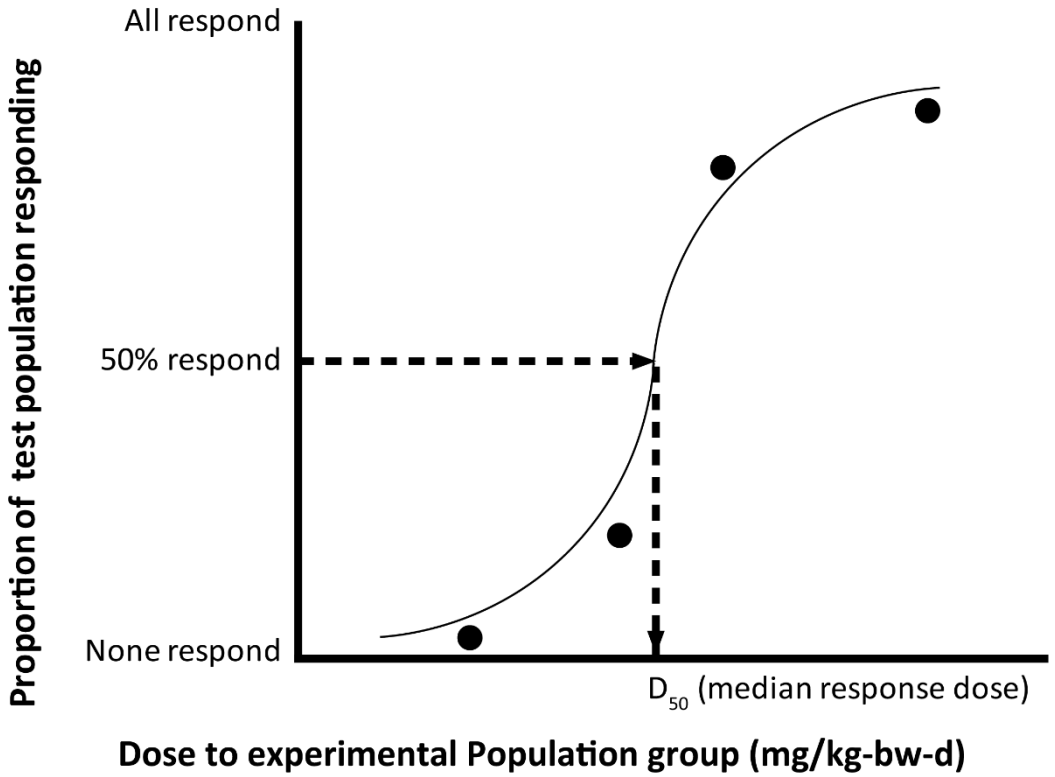

Figure 15 - Generic dose–response curve for a population group experiment (a quantal dose-response is not gradational, either a response is produced or it is not). This is illustrated as if four groups were given different doses. This approach can be used for acute (short-term) or chronic (long-term) health outcomes. For acute lethal toxicity, the LD_{50} (median lethal dose) is widely used to characterize the short-term toxicity of the chemical agent.

Generally, environmental health risk assessment is focused on low level environmental exposures that are below levels that would cause acute response, so the remaining discussion addresses chronic health effects that may arise at lower levels. An important feature of the lower environmental levels is that the dose scale must typically be shown on a log scale to cover the wide range of exposures that apply. Given this reality, it is important to recognize there is no zero on a log scale. Likewise, very low dose levels will often fall below a detectable response level (Figure 16). This approach can be used for acute (short-term) or chronic (long-term) health outcomes. For acute toxicity, the LD_{50} (median lethal dose) is widely used to characterize the short-term toxicity of the chemical agents. For agents that are deemed to exhibit a threshold below which no adverse effects occur, the lowest-adverse-effects level (LOAEL) and/or the no-adverse-effects level (NOAEL) have historically provided a basis for assigning a risk-based criterion for managing health risk from that agent, as is discussed in Section 4.3.5.

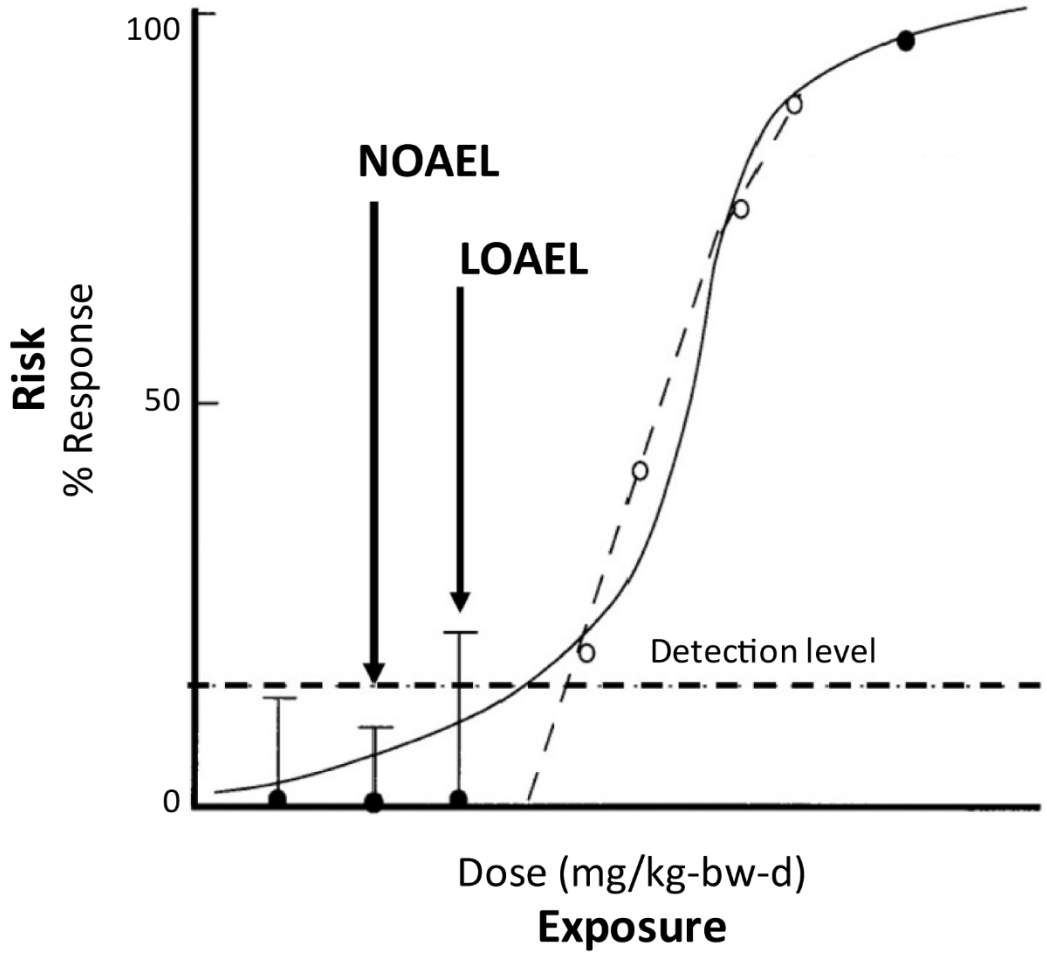

Figure 16 - Generic dose–response curve for a population-group experiment (a quantal dose-response is not gradational, either a response is produced or it is not). Four groups were given different doses to generate the data shown as open circles. The filled circles were estimated by modeling to define low dose responses including the LOAEL (lowest adverse effects level) and NOAEL (no adverse effects level). The detection level is shown as a bold dashed line.

This pragmatic approach has been criticized for failing to make full use of the experimental evidence, which has led to the so-called benchmark dose (BMD) approach (Crump, 1984; US EPA, 2012). The BMD approach involves determining a best-fit curve to the experimental data, then specifying a low-level response, typically 5 or 10 percent to define the benchmark dose (BMD_5 or BMD_{10}) and using the 95-percent confidence interval for the fitted model to determine a lower bound level (BMD_5 or BMD_{10}; Figure 17). Software has been developed to estimate these parameters for a given data set (US EPA, 2012). This approach has been widely adopted both for agents believed to exhibit a threshold as well as those for which a threshold has not been established, but the technical details are beyond the scope of this discussion. US EPA (2012) guidance on this topic alone cites 116 references.

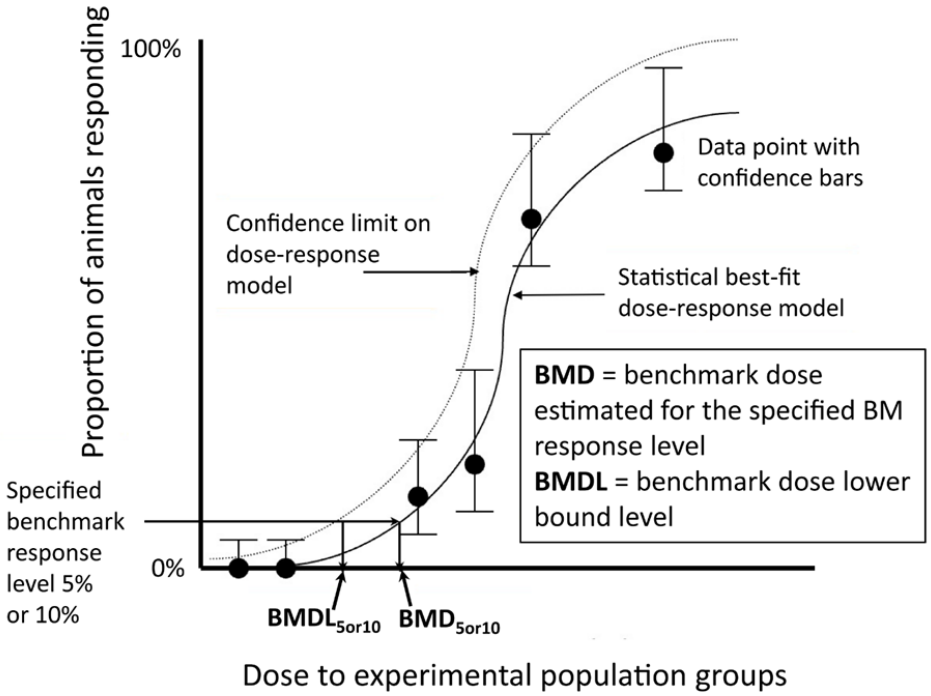

Figure 17 - Benchmark dose approach for a dose–response curve. The arrow indicating the specified benchmark response level is positioned at approximately 10% in this diagram, but in some cases 5% is used.

One major issue that has dominated the quantitative elements of risk assessment is the extrapolation of the response for the lowest experimental dose to environmentally relevant doses. That issue has been encountered most often with cancer-risk assessment for carcinogens where evidence of a threshold has not been obtained. In such cases, the precautionary assumption is that there may be no threshold—that is, any level of exposure may cause a non-zero cancer response. The substantial problems arising in this particular application are elaborated in Section 4.3.5, *Risk Characterization*, to introduce the wide range of challenges involved.

Sources of uncertainty that should be addressed at the dose–response assessment stage (NRC, 1994) include what is known about:

- biological mechanisms and dose–response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment;
- relationships between extrapolation models selected and available information on biological mechanisms;
- whether appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;
- basis for selecting interspecies dose scaling factors to account for scaling dose from experimental animals to humans;
- correspondence between the expected route(s) of exposure and the route(s) utilized in the hazard studies; and
- interrelationships of potential effects from different exposure routes.

4.3.4 Exposure Assessment

The critical importance of exposure assessment to supporting causal inference in epidemiology was raised in Section 3.3.5 "*Study Design for Showing Causation*". That importance applies equally well to risk assessment. The challenges in accurately characterizing exposure are substantial, yet, unlike dose–response assessment that faces intractable unknowns that can be addressed only by models and assumptions, exposure assessment can be improved with the application of available monitoring methods—it is primarily a matter of practical limits on investment of study resources.

That said, for a site-specific risk assessment, maximizing the evidence that can be obtained about exposures is often not prioritized in relation to making assumptions and applying predictive models. In one egregious example of a risk assessment for a contaminated site, major resources were invested into modeling the expected uptake of contaminants by vegetables grown in the garden of a nearby resident. The modeling was based on a single soil sample and generic contaminant transfer models rather than performing representative sampling and target analyses of the variety of vegetables that were actually being grown in the garden.

Exposure factors have been estimated and compiled for a variety of common exposure routes (e.g., drinking-water consumption rates, breathing rates), thereby allowing for relevant assumptions (enHealth, 2012b; US EPA, 2001). These provide a convenient source for exposure estimates in the absence of direct data.

As a way to illustrate the challenges of comprehensive exposure assessment, the relevant specific issue of human exposure to drinking-water DBPs are explored here. This topic is in its 50th year as an environmental health-risk issue (Hrudey & Fawell, 2015) with trihalomethanes (THMs: chloroform, bromodichloromethane, dibromochloromethane, and bromoform) having been identified as unintended by-products of drinking-water chlorination in 1974. Perhaps because of the pervasive exposure of drinking-water consumers to chlorination, the DBP issue has remained a focus of numerous health studies, many of which are remarkably poorly conceived. A study by Evlampidou and others (2020) that claimed to estimate the cases of bladder cancer caused by THMs in the European Union (EU)—4,518 cases per year in a total population of 482,682,585—by extrapolating from annual mean THM levels for each of 28 countries despite the marginal association of bladder cancer with THM exposure (Hrudey et al., 2015) is one example. Unfortunately, the fear that DBPs in drinking water cause cancer has contributed to several fatal drinking-water outbreaks where chlorine disinfection was absent or inadequate (Hrudey & Hrudey, 2004, 2014, 2019, 2021).

The complexity of exposure assessment for this pervasive exposure was the subject of a three-day workshop hosted by Health Canada (Arbuckle et al., 2002) involving 24 international experts. The workshop presented a long list of research needs worthy of attention (Box 3↴), most of which remain unresolved more than 20 years later. These gaps

in knowledge and approach to gathering evidence bear directly on the credibility of epidemiologic evidence for DBPs being causally associated with human health effects. If the number of issues listed seems like overkill, Figure 18 illustrates the complexity of DBP exposures in relation to exposure routes alone. Clearly, not all of the possible routes of exposure are likely to be major ones that warrant explicit measurement, but they should be considered and eliminated from further study if they are not substantial.

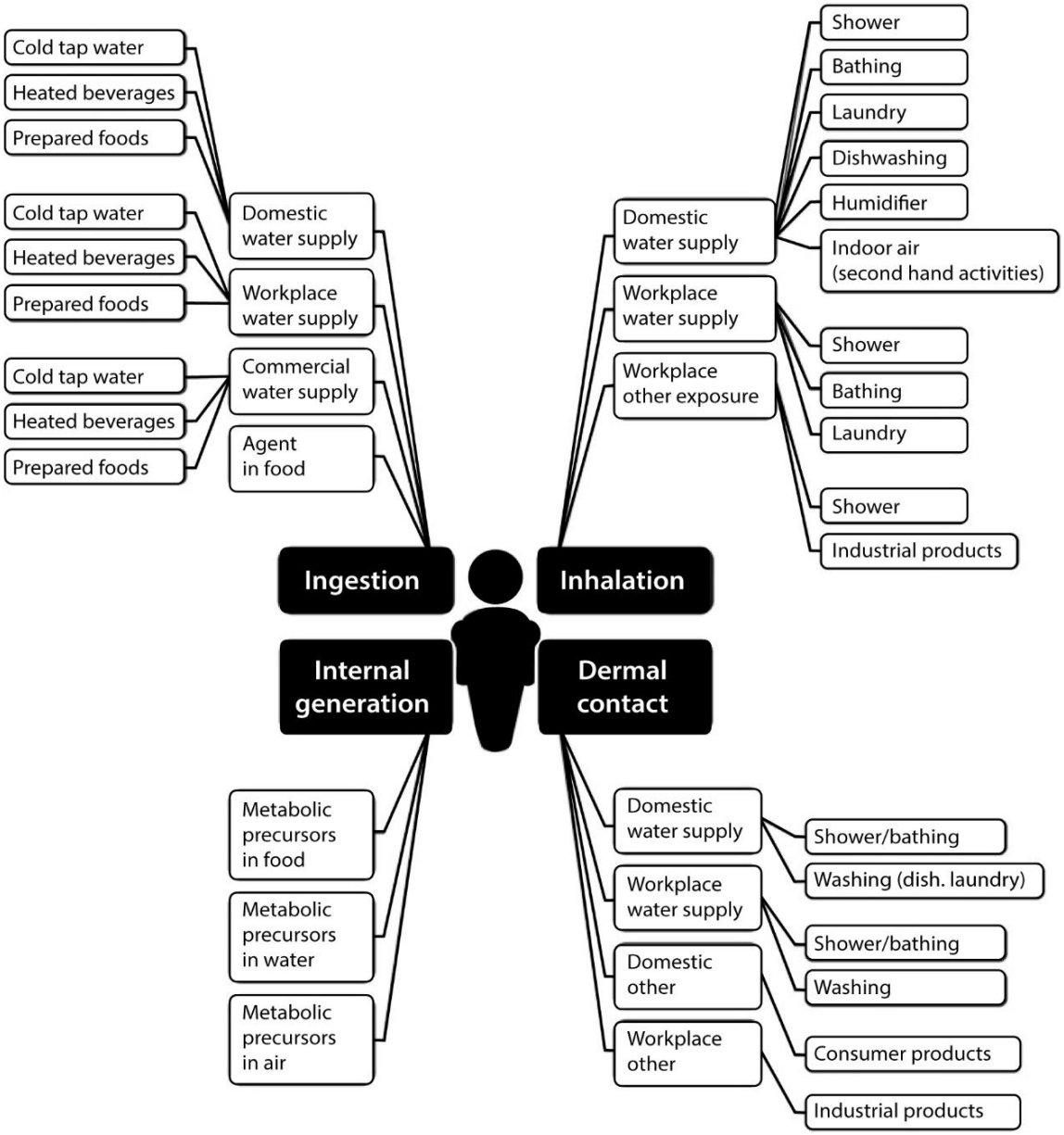

Figure 18 - Overview of possible individual exposure routes for DBPs.

Biomarkers were one major focus of attention in the research needs identified by Arbuckle and others (2002). Biomarker refers to a measurable parameter that could be monitored on an individual basis and might reliably provide evidence of exposure to a specified agent or agents. A major research effort (Bader et al., 2004; Froese et al., 2002; Zhang et al., 2009a,b) was directed at one promising biomarker for DBP exposure:

trichloroacetic acid (TCAA). TCAA offered the advantage of being readily detectible in chlorinated drinking water, being poorly metabolized such that it was largely excreted in urine. Humans are generally not exposed to TCAA by other routes These features suggested it could serve as a potentially reliable indicator of the consumption of chlorinated drinking water that could satisfy a critical missing link in individualized exposure estimates for epidemiologic studies of human populations.

Two pilot trials, one strictly observational (Froese et al., 2002) and the other experimental (Bader et al., 2004), showed enough promise to justify major investment in a larger-scale experimental trial. This involved student volunteers consuming controlled amounts of municipal drinking water already containing TCAA from a city with a population of 700,000 while providing daily first morning urine samples for TCAA analysis (Zhang et al., 2009a,b). The results confirmed the reliability of TCAA as a statistically significant biomarker for consumption of chlorinated tap water (Zhang, 2009b), but the scatter of these results from a substantially controlled exposure scenario offered little promise for resolving the dilemma of obtaining meaningful individual measures of exposure to chlorinated drinking water for a full-scale epidemiologic study (Figure 19).

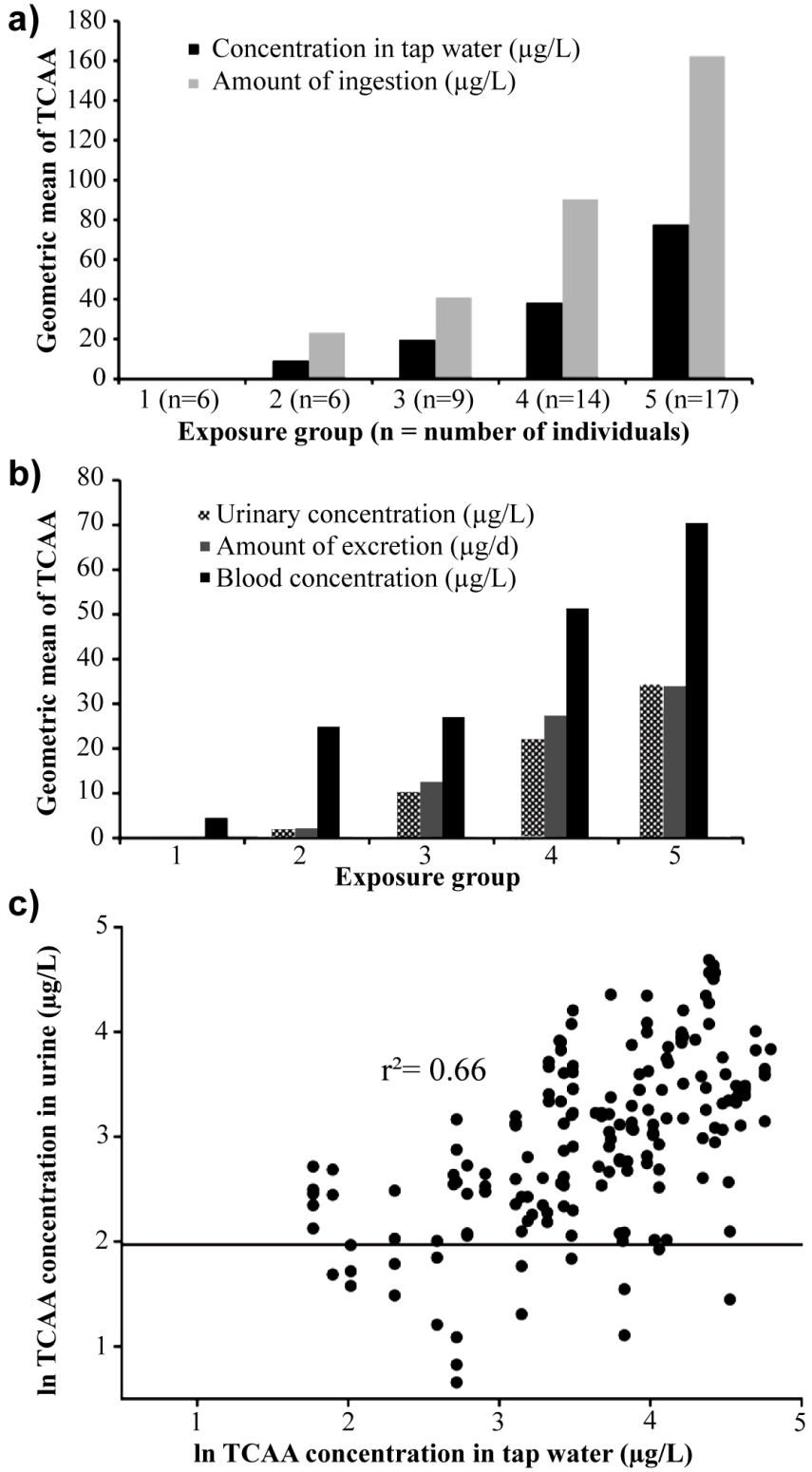

Figure 19 - Results from an experimental pilot trial for TCAA as a biomarker of exposure to chlorinated drinking water. a) Shows the increasing amount of TCAA consumed by exposure groups 2 through 5. Exposure group 1, received only bottled water but blood still showed a detectable level of TCAA. b) Shows increasing indicators of TCAA in urinary concentration, mass of TCAA excreted in urine and concentration of TCAA in blood. c) Shows a scattered correlation (r^2= 0.66) that is significant at $p < 0.001$). The axes are ln-ln scale (modified from Zhang et al., 2009a).

This research experience—conducted over a decade of focused research—raises a red flag about the feasibility of securing meaningful individual exposure assessment. Concerns about the poor exposure assessment in DBP research studies have been countered by an epidemiological argument that if an association is causal, weak exposure assessment that results in non-differential misclassification of exposure will bias the resulting RR toward the null value. That bias will show a weaker association than truly exists (Hrudey, 2012). This epidemiological argument can be true, although it requires that the misclassification is non-differential—which is not easy to verify—but the solution to the insensitivity of studies with poor exposure assessment can be resolved only by performing much better individualized exposure assessment, something that the TCAA biomarker research aimed to achieve.

Sources of uncertainty that should be addressed at the exposure–assessment stage include knowledge "*about the paths, patterns, and magnitudes of human exposure and number of persons likely to be exposed"* (NRC, 1994, p. 71).

4.3.5 Risk Characterization

As noted in the introduction to Section 4.3, *Overview of Guidance on Environmental Health Risk Assessment*, the distinction between risk assessment and risk management was first clearly and influentially formulated in the *Red Book* (NRC, 1983)—risk assessment being the data/evidence-intensive process of estimating health risks and risk management being the mostly pragmatic, policy-driven process of limiting risks to within goals established for this purpose.

Risk characterization serves as the bridge between risk assessment and risk management (US EPA, 1995). Risk assessors are cautioned that this distinction

> *"means that scientific information is selected, evaluated, and presented without considering issues such as cost, feasibility, or how the scientific analysis might influence the regulatory or site-specific decision. Assessors are charged with (1) generating a credible, objective, realistic, and scientifically balanced analysis; (2) presenting information on hazard, dose-response, exposure and risk; and (3) explaining confidence in each assessment by clearly delineating strengths, uncertainties and assumptions, along with the impacts of these factors (e.g., confidence limits, use of conservative/non-conservative assumptions) on the overall assessment"* (US EPA, 1995, p. 3).

In providing the bridge to risk management, risk characterization supplies the following (enHealth, 2012, p. 66):

- *"integrates the information from hazard identification, dose–response assessment and exposure assessment*
- *discusses chemicals of potential concern (COPC) and quantifies risks associated with these specified chemicals*

- *identifies the contributions to risk from all the relevant exposure pathways, and aggregates these risk estimates*
- *considers the possibility that multiple COPCs may have cumulative effects, and considers options for best integrating the effects of combined exposures*
- *describes the risks to individuals and populations in terms of nature, extent and severity of potential adverse health effects*
- *provides an evaluation of the overall quality of the assessment and the degree of confidence the risk assessors have in the estimates of risk and conclusions drawn; this should be based on appropriate uncertainty and sensitivity analyses*
- *communicates results of the risk assessment to the risk manager [and]*
- *provides key information for risk communication."*

Threshold Risk Estimation

Dose–response assessments that presume a threshold below which no adverse effects occur can express that threshold as a NOAEL or LOAEL or estimate it using the BMDL approach. A resulting toxicological reference value (TRV), tolerable daily intake (TDI) or reference dose (RfD) is determined by dividing the NOAEL, LOAEL, or BMDL by a set of uncertainty factors, which are also less accurately described as *safety factors*.

The TRV, TDI or RfD is calculated as shown in Equation (3).

$$\text{TRV TDI or RfD} = \frac{(\text{NOAEL, LOAEL, or BMDL})}{(\text{UF1})\,(\text{UF2})\,\ldots\,(\text{UFn})} \tag{3}$$

A TRV (expressed in units of dose or intake, mg of agent per kg-body-weight-day) derived from a toxicity bioassay can be used to estimate an indication of risk by dividing the estimated intake of the toxic agent in question from the exposure assessment by the TRV to yield a hazard quotient or hazard index shown in Equation (4).

$$\text{Hazard quotient or hazard index} = \frac{\text{Estimated daily intake } \left(\frac{\text{mg}}{\text{kg-bw-d}}\right)}{\text{TDI or TRV } \left(\frac{\text{mg}}{\text{kg-bw-d}}\right)} \tag{4}$$

Non-threshold Risk Estimation

Dose–response assessments that presume there may be no threshold for adverse effects should normally be reserved for genotoxic (DNA-reactive), initiator carcinogens. The assumption of no threshold is a cautious assumption that can be neither proven nor disproven but is conceptually based on the premise that a single DNA mutation of the necessary type—that is not repaired by natural DNA repair mechanisms—could

conceivably, by means of cell replication, be the initiating step in the formation of a cancerous tumor.

This notion was originally conceived by analogy with the cancer-initiating capacity of ionizing radiation. The reality that this tumor-initiating capacity has a low probability over a lifetime for any individual human is established by the reality that all humans are exposed to a non-zero level of background ionizing radiation but not all humans will experience cancer. Although the proportion of humans who will experience cancer is substantial, no one would seriously suggest that all such cases are caused by background ionizing radiation. If that was the sole cause, there would be little merit in the attention that our societies devote to reducing cancer risk from other carcinogens.

The dominant approach to quantitative cancer-risk assessment based on a no-threshold assumption used the so-called linearized multi-stage (LMS) model. Although it is well accepted that cancer is a multistage process, the LMS model is not derived from any attempt to model cancer mechanisms; it is a simple exponential expansion amenable to fitting data, such as obtained from a cancer bioassay, and is expressed as Equation (5).

$$p(d) = 1 - exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_k d^k)] \tag{5}$$

where:

p = the probability of tumor formation (unitless)

d = the dose of the agent under test (mg/kg-bw-d)

q = the exponential coefficient (units are inverse of associated term)

The extra risk above background—ER at dose d—is expressed by Equation (6).

$$\mathrm{ER}(d) = \frac{p(d) - p(0)}{1 - p(0)} \tag{6}$$

This expression simplifies at very low dose, using the upper 95-percent confidence limit for q_1 (i.e., $q_1{}^*$) to yield Equation (7).

$$\mathrm{ER}(d) = q_1{}^* \, d \tag{7}$$

where:

$\mathrm{ER}(d)$ = the excess, over background, lifetime cancer risk for dose, d (unitless)

d = the lifetime average daily dose (mg/kg-bw-d)

$q_1{}^*$ = the upper bound (95-percent confidence limit) cancer slope factor (CSF), also referred to as the cancer potency factor $(\text{mg/kg-bw-d})^{-1}$

This simplified calculation has allowed anyone who can multiply a few numbers to generate an upper bound estimate of lifetime cancer risk given an estimate of the lifetime average daily dose, leading to countless misrepresentations of cancer risk, including using this equation for a single point estimate for a one-time exposure (versus daily exposure for a 70-year lifetime).

Concerns arose throughout the 1980s and early 1990s about this approach for quantitative cancer-risk assessment, including those of Hrudey (1998). Specifically, Hrudey (1995) presented concerns to a one-day Royal Society (London) workshop organized by Sir Frederick Warner and attended by 55 British health and safety regulators and research experts, including cancer epidemiology icon Sir Richard Doll (who established smoking as a cause of lung cancer) and eminent statistician Professor D. J. Finney (who proposed probit analysis, the standard for analyzing bioassay data). Particularly troubling was the revelation reported by Krewski and others (1993) and NRC (1993) that demonstrated a remarkable negative correlation ($r = -0.941$) between estimates of the CSF and the maximum tolerated dose (MTD), the highest dose typically used for cancer bioassays chosen to maximize the likelihood of detecting tumors in an experimental animal bioassay (Figure 20). The other doses tested have typically been a fixed fraction of MTD.

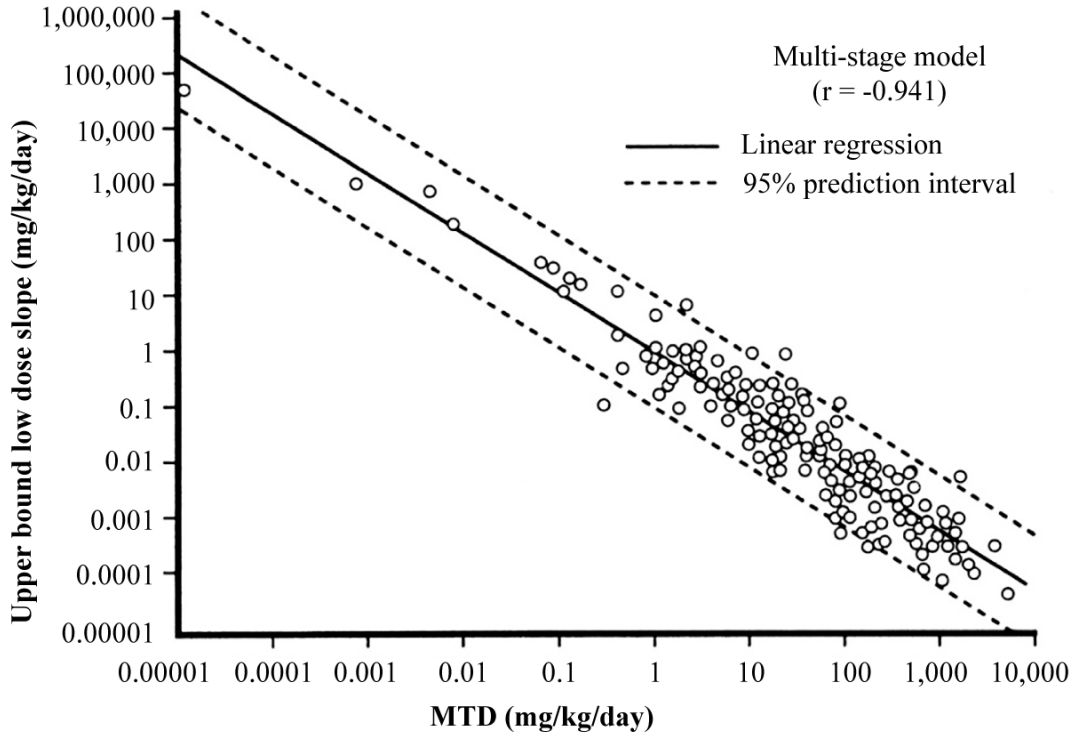

Figure 20 - Observed relationship between CSF and the MTD from cancer bioassays of 191 agents (after Krewski et al., 1993).

The finding by Krewski and others (1993) strongly suggests that the acute toxicity of an agent (as represented by MTD) is a major determinant of the predicted CSF. The values plotted almost entirely within a factor of ten higher or lower than the regression line

for the CSF values that span 10 billion-fold. This outcome is not surprising because the LMS model allowed the point of departure (POD) for the linear extrapolation to be defined by a fixed fraction of the MTD. The lower the MTD, the closer the POD for the linear extrapolation is to the origin (zero dose), constraining the CSF to be steeper than for a POD corresponding to a higher MTD.

These concerns have led to more common adoption of the BMD approach to select a POD, typically chosen as the $BMDL_{10}$, although some have advocated for $BMDL_5$ or lower. The BMD approach reduces but likely does not entirely eliminate the role of the MTD in influencing the estimation of the CSF. BMD has been used to identify the POD for such assessments since around the year 2000. However, it should be noted that many CSF values were estimated before 2000. As of 2023, the US EPA Integrated Risk Information System (IRIS) database currently lists 572 agents (not all are categorized as carcinogens), but more than 80 percent of the listed agents have not been updated since 2000.

Exercise 7 takes a closer look at chloroform and the risk of consuming the guideline level of chloroform over a lifetime.

Uncertainty in Risk Characterization

Uncertainty is a major issue at every stage of risk assessment and certainly must loom large for translating risk-assessment estimates into risk-management actions (Finkel, 1990; US EPA, 1995). While there is no absolute authority for categorizing uncertainty, there is a clear distinction between *true* uncertainty (sometimes referred to as knowledge uncertainty) and variability. This distinction is best understood by considering variability first.

Variability reflects true differences (heterogeneity) in the many parameters considered in the various stages of risk assessment (such as exposure levels and susceptibility). Variability creates uncertainty to the extent that the true differences that can be measured are not adequately measured or, if known, it may not clear which values are best used for predicting risk. Variability is distinguished by the fact that it can be resolved by more detailed analysis and data gathering.

Knowledge uncertainty is more challenging, as has been displayed by an infamous quote in 2002 attempting to justify the need to invade Iraq based on flawed intelligence about it having weapons of mass destruction.[19] Finkel categorizes uncertainty into parameter uncertainty (measurement errors, random errors, and systematic errors), model

[19] Response given by US Secretary of Defense Donald Rumsfeld, seeking to justify the 2003 invasion of Iraq, to a question at a news briefing on February 12, 2002, about the lack of evidence linking the Iraqi government to the supply of weapons of mass destruction to terrorist groups: "*Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say, we know there are some things we do not know. But there are also unknown unknowns—the ones we don't know we don't know. And if one looks throughout the history of our country and other free countries, it is the latter category that tends to be the difficult ones*."

uncertainty (surrogate variables, excluded variables, abnormal conditions, *incorrect model form* [emphasis added]), and decision-rule uncertainty. Despite guidance (US EPA, 1995) to consider and report uncertainty in risk-assessment estimates to inform risk-management decisions, the open-ended nature of all sources of uncertainty makes this need likely the most challenging aspect of risk characterization.

Kimball (1957) described an addition to the conventional Type 1 (false-positive error—e.g., convicting an innocent defendant) and Type 2 (false-negative error—e.g., failing to convict a guilty defendant) statistical errors. Kimball explained that so-called Type 3 statistical errors are the most problematic: errors caused by dealing with an issue so poorly understood that the underlying models are incorrect.

Uncertainty is inherently involved in any health-risk assessment because of numerous factors, including the following (Hrudey et al., 2012, p. 9–10).

- *"Uncertainty about the specific nature of a hazard (e.g., What adverse effect(s) occur(s)? What levels of exposure are required?).*
- *Uncertainty about the ability of a hazard to cause relevant adverse outcomes at plausible drinking-water exposure levels (e.g., What is the evidence of causation?).*
- *Probability estimates that are invariably less than 100 percent, making occurrence for any particular time and place uncertain.*
- *Probability estimates that must be based on subjective probabilities, often with little frequency-based evidence making for necessarily high uncertainty in probability estimates.*
- *Probability estimates that must be based on subjective probabilities, often with little frequency-based evidence making for necessarily high uncertainty in probability estimates.*
- *Uncertainty associated with analytical measurements. (Are samples representative?)*
- *Uncertainty about health effects from combinations of contaminants. (Are effects additive or could there be synergistic or antagonistic effects?).*
- *Variability in consequences because of individual differences in exposure (How much or does any individual drink the water?) or susceptibility (How susceptible is an individual to an adverse outcome?).*
- *Variability among individuals in their individual time windows (e.g., visitors versus long-term residents for short-term exposure; infants versus seniors for lifetime exposure).*
- *Variability in perspectives of what is most important among different individuals (e.g., How much is anyone willing to pay to reduce a very small risk even lower?)."*

Sources of uncertainty that should be addressed at the risk-characterization stage include the following (NRC, 1994, p. 72).

> *"What do other assessors, decision-makers and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment? What are the strengths and limitations of the assessment?*

1. *Numerical estimates should never be separated from the descriptive information that is integral to the risk assessment. For decisionmakers, a complete characterization (key descriptive elements along with numerical estimates) should be retained in all discussions and papers relating to an assessment used in decision-making. Differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk-management decisions in cases with ostensibly identical quantitative risks. That is, the number alone does not determine the decisions.*
2. *Consideration of alternative approaches involves examining selected plausible options for addressing a given uncertainty. The strengths and weaknesses of each alternative approach and as appropriate, estimates of central tendency and variability (e.g., mean percentiles, range, variance). The description of the option chosen should include the rationale for the choice, the effect of option selected on the assessment, a comparison with other plausible options, and the potential impacts of new research."*

Exercise 8 considers distinctions about uncertainty that bear on risk assessment and risk management and how these different types of uncertainty be dealt with in characterizing and managing risk.

4.3.6 Quantitative Microbial Risk Assessment (QMRA)

The concept or quantitative microbial risk assessment (QMRA) was thoroughly introduced by Haas and others (1999) and updated by Haas and others (2014). This approach provides a basis for setting health-based targets for pathogen-caused adverse health effects, a premise introduced by the WHO (2004) drinking water guidelines that first proposed water safety plans. The US EPA (2014), WHO (2016), and Health Canada (2018) have provided manuals describing the key elements of this approach for the purposes of guiding drinking water quality. WHO (2016) has outlined QMRA as consisting of four steps, similar to chemical risk assessment: problem formulation, exposure assessment, health effects assessment, and risk characterization. Collectively, these documents provide a well documented, detailed approach to applying QMRA to the particular exposure scenarios.

As with quantitative cancer risk assessment that dated back to the 1970s, QMRA had to acknowledge that it was not realistic to prescribe zero risk of the adverse outcomes, as a universal outcome, but the target could be set low enough that individual water consumers should not be likely to experience a serious illness from drinking water exposure. Because the nature of adverse outcomes from consuming pathogen contaminated drinking water involved various degrees of illness, as well as death, the concept of Disability-Adjusted Life Years (DALYs) can be applied as they had been used in quantifying differing disease outcomes for estimating burden of disease.

The essence of the DALY is that it combines both the years of life lost with the years of living with disability to judge the severity of a disease outcome as shown by Equation (8).

$$\mathrm{DALY} = \mathrm{YLL} + \mathrm{YLD} \tag{8}$$

where:

YLL = sum of years lost relative to life expectancy

YLD = sum of years living with specified disability

Experience in various jurisdictions has led to estimates of YLL and YLD for various pathogens and models to complete the steps necessary for application of the QMRA model. More detail about how water utilities can apply QMRA for pathogen risk management that goes beyond just satisfying the numerical water quality guidelines is provided for Australia by Walker and others (2015).

The application of this approach to groundwater systems—while definitely not intended to be generic guidance, but rather to serve as an illustration how QMRA can be applied to groundwater systems—is outlined (Walker et al., 2015). This water industry document proposed that groundwater systems could be judged to be Tier 1 (mandatory for all groundwater sources) or Tier 2 (where pathogen data is sufficient to perform QMRA).

Tier 1 involves clarifying whether the groundwater system is or is not groundwater under the influence of surface water (Walker et al., 2015, p. 27) as follows.

"***Sanitary Survey***

The sanitary survey should cover aspects such as:

- *hydrogeology - nature and thickness of strata, transmissivity (flux), recharge areas*
- *bore characteristics - depth to groundwater, depth to bore pump, drawdown characteristics*
- *pathogen sources - point and diffuse*
- *well-head protection - sealing, fencing, flooding.*

Vulnerability Assessment

Groundwater NOT under the influence of surface water will typically have the following characteristics:

- *protected headworks (fenced, above flood level)*
- *bore sealed from ingress (including flood events)*
- *depth to groundwater > 10 m*
- *depth to bore pump > 15m*
- *overlying material homogenous, sand, gravel*
- *TDS does not decrease following rainfall, high flow, or floods*
- *turbidity does not increase following rainfall, floods etc.*

Microbial Indicator Assessment

Where the vulnerability assessment indicates the source is not under the influence of surface water then this can be confirmed by raw water testing if it shows zero E. coli detected in raw water samples over a long period, including event-based samples.

Tier 2 is optional but can be used if suitable raw water pathogen data is available. *In this case, a QMRA can be performed on the source and the result used to complement (not replace) the Tier 1 assessment. The Tier 1 and Tier 2 assessments are combined to produce the final source water assessment and hence the log reduction requirements for bacteria, virus, and protozoa as per the surface water assessment."*

These requirements can be used to calculate log reduction criteria for the source water system under study (Section 2.4.3 "*Microbial Contaminants in Groundwater*").

5 Health Risk Management

5.1 Precautionary Bias of Public Health

The concept of disease prevention has always been a key element of public health practice. Horton (1998, p. 252) suggested a need to be more explicit and referred to a version of the precautionary principle he adapted from a 1990 UK Department of Environment declaration of that principle.

> *"We must act on facts, and on the most accurate interpretation of them, using the best scientific information. That does not mean we must sit back until we have 100% evidence about everything. Where the state of the health of the people is at stake, the risks can be so high and the costs of corrective action so great, that prevention is better than cure. We must analyse the possible benefits and costs of action and inaction. Where there are significant risks of damage to the public health, we should be prepared to take action to diminish those risks, even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it."*

Goldstein (2001) acknowledged Horton's advocacy while noting that public health interventions had often not been effective in this regard, citing examples such as the arsenic-induced disasters in Bangladesh in which public health authorities encouraged adoption of tube wells for drinking water to reduce the intolerable burden of waterborne disease associated with faecally contaminated surface waters. The result has been an epidemic of arsenic-associated disease, including cancer, because the groundwater was subsequently found to be contaminated by high naturally occurring levels of arsenic.

The precautionary principle was enshrined in the so-called Rio Declaration emerging from the 1992 United Nations Conference on Environment and Development (UN, 1992) and was stated as Principle 15 of that declaration.

> *"In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."* (UN, 1992, p. 3)

Although there have been many formulations and interpretations of the precautionary principle, the UN declaration is probably the most commonly cited. Kreibel and others (2001, p. 871) have expanded on this topic, providing an overview of the history and practice. They adopt a consensus statement attributed to Raffensperger and Tickner (1999): "*[W]hen an activity raises threats to harm human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically*."

They also note that the notion of the precautionary principle arose from an English translation of the German word *Vorsorgeprinzip*, which can be read as "foresight principle," although it is now commonly read as equivalent to the precautionary principle.

Who could argue with exercising foresight when seeking to manage environmental health risks? Yet, there are practical limits to how precautionary we can be before sensible pursuit of foresight becomes futile and counterproductive. Insights into those limits is outlined in the next section.

5.2 Approaches to Precaution and Practical Limits to Precaution

Public health and drinking-water safety are inherently interdisciplinary in scope, as evidenced by the preceding sections. One of the challenges of interdisciplinary activities is that terminology within one discipline may have a different meaning within another. Another challenge is that what may be well established knowledge in one discipline is not known or adequately understood in another. An important example of these challenges that has a dominant influence on the pursuit of precaution arises from established knowledge in medical diagnostics that has not been widely recognized within environmental sciences (Hrudey & Leiss, 2003).

First, with regard to terminology, there is considerable potential for misunderstanding about the capacity of monitoring (screening) evidence to reliably detect rare hazards. With respect to safe drinking water, measures are implemented to minimize, as far as possible, the occurrence of contamination that poses a health risk to consumers. A common, if not primary, risk-management measure is routine monitoring of drinking water for possible presence of hazardous contaminants.

Analytical chemists and environmental scientists refer to the capabilities of monitoring methods in terms of their sensitivity and specificity. In analytical chemistry, the basic science underlying detection of contaminants, sensitivity means the ability to detect the signal indicative of a contaminant under analysis above the noise level—that is, how little of a contaminant can be reliably detected. In analytical chemistry, specificity refers to the ability to distinguish the signal for a specific contaminant from the signals from other similar contaminants. However, in the field of medical diagnostics—which relies on analytical chemistry for many, if not most, of its techniques—sensitivity and specificity have different, more explicit definitions.

In terms relevant to our purpose, diagnostic sensitivity is the conditional probability that the evidence will identify a true hazard given that the hazard is present (Hrudey & Leiss, 2003; Hrudey & Rizak, 2004; Rizak & Hrudey, 2006). Diagnostic specificity is the conditional probability that the evidence will identify the absence of a hazard given that it is truly absent.

Finally, the analytical scheme for medical diagnostics defines two valuable parameters: the positive predictive value (PPV) and the negative predictive value (NPV).

PPV is the conditional probability that something is a true hazard given that the evidence identifies it as a hazard. NPV is the conditional probability that something is truly no hazard given that the evidence identifies it as a non-hazard. These characteristics are found to be determined by the false-positive rate, the false-negative rate, and the frequency of the hazard occurrence—i.e., how rare the hazard is. Despite being an unavoidable statistical reality, the relationships among these parameters give rise to counter-intuitive interpretations among most who are not familiar with these realities.

Rizak and Hrudey (2006) found that even experienced drinking-water professionals are more likely than not to misunderstand the meaning of rarely occurring contaminants being detected in drinking water. These findings do not invalidate the need for, or value of, drinking-water monitoring. They do, however, point to the need for health-risk management of drinking water to focus on more than endpoint testing of treated drinking water. The existence of quantitative criteria for drinking-water quality expressed as treated-water guidelines or standards is easy to misinterpret as the primary means for ensuring that drinking water is safe. However, careful consideration of this approach reveals some of its limitations as follows.

- There are economic limits to the number of contaminants that can be measured on a frequent basis.
- Even when contaminants are monitored, results are not reported in real time and in many cases not until days or weeks after the water has been produced and consumed.
- Most of the contaminants listed by drinking-water guidelines or standards have not shown to be the cause of documented drinking-water disease.
- Most of the contaminants listed by drinking-water guidelines or standards are expected to occur only rarely, if at all, creating the false-positive conundrum outlined above.

For all of the foregoing reasons, there has been a constructive trend toward focusing risk management on ensuring adequate barriers to contamination are in place for the hazards a given water supply faces and on ensuring the barriers are operating as intended so they can prevent contaminants from reaching treated water in dangerous quantities. These risk-management approaches—generically described as drinking-water safety plans—are discussed in Section 5.5, *Drinking Water Safety Plans*.

Another main message to discern from the quandary that exists with reliably detecting very rare hazards is that a pursuit of zero is futile; diminishing returns inevitably arise in trying to detect rare hazards. In other words, a precautionary approach that seeks to limit exposures to toxic agents to zero is doomed to failure.

Exercise 9 examines the interpretation of an analytical test for a pesticide in a drinking water supply. The exercise solution goes on to provide information showing that most water professionals do not know how to accurately interpret the data, but they are

not alone as similar misinterpretation has been observed in health care professionals. This demonstrates the need to improve understanding of risk assessment not only in the general public, but also among the professionals that the public relies on to make such assessments.

5.3 Setting Environmental Health Criteria

Key issues to consider in setting environmental health criteria (adapted from EnHealth, 2002) are presented in the form of questions in the following list.

- Why is a criterion being proposed?
- Is a criterion necessary? Are there viable alternative means to achieve the objective?
- How will the criterion be used (as a guideline or standard)?
- Is the criterion limited to a specific situation or for general application?
- Who will be setting the criterion? Are they capable of addressing all the issues?
- What populations will be affected?
- Are there any sensitive or susceptible sub-populations exposed?
- Over what period of time will the population(s) be exposed?
- What patterns of exposure are likely to occur? Are there likely to be short- or long-term fluctuations?
- Are relevant and accurate background exposure data attainable?
- What are the implications of setting criteria at or near the limits of detection?
- Are there viable options to translate from one exposure to another and are all routes credible?
- How will multiple routes of exposure be dealt with?
- Are there defensible default criteria that could be applicable?
- Are there feasible means to measure and meet the possible criterion?
- What are the critical health effects? What is known about their nature, severity, and reversibility?

5.4 Developing Drinking-water Guidelines and Standards (WHO, EU, USA, Canada, and Australia)

The following sections briefly summarize the major international references for drinking-water guidelines, including WHO, the EU, USA, Canada, and Australia. Quantitative criteria for chemical contaminants in drinking water are summarized for these sources in Box 1.

As an aside, it is worth noting a paradox of the standard protocols for guideline derivation. Substances that have been well characterized toxicologically will normally have fewer and smaller uncertainty/safety factors applied in deriving the guideline number. Those substances for which data are limited in quality or quantity will normally get larger safety factors applied, which results in a lower, more stringent guideline value. This

practical reality undermines the merits of comparing guideline numbers between parameters without carefully considering the evidence that was used in deriving the guideline. For example, a jurisdiction that made greater use of the best evidence might conceivably develop a higher guideline number compared to another jurisdiction that made less use of available evidence, preferring to use larger or more uncertainty/safety factors instead.

5.4.1 World Health Organization Guidelines for Drinking-Water Quality

The fourth edition of the WHO Guidelines for Drinking-Water Quality were published in 2022, incorporating the first and second addenda (WHO, 2022a). Box 1 lists the WHO guidelines. WHO has adopted a process for updating guidelines by providing addenda without requiring issuance of an entirely new edition. Because WHO is an advisory and not a regulatory body, the documents are produced as guidelines. Compliance is voluntary, reflecting also the diverse nature of jurisdictions worldwide and their differing resource capacity to implement guidelines.

The structure of the WHO guidelines is summarized in Table 11, which shows four types of targets: health outcome, water quality, performance, and specified technology. The health-outcome target was introduced to orient the quantitative criteria specified or sought in the subsequent three types of targets. The health-based target approach is expressed in terms of DALYs—disability adjusted life years—(Havelaar & Melse, 2003; Gibney et al., 2013) with the target of 10^{-6} DALY (i.e., 1 μDALY) per person per year. Practical details for implementing the health-based target approach are described by Walker and others (2015), an approach recommended in Australia.

Table 11 - Nature and application of health-based targets in WHO (2022).

Type of target	Nature of target	Typical applications	Notes
Health outcome	Defined tolerable burden of disease	High-level policy target set at national level to inform derivation of performance, water quality, and specified technology targets	These guidelines define a tolerable burden of disease of 10^{-6} DALY per person per year
	No adverse effect or negligible risk	Chemical or radiological hazards	Derived from international chemical or radionuclide risk assessments
Water quality	Guideline values	Chemical hazards	Based on individual chemical risk assessments
		Microbial water quality targets are not normally applied	*Escherichia coli* is used as an indicator of faecal contamination and to verify water quality
		Radiological water-quality targets are not normally applied	Radiological screening levels are applied
Performance	Specified removal of hazards	Microbial hazards (expressed as log reductions)	Specific targets set by water supplier based on quantitative microbial risk assessment and health-outcome targets or generic targets set at national level
		Chemical hazards (expressed as percentage removal)	Specific targets set by water supplier based on chemical guideline values or generic targets set at national level
Specified technology	Defined technologies	Control of microbial and chemical hazards	Set at national level; based on assessments of source water quality, frequently underpinned by established or validated performance of the specified technology (e.g., requirement of filtration for surface water)

5.4.2 United States Safe Drinking Water Act Regulations (US DWA)

The US sets regulated drinking-water standards under the US SDWA, originally passed in 1974 and amended in 1986, 1996, and 2016 (US EPA, 2004)[20]. Box 1 lists the US guidelines and standards. Currently, more than 90 contaminants are regulated under the SDWA. The process for adding new contaminants to the regulated contaminants includes steps for identifying unregulated contaminants that are published on a candidate contaminant list (CCL) that is then prioritized based on comprehensive monitoring data (unregulated contaminant monitoring rule—UCMR) with risk assessments and other relevant information. The evaluation considers whether the contaminant may have an adverse effect on human health, whether it is known to occur and is likely to occur in public water systems frequently enough and at levels of public health concern, and whether there is a meaningful opportunity to reduce health risk among consumers of public water systems. Consultation steps include publishing a preliminary determination in the *Federal Register*, followed by public comments and consultation with states and other federal agencies. Following review of the comments, recommendations are published in a final notice in the *Federal Register*. The *Federal Register* is the official journal of the federal government of the United States that contains government agency rules, proposed rules, and public notices.

If regulation is recommended, rule-making for a National Primary Drinking Water Standard is initiated, including an economic analysis, with these being reviewed every six years. Regulated contaminants will have a maximum contaminant level (MCL) specified. For a contaminant with no threshold, below which no adverse health effect can be found, it can be assigned a maximum contaminant level goal (MCLG) that is typically specified as zero for carcinogens. The issue of having a goal of zero is discussed in Section 6, *Health Risk Perception and Consequences*.

If a decision is made to not regulate, a health advisory may be issued or no additional action may be adopted. The regulatory program under SDWA includes, in addition to the primary regulated contaminants, secondary standards for aesthetic contaminants, consumer confidence reports, treatment and operational requirements for microbial contaminants and DBPs, operator certification, special programs for small water systems, and requirements on states to perform source-water assessments.

A constructive illustration of the process was engaged by Hrudey and others (2013) following the listing of five selected nitrosamines on a CCL, leading to extensive monitoring for six nitrosamines under UCMR2 and evidence that drinking water provided a limited route of exposure to carcinogenic nitrosamines (Fristachi & Rice, 2007). N-nitrosodimethylamine (NDMA) was discovered as a drinking-water DBP in Oshweken, Ontario, Canada, in 1989 (Jobb et al., 1993), ultimately leading to WHO, Australian, and

[20] US drinking-water regulations↗

Canadian drinking-water guidelines and extensive published research on its occurrence and removal from drinking water (e.g., Charrois & Hrudey, 2007; Charrois et al., 2007; Qian et al., 2015a; Wu et al., 2014; Zhou et al., 2009; Zhao et al., 2008).

Hrudey and others (2013) extended the estimates of Fristachi and Rice (2007), taking advantage of the results from the UCMR2 that included six nitrosamines, NDMA, *N*-nitrosodiethylamine (NDEA), *N*-nitrosodipropylamine (NDPA), *N*-nitrosopyrrolidine (NPYR), *N*-nitrosomethyl-ethylamine (NMEA), and *N*-nitrosodibutylamine (NDBA) from over 18,000 raw and treated water samples. Hrudey and others (2013) validated the findings of Fristachi and Rice (2007) that drinking water contributed less than 2.8 percent of ingested NDMA and, furthermore—based on evidence of endogenous formation of nitrosamines—drinking water was estimated to produce less than 0.02 percent of total human exposure. These findings provided a compelling case that drinking-water regulation would fail to provide a meaningful public health benefit by only being able to reduce such a low fraction of total human exposure to NDMA. As of the date of publication of this book, no regulation of nitrosamines has occurred under the US SDWA.

5.4.3 Guidelines for Canadian Drinking Water Quality (GCDWQ)

The GCDWQ are established by a federal, provincial, and territorial committee on drinking water (CDW)[21] comprised of representatives from each province and territory, with a secretariat provided by Health Canada. This structure reflects that management of drinking water is a provincial responsibility under the Canadian constitution. Guidelines can be developed specifically for contaminants that meet the following three criteria.

1) Exposure to the contaminant could lead to adverse health effects in humans.
2) The contaminant is frequently detected or could be expected to be found in a large number of drinking-water supplies throughout Canada.
3) The contaminant is detected, or could be expected to be detected, in drinking water at a level that is of possible human health significance.

For those contaminants that are deemed to not meet all these criteria, Health Canada and the CDW may elect to not set a numerical guideline or issue a guideline technical document. In some cases, a health advisory or operational advice may be offered for issues that are more localized concerns.

Because of the provincial jurisdiction for drinking water, the Canadian guidelines are just that—guidelines. Many Canadian provinces may adopt them by reference for regulatory standards (at least for health-based contaminants), but some provinces have produced their own provincial standards that may refer to the national guidelines.

Currently, Canada has health-based maximum acceptable concentrations (MAC) specified for 55 chemical or physical contaminants, five radiological agents, and 18 aesthetic objectives (OG), with some such as iron and manganese also having health-based MACs.

[21] CDW↗

Box 1 lists Canada's guidelines and standards. For microbiological contaminants, *E. coli* and total coliforms are indicators of potential faecal contamination that should be completely inactivated by functioning disinfection and have an MAC of zero in a 100-mL sample. Four chemical guidelines are annotated to be ALARA (as low as reasonably achievable): arsenic, haloacetic acids, lead, and vinyl chloride. These are all contaminants that have been suggested as possibly not having a threshold below which a safe level can be specified (two are carcinogens, one group includes suspected carcinogens, and the other is lead). Two other contaminants that are listed as human carcinogens—benzene and benzo[a]pyrene—are not listed as ALARA. The topic of no safe level being available to specify is discussed further in Section 6.

Enteric protozoa (*Giardia* and *Cryptosporidium*) have a treatment goal of 3-log removal or inactivation (i.e., a 99.9% reduction in microorganisms). Enteric viruses have a treatment goal of 4-log removal or inactivation (99.99% reduction). Turbidity has treatment limits specified according to treatment technology: conventional and direct filtration (≤ 0.3 NTU[22]), slow sand and diatomaceous earth filtration (≤ 1.0 NTU), and membrane filtration (≤ 0.1 NTU).

Draft guideline proposals (new or updated) are made available for public comment, typically for two months. There are also 12 guidance documents provided on a variety of issues and operational considerations for the benefit of drinking-water providers. Current documentation on Canadian drinking-water guidelines has been provided by O'Keefe (2023).

5.4.4 Australian Drinking Water Guidelines (ADWG)

The ADWG draw on expert input from a water-quality advisory committee comprised of experts in the fields of microbiology, toxicology, water-quality risk assessment and management, water chemistry and recycling, and groundwater hydrology, with guidelines development methodology from academia, practice, and those who have experience with implementation from relevant jurisdictions.

The ADWG was subject to a major revision and restructuring for the edition ultimately released in 2004 to incorporate a quality-management framework to provide performance guidance well beyond the numerical limits specified for individual contaminants. The direction of the restructuring had much in common with the WHO Water Safety Plan approach, in part because of a week-long meeting in Adelaide, Australia, in May 2001 between the WHO expert group and an NHMRC working group that led the Australian revisions (Rizak et al., 2003). Because this restructuring made an already large document much larger (1,223 pages at time of writing), a set of guiding principles was adopted. These were provided with a view to being *read me first* guidance for all that followed. These principles (NHMRC, 2023) are listed here.

[22] Nephelometric turbidity units

- The greatest risks to consumers of drinking water are pathogenic microorganisms. Protection of water sources and treatment are of paramount importance and must never be compromised.
- The drinking-water system must have, and continuously maintain, robust multiple barriers appropriate to the level of potential contamination facing the raw water supply.
- Any sudden or extreme change in water quality, flow, or environmental conditions (e.g., extreme rainfall or flooding) should arouse suspicion that drinking water might become contaminated.
- System operators must be able to respond quickly and effectively to adverse monitoring signals.
- System operators must maintain a personal sense of responsibility and dedication to providing consumers with safe water and should never ignore a consumer complaint about water quality.
- Ensuring drinking-water safety and quality requires the application of a considered risk-management approach.

The ADWG provides 16 information sheets covering topics including disinfection, sampling, and statistics. Individual contaminants are addressed with fact sheets grouped according to microorganisms, physical and chemical characteristics, and drinking-water treatment chemicals. The microorganisms are further grouped as microbial indicators (six are named but numerical limits are specified only for *E. coli* and thermotolerant coliforms [zero per 100 mL]), bacteria (13, none with numerical limits set), protozoa (six, no numerical limits set), cyanobacteria and their toxins (four toxins with a numerical limit specified only for microcystins), and viruses (five, none with numerical limits).

Physical and chemical characteristics total 219 with 187 having specified numerical health-based limits; 28 having aesthetic, nuisance, or operational based limits; 14 having insufficient evidence to set a limit (two asking for supplementary monitoring); and 12 that have both aesthetic and health-based limits. Box 1 lists the ADWG guidelines and standards.

Overall, the ADWG provides assessments of more contaminants than any other agency, so it may provide a useful reference in jurisdictions where guidance for a particular contaminant is not available. In the case of pesticides, it may be necessary to consider that Australia has a different name for a product than encountered elsewhere. The ADWG also includes fact sheets on 35 chemicals or substances that may be used in water-treatment processes. These provide useful information on their characteristics, including possible contaminants that some of them may contain.

The ADWG is subject to a continuous rolling revision with timely updates provided as additions to the most recent edition of the guidelines.

5.4.5 European Union Water Directive

The EU Water Directive (EU, 2020) on drinking water is somewhat more bureaucratic and legalistic than the other documents listed above and provides far less technical and scientific information. The numerical criteria that have been set are provided in Annex I of the document.

Annex I provides two microbiological parameters—intestinal enterococci and *E. coli*— both of which are specified to be zero in a 100-mL sample. A total of 34 chemical parameters have numerical limits specified (Box 1; presumably health-based), and 18 indicator parameters (including chemical, physical, and microbiological) are listed (11 with numerical limits) covering aesthetic and operational considerations. Finally, two parameters (*Legionella* and lead) have numerical limits applicable to domestic distribution systems.

5.4.6 Calculation of Drinking Water Guideline/Standard Concentrations

Each jurisdiction has its own protocols for calculating guideline/standard concentrations for the health-risk data obtained from toxicological and/or epidemiological data for the contaminant in question. Although there are slight differences among jurisdictions in performing these calculations, the general format is similar among the five jurisdictions described above.

For this book, the procedure will be illustrated using the format in the Guidelines for Canadian Drinking Water Quality. These approaches differ slightly depending upon whether the contaminant in question is considered to exhibit a threshold. Carcinogens are generally treated as non-threshold contaminants unless there is credible evidence—normally based on an understanding of the mechanism of action (MOA)—that the contaminant has a threshold.

Threshold Risk Estimation

For contaminants judged to exhibit a threshold (i.e., an exposure dose below which no identified toxic effect is expected), the calculation of a health-based guideline or standard limit in mg/L is accomplished using Equation (9).

$$\text{Health-Based Value (HBV)} = \frac{\text{TDI BW AF}}{\text{CR}} \tag{9}$$

where:

TDI = tolerable daily intake or toxicological reference value (mg/kg-bw-d)

BW = body weight (as mass, kg-bw)

AF = allocation factor, a policy-determined factor to estimate the proportion of total exposure that occurs from drinking water consumption (unitless)

CR = consumption rate (L/d)

For drinking water contaminants that have appropriate physical and/or chemical characteristics (e.g., volatility, ability to absorb through skin), factors to consider exposure by inhalation or skin absorption can be added.

Non-threshold Risk Estimation

For contaminants judged to exhibit no threshold (i.e., any exposure dose is judged to pose a non-zero health risk [e.g., an initiator carcinogen]), the calculation of a health-based guideline or standard limit employs Equation (10).

$$\mathrm{ER}(d) = q_1^{*}\, d \tag{10}$$

where:

$\mathrm{ER}(d)$ = the excess lifetime cancer risk for a dose, d, (unitless)

d = the lifetime average daily dose, (mg/kg-bw-d), which is (CR MAC)/bw, CR is the consumption rate (L/d) and MAC is the maximum acceptable concentration (mg/L)

q_1^{*} = the upper bound (95-percent confidence limit) cancer slope factor (CSF), also referred to as the cancer potency factor $(\text{mg/kg-bw-d})^{-1}$

5.4.7 Threshold of Toxic Concern (TTC)

A major challenge for assessing the toxic threat of low-level exposures to chemicals is the enormous number of chemicals, the limits of toxicological evidence for most chemicals, and the scientific resources that toxicological testing demands. Up to 350,000 chemicals or mixtures of chemicals have been registered for production and use across several nations (Wang et al., 2020). The nature of this concern is effectively captured by the European Food Safety Administration–World Health Organization (EFSA–WHO, 2016, p. 1):

> *"In light of improving analytical methods, it can be expected that many more unintended chemicals will be detected in our environment, including food and drinking water, and in our bodies. The TTC (Theshold of Toxic Concern) approach is a screening and prioritization tool for the safety assessment of chemicals when hazard data are incomplete and human exposure can be estimated."*

The TTC approach to dealing with this challenge was first proposed by Cramer and others (1978) to ask a series of focused questions about a substance that would allow classification of chemicals into three tiers of concern for likely toxic effect. Their concern is evident in their statement that is presented here.

> *"Safety evaluation is caught in a frustrating circle. It is neither possible nor sensible to try to obtain the information needed to assess every imaginable toxic risk associated with every substance, and pursuit of greater safety therefore demands the setting of*

> *priorities as well as sensible limits for investigation. To do this with confidence requires possessing the very information that is lacking and that can be won only slowly on a few substances at a time, with significant uncertainty and at considerable cost. This requires priorities, and completes the circle of frustration. Individual toxicologists deal with this problem by using 'experience', a personal synthesis of accumulated knowledge of structure–activity relationships, metabolic mechanisms, chemical reactivity, human exposure, and other relevant information. Such expert judgement is often very effective in distinguishing potential risks worth pursuing from problems on which effort would be wasted but, because it is usually so inexplicit and subjective, it is seldom able to invoke the public confidence most decisions now require."* (Cramer et al., 1978, p. 255)

Munro (1990) extended the Cramer concept to address health risks from food additives and it was further refined for health risk assessment as the TTC (Munro et al., 2008). TTC was critically reviewed in a European workshop reported by Dewhurst and Renwick (2013), ultimately forming the basis for the review of TTC by EFSA–WHO (2016) that has recommended cautious adoption of this detailed prioritization process with updated refinements.

5.5 Drinking-water Safety Plans

Drinking-safety plans offer a *know-your-own-system* preventive approach for managing drinking-water risks to improve upon the all-too-common emphasis on and reliance upon monitoring of treated water for compliance with numerical water-quality guidelines or standards. This quality-management approach was concurrently developed by WHO and the Australian NHMRC, beginning in the 1990s, and ultimately being captured in their respective drinking-water guidelines, both published in 2004 (Hrudey et al., 2024).

WHO has promoted the drinking-water safety plan concept, and formally introduced it with the third edition of the WHO DWG in 2004—which has since been updated (WHO, 2022a) —and including it in other supporting documentation (WHO, 2023, 2022b, 2012). WHO initiated consideration of a need to improve the preventive features of drinking-water guidelines, taking notice of a proposal by Havelaar (1994) to adopt the established food safety management system—awkwardly named Hazard Analysis and Critical Control Point (HACCP)[23]—as an approach for ensuring drinking-water safety. As indicated in the ponderous and unwieldly title, a key feature of the HACCP approach is

[23] Hazard Analysis and Critical Control Point is not accurately named because mainstream risk-assessment and risk-management practice recognizes hazards as the potential to cause harm, while risks are the probability of any identified hazards affecting safety (Kaplan & Garrick, 1981). Hazards are open-ended and cannot all be practically managed. Hazards that are identified can be assessed to determine the likelihood (probability) and consequences of their occurrence that allow them to be considered as risks, with the greatest risks warranting the highest priority for management.

the identification, monitoring, and management of so-called critical control points (CCPs; Food and Agriculture Organization of the United Nations & WHO, 2023). CCPs are locations in the overall process at which priority risks can be controlled to acceptable levels. As such, HACCP properly places a focus on operations rather than solely on treated water monitoring and apparent compliance with numerical guidelines or standards because the latter is not preventive.

Although many of the details of HACCP needed to be adapted to be workable for ensuring drinking-water safety, the orientation toward the management of operational practice provided a focus for the development of drinking-water safety plans. The concepts were refined at an expert meeting in September 1999 in Stockholm that included many Australian participants, as described by Bartram and others (2001) and Deere and others (2001), before being published in the third edition of the WHO DWG in 2004.

The NHMRC incorporated a Framework for Management of Drinking Water Quality (Rizak et al., 2003), initiated in 1999, into substantially restructured and revised national drinking-water guidelines, ultimately published in 2004, that have been continuously updated with rolling revisions (NHMRC, 2023). The Framework was developed by reviewing a range of national and international quality-management frameworks to develop a draft framework. The process involved extensive consultation with Australian water professionals and key stakeholders, including federal and state regulators, watershed managers, environmental groups, and the Australian Consumers' Health Forum.

The concepts presented at a 1999 national meeting in Adelaide, South Australia, were followed by desktop trials in 2001 with four drinking-water suppliers to evaluate their practicality. Concurrently, the NHMRC working group held a week-long joint session in Adelaide with Dr. Bartram's WHO expert group on microbiological risks to drinking water, during which WHO and NHMRC experts shared their respective progress on revising drinking-water guidelines toward a preventive risk-management approach. Two members of the NHMRC working group also worked directly on drafting the 2004 edition of the WHO DWG.

More than a decade after the formal publication of the water safety plan concept in 2004, WHO (2017a) published a survey that found 93 countries, worldwide, had adopted water safety plans to some degree. A compilation of resources for implementation of water safety plans has been provided (WHO, 2017b), and the second edition of the water safety plan manual has been published (WHO, 2023).

An illustration of the misunderstanding about the capability of numerical limits alone for ensuring safe drinking water was outlined by Hrudey and others (2012). The misconceptions were presented in a report prepared for the David Suzuki Foundation (Boyd, 2006) that compared the GCDWQ with guidelines or standards from Australia, the

European Union, the US EPA, and WHO. First among Boyd's nine recommendations (Boyd, 2006, p. 24) was the following.

> *"The Canadian Guidelines for Drinking Water Quality should be replaced by a set of health-based long-term objectives for drinking water quality, and legally binding national standards for drinking water quality that are equal to or better than the highest standards provided in any other industrialized nation."*

Recommendation 1 was based on a table of 53 parameters showing the then-current Canadian MAC for each and a more stringent recommendation based on the lowest limit published by any other jurisdiction. Of the 53, 22 parameters have been withdrawn for no longer being relevant for Canada.[24] Although the idea proposed by Boyd (2006) seems logical on the face of it, few municipalities, especially medium to smaller-sized communities, can afford to monitor for all of these chemicals versus investing adequately in personnel and treatment performance. Even for larger communities, the adopted frequency of monitoring may be only once a year. Some of the MACs mentioned, especially the older ones, were not set by a thorough health risk assessment and may have simply been set to the then-current detection limit. Boyd (2006) was accurate in explaining that the greatest health risk to drinking-water consumers was posed by microbial pathogens rather than by chemicals.

Finally, a practical illustration of how to avoid allowing seemingly logical economic arguments to drive decisions that undermine safe drinking water has recently been provided by Walker (2023). Walker's paper makes the case that ensuring the most basic treatment barriers—such as disinfection—are provided and assured to be functional is the most sensible way to ensure safe drinking water. This approach could have prevented the 2016 fatal drinking-water outbreak in Havelock North, New Zealand (Graham et al., 2023).

[24] Guidelines are withdrawn for parameters that are no longer found in Canadian drinking-water supplies at levels that could pose a risk to human health, including pesticides that are no longer registered for use in Canada.

6 Health Risk Perception and Consequences

6.1 Misunderstanding Health Risk Evidence and Risk Perception

An inescapable reality of issues involving health-risk assessment and risk management is encountering a range of views about the credibility of and, more importantly, the willingness of affected and interested parties to believe estimates of risk provided by professional risk assessors. A common, if not universal, response by professional risk assessors is to dismiss or undervalue the concerns of the affected parties, often under the rubric of such beliefs being only *perceived* risks.

This attitude was evident in the title assigned to proceedings of a workshop—The Analysis of *Actual* Versus *Perceived* Risks [emphasis added]—of an interdisciplinary group of scientists (Covello et al., 1983) that ultimately became the Society for Risk Analysis (SRA). More commonly, this divergence has been cast as *real* versus *perceived* risks. A compelling explanation of how to address this characterization of risk was provided by Kaplan and Garrick (1981) in the inaugural issue of the SRA journal *Risk Analysis*. Their paper "*On the quantitative definition of risk*" described risk as the answer to three questions:

1) What can go wrong?
2) How likely is it?
3) What are the consequences?

This description of risk leads to it being defined as a multi-dimensional entity consisting of at least

- a hazard (the source of danger),
- uncertainty of occurrence and outcomes (expressed by the probability or chance of occurrence), and
- adverse consequences (the possible outcomes).

Hrudey (2000) added two other elements to this list of risk dimensions:

- a time frame for evaluation of risk and
- the perspectives of those affected about what is important to them.

In the context of their definition of risk, Kaplan and Garrick (1981, p. 12) addressed the issue of real versus perceived risk as follows.

> *"Connected to this thought is the idea that risk is relative to the observer. We had a case in Los Angeles recently that illustrates this idea. Some people put a rattlesnake in a man's mailbox. Now if you had asked that man: 'Is it a risk to put your hand in your mailbox?' He would have said, 'Of course not.' We, however, knowing about the snake, would say it is very risky indeed.*
>
> *"Thus risk is relative to the observer. It is a subjective thing—it depends upon who is looking. Some writers refer to this fact by using the phrase 'perceived risk.' The problem with the phrase is that it suggests the existence of some other kind of risk*

> *other than perceived. It suggests the existence of an 'absolute risk.' However, under attempts to pin it down, the notion of absolute risk always ends up being somebody else's perceived risk."*

Put another way, risk in the context of risk assessment and risk management is inevitably a prediction, based to some degree on an individual's or a group of individuals' awareness, understanding, and judgment of evidence. A prediction cannot be considered *real* or *actual*. We can have varying degrees of confidence in a prediction, but if risk predictions were truly real, we would know the future without uncertainty and we should all be able to thrive on the stock market.

Kaplan and Garrick (1981, p. 13) also challenge another common misconception about risk as delineated here.

> *"One often hears it said that 'risk is probability times consequence.' We find this definition misleading and prefer instead, … to say that 'risk is probability and consequence.' In the case of a single scenario the probability times consequence viewpoint would equate a low-probability high-damage scenario with a high-probability low-damage scenario—clearly not the same thing at all."*

Applying the Kaplan and Garrick comment to drinking-water safety might lead to equating the risk of a Walkerton-type of fatal drinking-water outbreak (low probability–high consequence) with a small water leak (high probability–low consequence). There is ample evidence that uncritically adopting the concept of risk being simply probability times consequences, as is often done with risk matrices, can misinform risk management (Graham et al., 2023; Lane & Hrudey, 2023; Vatanpour et al., 2015).

A consistent argument for pursuing risk assessment is that being able to assign quantitative values to risks will allow prioritization of risk-management actions. While this goal is attractive, the challenges of being able to inform priorities should never be underestimated. First, if we accept that risk is a multidimensional parameter, we need to recognize that there is no single, absolutely objective way to rank the magnitude of multidimensional parameters.

Consider two quantitative, hypothetical, three-dimensional risk estimates, A and B, with a level of risk assigned to each of the three components of risk and the quantitative dimensions normalized to a range from 1 to 10.

$$A = (6, 1, 3)$$

$$B = (4, 2, 4)$$

Which risk is larger—A or B? Some might argue that you could weight each dimension equally then sum the values of the dimensions. In this case, that would yield a value of 10 for both A and B. That choice might be viewed as rational, but it is not strictly objective because not everyone will value all dimensions equally. If we accept that risk

involves more than one dimension, there is no strictly objective, simple way to rank the risks according to magnitude.

Likewise, uncertainty is inevitable in estimating probability or consequences of a risk. Typically, uncertainty in a given parameter may be estimated as a confidence interval. Figure 21 illustrates the resulting problem.

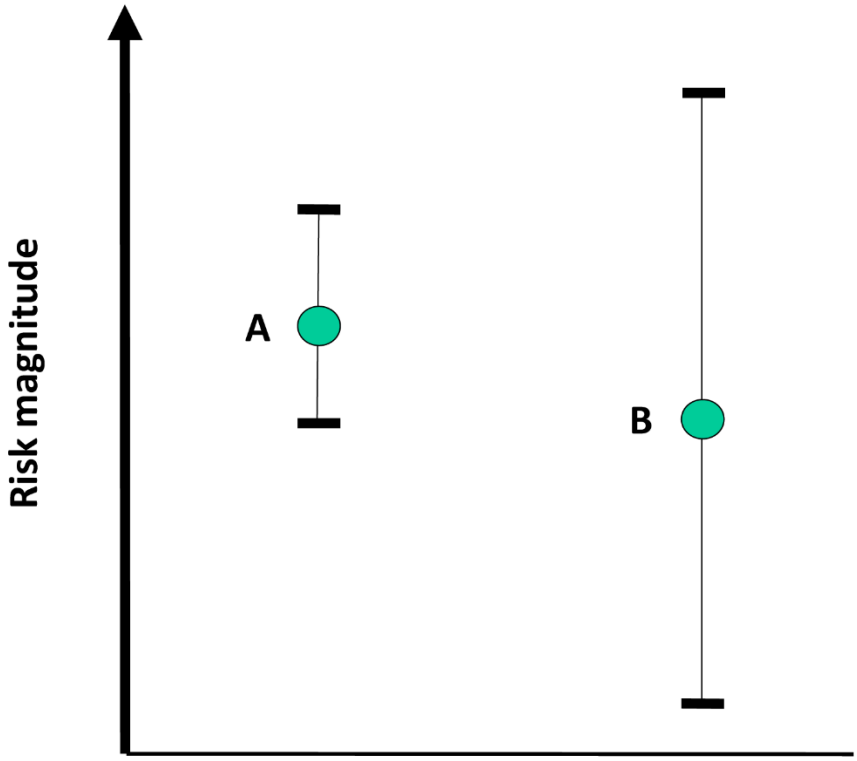

Figure 21- Risk comparisons considering uncertainty (confidence) intervals.

Which risk is greater—A or B? If we judge the median estimate as the best measure of risk magnitude, we will choose A. But if, as is common among the affected parties, the upper bound or worst case is chosen as the best measure of risk magnitude, then B is the greater risk.

We could dig much deeper into the realities of risk estimation, but the reader should appreciate by now that there is no strictly objective way to rank the magnitude of realistic risk estimates. Likewise, the simplistic notion of *real* versus *perceived* risk is neither accurate nor helpful for effectively managing environmental health risks. The focus must always be upon what is the evidence for any estimate of risk.

The foregoing realities do not make a case for ignoring perceptions of risk. Rather, they indicate a need to evaluate how risks are understood by all parties who may have a valid interest in risk management. There have been decades of research on risk perception, some of which has been cynically aimed at manipulating public concerns, and much of which provides no basis for opening a meaningful dialogue with parties potentially affected by a risk-management decision.

Wildavsky (1979, p. 32) noted the irony that American society seemed to be increasingly afraid of technological risk despite the obvious benefits to health and wellness compared to previous generations: "*How extraordinary! The richest, longest-lived, best-protected, most resourceful civilization, with the highest degree of insight into its own technology, is on its way to becoming the most frightened*." As noted in the discussion of the history of safe drinking water (Section 2.1 of this book), society used to face prevalent risks of illness and death from waterborne disease outbreaks that have been largely controlled by the introduction of water disinfection and filtration. Yet, modern fatal outbreaks in Walkerton, Ontario, Canada, in May of 2000 (Hrudey & Hrudey, 2004, 2014; O'Connor, 2002a) and Havelock, North, New Zealand, in August of 2016 (Graham et al., 2023; Gilpin et al., 2020) have occurred, in part, because of unwarranted fear of adverse health effects of chlorination DBPs—a topic addressed in Section 6.2.1, *Misunderstanding Health Risk Evidence and Risk Perception*, and Box 2.

Slovic (1987) provided a seminal introduction to focused research on understanding risk perception, highlighting that perception of risk is influenced by many socially relevant characteristics grouped as *unknown* (e.g., not observable, effect delayed, new or unknown to science) and *dread* (e.g., uncontrollable, global, fatal consequences, not equitable, catastrophic, high risk to future generations, not easily reduced, evidently increasing, involuntary). While information on these factors may be inaccurate for the risk under evaluation, most of the perceptions of risk are not irrational. Slovic (1991) elaborated on these matters by listing many examples where public understanding of risk is inconsistent with available evidence. Slovic noted challenges associated with communicating evidence to influence public understanding of risk. Among the factors Slovic discussed were the limitations of risk assessment, as discussed in the previous sections of this book. Slovic elaborated on the challenges of communicating evidence of risk to the public including that:

- risk evidence is sometimes inaccurate,
- risk information can be frightening and frustrating,
- strong beliefs are difficult to modify, and
- naive views are easily manipulated by presentation format.

Slovic (1993) discussed how risk controversies are imbedded in broader social issues that are increasingly politicized, a feature that was evidenced during the COVID-19 pandemic.

Trust is particularly influential. Earle and Cvetkovich (1995) explain trust as a complexity reduction mechanism. Complex risk issues are difficult even for full-time risk-assessment professionals to completely understand, and no one can pursue every element of evidence to its original source. At some point, we all have to trust, as much as can be rationalized based on judging the evidence, what we can learn from others.

Unfortunately, in the age of social media, it is far too easy for individuals to access unreliable, if not intentionally inaccurate and manipulative, misinformation about risk issues. Many social scientists have provided useful perspectives on this topic, including

Fischoff and others (1993), Kasperson (2022), Renn (1992), and Tversky and Kahneman (1981). Readers who seek to practice environmental health-risk assessment and risk management are encouraged to explore these sources and the expansive literature on this topic to improve their own ability to accurately communicate evidence about risk.

6.2 Misinformation versus Reality

When it comes to environmental health risks and misinformation, there is so much material from the past 50 years that we could write a book on this topic alone. However, to illustrate with an example that is directly relevant to the topic of this book, the subject of drinking water disinfection by-products and human health is explored.

6.2.1 Disinfection By-products and Human Health

Although countless individual chemical substances can be generated, unintentionally, by the use of disinfection processes (chlorination, chloramination, ozonation, chlorine dioxide, or ultraviolet [UV] light), a 50-year-old publication (Rook, 1974) about the formation of four halogenated-methanes (chloroform, bromodichloro-methane, dibromochloromethane, and bromoform)–collectively labeled as THMs or THM_4 has dominated the topic, with chloroform originally attracting the most attention. This story, originally adapted from enHealth (2012a) and Hrudey (2009), and updated from Hrudey and others (2015a,b) and with subsequent experience, is provided in Box 2.

The end of Box 2 explains that the Chowdhury and Hall (2010) paper was retracted when the journal was informed that its ethics policy had been breached because the lead author failed to inform the journal of a major error by misusing an RfD value as a CSF, invalidating all of the reported cancer case numbers. There have been at least ten subsequent citations of the inaccurate, retracted paper by Chowdhury and Hall (2010), but only Grellier and others (2015) noted that it had been retracted and also mentioned errors in it and a subsequent parallel publication (Chowdhury et al., 2011). The latter claimed to report cancer cases by Canadian province rather than by Canadian city. Bull and others (2012) noted that Chowdhury and others (2011, p. 382) stated "*To be protective against cancer risks, this study used* [sic] *previously reported slope factor for chloroform,*" despite having acknowledged that no CSF for chloroform was reported in the US EPA IRIS database, as was erroneously claimed in the retracted Chowdhury and Hall (2010) paper. No reference was reported in Chowdhury and others (2011) for the "*previously reported slope factor for chloroform*" that was claimed to have been used.

As if this fundamental error was not enough, Chowdhury and others (2011), as with Chowdhury and Hall (2010), applied the US EPA approach using a slope factor calculation that yielded a lifetime (70-year) cancer risk, but they presented the calculations as annual cancer risks—an overwhelming misrepresentation of what regulators intended to be an already cautious *upper bound* cancer risk estimate.

In case readers imagine that abuse of cancer-risk calculations has been limited to the cases described above, Cotruvo and others (2020) critiqued a paper from Evlampidou and others (2020) that had 30 co-authors from 18 European nations, including several prominent epidemiologists. The paper purported to show THM levels in 28 European countries (total population of 404,672,106 with 134,976 cases of bladder cancer per year), accounting for 6,561 (95 percent confidence interval: 3,389 to 9,537) bladder cancer cases per year. Unlike the case of Chowdhury and others (2011) that was based on erroneous application of cancer-risk assessment models based on outdated and inaccurate animal toxicology studies, the paper from Evlampidou and others (2020) was based on questionable application of limited human epidemiology studies applied to extremely generic exposure-assessment data. These authors acknowledge that sufficient information for causality between THMs in drinking water and bladder cancer has not been established by either IARC or WHO. Even the US EPA acknowledges that THM contribution to cancer risk could be zero.

Evlampidou and others (2020) performed their cancer-case calculations by using an analysis of Costet and others (2011), which performed a meta-analysis[25] of three case-control studies from France (1985-1987), Finland (1991–1992), and Spain (1998–2001), involving a total of 2,381 cases and 3,086 controls. This approach was used to develop an exposure response function odds ratio (OR) of 1.004 for each 1 μg/L increase of THM exposure that was adjusted for each country to obtain a country-specific population attributable fraction (PAF) for bladder cancer incidence. These were applied to national annual average THM exposures levels estimated for each country (some based on monitoring, others based on estimation) to calculate the estimated annual bladder cancer case numbers.

This is a classic case of aggregating data across an entire population (of Europe) and then estimating bladder cancer case numbers to a single case. Evlampidou and others (2020) determined a PAF for THMs and bladder cancer of 0 percent for Denmark and 0.1 percent for the Netherlands, yet 2020 bladder cancer statistics (age-standardized incidence rates) show that the Netherlands and Denmark rank second and fourth, respectively, among 25 countries for age-standardized bladder cancer incidence per 100,000 (World Cancer Research Fund International, 2023). These actual bladder cancer case data reveal only that there are dominant causes of bladder cancer other than hypothetical cases caused by DBPs but they do not allow for judgment about whether DBPs cause bladder cancer.

[25] A meta-analysis is a statistical analysis that combines the results of multiple epidemiological studies and is most credible when applied to clinical trials that have all used similar methodology. The credibility of meta-analysis applied to very different study designs is questionable.

6.2.2 Other Drinking Water Health Risk Controversies

Although there have been countless cases of marginal evidence of contaminants in drinking water causing adverse health effects—too many to document here—the adverse consequences of an overzealous response to a situation where there is consensus agreement that a drinking-water contaminant can contribute to adverse health consequences is worthy of mention.

Roy and others (2023) discuss the issue of blood lead levels in children and its role in causing a decrease in intelligence quotient. The issue of lead poisoning in children has been studied for more than 50 years, driven in part by children's high exposures from lead-based paints and contributing to the regulatory decision to ban the use of leaded gasoline, which contributed to environmental contamination by airborne emissions from motor vehicles. As these large environmental sources of lead contamination have been eliminated, Roy and others (2023) reported that blood lead levels in the US declined from an estimated mean of 27 to 58 μg/dL in the 1930s and 1940s to 3.5 μg/dL in 2021, a clear testament to sensible risk-management actions for reducing lead in the environment.

Egan and others (2021, p. 037003-1) noted that, to date, a *blood lead level that avoids a negative effect on cognition has not yet been demonstrated*.

The US EPA (2023c, p. x) inaccurately states about the same issue:

> *"The MCLG [maximum contaminant level goal] for lead is zero. EPA has set this level based on the best available science which shows there is no safe level of exposure to lead [emphasis added]."*

Although the distinction between these two statements may appear subtle and they may even appear to say the same thing, there is a huge difference between stating that health studies have been unable to identify, so far, a level of exposure that yields no adverse health effects and stating that no such level exists. This is similar to the issue about whether there can be a safe level of exposure to a carcinogen (Hrudey & Krewski, 1995) as discussed in Section 4.2. The magnitude of that difference is explained by noting that the CDC detection limit for lead in blood is 0.07 μg/dL, a level below which will be presumed by some to mean that no lead is present versus the reality that none has been detected by available analytical methods. That 0.07 μg/dL detectable concentration corresponds to $35x10^{14}$ (3,500,000,000,000,000—about 3.5 quadrillion) atoms of lead per dL, a huge difference from zero.

Just as there is a limit to what current analytical technology can reliably detect, there are more compelling limits to what epidemiological studies can reliably document for something as challenging to demonstrate as cognitive deficit at very low levels of lead exposure. Roy and others (2023) go on to argue that the misleading messages about "*no safe level*" can have the negative effect of misleading the public into believing that any level of exposure is dangerous and, by illogical extension, the actual level of exposure does not matter—a thoroughly dangerous belief.

Hrudey (2024) has described an extreme example of the foregoing misguided logic whereby the US EPA (2023b) has proposed under regulations for the SDWA that drinking-water utilities should be prohibited from advising their consumers, under mandatory reporting requirements, that the drinking water they are being provided is "*safe*." The expressed rationale for this proposed prohibition includes the foregoing US EPA misinterpretation that there is "*no safe level*" of exposure to lead.

6.3 Off-flavors, Aesthetics, and Risk Perception

One of the most serious errors among those who believe themselves to be experts—or at least knowledgeable about drinking-water safety—is a tendency to judge aesthetic issues with water (color, off-flavors) as being minor issues. Consumers do not have easy access to analytical techniques for measuring trace contaminants. However, consumers can see with their own eyes if water is discolored or if it has a detectable taste or odor; they know intuitively that safe water should have none of these aesthetic impairments.

Water utilities, regulators, and public health authorities will discount such issues at their peril because consumer confidence in the safety of their drinking water can certainly be undermined by such aesthetic problems. At one extreme are documented cases where consumer detection of aesthetic issues provided the first warning of contamination that ultimately caused a drinking-water disease outbreak (Hrudey & Hrudey, 2007) showing that aesthetic complaints should not have been ignored. At the other extreme, outbreaks, some fatal, have been caused by inadequate or no disinfection, which occurred—at least in part—because consumers objected to chlorine taste or odor (Hrudey, 2017). The ability of water professionals to misunderstand or dismiss such concerns was revealed to us by negative reviewer comments questioning the relevance of a paper we received for our initial submission to a drinking water industry journal. The paper proposed practical consumer options for removing objectionable chlorine off-flavors at their own taps, which the reviewer dismissed as not being relevant. We ultimately published the research elsewhere (Qian et al., 2015b).

6.4 Judgment and Ethical Risk Management

Using risk assessment to guide management of environmental health risks is not a simple, straightforward matter. There is no shortage of advice about how best to navigate this complicated maze, with bad advice likely dominating good advice. However, a valuable overview of this challenge came from a presidential/congressional commission on risk assessment and risk management (Omenn et al., 1997). This report resulted from a panel that involved a diverse range of stakeholders and was not dominated by academic

theorists, consulting practitioners, or government regulators engaged in environmental health-risk assessment and risk management.

Omenn and others (1997) may be best known for the graphic used to define the guiding framework that some critics described as a never-ending wheel of death (Figure 22). Although there is clearly some merit in having a concern over the *never-ending* message it conveys, there is also some truth that such problems can take on an extended life of their own that participants in the process need to recognize. This reference is raised here because it provides some useful context as to how to judge the characteristics of a good risk-management decision.

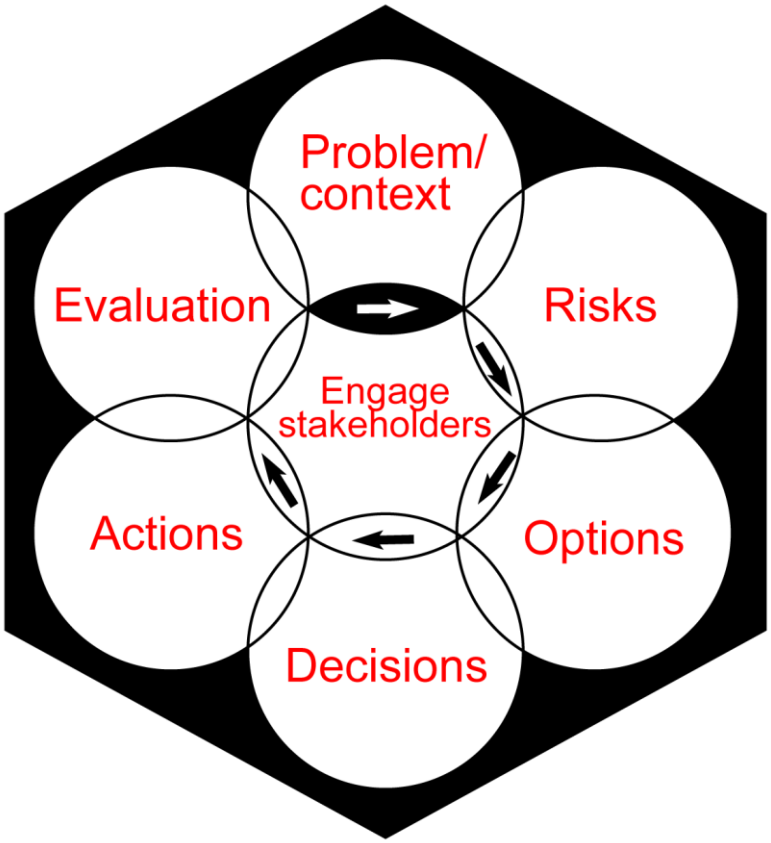

Figure 22 - The framework for environmental health-risk management (Omenn et al., 1997).

The characteristics of a good risk-management decision (Omenn et al., 1997, p. 4) are such that it:

- *"addresses a clearly articulated problem in its public health and ecological context;*
- *emerges from a decision-making process that elicits the views of those affected by the decision, so that differing technical assessments, public values, knowledge and perceptions are considered;*
- *is based on a careful analysis of the weight of scientific evidence that supports conclusions about a problem's potential risks to human health and the environment:*

- *is made after examining a range of regulatory and nonregulatory risk-management options; and*
- *reduces, or essentially eliminates, risks in ways that:*
    - *are based on the best available scientific, economic, and other technical information;*
    - *account for their multisource, multimedia, multichemical and multi-risk contexts;*
    - *are feasible with benefits reasonably related to their costs;*
    - *give priority to preventing risks not just controlling them;*
    - *use alternatives to command-and-control regulation;*
    - *are sensitive to political, social, legal, and cultural factors;*
    - *include incentives for innovation, evaluation, and research;*
    - *can be implemented effectively, expeditiously, flexibly and with stakeholder support;*
    - *can be shown to have a significant impact on the risks of concern;*
    - *can be revised and changed when significant new information becomes available while avoiding 'paralysis by analysis'."*

These features of good risk management must operate in the reality that there are pervasive limits to the quality and quantity of evidence available to guide environmental health-risk-management decisions. Likewise, there are pervasive limitations to the ability of scientific (i.e., experimental) evidence to guide decisions under uncertainty.

Given the illusiveness of certain evidence of truth in making predictions about environmental health risks, there is a need to seek sensible generic guidance for risk management and to operate with awareness of ethical principles to guide risk-management decision-making. Marcus (1988) described a wide range of the challenges facing environmental health-risk management, including the challenge of making decisions in the face of substantial uncertainty. Marcus describes the two extremes:

- total uncertainty (perfect ignorance)—any decision will be essentially random and
- no uncertainty (perfect, complete knowledge)—risk-management decisions can be totally rational.

This perspective can be translated into a modest proposal of general guidance for risk-management decisions: *Effective management of risk for protecting public health in the face of uncertainty should seek a high level of confidence, versus a low level of confidence*. That is, confidence in risk-management actions should be:

- *lowest* when uncertainty about evidence is enormously *large* and
- *highest* when uncertainty about evidence is negligibly *small.*

Before considering a drinking-water safety case, the point can be illustrated by a controversy that has grown recently. Vaccination of children has been mostly non-controversial since vaccination was successfully introduced against infectious

diseases, such as polio, in the 1950s; some infectious diseases have been virtually eliminated in higher income countries.

However, recent outbreaks of measles in children have been attributed to parents who have avoided vaccinating their children. This phenomenon has grown since Wakefield and others (1998) published claims to have found that eight of 12 children administered the MMR (measles, mumps, rubella) vaccine developed autism. This paper was exposed as "*research fraud*" and was retracted by the journal *Lancet* in February 2010, 12 years after publication (Deer, 2020; Omer, 2020). The author's claim of a link between the MMR vaccine and autism was judged by a major inquiry of the UK Medical Register to be "*utterly false*." Dr. Wakefield was removed from the UK Medical Register in 2010 after being found guilty of three dozen charges, including "*dishonesty*."

Dozens of credible studies have demonstrated no causal connection between the MMR vaccine and autism in children. For example, Hviid and others (2019) performed a cohort study of five million person-years and concluded that "*[t]he study strongly supports that MMR vaccination does not increase the risk for autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination*" (p. 513). Yet, Wakefield has become a media personality in the anti-vaccine community in the US and has produced a widely viewed, pseudo-scientific 2016 film, *Vaxxed* (Deer, 2020), that has attracted substantial public support.

This anti-evidence phenomenon has continued with opposition to vaccination for COVID-19 that has inevitably allowed thousands of preventable deaths (Figure 23) with death rates per 100,000 being four times higher among unvaccinated persons versus vaccinated persons.

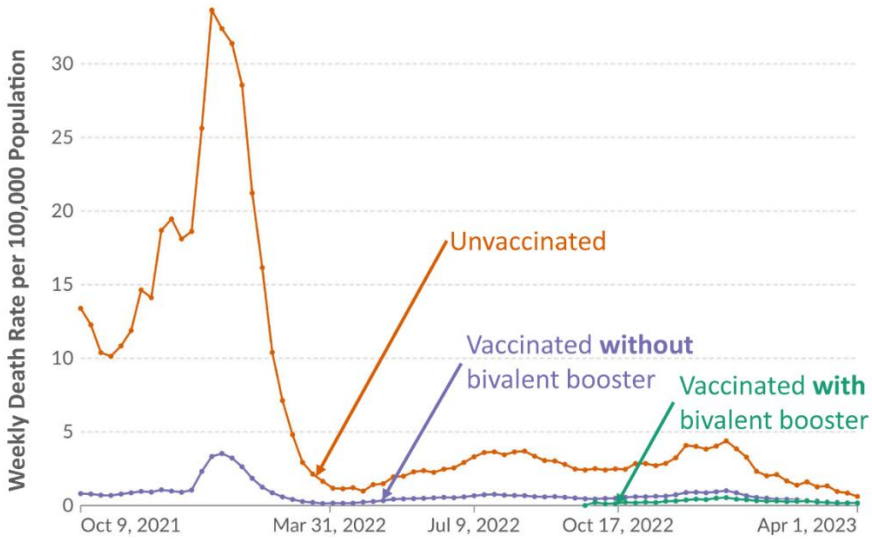

Figure 23 - United States COVID-19 weekly death rate by vaccination status, all ages. This is given per 100,000 people. The mortality rate for 'All ages' group is age-standardized to account for different vaccination rates among older and younger people (OurWorldinData.org: https://ourworldindata.org/grapher/united-states-rates-of-covid-19-deaths-by-vaccination-status↗; data source: Centres for Disease Control and Prevention, Vaccine Breakthrough/Surveillance and Analytics Team).

A relevant example for invocation of the modest proposal for confidence in risk-management decisions about drinking water is the trade-off between health risks from drinking-water DBPs versus failure to disinfect drinking water. Figure 24 shows the decline in the death rate from infectious diseases following a variety of medical interventions.

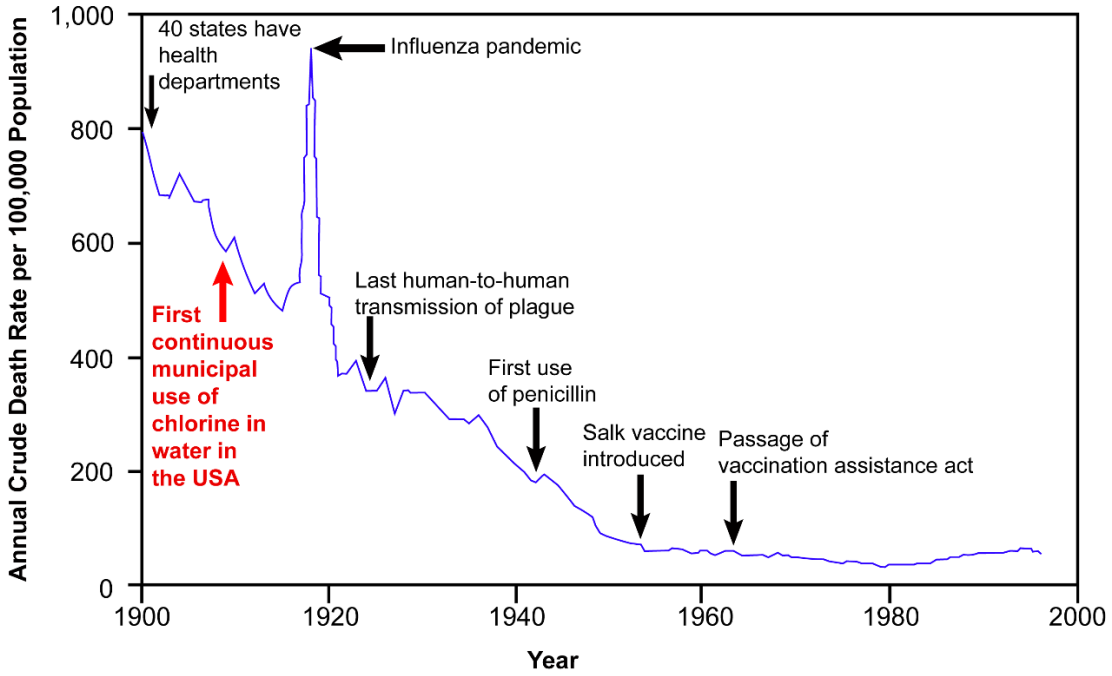

Figure 24 - US crude death rates (per 100,000 population per year) for infectious diseases since 1900. The 1918 influenza pandemic is a striking spike (CDC, 1999).

The intervention shown at around 1910 was the first continuous use of chlorine for disinfecting US drinking water. More explicitly, Figure 25 shows the annual average cases of typhoid caused by drinking-water outbreaks in the USA from 1920 to 1980.

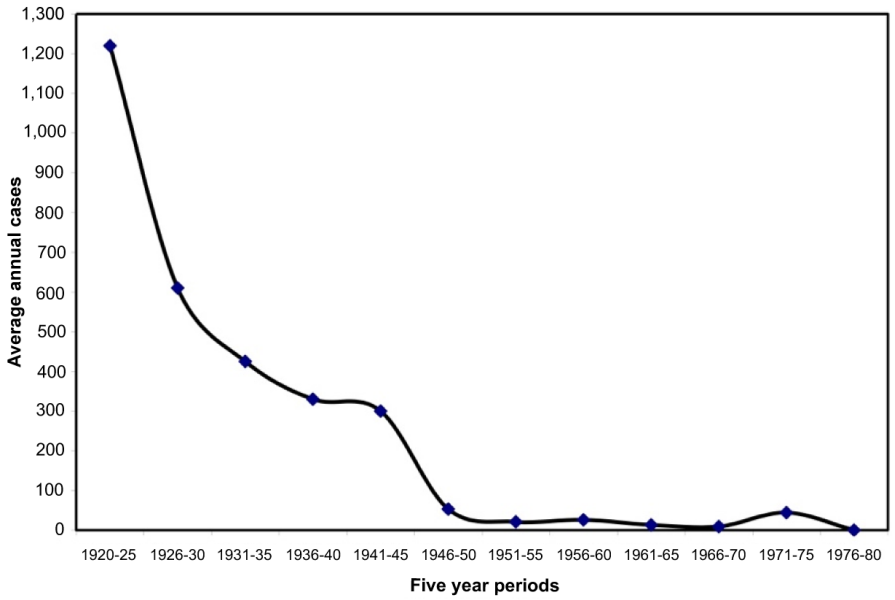

Figure 25 - Average annual cases of waterborne typhoid in the USA 1920 to 1980 (after Craun, 1986).

Drinking-water–borne outbreaks caused by microbial pathogens continue to occur (Hrudey & Hrudey, 2021, 2019, 2014, 2004) because of system failures—commonly failures of disinfection or failures to provide any disinfection. Worldwide, WHO (2023) states:

> *"In 2022, globally, at least 1.7 billion people use a drinking water source contaminated with faeces. Microbial contamination of drinking-water as a result of contamination with faeces poses the greatest risk to drinking-water safety … Microbiologically contaminated drinking water can transmit diseases such as diarrhoea, cholera, dysentery, typhoid and polio and is estimated to cause approximately 505 000 diarrhoeal deaths each year."*

There is no uncertainty that microbial pathogens are capable of causing human disease and even death by means of drinking-water exposure; the only uncertainty is whether sufficient pathogen contamination will occur in any specific drinking-water scenario. Effective disinfection of drinking water is capable of ensuring that such sufficient exposure to undisinfected drinking water is prevented. In contrast, as outlined in Box 2 (associated discussions about DBPs), there is considerable uncertainty that DBPs cause serious health effects under regulated exposure scenarios. This provides a clear case of *low* confidence–*high* uncertainty for DBP health risk versus *high* confidence–*low* uncertainty for microbial pathogen risk, a comparison that fully justifies recognition of microbial pathogens as a much more important health risk than DBPs.

The harsh reality is that risk assessment and corresponding risk management can be exercised with confidence only when risks are either very high and correspondingly obvious or very low such that it is possible to be confident that risks are insufficiently substantial to warrant specific risk management. Unfortunately, most controversial risk issues fall between these extreme boundaries. In such cases, additional guidance is likely necessary to inform decision-making for risk management.

Hattis (1996) addressed the possibility of invoking ethics to assist in difficult decision making, something that is common in matters such as medical interventions, which are never without risk. The minimum ethical requirement in such decisions is to have informed consent from the person who is at risk.

Hattis proposed four ethical principles. I have slightly modified these and added two others that should also be considered. A key feature of these principles is that some may seem to work against others and it is likely not possible to easily maximize consideration of all of them simultaneously. This reflects the reality of making difficult decisions.

6.4.1 Ethical Principles to Guide Risk Management

1. Do more good than harm: A principle adapted from the Hippocratic oath for physicians. A translation from Greek is *"I will prescribe regimen for the good of my*

patients according to my ability and my judgment and never do harm to anyone."[26] Because zero risk must be recognized as unachievable, all risk-management decisions involve trade-offs. The quantity and quality of good that can be achieved with active risk management versus the harm that may arise with no action must be weighed. The ultimate goal of risk management should be to prevent harm to the degree feasible, but certainly such harm must be minimized. Because it is an exercise in balancing uncertain estimates of probabilities, this will be challenging.

2. Fair process of decision making: Fairness is a core value and is captured in the legal system as *natural justice*. In a democratic society, the principle of natural justice appears at or near the top of requirements for public institutions. A perceived lack of fairness underlies most, if not all, risk disputes in society. If the pursuit of fairness can keep the focus of discussion and debate on the quality of evidence and inference about risk, there will be a greater chance of achieving constructive solutions.
3. Insure an equitable distribution of risk: Equity or equality are basic ideals in a democratic society. Inequitable treatment including risks often underly public-risk controversies. Because of inevitable qualitative differences among the elements of risks, true equity is difficult to achieve. Pursuit of equity must involve considering who benefits and who is harmed by any risk situation.
4. Seek optimal use of limited risk-management resources: Utility is a measure of efficiency or optimal use of resources. Inevitably, our resources (intellectual, tangible, and financial) for achieving effective risk management will be limited. Optimal risk management requires using limited resources where they will achieve the most risk reduction or overall benefit, but this is not simply economic cost–benefit analysis. The likely inevitable trade-offs between individual risk and population risk may be challenging.
5. Promise no more risk management than can be delivered: Honesty is always a critical aspect of human relations. Creating expectations for risk management that realistically cannot be met will almost certainly generate avoidable conflict. If we fail to understand the limitations to our knowledge, our ability to make difficult decisions under uncertainty will be impaired. Misguided confidence in risk-assessment predictions may be the largest single problem for effective risk management and risk communication.
6. Impose no more risk than you would tolerate yourself: The Golden Rule may be the most effective guidance for governing civil society. Society has been extremely well served by the Golden Rule as a guide for civilized human behavior.

[26] https://www.wikidoc.org/index.php/Hippocratic_Oath↗.

This guidance forces decision makers to abandon complete detachment from their decisions so they may understand the perspectives of those affected. Of course, actually honoring this principle may be the most difficult principle of all. The truth of this does not reduce the merit of the Golden Rule.

Exercise 10 addresses the issue of confidence in risk management decisions.

6.5 Making More of What We Know

Hrudey and others (2011, 2012) suggested an approach specifically for ensuring safe drinking water that seeks to maximize the knowledge we have gained over decades of experience and study. Uncertainty can seem overwhelming, but that reality should not cause us to ignore all we have learned about water quality and water treatment. Individual water-quality parameters have basic properties that predict how they will behave in water-treatment processes. These processes are designed for specific treatment purposes, but they will also remove other parameters with similar physical, chemical, or biological properties. These realities justify a focus on ensuring that treatment processes are functional for their intended purpose at all times.

For example, microbial pathogens are all small (fine particles), so a treatment process that maximizes removal of very fine particles will remove microbial pathogens regardless of their species identity or genetic complement.

Hrudey and others (2011, 2012; p. 15–16) proposed a risk-hierarchy approach to incorporate uncertainty, with health risk being pre-eminent:

> *"1. Highly certain and pervasive risks require action for any water system—these are best represented by the microbial pathogens that are known to cause human disease via drinking water exposure and because of their faecal origin present a pervasive risk to all surface water systems, many groundwater sources and to all distribution systems.*
>
> *2. Reasonably certain but less pervasive risks (appearing in some drinking water systems) should be identified and addressed as demonstrably necessary—various parameters have provided essentially certain evidence of causing human illness (or adverse effect) via drinking water exposure at some time, somewhere in the world (e.g., arsenic, fluoride, nitrates, lead). These will be site-specific and only apply to some water providers.*
>
> *3. Common but comparatively uncertain risks (e.g., produced in water treatment) require a rational precautionary response—various parameters (e.g., DBPs, aluminum, water treatment chemicals) warrant scrutiny because they are produced or added in the water treatment process, are very common and may be amenable to reduction through process refinements.*

4. Site-specific contaminants with noteworthy toxic potential require localized plans commensurate with risk—various parameters (e.g., pesticides, cyanobacterial toxins) with toxic potential relevant to drinking water exposure and that can be found in water need to be assessed to determine site-specific relevance and appropriate local action.

5. Emerging contaminants require research to characterize the nature of problem—advances in analytical chemistry guarantee that many contaminants will continue being identified in drinking water … and these require research to characterize their nature to determine if they pose a drinking water health problem [versus] a hypothetical problem. Once research has adequately characterized the risks, and the importance of drinking water relative to other sources of human exposure, such emerging contaminants may be classified into an appropriate category above. In the meantime, treatment barriers should not be altered unless there is reasonable certainty that such alterations will not simply create other, as yet uncharacterized risks."

Figure 26 illustrates the underlying logic categorized with a horizontal scale of confidence in the ability of a given hazard to cause human illness specifically by means of drinking-water exposure and a vertical scale of risk magnitude (simplified as probability and consequences for exposure levels known to have occurred in drinking water). Those risks that are pervasive or highly prevalent will generate a higher probability for the estimation of risk magnitude.

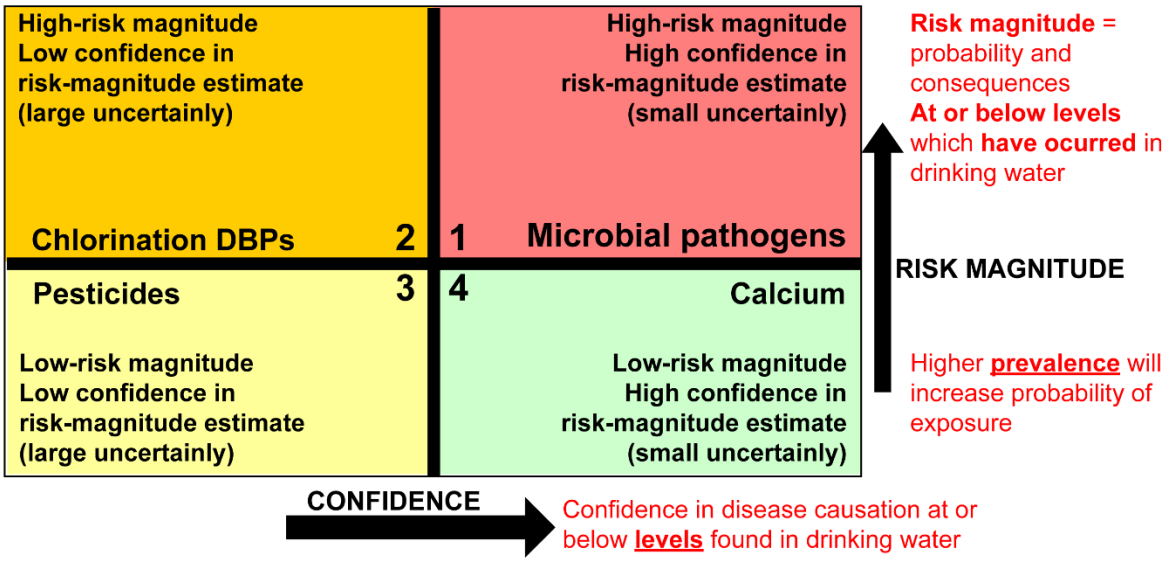

Figure 26 - Categorization of risks according to risk magnitude and uncertainty (Hrudey et al., 2012). Judgements on risk associated with drinking water need to be made at contaminant concentrations that have occurred in drinking water because many substances can be dangerous at high concentrations that do not arise in drinking water. Thus, the upper right quadrant includes clearly defined risk at levels found in drinking water. The lower right quadrant includes substances that are prevalent in drinking water, making exposure more likely, but have not been identified as being hazardous at those concentrations. Probability and consequences are considered for establishing risk magnitude, but as noted throughout this book, these do not fully characterize risk.

The risk hierarchy presented in this section deals with risks falling in quadrants 1 or 2 of Figure 26. Well-characterized microbial pathogens (e.g., *Campylobacter*, *Cryptosporidium*) would generally fit in quadrant 1. DBPs would fit in quadrant 2 because of their widespread population exposure. Although they have had serious suspected outcomes, the major uncertainty of the evidence that they have caused human disease via drinking-water exposure places them in quadrant 2. Most trace contaminants (e.g., pesticides) would normally fit in quadrant 3 because the exposure level typically found in drinking water is very low, they are usually not widespread, and there is low confidence that such low-level exposures can cause human health effects. Emerging contaminants may belong in quadrant 2 or 3, if environmental health research is to be valuable, future study will eventually reduce uncertainty to allow more confident reassignment to quadrants 1 or 4. Substances with well known but very limited toxic properties (e.g., iron, calcium) would fit in quadrant 4. The latter risks are logically at the bottom of any risk comparison because of their characteristics of being low-risk-magnitude with a high degree of certainty.

7 Concluding Thoughts

7.1 Overview

This book seeks to address how we can ensure safe drinking water. The challenge is complicated by the apparent reluctance of responsible regulatory agencies to define *safe* or *safe drinking water*. Drinking water that makes consumers ill is clearly unsafe. Because there is not a sharp transition from unsafe water to water that is very unlikely to make any consumer ill, determining when drinking water can be deemed safe requires a judgment that many regulatory agencies appear reluctant to commit to make. This reluctance prevails with some (e.g., US EPA) making claims that there are contaminants (carcinogens, lead) for which there is no safe level. Such claims are not accurate in any practical sense and are surely not defensible by any party or agency that also declines to define what it considers safe.

Safe is not and cannot be zero-risk. However, a careful analysis reveals there must be levels of non-zero risk that are too small to warrant change of behavior or diversion of resources—meaning they are effectively safe. The misconceptions about various chemicals having no safe level of exposure may have contributed to a common perspective that chemical contaminants in drinking water pose a greater health risk than microbial pathogens. That perspective is demonstrably inaccurate given the ongoing toll of disease and death around the world caused by pathogens arising from faecal contamination of drinking water versus the site- and circumstance-specific cases of human illness that can be reliably attributed to chemical contamination of drinking water.

Among the popular misconceptions that are addressed in this book is the belief that natural is healthy and that chemicals somehow present a human-created risk that is inherently dangerous. The reality that is misperceived is that microbial pathogens are entirely natural, yet they pose by far the greatest human health risk for drinking-water contamination. Any water utility, no matter what technology it employs, can experience microbial contamination. It arises from humans and animals (livestock, pets, and wildlife), so a microbial contamination risk exists everywhere there are humans and animals. Furthermore, unlike chemical contaminants, human pathogens can reproduce in the human body.

The basic sciences employed in assessing public health risks are toxicology and epidemiology. These disciplines are complex and nuanced in their respective capabilities to define and characterize human health risks. Because ethics largely preclude the possibility of experimental exposure of humans to prospective health risks, these sciences must be applied in an indirect and inferential manner. The processes for assessing human health risks have been developed largely over the past 50 years. Despite considerable attention aimed at improving the processes involved, they are invariably subject to limited evidence and considerable uncertainty for the purposes of making a prediction of what

may go wrong. There are many sources of detailed guidance for performing health-risk assessment, but the available evidence that can be used to make predictions is normally much less than desirable, meaning that predictions are inherently uncertain. This may not be sufficiently evident because risk-assessment guidance can be interpreted as being prescriptive, which leads to overconfidence in the predictions. Such overconfidence will be readily evident if predictions are expressed quantitatively in more than two significant figures (one significant figure is often a stretch). Uncertainty must generally be addressed by consistently making cautious assumptions. Practitioners will commonly call such assumptions *conservative*, a clear example of using an ambiguous description that can convey an unintended, politically charged meaning to anyone outside the circle of risk assessors.

Health-risk management needs to be informed by health-risk assessment, something that is not always achieved effectively. Risk management for drinking water is generally achieved by following guidelines or regulations specifying limits on contaminants in treated water. This emphasis is understandable to some degree because of the large number of contaminants that have numerical limits.

However, the concept of ensuring safe drinking water by monitoring for contaminants in treated water suffers from the reality that few contaminants can be reported in real time. Most trace contaminants, which are expensive to track, are reported only days to weeks after sampling, meaning that consumers have already been exposed. This approach is inherently reactive rather than preventive.

Understanding this reality has led over the past 20 years toward more emphasis on operational guidance aimed at ensuring that treatment barriers capable of removing contaminants that threaten a given system are ensured to be functional to achieve the treatment performance they are designed for. The drinking-water safety plan approach is advocated by WHO and the ADWG as part of a comprehensive, "know your own system" quality-management approach and offers the best assurance of providing safe drinking water, notwithstanding clear evidence that such plans can and do fail (Graham et al., 2023; Lane & Hrudey, 2023; Walker, 2023).

Health-risk assessment and risk management face a growing, technologically driven challenge because of misinformation. Inaccurate beliefs about drinking-water safety date back to the discovery by Snow that faecal contamination of drinking water was responsible for cholera epidemics in London, England, in the 1800s. His discovery was at odds with the prevailing views of public health authorities that cholera was caused by foul-smelling air, so-called miasma. Further, we live in a world that is increasingly subject to the spread of misinformation via social media, as evidenced by the degree to which anti-vaccine movements contributed to hundreds of thousands of avoidable deaths during the COVID-19 pandemic. Overcoming the challenges of misinformation will not be achieved by ignoring the underlying beliefs but inevitably depends upon ensuring that

those responsible for providing drinking water make the most of what we know about health risks from drinking water. That knowledge must be consistently applied in a rational manner. Section 7.2 lists some of the many things we know, or can reasonably infer, about health risk.

7.2 Principles, Foundations and Concepts About Health Risk

7.2.1 Risk and Health Risk

Risk is a much broader concept than the frequently used, simplified concept of risk being the numerical product of probability and consequences.

1) Risk cannot be objectively captured by a single number calculated in this manner.
2) A realistic and comprehensive notion of risk is a prediction of the likelihood (probability) of an event or set of circumstances (a hazard) leading to adverse consequences over a specified time period. This comprehensive concept consists of five key elements, namely:
    - hazard (the source of danger),
    - consequences (adverse outcomes caused by a hazard),
    - probability (the likelihood of a hazard causing adverse outcomes),
    - time frame (over which the likelihood is considered),[27] and
    - perspective (of how important those affected judge the risk to be).
3) There are three absolute certainties with regard to health risk:
    - Everyone has a lifetime probability of death equal to 1.0 (that is, certainty).
    - Given the foregoing reality, ZERO human health risk cannot be achieved.
    - Risk management can seek only to minimize preventable health risks and "premature"[28] death, but tradeoffs (risk versus risk) are inevitable in any risk-management decision.
4) Health, as experienced by humans, is a much broader concept than merely absence of disease.
5) Consequences of specific health risks elaborated on by direct scientific inquiry (humans by means of epidemiology, animals by means of toxicology) can only infer possible health risks and, then, only for populations.
6) Individual health risk is entirely an abstract quantity that can only be inferred; it can never be known with certainty for any individual, rather it must be inferred by relying on evidence gathered about population health risk, if such can be found.

[27] The probability of something happening in one day, or even a year, is vastly different from the probability of occurrence in a lifetime.
[28] An individual's normal life expectancy cannot be known so that the concept of premature death is abstract at best.

7.2.2 Evidence of Causation, Epidemiology, and Toxicology

1) There is a chain of causation for environmentally linked disease that is interactive between the host and the disease agent(s) via environmental pathways.
2) A chain of causation, as noted above, results in perceived or measurable consequences for the host.
3) A *sufficient* cause is one that will inevitably lead to the disease, whereas a *necessary* cause is one that must be present for the disease to occur but will not guarantee the disease, while *contributory* causes increase the likelihood of causation through risk factors but need not be either necessary nor sufficient causes.
4) Epidemiological studies can possibly demonstrate association (correlation) of disease with exposure to risk factor(s), but—strictly by themselves—epidemiological studies cannot prove causation. However, epidemiological evidence is an essential element that must be considered in causal inference that requires judgment applied to a variety of factors, including biological plausibility based on an understanding of the mechanism of toxic action (MOA).
5) Statistical inference is distinctly different from causal inference, even though statistical inference is used to judge aspects of the strength of evidence in support of causal inference. Finding statistical significance can support causal inference but alone does not prove causation.
6) There is a hierarchy in epidemiological study designs. Analytical designs (case-control, cohort, or experimental designs) are needed to provide meaningful evidence for causal inference. These designs require knowledge of both individual health outcome and individual exposure to the hypothesized causal agent, which is difficult to characterize in drinking water studies. Designs with lesser capability can be considered hypothesis-generating but not hypothesis-testing for causation.
7) The dose makes the poison; all substances are toxic in sufficient dose. Sufficiency of dose involves individual variability in tolerance to adverse effects.
8) Toxicology is both a science and an art. The science goes with documenting the observational and experimental activities in relation to specified hypotheses, while the art goes with interpreting the applicability of the findings and making predictions (risk assessment).
9) As the quantity of exposure to a substance within its harmful range increases, the probability and severity of adverse effects will increase, forming the basis for a quantitative dose–response relationship. The latter is needed to make quantitive predictions about adverse outcomes for a specified level of exposure.
10) Animal models are useful to determine toxic effects in humans—given that humans are animals—provided the relevant physiological differences are taken into account in seeking to understand a biological MOA, that is, mechanism of toxic action for humans.

11) Adverse effects of substances will not be universal in character. Rather, they will be specific to one or more MOA giving rise to various specific adverse effects, including the possibility of different effects at different sites of action.
12) Adverse health effects resulting in toxicity occur via molecular-level chemical reactions and physical processes. Although these effects are classified as adverse because of their outcome on the function of the host, most of these chemical reactions are not otherwise distinguishable from reactions that occur in normal life processes.

7.2.3 Exposure Assessment is Essential

1) Contaminants will broadly partition in the environment and in the body in accordance with the basic physical and chemical properties they possess. Those characteristics need to be considered in judging the likelihood of a given contaminant posing a tangible human health risk.
2) Exposure assessment is necessary to determine plausible doses, including routes of exposure and distribution of dose according to physiological processes and physical/chemical properties.
3) Dose may be defined in many ways, including various time frames and at various levels of specificity. Ultimately, the most relevant measure of dose is the biologically effective dose at the site of toxic action.
4) Knowledge of the exposure (the dose) and the toxic potency of a substance, along with bioavailability and environmental and social factors, will provide a basis for predicting the likelihood of adverse health effects.
5) The consequences of any specified level of toxic exposure depend on toxicokinetics (absorption, distribution, metabolism, and excretion) and toxicodynamics (MOA at the target site), which depend on the physical/chemical properties of the contaminant. For this reason, health risk to an individual is dependent upon the route of exposure, with different routes of exposure yielding different nature and degrees of health risk.

7.2.4 Cancer Risk and Thresholds of Dose–Response

1) Cancer is not a single, homogenous disease. Rather, cancer is a family of a diverse range of diseases that have the common feature of abnormal, unregulated cell replication that otherwise have a wide range of characteristics including the likelihood of being treatable versus being fatal.
2) Carcinogenesis is a complex disease expression involving multiple processes in stages ranging from initiation of a tumor (involving alteration of a cell's genetic material) through promotion of tumor growth, to progression of tumor growth and spread. These factors depend upon individual metabolism, physiological processes (including immune response), and the inherent aggressiveness of the specific tumor.
3) The practice of risk assessment has, until recently, clearly distinguished toxic substances for which a threshold is expected from those for which there may be no

measurable threshold. Only in the latter case have mathematical models been properly used to express risk at low dose in terms of probability of adverse outcome.

4) For threshold substances, doses below the presumed no-effect levels are interpreted as having no estimable probability of harm. The merits of the assumption that some contaminants have no threshold have been increasingly questioned by toxicologists and risk assessors as more knowledge is gained about the mechanisms of toxicity.
5) The case for or against a threshold for any toxic process cannot be resolved strictly on the basis of scientific experiment or argument. If there is no plausible mechanism for biological amplification of adverse effects from very low doses, such as cell replication with damaged genetic material, then a toxic substance must effectively have a threshold, even if it has not yet been quantified.
6) For the purposes of health-risk assessment, thresholds must be distinguished in terms of whether they refer to harm ultimately affecting the entire organism versus damage only to a single cell or an individual organ that has sufficient reserve capacity to avoid those adverse consequences harming the whole organism.

7.2.5 Uncertainty and Managing Risk

1) The relationship between the means of knowing about health risk and the comparative uncertainty and confidence in the evidence is illustrated in Figure 4 and Figure 10 .
2) Uncertainty can be comprised of two types:
    a. Variability (heterogeneity) refers to possible differences in key elements of exposure or susceptibility (such as differences in age, gender, and degree of exposure) that exist but are not known with certainty.
    b. Knowledge uncertainty (ignorance) is the absence of knowledge about the true values of key aspects of the toxic effects (such as MOA, existence of a threshold, and quantitative dose-response).

7. Knowledge uncertainty can be reduced by further study to learn what can be known, whereas variability can be better characterized but it cannot be reduced.

3) We must confront uncertainty in risk management to confront reality. Knowledge uncertainty deals with our level of confidence in our knowledge of risk character while variability deals with who or what may be affected by risk and to what extent.
4) Risk cannot be characterized without an accurate understanding gained from hazard identification, exposure assessment, and dose-response assessment because risk is a composite of the elements that these activities seek to identify and assess.
5) Risk management needs the best available scientific inputs to allow us to make effective decisions, but the best available science alone can never resolve all, or even most, of the necessary risk-management choices. The best possible scientific knowledge about a health risk cannot ensure the absence of risk controversy.

6) Effective management of risk for protecting public health in the face of uncertainty requires a high level of confidence versus a low level of confidence in the evidence supporting risk-management decisions. Confidence in risk-management actions should be lowest when uncertainty about evidence is enormously large and highest when uncertainty about evidence is negligibly small.
7) Resolving competing risks (e.g., pathogen infection vs. exposure to disinfection by-products) should be informed by the negligible uncertainty about pathogens being able to cause human illness vs. the substantial uncertainty of drinking water levels of exposure to disinfection by-products causing human illness.
8) Knowing what to ultimately do with the "truth" can be as hard as knowing what the truth is.

7.3 Summary

Public health risk assessment seeks to inform risk management to ensure safe drinking water. This topic has received increasing attention over the past 50 years which has revealed the complexity of the inputs and relationships that bear on estimating health risks associated with contamination of drinking water (Figure 27). Given the substantial role for scientific evidence in characterizing the inputs and relationships there is a common expectation of quantitative certainty in assessing health risk. The realities of health risk assessment of drinking water reveal that there are many uncertainties that cannot be simply resolved by evidence that can be realistically obtained.

Expectations for certainty must be tempered by the realities of scientific evidence. In this situation, it is vitally important to recognize what we can know with confidence (e.g. pathogens pose the greatest health risk to drinking water safety) and to ensure these risks are managed as completely as possible. Otherwise, the most we can expect from scientific evidence is that it assists us in understanding the dimensions and details of a problem.

A fundamental reality of risk assessment is that there is no possibility of zero risk meaning that safety cannot be equated with zero risk. The knowledge derived from maximizing scientific evidence can help us better understand estimates of health risk from drinking water contamination. However, the scientific evidence cannot tell us how to judge uncertainties or how low the risk must be to judge it to be safe. The latter is a value judgement for society to make.

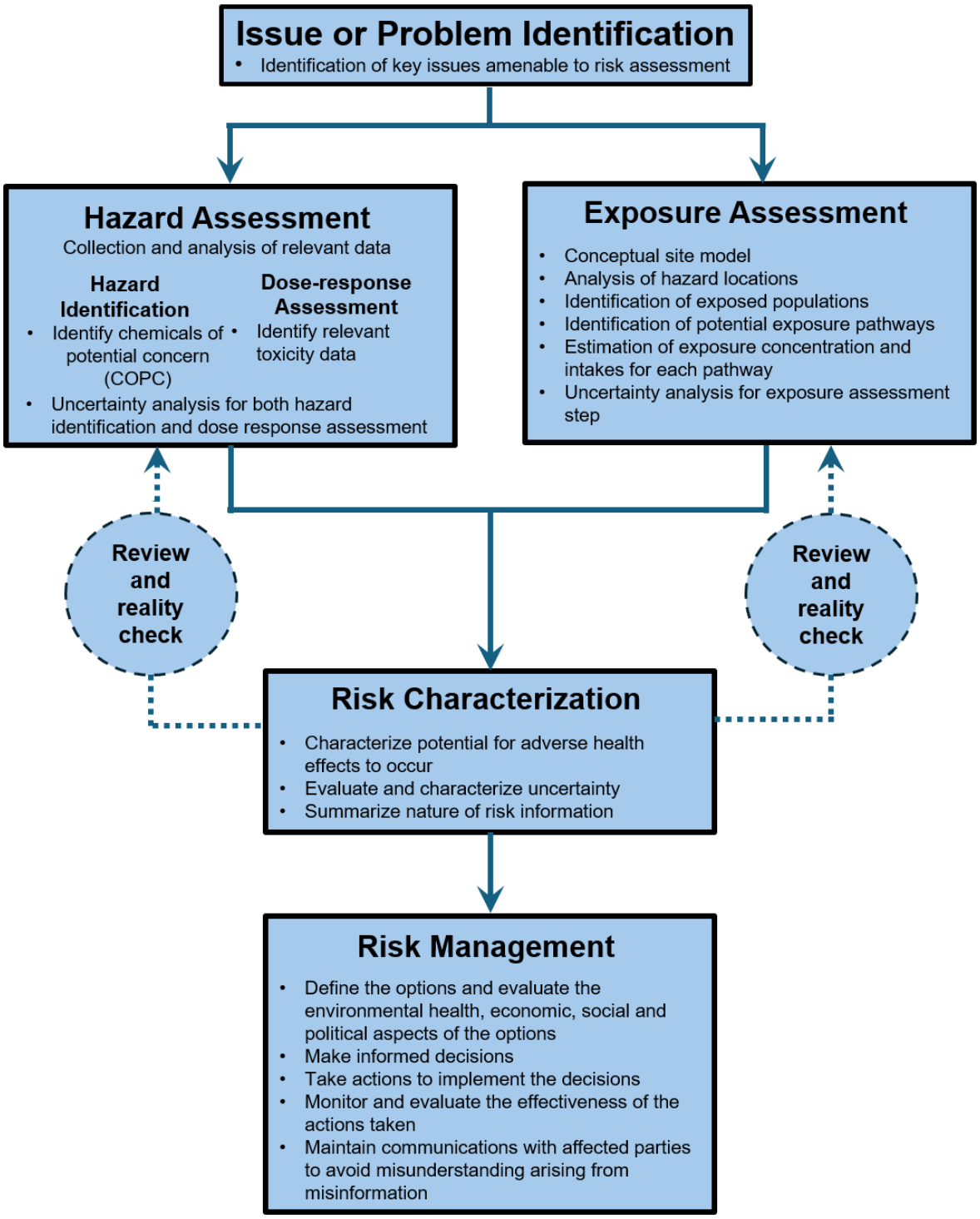

Figure 27 - Overview of environmental health risk assessment and risk management (adapted from EnHealth 2012a).

8 Exercises

Exercise 1

Describe the chain of causation that applies to environmental health risks.

Solution to Exercise 1

Return to where text linked to Exercise 1

Exercise 2

There is a relationship between the methods of gaining evidence about human health risks and the comparative degree of uncertainty. Describe what that relationship is and explain why this relationship exists.

Solution to Exercise 2

Return to where text linked to Exercise 2

Exercise 3

What is the difference between statistical inference and causal inference? What is needed to use statistical inference to demonstrate causal inference?

Solution to Exercise 3

Return to where text linked to Exercise 3

Exercise 4

Why can the consequences of specific human health risks only be inferred and only for populations and not for individuals?

Solution to Exercise 4

Return to where text linked to Exercise 4

Exercise 5

There are many epidemiological study designs. Why are some designs more capable of contributing evidence toward demonstrating causation? What feature is essential for any study design to be able to provide evidence in support of causation? Why are such lines of evidence not able to provide certain predictions of any individual's health risk?

Solution to Exercise 5

Return to where text linked to Exercise 5

Exercise 6

Many risk assessments will try to guide risk management by calculating risk as a product of probability and a quantitative estimate of consequences. Is that a useful, realistic concept of risk for authentic risk management scenarios? If not, what is a more realistic concept of risk?

Solution to Exercise 6

Return to where text linked to Exercise 6

Exercise 7

Chloroform, the most prevalent disinfection by-product caused by chlorination, had been historically treated as a carcinogen, by any route of exposure. In the past 25 years, chloroform has been one of only a few carcinogens to be reviewed for the plausibility of its assignment as a non-threshold (genotoxic) carcinogen. In that update (US EPA, 2001, p. 10, 24), chloroform was described as follows.

"II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996; U.S. EPA, 1999), chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b).

Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. This weight-of-evidence conclusion is based on

1) observations in animals exposed by both oral and inhalation pathways which indicate that sustained or repeated cytotoxicity with secondary regenerative hyperplasia precedes, and is probably required for, hepatic and renal neoplasia;

2) there are no epidemiological data specific to chloroform and, at most, equivocal epidemiological data related to drinking water exposures that cannot necessarily be attributed to chloroform amongst multiple other disinfection byproducts; and

3) genotoxicity data on chloroform are essentially negative, although there are some scattered positive results that generally have limitations such as excessively high dose or with confounding factors.

Thus, the weight-of-evidence of the genotoxicity data on chloroform supports a conclusion that chloroform is not strongly mutagenic, and that genotoxicity is not likely to be the predominant mode of action underlying the carcinogenic potential of chloroform.…

II.B.1. Summary of Risk Estimates

A dose of 0.01 mg/kg/day (equal to the RfD) can be considered protective against cancer risk. (emphasis added)

II.B.1.1. Oral Slope Factor — Not applicable….

II.B.1.2. Drinking Water Unit Risk — Not applicable."

a) If the invalid, outdated carcinogenic potency factor, $q_1{}^*$ (based upon an expectation of no threshold) for chloroform was 6.1×10^{-3} $(\text{mg/kg-bw-d})^{-1}$, calculate the risk for an average American dose of chloroform at the SDWA maximum contaminant level (MCL) of 0.08 mg/L via average drinking water consumption levels of 1.5 L/d, assuming an average body mass of 70 kg.
b) Considering the risk level calculated in part a), how many cases of cancer might occur on average per year in the USA (population of 330 million) if everyone was exposed to that specified level for their entire lifetime.
c) Is the calculation in part b), if it was valid (it is not), likely to match with observed values of cancer occurrence? Why or why not?
d) Can you reconcile the calculation in part b) with the statement in the US EPA (2001) IRIS risk profile for chloroform that states, "*A dose of 0.01 mg/kg/day (equal to the RfD) can be considered protective against cancer risk?*"
e) The current drinking water guideline in Canada for THMs, which can be reliably assumed to be mainly composed of chloroform (unless the source water is high in bromide, which generally is limited to water supplies impacted by saline water), is 100 μg/L. Assuming average daily consumption of 1.5 L of drinking water at the guideline maximum with 100 percent of THM as chloroform, what is the risk of consuming this guideline level of drinking water for a lifetime?

Solution to Exercise 7

Return to where text linked to Exercise 7

Exercise 8

Uncertainty is pervasive in risk assessment and risk management. What are the important distinctions about uncertainty that bear on risk assessment and risk management? How can these different types of uncertainty be dealt with in characterizing and managing risk?

Solution to Exercise 8

Return to where text linked to Exercise 8

Exercise 9

Monitoring evidence for a drinking-water supply has indicated that in treated drinking water, a pesticide—say, atrazine—is truly present above the recognized standard methods detection limit only once in every thousand water samples from the treated water.

The analytical test for the pesticide has the following characteristics:

ninety-five percent of tests will be positive for detection when the contaminant is truly present above the detection limit, and

ninety-eight percent of tests will be negative for detection when the contaminant is truly not present above the detection limit.

With these characteristics, and given only one positive result (detection) in 1000 analyses for the pesticide in the drinking-water system, how likely is it that this positive result is true? Provide either a probability estimate or your scale of agreement using the following categories:

almost certain (95 to 100 percent)
very likely (80 to 95 percent)
very unlikely (5 to 20 percent)
extremely unlikely (0 to 5 percent)
more likely than not (50 to 80 percent)
less likely than not (20 to 50 percent)
don't know

Solution to Exercise 9

Return to where text linked to Exercise 9

Exercise 10

Confidence in risk-management decisions is important. Provide logic to maximize confidence in risk-management decisions in relation to inevitable uncertainty in evidence.

Solution to Exercise 10

Return to where text linked to Exercise 10

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10 Boxes

Box 1 - Drinking-water guidelines and standards are dominated by chemical contaminants

This summary is provided only for an overview comparison. For application to any specific water safety issue, the most recent version of criteria applicable to your jurisdiction must be consulted.

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Acephate (organophosphate class)	-	-	0.008	-	-
Acrylamide	0.0005	TT	0.0002	-	0.0001
Alachlor (methoxymethylacetanilide)	0.02	0.002	-	-	-
Aldicarb (carbamate class)	0.01	-	0.004	-	-
Aldrin and dieldrin	0.00003	-	0.0003	-	-
Aluminum	-	-	-	2.9 (0.1)**OG**	
Ametryn (triazine class)	-	-	0.07	-	-
Amitraz (amidine class)	-[a]	-	0.009	-	-
Amitrole (triazole class)	-	-	0.009	-	-
Antimony	0.02	0.006	0.003	0.006	0.01
Arsenic	0.01 (A,T)	0.01	0.01	0.01	0.01
Asbestos fiber (> 10 µm)	-	$7x10^6$ /L	-	-	-
Asulam (carbamate class)	-	-	0.07	-	-
Atrazine (triazine class)	0.1	0.003	0.02	0.005	
Azinphos-methyl (organophosphate class)	-	-	0.03	-	-
Barium	1.3	2	2	2.0	-
Benomyl (benzimidazole class)	-	-	0.09	-	-
Bentazone (benzimidazole class)	-	-	0.4	-	-
Benzene	0.01	0.005	0.001	0.005	0.001
Benzo[a]pyrene	0.0007	0.0002	0.00001	0.00004	0.00001

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Beryllium	-[a]	0.004	0.06	-	-
Bioresmethrin (pyrethroid class)	-	-	0.1	-	-
Bisphenol A	-	-	-	-	0.0025
Boron	2.4	-	4	5	1.5
Bromacil (urea group)	-	-	0.4	-	-
Bromate	0.01 (A,T)	0.01	0.02	0.01	0.01
Bromodichloromethane	0.06	-	-	-	-
Bromoform	0.1	-	-	-	-
Bromoxynil (hydroxybenzonitrile class)	-	-	0.01	0.03	-
Cadmium	0.003	0.005	0.002	0.007	0.005
Captan (phthalimide class)	-	-	0.4	-	-
Carbaryl (carbamate class)	-[a]	-	0.03	-	-
Carbendazim/thiophanate-methyl (benzimidazole class)	-	-	0.09	-	-
Carbofuran (carbamate class)	0.007	0.04	0.01	-	-
Carbon tetrachloride	0.004	0.005	0.003	0.002	-
Carbophenothion	-	-	0.0005	-	-
Carboxin (carboxamide class)	-	-	0.3	-	-
Carfentrazone-ethyl (triazolinone class)	-	-	0.1	-	-
Chloral hydrate (Trichloroacetaldehyde)	-[a]	-	0.1	-	-
Chloramines (as Cl_2)	-	4(MRDL)	-	-	-
Chlorantraniliprole (anthranilic diamide)	-	-	6	-	-
Chlordane (cyclodiene class)	0.0002	0.002	0.002	-	-
Chlorfenvinphos (organophosphate class)	-	-	0.002	-	-
Chlorine	5(C)	4	5 (0.6)	-[c]	-
Chlorine dioxide	-	0.8(MRDL)-	-	-	-
Chlorate	0.7(D)		-	1	0.25
Chlorite	0.7(D)	1.0	0.8	1-	0.25

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Chloroacetic acid	-	-	0.15	-	-
Dichloroacetic acid	0.05	-	0.1	-	-
Trichloroacetic acid	-	-	0.1	-	-
Chlorobenzene	-[a]	0.1	0.3 (0.01)	-	-
Chloroform	0.3	-	-	-	-
2-Chlorophenol	-[d]	-	0.3 (0.0001)	-	-
2,4-Dichlorophenol	-[d]	-	0.2 (0.0003)	-	-
2,4,6-Trichlorophenol	0.2	-	0.02 (0.002)	-	-
Chlorothalonil (chloronitrile class)	-[a]	-	0.05	-	-
Chlorotoluron (phenlyurea class)	0.03	-	-	-	-
Chlorpyrifos (organophosphate class)	0.03	-	0.01	0.09	-
Chlorosulfuron (sulfonylurea class)	-	-	0.2	-	-
Chromium[e,f]	0.05[e]	0.1[e]	0.05[f]	0.05[e]	0.025
Clopyralid (pyridinecarboxylic acid class)	-	-	2	-	-
Copper	2	1.3(AL) TT	2 (1)	2 (1) [g]	2
Cyanide	-[a]	0.2	0.08	0.2	0.05
Cyanazine (triazine class)	.0006	-	-	-	-
Cyanogen chloride	-[a]	-	0.08	-	-
Cyanobacterial toxins	-[h]	-	-[h]	0.0015[i]	-
Cyfluthrin, ß cyfluthrin (pyrethroid class)	-	-	0.05	-	-
Cylindrospermopsins (cyanobacterial toxins)	0.0007(P)	-	-	-	-
Cypermethrin isomers (pyrethroid class)	-[a]	-	0.2	-	-
Cyprodinil (anilinopyrimidine class)	-	-	0.09	-	-
Dalapon	-	0.2	-	-	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
2,4-D (2,4-Dichlorophenoxy acetic acid)	0.03	0.07	0.03	0.1	-
2,4-DB (2,4-Dichlorophenoxy butyric acid)	0.09	-	-	-	-
DDT (1,1,1-trichloro-di(4-chlorophenyl) ethane) and metabolites	0.001	-	0.009	-	-
Deltamethrin (pyrethroid class)	-[a]	-	0.04	-	-
Diazinon (organophosphate class)	-[a]	-	0.004	-	-
Dibromoacetonitrile	0.07	-	-	-	-
Dibromochloromethane	0.1	-	-	-	-
1,2-Dibromo-3-chloropropane (DBCP)	0.001	0.0002	-	-	-
1,2-Dibromomethane	0.0004(P)	-	-	-	-
Dicamba (chlorophenoxy class)	-	-	0.1	0.11	-
1,2-Dichlorobenzene	1(C)	0.6	1.5 (0.001)	-	-
1,4- Dichlorobenzene	0.3(C)	0.075	0.04	0.005	-
1,2-Dichloroethane	0.03	0.005	0.003	0.005	0.003
1,1-Dichloroethene	-[a]	0.007	0.03	-	-
1,2-Dichloroethene	0.05	0.07[j] or 0.1[j]	0.06	-	-
Dichloromethane	0.004	0.005	0.004	0.05	-
1,2-Dichloropropane	0.04(P)	0.005	-	-	-
1,3-Dichloropropene	0.02	-	0.1	-	-
Dichlorprop/Dichlorprop-P (phenoxycarboxylic acid class)	0.1	-	0.1	-	-
Dichlorvos (organophosphate class)	-[a]	-	0.005	-	-
Diclofop-methyl (arylphenoxy propionate and chlorophenoxy class)	-	-	0.005	-	-
Dicofol (related to DDT)	-[a]	-	0.004	-	-
Di(2-ethylhexyl) adipate (DEHA)	-	0.4	-	-	-
Di(2-ethylhexyl) phthalate (DEHP)	0.008	0.006	0.01	-	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Diflubenzuron (benzoylurea class)	-	-	0.07	-	-
Dimethoate (organophosphate class)	0.006	-	0.007	0.02	-
Dinoseb	-	0.007	-	-	-
Dioxin (2,3,7,8-TCDD)	-	0.00000003	-	-	-
1,4-Dioxane	0.05	-	-	0.05	-
Diquat(ion), Diquat dibromide (bipyridilium class)	-[a]	0.02	0.007	0.05	-
Disulfoton (organophosphate class)	-	-	0.004	-	-
Diuron (urea class)	-	-	0.02	-	-
2,2-DPA (2,2-dichloropropionic acid)	-	-	0.5	-	-
Endosulfan (cyclodiene class)	-[a]	-	0.02	-	-
Endothall (dicarboxylic acid class)	-	0.1	0.1	-	-
Endrin	0.0006	0.002	-	-	-
Epicrohydrin	0.0004(P)	TT	0.0005	-	0.0001
EPTC (S-ethyl-dipropylthiocarbamate)	-	-	0.3	-	-
Esfnevalerate (pyrethroid class)	-	-	0.03	-	-
Ethion (organophosphate class)	-	-	0.004	-	-
Ethoprophos (organothiophosphate class)	-	-	0.001	-	-
Ethylbenzene	0.3(C)	0.7	0.3 (0.003)	0.14 (0.0016)	-
Ethylene thiourea (ETU) – degradation product of Mancozeb	-[a]	-	0.009	-	-
Ethylenediamine tetraacetic acid (EDTA, Edetic acid)	0.6	-	0.25	-	-
Ethylene dibromide	-	0.00005	-	-	-
Etridiazole (thiazole class)	-	-	0.1	-	-
Fenamiphos (organophosphate class)	-[a]	-	0.0005[a]	-	-
Fenarimol (pyrimidine class)	-	-	0.04	-	-
Fenitrothion (organophosphate class)	-[a]	-	0.007	-	-
Fenoprop	0.009	-	0.01[a]	-	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Fenthion (organophosphate class)	-	-	0.007	-	-
Fenvalerate (pyrethroid class)	-	-	0.06	-	-
Fipronil (phenylpyrazole class)	-	-	0.0007	-	-
Flamprop-methyl (arylaminoproprionic acid class)	-	-	0.004	-	-
Fluometuron (phenylurea class)	-	-	0.07	-	-
Fluoride	1.5	4	1.5	1.5	1.5
Flupropanate (alkanoic acid class)	-	-	0.009	-	-
Formaldehyde	-	-	0.5	-[a]	-
Glyphosphate (aminophosphonic analogue of glycine)	-[a]	0.7	1	0.28	-
Haloacetic acids - Total	-	0.06	-	0.08	0.06
Haloxyfop (aryloxyphenoxypropionate class)	-	-	0.001	-	-
Heptachlor	-[a]	0.0004	0.0003	-	-
Heptachlor epoxide	-[a]	0.0002	0.0003	-	-
Hexachlorobenzene	-	0.001	-	-	-
Hexachlorocyclopentadiene	-	0.05	-	-	-
Hexachlorobutadiene	0.0006	-	0.0007	-	-
Hexazinone (triazinone class)	-	-	0.4	-	-
Hydroxyatrazine	0.2	-	-	-	-
Imazapyr (imidazolinone class)	-	-	9[a]	-	-
Iodide	-	-	0.5	-	-
Iprodione (dicarboximide class)	-	-	0.1	-	-
Isoproturon	0.009	-	-	-	-
Lanthanum	-	-	0.002	-	-
Lead	0.01(A,T)	TT, AL 0.015[k]	0.01	0.005	0.005
Lindane (cyclodiene class)	0.002	0.0002	0.01	-	-
Malathion (Maldison) organophosphate class)	-[a]	-	0.07	0.19	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Manganese	0.08(P)	-	0.5 (0.1)	0.12 (0.02)	-
Mecoprop	0.01	-	-	-	-
2-methyl-4-chlorophenoxyacetic acid (MCPA)	-[a]	-	0.04	0.35	-
Mercury	0.006	0.002	0.001	0.001	0.001
Metaldehyde (aldehyde class)	-	-	0.02	-	-
Methylisocyanate (MITC), Metham	-	-	0.001	-	-
Methidathion (organophosphate class)	-	-	0.006	-	-
Methiocarb (carbamate class)	-	-	0.007	-	-
Methomyl (carbamate class)	-[a]	-	0.02	-	-
Methoxychlor	0.02	0.04	0.3-	-	-
Methyl bromide		-	0.001	-	-
Metolachlor / s-Metolachlor (chloroacetamide class)	0.01	-	0.3	-	-
Metribuzin (triazinone class)	-	-	0.07	0.08	-
Metsulfuron-methyl (sulfonylurea class)	-	-	0.04	-	-
Mevinphos (organophosphate class)	-	-	0.005	-	-
Microcystins (cyanobacterial toxins)	0.001(P)-	-	0.0013[m]	0.0015	0.001
Molinate (thiocarbamate class)	0.006	-	0.004	-	-
Molybdenum	-[a]	-	0.05	-	-
Monochloramine	3	-	3	-	-
Monochloroacetate	0.02	-	-	-	-
Napropamide (alkanamide class)	-	-	0.4	-	-
Nicarbazin 4.4'-dinitrocarbanilide and 2-hyrdoxy-4,6-dimethylpyrimidine	-	-	1	-	-
Nickel	-0.07	-	0.02	-	0.02
Nitrate and nitrite (as nitrate, NO_3)	50	10 (as NO_3-N)	50	45[n]	50
Nitrilotriacetic acid (NTA)	0.2	-	0.2	0.4	-
Nitrite (as nitrite, NO_2)	3	1 (as NO_2-N)	3-	3	0.5

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
N-Nitrosodimethylamine (NDMA)	0.0001-	-	0.0001	0.00004	-
Norflurazon (pyridazinone class)	-	-	0.05	-	-
Omethoate (organophosphate class)	-	-	0.001	-	-
Oryzalin (dinitroaniline class)	-	-	0.4	-	-
Oxamyl (carbamate class)	-[a]	0.2	0.007	-	-
Paraquat (bipyridinium class)	-	-	0.02	-	-
Parathion (ethyl parathion) (organophosphate class)	-[a]	-	0.02	-	-
Parathion-methyl (organophosphate class)	-	-	0.0007	-	-
Pebulate (thiocarbamate class)	-	-	0.03	-	-
Pendimethalin (dinitroaniline class)	0.02	-	0.4	-	-
Pentachlorophenol	0.009(P)	0.001	0.01	0.06 (0.03)	-
Pesticides	-	-	-	-	0.0001[o]
Pesticides - total	-	-	-	-	0.0005
PFAS – sum of	-	-	-	0.00003 (objective)-	0.0001[p]
PFOS+PFHxS (perfluorinated class)	-	-	0.00007		-
PFOA (perfluorinated class)	-	-	0.00056		-
Permethrin (pyrethroid class)	-	-	0.2	-	-
Picloram (pyridinecarboxylic acid class)	-	0.5	0.3	-	-
Piperonyl butoxide	-	-	0.6	-	-
Pirimicarb (carbamate class)	-	-	0.007	-	-
Pirimiphos methyl (orthophosphate class)	-	-	0.09	-	-
Polihexanide – chlorhexidine polymer	-	-	0.7	-	-
Polychlorinated biphenyls (PCBs)	-	0.0005	-	-	-
Polycyclic aromatic hydrocarbons	-	-	0.00001-	-	0.0001[r]
Profenofos (organophosphate class)	-	-	0.0003	-	-
Propachlor	-	-	0.07	-	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Propanil (anilide class)	-[s]	-	0.7	-	-
Propargite (sulfite ester acaricide)	-	-	0.007	-	-
Propazine (triazine class)	-	-	0.05	-	-
Propiconazole (triazole class)	-	-	0.1	-	-
Propyzamide (benzamide class)	-	-	0.07	-	-
Pyrasulfotole (benzoylpyraole class)	-	-	0.04	-	-
Pyrazophos (phosphorothiolate class)	-	-	0.02	-	-
Pyroxsulam (triazolopyrimidine class)	-	-	4	-	-
Quintozene (nitroaniline class)	-	-	0.03	-	-
Saxitoxins (cyanobacterial toxins)	0.003	-	-	-	-
Selenium	0.04(P)	0.05	0.01	0.05	0.02[t]
Silver	-	-	0.1	-[u]	-
Simazine (triazine class)	0.002	0.004	0.02	-	-
Spirotetramat (tetramic acid / cyclic ketoenol class)	-	-	0.2	-	-
Strontium	-	-	-	7	-
Styrene	0.02(C)	0.1	0.03	-	-
Sulprofos (organophosphate class)	-	-	0.01	-	-
Temephos (organophosphate class)	-	-	0.4	-	-
Terbacil (uracil class)	-	-	0.2	-	-
Terbufos (organophosphate class)	-	-	0.0009	-	-
Terbuthylazine (triazine class)	0.007	-	0.01	-	-
Terbutryn (triazene class)	-	-	0.4	-	-
Tetrachloroethene (tetrachloroethylene)	0.1	0.005	0.05	0.01	-
Tetrachloroethene + Trichloroethene	-	-	-	-	0.01
Thallium	-	0.002	-	-	-
Thiobencarb (thiocarbamate class)	-	-	0.04	-	-
Thiophenate	-	-	0.005	-	-
Thiram (dimethyldithiocarbamate class)	-	-	0.007	-	-

Chemical Chemicals with documented adverse human health outcomes via drinking-water exposure shown in bold	**World Health Organization Drinking-Water Guidelines (WHO 2022a) mg/L**	**US Primary Regulations - Safe Drinking Water Act (US 2023) mg/L**	**Australian Drinking Water Guidelines (NHMRC 2023) mg/L**	**Guidelines for Canadian Drinking Water Quality (Health Canada 2024) mg/L**	**European Union Water Directive (EU 2020) mg/L**
Toltrazuril (triazinetrione class)	-	-	0.004	-	-
Toluene	0.7(C)	1	0.8 (0.025)	0.06 (0.024)	-
Toxaphene	-	0.003	-	-	-
Triadimefon (triazole class)	-	-	0.09[a]	-	-
2,4,5-Trichlorophenoxyacetic acid, Fenoprop	0.009	0.05	0.01	-	-
Tributyltin oxide	-	-	0.001	-	-
Trichlorfon (organophosphate class)	-[a]	-	0.007	-	-
Trichloroacetate	0.2	-	-	-	-
Trichlorobenzenes (sum of all isomers)	-[a]	0.07	0.03 (0.005)	-	-
1,1,1-Trichloroethane	-	0.2	-	-	-
1,1,2-Trichloroethane	-	0.005	-	-	-
Trichloroethylene (1,1,1-Trichloroethene)	0.008	0.005	-[d]	0.005	-
2,4,6-Trichlorophenol	0.2(C)	-	-	0.005 (0.002)	-
Tricopyr (pyridinecarboxylic acid class)	-	-	0.02	-	-
Trifluralin (dinitroaniline class)	0.02	-	0.09	-	-
Trihalomethanes - total (THMs)	-	0.08[v]	0.250[w]	0.1[v]	0.1
Uranium	0.03(P)	-	0.02	0.02	0.03
Vernolate (thiocarbamate class)	-	-	0.04	-	-
Vinyl chloride	0.0003-	0.002	0.0003[x]	0.002	0.0005
Xylenes	0.5(C))	10	0.6 (0.02)	0.09 (0.02)	-

Maximum Residual Disinfectant Level (**MRDL**): The highest level of a disinfectant allowed in drinking water. There is convincing evidence that addition of a disinfectant is necessary for control of microbial contaminants**.** Action Level (**AL**). Operational Goal (**OG**).

Jurisdictions that only provide an aesthetic limit are not listed. If an aesthetic limit is provided in addition to a health-based limit, the aesthetic limit is shown in (..)

A, provisional guideline value because calculated guideline value is below the achievable quantification level; **C**, concentrations of the substance at or below the health-based guideline value may affect the appearance, taste or odor of the water, leading to consumer complaints; **D**, provisional guideline value because effective disinfection may result in the guideline value being exceeded; **P**, provisional guideline value because of uncertainties in the health database; **T**, provisional guideline value

because calculated guideline value is below the level that can be achieved through practical treatment methods, source protection, etc. X, The sum of the ratio of concentration of each to its respective guideline value should not exceed 1.0

- No numerical limit reported or set

[a]- Rarely or unlikely to be found in drinking water at concentrations of health concern—except for product spills

[b] A provisional reference value may be useful to guide actions by member states when there is reason for local concern, although available data are inadequate to permit derivation of a health-based guideline value.

[c]- A guideline value is not necessary due to low toxicity at concentrations found in drinking water.

[d]- limited toxicity data, insufficient to set guideline value

[e] Total chromium

[f] Hexavalent chromium

[g] Aesthetic objective only

[h]- Cyanobacterial toxin limits set for specific toxins or toxin groups

[i]- Cited limit is for total microcystins (intra- and extra-cellular)

[j] 0.07 mg/L for cis-1,2-dichloroethylene and 0.1 mg/L for trans-1,2-dichloroethylenea

[k] Lead and copper are regulated by a treatment technique that requires systems to control the corrosiveness of their water. If more than 10 percent of tap water samples exceed the action level, water systems must take additional steps. For copper, the action level is 1.3 mg/L and for lead it is 0.015 mg/L.

[l] The parametric value of 0.005 mg/L shall be met, at the latest, by 12 January 2036. The parametric value for lead until that date shall be 0.01 mg/L. After that date, the parametric value of 0.005 mg/L for lead shall be met at least at the point of supply to the domestic distribution system.

[m] Microcystin-LR toxicity equivalents (TE)

[n] For nitrate only, separate limit specified for nitrite

[o] Pesticides: organic insecticides, organic herbicides, organic fungicides, organic nematocides, organic acaricides, organic algicides, organic rodenticides, organic slimicides, related products (interalia, growth regulators), and their metabolites. The parametric value of 0.0001 mg/L shall apply to each individual pesticide. In the case of aldrin, dieldrin, heptachlor, and heptachlor epoxide, the parametric value shall be 0.000030 mg/L.

[p] "PFAS - sum of" means the sum of per- and polyfluoroalkyl substances considered a concern as regards water intended for human consumption. This is a subset of PFAS total substances that contain a perfluoroalkyl moiety with three or more carbons (i.e., –CnF2n–, n ≥ 3) or a perfluoroalkylether moiety with two or more carbons (i. e., –CnF2nOCmF2m–, n and m ≥ 1).

[q] For PFOS only

[r] Sum of concentrations of the following specified compounds: benzo(b)fluoranthene, benzo(k)fluoranthene, benzo (ghi)perylene, and indeno(1,2,3-cd)pyrene

[s] Readily transformed into metabolites that are more toxic; a guideline value for the parent compound is considered inappropriate, and data are inadequate to enable the derivation of guideline values for the metabolites.

[t] A parametric value of 0.030 mg/L shall be applied for regions where geological conditions could lead to high levels of selenium in groundwater.

[u] Guideline values not required, as drinking water contributes negligibly to an individual's daily silver intake.

[v] Expressed as a locational running annual average of quarterly samples

[w] Trihalomethane concentrations fluctuating occasionally (for a day or two annually) up to 1 mg/L are unlikely to pose a significant health risk.

[x] No safe concentration for vinyl chloride in drinking water can be confidently set, according to NHMRC (2023). However, for practical purposes, the concentration should be less than 0.0003 mg/L, which is the limit of determination.

Return to where text linked to Box 1

Box 2 - Chloroform and THMs - A true story of regulatory evolution of DBPs

(Adapted and updated from enHealth, 2012a; Hrudey, 2009; Hrudey et al., 2015a,b).

Chloroform and the related trihalomethanes (THMs) were first identified as by-products of chlorine disinfection by Johannes Rook, a Dutch water chemist (Rook, 1974). Rook had consistently identified chloroform in treated—but not raw—water samples. He chose not to publish the identity of the large chloroform peak until he had figured out what was causing its formation, but he was not troubled about consumer health risk, noting "*Our health officer told us chloroform was a normal constituent of cough syrups and was not known to be particularly toxic*." (Symons, 2001, p. 21)

There was also originally little health concern about chloroform at the US EPA (Symons, 2001) because of the widespread use of chloroform in consumer products, but they confirmed finding higher levels of THMs with increasing chlorine contact during disinfection (Bellar et al., 1974). The concern about chloroform started to escalate only when it was recognized that THMs were being formed from the reaction of chlorine with natural organic material, a constituent that is ubiquitous in surface water supplies.

Shortly after a growing body of evidence showed that chloroform appeared in chlorinated drinking-water supplies, the National Cancer Institute (NCI) published results of a rodent cancer bioassay on chloroform (NCI, 1976). This bioassay was conducted in accordance with the practices of that day; it was designed to determine the potential for chemical substances to cause cancer in mammals and was designed to maximize the ability of the experiment to reveal any carcinogenic effect by using the MTD.

Dosing in this experiment was done as a daily bolus dose of chloroform dissolved in corn oil. The initial high dose in female rats of 250 mg/kg-bw-d (milligrams per kilogram of body weight per day) had to be reduced to 180 mg/kg(bw)/d after 22 weeks because of the obvious toxic effects that were observed. Mice proved more tolerant to chloroform, so their initial doses of 200 and 400 mg/kg-bw-d were increased after 18 weeks to 300 and 500 mg/kg-bw-d. For comparison, a human dose of chloroform equivalent to the highest dose rate would correspond to more than 25,000 times the daily dose achieved by consuming 2 L per day of drinking water containing 100 μg/L of chloroform daily for a lifetime. Furthermore, delivering a bolus dose once per day in a vehicle such as corn oil provides a higher peak loading to the liver than consuming water with an equivalent dose of dissolved chloroform spread out over a day.

The results of this high dosing showed strong evidence of liver tumors in mice (98 percent of males and 95 percent of females at lifetime average doses of 277 mg/ kg-bw-d and 477 mg/ kg-bw-d, respectively; 36 percent of males and 80 percent of females at lifetime average doses of 138 and 238 mg/kg-bw-d, respectively) in the mouse experiments. These high dose levels were from 27 to 115 percent of published LD_{50}s for the mice (Hill et al.,

1975), suggesting that the B6C3F1 strain of mouse used in these cancer bioassays was unusually tolerant of chloroform. The rats dosed at up to 200 mg/kg-bw-d failed to show a significant excess of liver tumors relative to controls. Rats exhibited a significant increase in kidney tumors, but mice did not.

Within four months of the publication of the NCI bioassay results, the US Food and Drug Administration banned the use of chloroform in cosmetics. This was a dramatic change in relation to chloroform, which had been widely used as an anaesthetic from the mid-1800s, ironically due to the efforts of Dr. John Snow who used chloroform on Queen Victoria for childbirth. He has been widely considered the inventor of epidemiology for showing that sewage-contaminated drinking water caused cholera epidemics in London.

Health concerns associated with chloroform and THMs rapidly led to the adoption of drinking-water guidelines and standards; Canada was first in 1978 to adopt a guideline maximum value for THM4 (i.e., chloroform, bromodichloromethane, dibromochloromethane, bromoform) of 350 μg/L. Then in 1979, the USA adopted a regulatory standard for THM4 under the SDWA of 100 μg/L as a running annual average of four quarterly samples. In 1984, WHO proposed a guideline for chloroform of 30 μg/L based on an estimate that this would assure a less than 1 in 100,000 lifetime cancer risk, assuming a linear extrapolation to zero dose of chloroform. Australia established a drinking-water guideline value of 250 μg/L in 1996 (NHMRC, 2023)—based on the NOAEL for kidney toxicity in a 90 d rat study—and concluded that "*In view of the safety factors used in the derivation of the guideline value, it is unlikely that short-term consumption of water containing significantly higher concentrations of trihalomethanes would pose a health risk*" (p. 1037). This value was confirmed when reviewed in 2004 and subsequently.

The initial extremely high-dose bioassay results on chloroform (NCI, 1976) provided the expectation that was widely cited throughout the late 1970s and early 1980s that chloroform and, by extension, THMs, were carcinogenic. The NCI results were obtained by a method (high dose of chloroform in corn oil) that was later found to be much more toxic than the equivalent dosing of chloroform in water (Bull et al., 1986). The comparison of corn oil versus water as a vehicle was undertaken to explain the results from a study providing high concentrations of chloroform (up to 1,800,000 μg/L) dissolved in drinking water (Jorgenson et al., 1985) that produced no significant carcinogenic response.

The impact of extremely high doses of chloroform in corn oil to the liver was first noted as evidence of cytotoxicity on liver cells. Larson and others (1994, 1995) demonstrated by direct experimentation that the corn oil gavage delivery of chloroform induced cytotoxicity and cell proliferation in the liver for mice and the kidney and liver for rats. The mouse experiments found this effect for the corn oil gavage but not for direct delivery of similar daily doses orally by drinking water. These findings on a plausible mechanism for chloroform carcinogenicity were supported by extensive evidence of virtually no mutagenic activity for chloroform (Golden et al., 1997). The earlier noted distinction in

mechanism of tumor formation from cytotoxicity rather than genotoxicity justifies a threshold approach to risk assessment rather than a no-threshold approach for THMs (Fawell, 2000).

According to the US SDWA, the maximum contaminant level goal (MCLG) is the maximum level of a contaminant in drinking water at which no known or anticipated adverse health effects would occur and that allows an adequate margin of safety. US EPA policy for carcinogens in drinking water had required a MCLG to be zero, apparently ignoring the possibility of a non-genotoxic carcinogen having a threshold. However, the foregoing toxicological evidence on the mode of action of chloroform resulted in a US EPA expert review panel recommending the abandonment of the MCLG of zero and replacement with a limit based on an estimated threshold. Thus in 1998, the US EPA (1998a) proposed to raise the MCLG to 300 μg/L in accordance with this expert advice. Because many intervenors protested this precedent-setting measure, the US EPA Final Rule (1998b) withdrew the proposal to change the MCLG for chloroform (Pontius, 2000).

The Chlorine Chemistry Council sought a court review of the US EPA decision because the SDWA requires the US EPA to use the best available science in setting standards and regulations. Although the US EPA acknowledged that the best available science called for raising the MCLG above zero, it had nevertheless decided to retain the zero MCLG. On March 31, 2000, the US District Court ruled that the US EPA had violated the SDWA by failing to use the best available science. The court found the EPA action of setting the MCLG of chloroform at zero to be "*arbitrary and capricious*" and exceeded statutory authority. The US EPA withdrew the zero MCLG in May 2000, subsequently replacing it with a MCLG of 70 μg/L in 2003—just below the MCL negotiated for the SDWA of total THMs at 80 μg/L.

Meanwhile, WHO had changed its drinking-water guideline for chloroform from 30 μg/L in its first edition of Guidelines for Drinking-Water Quality (WHO, 1984) to 200 μg/L in the second edition (WHO, 1993). Recognizing that chloroform exhibited a threshold for acting as a carcinogen justified this change.

The initial NCI (1976) carcinogenic finding on chloroform—taken together with the background expectation that substantial numbers of human cancers could be explained by environmental contamination—resulted in more than 65 epidemiology studies of varying quality from 1977 to 2008. These sought to determine if some measure of chlorination DBPs was associated with an increase in one or more types of cancer.

The epidemiological evidence regarding cancer has been reviewed at various times (IARC, 1991; Mills et al., 1998; ICPS, 2000; IARC, 2004; Hrudey et al., 2015a,b; Hrudey & Fawell, 2015). Overall, the epidemiologic evidence has generally been found to be insufficient to declare chlorination DBPs to be carcinogenic in humans (Hrudey et al., 2015a,b; Hrudey, 2012). The evidence for colon and rectal cancer has been suggestive of a causal association, while the evidence for bladder cancer has been the most consistent,

providing the greatest likelihood of being causally associated with chlorination DBPs (Mills et al., 1998).

There is now common understanding among experts on DBPs and health evidence that chloroform, in particular, and THMs, in general, are at best surrogates for some DBPs as yet unidentified in chlorinated drinking water that may pose a drinking-water cancer risk. Despite the original focus on THMs as carcinogens in drinking water, almost 50 years of evidence now fails to show these chemicals are a cancer risk at realistic drinking-water exposure levels.

Despite these realities, publications continued to claim that chloroform, in particular, and THMs, in general, cause tangible numbers of cancer cases. A particularly striking case was a Chowdhury and Hall paper (2010) that claimed 94 cancer cases per year for Montreal and 54 per year for Toronto based on routine regulatory reporting of THM levels. The paper was retracted when the journal was informed that its ethics policy had been breached because the lead author failed to inform the journal of a major error in claiming that the cancer cases were calculated using a CSF (cancer slope factor) for chloroform of 0.01 $(mg/kg\ day)^{-1}$ obtained from the Integrated Risk Information System (IRIS; US EPA, 2001). That reference source did not provide a CSF for chloroform; rather, it provided a reference dose (RfD), stating "*A dose of 0.01 mg/kg/day (equal to the RfD) can be considered protective against cancer risk*" (p. 24).

In other words, oral exposure to chloroform has been found to exhibit a threshold below which no cancer risk is expected. Chowdhury and Hall (2010) misused this RfD as a CSF, which requires units of **(**$mg/kg\ day)^{-1}$ rather than RfD units of mg/kg day to calculate all the claimed number of cancer cases, invalidating all of the cancer case numbers claimed.

Notwithstanding the retraction, ten papers have since cited it (Cheshmekhezr et al., 2021; Egorova et al., 2013; Grellier et al., 2015; Kumari & Gupta, 2018; Lee et al., 2013; Stepanova et al., 2018; Uddameri & Vendataraman, 2013; Vendataraman & Uddameri, 2012; Yang et al, 2015; Zhang et al., 2018), two showing it as "*retracted*" in the reference list and only one noting that it was in error (Grellier et al., 2015).

The issue of the challenge of dealing with evaluating mixtures was raised in Section 4.3.2 in the discussion of hazard identification. The U.S. EPA chose DBPs as an issue to invest major research resources in assessing whether mixtures of contaminants would show combined toxicity that exceeded expectations based on the toxicity of the individual DBPs. Simmons and others (2008) provided the introduction of a special issue of the *Journal of Toxicology and Environmental Health, Part A* that provided seven other papers describing some of the individual research studies in this program. The results of this research program did not reveal any substantive findings of any excessive mixture toxicity and were largely negative. Parvez and others (2017) reported: "*Although a modest but significant delay in puberty acquisition was observed in WM-treated female rats, we cannot discern a difference between the nine DBPs in the DM* (defined mixture) *and the WM* (whole mixture). Narotsky

and others (2013) reported on their study: "*Overall, it is reassuring that multigenerational reproductive and developmental toxicity testing of an environmentally relevant whole mixture of drinking water DBPs yielded predominantly negative results. Nonetheless, slight but significant effects on puberty, sperm production, and thyroid cells warrant further investigation.*"

Return to where text linked to Box 2

Box 3 - Research needs for DBP-exposure assessment issues (Arbuckle et al., 2002)

Sampling, analysis, and distribution monitoring research needs

More and better data on occurrence and toxicity for:

- Chlorine DBPs, both halogenated and non-halogenated (e.g., aldehydes)
- Ozone DBPs
- Chlorine dioxide DBPs
- Chloramine DBPs

Exposure reconstruction by exploiting site-specific correlations among:

- Trihalomethanes (THMs), 174 haloacetic acids, and other DBPs
- Brominated species and bromide
    - Potential surrogate measure for bromide [e.g., chloride]
- DBPs and other measures (chlorine demand, SUVA)

New identifications of:

- Polar and non-volatile DBPs
- Thermally labile DBPs
- Higher molecular weight DBPs

Standards and standardized analytical methods for DBPs that are not routinely analyzed

Models to predict historic DBP formation in treatment plants and distribution systems: factors that should be considered in model development are the capability to:

- Represent variability in raw water sources
- Utilize historically available water quality parameters
- Estimate specific DBPs
- Incorporate changes in treatment practices over time
- Measure residence time by location in distribution system better than has been possible to date
- Deal with the reality that some historic DBP monitoring data were collected without the use of dechlorination agents
- Deal with improvements in analytical detection limits over time

Kinetic models interfaced with hydraulic network models to describe DBP behavior: factors that should be considered in model development are:

- Parameters need to be site-specific
- Models must be calibrated and validated, and
    - Represent sufficient time frame for exposure analysis

- Address diurnal variations in water demands and pumping/distribution practices
- Address blending issues
  - Surface and ground water sources
  - Water from different treatment plants
  - Water from different systems (wholesaler versus retailer)

Improved methods for water-sample collection:

- To arrest (quench) reactions to form additional DBPs
- Choice of dechlorination (quenching) agent and preservation pH[29]

Improved methods to determine chlorine dose in treatment plant:

- Considering that chlorine dose can vary significantly during the course of the day[30]

Identification of chemical reactions occurring in hot water tanks and during boiling of water:

- Considering that increases in temperature and other storage conditions affect formation and stability of DBPs

Evaluation of the effectiveness of surrogates for improving DBP data exposure estimates:

- UV absorbance[31]
- Conductivity[32]

Adaptation of monitoring protocols to collect data more useful for future epidemiologic studies

Information to collect by questionnaire for epidemiological studies

Water consumption characteristics and water use activities diary for critical exposure period:

- Type of activity (e.g., showering, bathing, operation of dishwashers and washing machines, use of swimming pools and hot tubs)
- Source of water
  - Tap or bottled
  - Home or other location
  - Ground or surface (river or lake)

[29] Some DBPs, if not properly preserved, will degrade during sample storage; in some cases, the degradation by-products are other DBPs, such as the trihalomethanes.
[30] Sunlight-catalyzed destruction of chlorine in open treatment basins requires adjustments in the dose during the daylight hours.
[31] Indicator of reactivity of total organic carbon to form DBPs.
[32] Used as a tracer of source waters in blended distribution systems.

  - Hot or cold tap or boiled water
- Supplier (e.g., name of utility, private well)
- Volume consumed (ingestion), duration of shower/bath (inhalation or dermal exposure)
- Water temperature
- Air circulation level (e.g., in bathroom)

Factors potentially modifying concentration:

- Water filters[33]
- Boiling of water[34]
- Use of bottled water[35]
- Allowing water to stand (stored versus directly from tap)
- Time of day, season

Other sources of exposure:

- Foods and beverages[36]
- Pharmaceuticals (direct agents and metabolites)
- Occupation and full range of workplace activities

Epidemiological study design research needs

Improved methods for measuring water consumption and use patterns:

- Standardized questions that are:
  - Valid and reliable (accurate recall)
  - Tested in different geographical areas
- Development of a "Gold Standard" to test against
- Further testing on usefulness of water meter data loggers

Strategies to accurately estimate past activities (e.g., look at differences in population activity patterns by age and locale)

Development of perspectives on:

- How much exposure misclassification is tolerable?
- What level of accuracy is needed to achieve that tolerable level?

Direction on valid means of combining exposure data based on such factors as:

- Diversity of individual DBPs

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[33] Type, location, maintenance schedule.

[34] Do not assume that all DBPs are volatilized off; moreover, some may form during the boiling process as residual chlorine reacts at an elevated temperature with DBP precursors in the water.

[35] Do not assume bottled water to be free of DBPs.

[36] Including those prepared with tap water having disinfectant residual.

- Metabolic pathways
- Toxicity mechanisms
- Routes of exposure

New cancer studies that can exploit emerging biomarkers of susceptibility to relevant cancer sites

Biomarkers of DBP exposure research needs

Better understanding of absorption, distribution, metabolism and excretion of specific DBPs and how these are affected by:

- Chemistry of compound
- Route of exposure
- Prior or continuous exposure
- Metabolic precursors of DBPs

Information on population differences in:

- Biomarker production by metabolism
- Biological residence time (elimination and excretion half life)
- Indicators of susceptibility (e.g., genetic markers, presence/absence of specific enzymes such as glutathione S-transferases)

Physiologically based toxicokinetic models for humans for the most relevant DBPs

Toxicity of DBPs and metabolites:

- Need to know which agents are of toxicologic concern to focus efforts (i.e., rapid screening tests)
- Markers of longer-term exposure such as DNA or protein adducts
- Possible integrated surrogate measures of exposure to multiple DBPs (e.g., analogous to total organic halogen tests on urine)

Valid and reliable instructions for participants on biomarker sample collection

Population baseline data on occurrence of DBPs in biological fluids/media

Identification of other appropriate biological media to sample (e.g., saliva, sweat)

Identification of important biomarkers of susceptibility:

- Need to examine many candidate genes to see how these polymorphisms affect risk when taken into consideration with exposure

Collection and archiving of human tissue samples for future biomarker development needs:

- Protocols on collection and storage of such samples
- Development of the basis to include such plans into approvals for studying human subjects

DBP personal exposure modeling and uncertainty analysis research needs

Valid human exposure models:

- Many individual components have been evaluated; however, most models have not been evaluated when these components are aggregated
- Results of simulation models can be used to improve epidemiologic questionnaires by pinpointing the most important environmental and water use activities affecting DBP exposure

Methods to evaluate contribution to exposure from various sources and routes of exposure:

- Will vary by type of DBP (e.g., volatile versus non-volatile)
- Currently chloroform model used, but validity for other DBPs is unknown
- What is effect of home treatment devices on total DBP exposure?
- how much do DBP exposures occurring outside the home contribute to total exposure?

Models to predict historical exposure from decades ago:

- Specific for individual DBPs
- Represent variability in personal exposures, considering all relevant routes

Sensitivity and uncertainty analysis should be done to:

- Determine exposure to individual DBPs (e.g., brominated species) as health effects are likely caused by particular species or combinations thereof rather than total exposure to all DBPs
- Identify activities that will differentiate individuals for exposures of interest versus activities that vary little among individuals

Exposure models for mixtures of DBPs:

- Better understanding of the relationship between water concentration and actual DBP uptake
    - Should resources be expended on collecting more and better data on personal habits or on increasing number of participants in study?
    - What is the relative contribution of tap water compared to all other possible sources of exposure to specific DBPs (e.g., bottled water, other beverages, and foods)?

Integrated exposure models with physiologically based pharmacokinetic models

Return to where text linked to Box 3

11 Exercise Solutions

Solution Exercise 1

The chain of causation is depicted in Figure 3, which shows involvement of an agent (the contaminant), exposure via environmental media, and a causal mechanism that involves a dose–response relationship giving rise to an adverse effect. The means for knowing about this causal chain include experimental, predictive toxicology, and observational epidemiology. The adverse outcomes can be documented with biostatistics (for example, the number of deaths or cases of specified diseases).

Return to Exercise 1

Return to where text linked to Exercise 1

Solution Exercise 2

The hierarchy of health-risk evidence and its relationship to means of learning about health risk (in this case, death) is shown in Figure 4. This shows that the most certain evidence is about the total number of deaths based on direct evidence from the total number of death certificates filed.

However, the cause of death reported on the death certificate is much less certain. This information may be quite certain if the deceased person dies from obvious trauma (e.g., motor vehicle crash) but is much less certain if the person dies in their sleep with no evident cause. Autopsies can provide evidence, but they are not totally certain.

Lacking direct evidence, epidemiology seeks to understand the cause of human disease and death, but it does so through study of a sample of the human population. Epidemiological methods have a range of power to support causation with inevitable uncertainty. Even strong evidence acquired using strong methods applies to a sample of the population, and there is inevitable uncertainty involved with inferring overall population risk.

Lacking epidemiological evidence, toxicology-based risk assessments rely on experimentation using a small sample of animals. Results are uncertain because they must be translated to health risk for the overall population of animals and, further uncertainty arises in transferring the findings from animals to humans.

A range of even-less-certain methods seeks to predict risk, which is not addressed in Section 3.1 where this exercise is presented. These are discussed in Section 3.3.5 and their strength of evidence is illustrated in Figure 10.

Return to Exercise 2

Return to where text linked to Exercise 2

Solution Exercise 3

Statistical inference involves interpreting the analysis of statistical characteristics of data from a sample of organisms under study. The statistical tests used in these analyses can provide estimates of the likelihood of observations occurring by chance alone but not the probability of being true because of a hypothesized relationship. Statistical analyses are essential but not sufficient to establish a hypothesized relationship because of various factors that cannot be totally accounted for in the statistical analyses. Even with a maximal degree of accounting for such factors, there is always a need to apply judgment to translate sample results to a relevant population. This involves what is termed external validity, the applicability of study findings to a broader external population rather than just the internal validity of applying it to the study population.

Causal inference is a far more complex process that includes statistical inference as one important component among many other critical issues that are discussed in Section 3.3.6, *Weighing Epidemiological Evidence for Causation*.

Return to Exercise 3

Return to where text linked to Exercise 3

Solution Exercise 4

As anyone who has ever discussed personal health issues with a physician will know, clear conclusions about health arise only after physical injury has happened (e.g., a broken limb or a tumor being discovered). The question was about health risk for an individual. Risk is a prediction of what will happen. Once something has happened (a broken limb or the occurrence of a tumor), it is no longer a prediction; it is a reality. Discussions with a physician about risks, whether about the risks that come with smoking or poor diet, will inevitably lead to recourse to evidence from epidemiological studies that are based on population samples that have been studied, usually with variable results and sometimes with contradictory results (except for smoking, which has about the most compelling human health-risk evidence about an activity that can ever be obtained by epidemiological study).

The most that any physician can do is try to interpret how well the epidemiologic evidence applies to any individual in terms of factors such as age, gender, and health status. Such an analysis can, at best, result in an informed opinion about how the evidence applies to any specific individual. The validity of that opinion is dependent on how good the evidence is, how well it applies to the individual, and how detailed and comprehensive the analysis is that goes into forming the opinion.

In a starker analysis of the difference between individual and population risk, Thomas and Hrudey (1997) used comprehensive Statistics Canada data to estimate the probability of death in Canada on the basis of the two most influential variables affecting death: age and gender. The estimate for 1994 Canadian evidence predicted that my chance of dying in the next year (based on my age at that time) was 1 in 320.

As I write this book 30 years later, I obviously did not die in 1995, which neither proves nor disproves the validity of the risk estimate. There are only two possible outcomes for this analysis: either I die or I do not—a binary outcome, neither of which proves or disproves the risk estimate. Testing the actual estimate could be achieved only by an impossible experiment—that is, following at least three times 320 clones or identical twins (960 clones) of me who have lived exactly as I have for their entire lives and then following each for the next year to demonstrate that three of them would have died. The three-times factor is to allow for an estimate of statistical significance.

As an aside, my current risk estimate of dying in the coming year (based on 2022 data, Mortality rates by age group↗) is 1 in 33—odds that I might otherwise find attractive enough to purchase a lottery ticket.

Return to Exercise 4↑

Return to where text linked to Exercise 4↑

Solution Exercise 5

The many issues bearing on the ability of epidemiological studies to contribute evidence for causation are discussed in detail in Section 3.3, *Epidemiology for Risk Assessment*, including dealing with confounding, bias, validity, and reliability. The specific capabilities of particular study designs are addressed in Section 3.3.5, *Study Design for Supporting Causation*, noting that some observational descriptive studies can be considered to be hypothesis-generating, some observational analytical studies can be considered hypothesis-testing, and some experimental studies offer the greatest potential capability for testing hypotheses but are limited by ethical and practical limitations of human studies.

Section 3.3.6, *Weighing Epidemiological Evidence for Causation*, addresses specific considerations for weighing causal evidence, including temporal relationships, plausibility, consistency, dose–response relationships, strength of association, reversibility, and overall judgment of the evidence.

For any study design to provide evidence in support of causation, it is essential that data be obtained at an individual level in terms of both exposure and outcome. Both the individual exposure status and the health outcome must be known for each individual to avoid anomalies in which individuals who are not exposed are counted for their adverse outcome and vice versa for individuals who are exposed but are counted for their absence of an adverse health outcome. Many, if not most, studies in environmental epidemiology range from completely inadequate to weak in their accounting for individual exposure. For example, how much and what type of water is consumed for every individual is often not known with any reliability or specificity for drinking-water epidemiological studies.

Epidemiological study results are unable to predict individual health risk because epidemiological studies are based on samples drawn from a specified population that may or, more likely, may not be applicable to a specific individual who was not part of the study.

In any case, all health-risk predictions are just that: predictions of what may happen. As such, an individual's health risk cannot be stated with certainty, as illustrated in the answer to Exercise 4.

Return to Exercise 5

Return to where text linked to Exercise 5

Solution Exercise 6

Risk, in reality, is far more complex than can be captured by a single number, as is generated by multiplying probability and some quantitative measure of consequences.

An authentic concept of risk can be based on an expansion (Hrudey, 2000) of the seminal definition of risk provided by risk-assessment pioneers, Kaplan and Garrick (1981). This explains that risk is a prediction of the likelihood (probability) of an event or set of circumstances (a hazard) leading to adverse consequences over a specified time period. This concept consists of several key elements, namely:

hazard (source of danger),
consequences (adverse outcomes caused by hazard),
probability (likelihood of hazard causing adverse outcomes),
time frame (over which the likelihood is considered),
perspective (how important those affected judge the risk to be).

Return to Exercise 6

Return to where text linked to Exercise 6

Solution Exercise 7

a) This question requires the use of Equation (7) for the excess, over background, lifetime cancer risk for a dose, d

$$ER(d) = q_1{}^* \, d$$

where:

$q_1{}^*$ = $6.1\text{x}10^{-3}$ (mg/kg-bw-d)$^{-1}$

dose = CR/bw

The average drinking water consumption rate (CR) is 1.5 L/d, average body weight is 70 kg, and the maximum contaminant level is 0.08 mg/L of chloroform.

$$ER(d) = 6.1\text{x}10^{-3} \frac{\text{kg-bw-d}}{\text{mg}} \quad \frac{1.5 \frac{\text{L}}{\text{d}} \; 0.08 \frac{\text{mg}}{\text{L}}}{70 \text{ kg-bw}} = 0.00001046$$

or ≈1 in 100,000 lifetime cancer risk

The value 0.00001046 is rounded to one significant figure given the enormous uncertainties built into the assumptions underlying this calculation.

b) This invalid, outdated excess cancer risk calculation for chloroform exposure by ingestion would correspond to:

$$(1\text{x}10^{-5})\ 3.3\text{x}10^{8} = \text{3,300 cases over 70 years or, on average, 47 cases per year}$$

c) Recognizing that the foregoing calculations no longer have validity for determining cancer risk, hypothetically, if they did apply then the predictions would estimate an upper 95-percent cancer risk, not an expected cancer risk. Consequently, even if the calculated numbers were valid, the number of predicted cancer cases per year (47) in the USA would be challenging to track within a total of about 1.9 million new cases of cancer in the USA in 2022 (American Cancer Society, 2022). This would be a challenge even if chloroform was known, with confidence, to cause only bladder cancer (it is not: Hrudey et al., 2015b). The USA has about 81,000 new cases of bladder cancer per year (American Cancer Society, 2022). The upper bound (95%) estimate of an average of 47 cases per year would correspond to about 0.06 percent of all bladder cancer cases, a level that could not be reliably detected by epidemiological studies.

d) Unlike most carcinogens that have been quantitatively regulated, chloroform has undergone extensive detailed toxicological and epidemiological risk assessment such that the mechanism of cancer observed in animal toxicology experiments has been clearly established as being attributed to the high chloroform doses used in original cancer bioassay experiments. The high doses cause cell death that inevitably leads to cell regeneration that has a non-zero DNA replication error rate that can initiate tumors. That

inference justifies the conclusion that there is a threshold dose (reference dose: RfD) of 0.01 mg/kg-d that poses no cancer risk below the RfD.

e) The Canadian MAC for chloroform of 100 mg/L would yield a daily dose of:

$$d = \frac{1.5\,\frac{\text{L}}{\text{d}}\;\;0.100\,\frac{\text{mg}}{\text{L}}}{74\ \text{kg-bw}}$$

$$d = 0.002\,\frac{\text{mg}}{\text{kg-bw-d}}$$

The currently valid cancer evaluation for chloroform (US EPA, 2001) states that below 0.01 mg/kg-d of chloroform poses no cancer risk, so the calculated chloroform dose of 0.002 mg/kg-bw-d is only 20 percent of that cancer-free risk level. This evaluation suggests that meeting Canada's drinking water guideline for chloroform poses no cancer risk to Canadian consumers.

Return to Exercise 7

Return to where text linked to Exercise 7

Solution Exercise 8

Uncertainty in risk estimates consists of two major classes: variability (heterogeneity) versus knowledge uncertainty (ignorance). Variability refers to possible differences in key elements of exposure or susceptibility (such as differences in age, gender, and degree of exposure) that exist but are not known with certainty. Knowledge uncertainty is the absence of knowledge about the true values of key elements. This type of uncertainty can be reduced by further study to learn what is not known, whereas variability uncertainty can be better characterized to be better known but cannot be reduced.

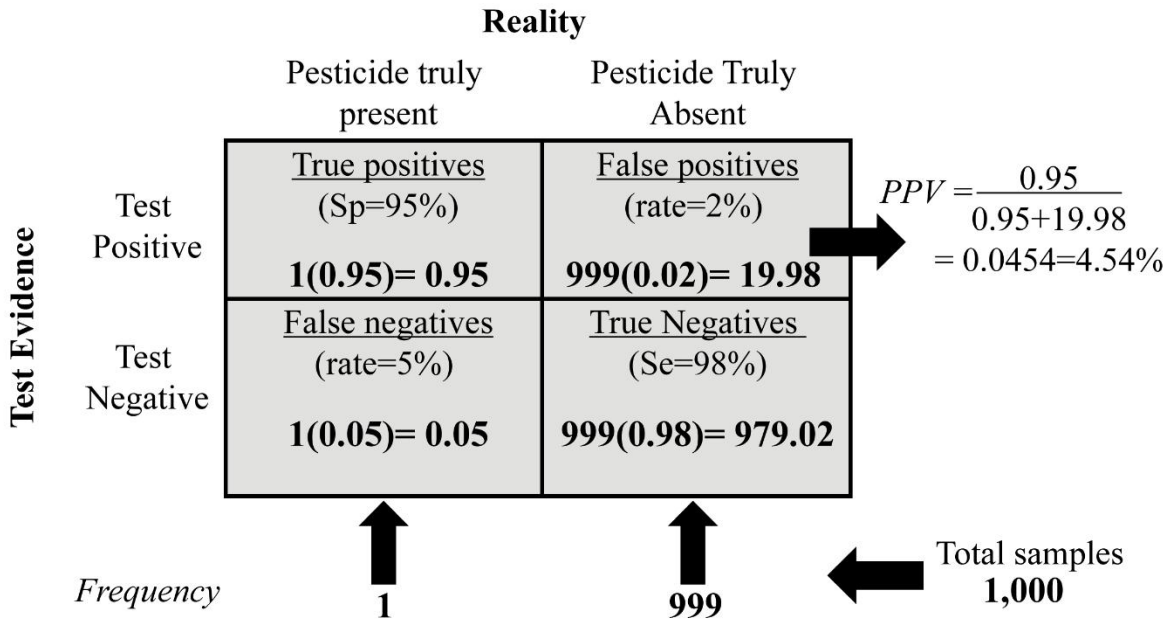
Return to Exercise 8

Return to where text linked to Exercise 8

Solution Exercise 9

Only about one in 1,000 water samples at this site contains the pesticide at a detectable level. This statistic is not truly knowable, but monitoring experience and other sources of evidence can allow it to be estimated. This means that for every true-positive result, there will be 999 true-negative results. Applying the false-positive rate (when the pesticide is truly not present at detectable levels) and false-negative rate (when the pesticide is truly present at detectable levels) to these values, we obtain 19.98 false-positive results (999x0.02) for every 0.95 true-positive result (1x0.95) or a ratio of 0.95/(0.95+19.98) = 0.0454 (i.e., 4.54 percent) true-positive results among total positive results (i.e., the sum of true positives plus false positives). This ratio (4.54 percent for this example) is termed the positive predictive value (PPV).

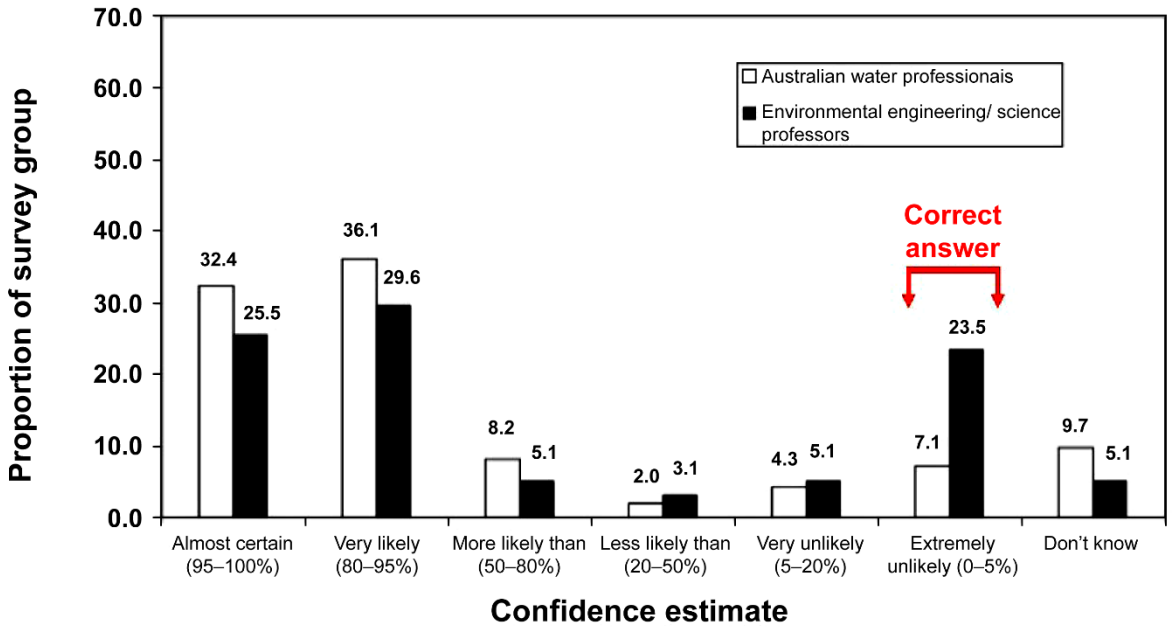
An expanded explanation of the true result is provided in the image below based on the information provided in the exercise and the underlying statistical reality. The logic is captured in a 2x2 table that applies Bayes' theorem. The characteristics of the analytical method described in the scenario provided for a false-negative rate of 5 percent (corresponds to a diagnostic sensitivity of 95 percent—that is, 95 percent of water samples will report positive when the pesticide is truly present above the detection limit) and a false-positive rate of 2 percent (corresponds to a diagnostic specificity of 98 percent—that is, 98 percent of water samples will report negative when the pesticide is truly not detectable above the detection limit).



Calculation of PPV (positive predictive value) for the hypothetical example provided to water professionals and environmental academics (Rizak & Hrudey, 2006).

Further information illustrating the extremely different interpretation of these data among professionals:

Rizak and Hrudey (2006) demonstrated the misinterpretation of this monitoring scenario among two groups that were surveyed: Australian water professionals and members of the Association of Environmental Engineering and Science Professors (mostly American). Each group was presented with the hypothetical monitoring scenario. The results are summarized in the following image, which shows their estimated confidence in the accuracy of a positive monitoring detection as outlined in the scenario described above.



Ratings of confidence in results for a hypothetical drinking-water monitoring scenario where the correct result was 4.54 percent, i.e., extremely unlikely (Rizak & Hrudey, 2006).

The water professionals comprised 352 respondents from Australian Water Association specialist groups: 39.2 percent of these were affiliated with a water utility; 22.4 percent with a consulting firm; 10.3 percent with a local, state, or federal government regulatory agency; 2.5 percent with an analytical laboratory; 8.0 percent with a research organization or academic institution; and 17.3 percent with other entities. With regard to experience, 38.1 percent had more than 20 years in the water industry, 25.3 percent had ten to 20 years of experience, 19.3 percent had five to ten years of experience, and 17.1 percent had limited experience in the water industry (less than five years). A large number of respondents (42.3 percent) indicated they were directly involved in evaluating monitoring results and/or making decisions regarding responses to be taken to protect public health.

For the 98 respondents who were members of the Association of Environmental Engineering and Science, most were at American institutions either at professor or associate professor rank. With regard to experience, 48.0 percent had more than 20 years in environmental engineering and in science, 41.8 percent had ten to 20 years of experience, 8.2 percent had five to ten years of experience, and 1.0 percent had limited experience in

environmental engineering and science (less than five years). The better performance of the academics in providing the correct answer (23.5 percent versus 4.5 percent for water professionals) may have been influenced by having read either articles by Hrudey and Leiss (2003) or Hrudey and Rizak (2004) that were published prior to the survey in *Environmental Health Perspectives* and *Journal of the American Water Works Association*, two American journals that American environmental academics interested in drinking water may have followed.

The foregoing result was not unexpected. Similar results have been obtained among professionals that had, or should have received, training in the underlying statistical reality. Hoffrage and others (2000) discussed examples of misinterpretation from the medical and legal professions, including citing an example of professionals from Harvard Medical School (Casscells et al., 1978. p. 999) who were asked what the chance was that *"a person found to have a positive result actually has the disease, assuming that you know nothing about the person's symptoms or signs?"* in "*a test to detect a disease whose prevalence is 1/1000, that has a false positive rate of 5 percent*." The estimates varied wildly, ranging from the most frequent estimate—95 percent likely to have the disease (given by 27 out of 60 participants)—to the correct answer: 2 percent likely to have the disease (given by 11 out of 60 participants).

Return to Exercise 9

Return to where text linked to Exercise 9

Solution Exercise 10

Effective management of risk for protecting public health in the face of uncertainty should seek a high level of confidence versus a low level of confidence. Confidence in risk management actions should be lowest when uncertainty about evidence is large and highest when uncertainty about evidence is negligibly small.

Return to Exercise 10

Return to where text linked to Exercise 10

12 Glossary

Anon.	=	anonymous
ADME	=	absorption, distribution, metabolism, and excretion
ADWG	=	Australian Drinking Water Guidelines
ATSDR	=	Agency of Toxic Substances and Disease Registry
BCMOH	=	British Columbia Ministry of Health
BDCM	=	bromodichloromethane
BMD	=	benchmark dose
CCL	=	candidate contaminant list
CCP	=	critical control point
CDC	=	US Centers for Disease Control and Prevention
CDW	=	Committee on Drinking Water
CERCLA	=	Comprehensive Environmental Response Compensation and Liability Act
COPC	=	chemicals (contaminants) of potential concern
CSF	=	cancer slope factor
DALY	=	disability adjusted life years
DBP	=	disinfection by-product
DBCM	=	dibromochloromethane
dL	=	deciliter
ER(d)	=	extra risk above background
GCDWQ	=	Guidelines for Canadian Drinking Water Quality
HAA	=	haloacetic acids
HACCP	=	Hazard Analysis and Critical Control Point
HQ	=	hazard quotient
IARC	=	International Agency for Research on Cancer
ICD	=	International Classification of Disease
In vitro	=	in a non-living system
In vivo	=	in a living system
IPCS	=	International Programme on Chemical Safety
IQ	=	intelligence quotient
IRIS	=	Integrated Risk Information System (US EPA)
LADD	=	lifetime daily dose

LD_{50}	=	median lethal dose
LMS	=	linearized multistage model
LOAEL	=	lowest adverse effect level
LOEL	=	lowest effect level
LYL	=	life years lost
MAC	=	maximum acceptable concentration
MCL	=	maximum contaminant level (SDWA)
MCLG	=	maximum contaminant level goal (SDWA)
MOA	=	mode or mechanism of action for a toxic substance
MTD	=	maximum tolerated dose to avoid mortality in an animal bioassay
NCI	=	National Cancer Institute
NDMA	=	N-nitrosodimethylamine
NHMRC	=	National Health and Medical Research Council
NOAEL	=	no adverse effect level
NOEL	=	no effect level
NOM	=	natural organic matter
NPDWR	=	national primary drinking water rule under the SDWA
NPV	=	negative predictive value; given that a hazard is not detected, the non detection is accurate
GCDWQ	=	Guidelines for Canadian Drinking Water Quality
HAA	=	haloacetic acids
NRC	=	National Research Council
NTU	=	nephelometric turbidity units
OR	=	odds ratio
PAF	=	population attributable fraction
PB-PK	=	physiologically based-pharmacokinetic model
P(d)	=	probability of tumor formation at dose d
POD	=	point of departure
PPV	=	positive predictive value; the conditional probability that given a hazard is detected the detection is accurate
$q_1{}^*$	=	upper bound (95 percent confidence limit) of the cancer slope factor
QMRA	=	quantitative microbial risk assessment
RCRA	=	Resource Conservation and Recovery Act
RfD	=	reference dose

RR	=	rate ratio, risk ratio, or relative risk
SDWA	=	US Safe Drinking Water Act
SF	=	safety (uncertainty) factor
SRA	=	Society for Risk Analysis
TCAA	=	trichloroacetic acid
THM	=	trihalomethane
TOC	=	total organic carbon
TOX	=	total organic halogen
TRV	=	toxicological reference value
TSCA	=	Toxic Substances Control Act
UCMR	=	unregulated contaminant monitoring rule
UF	=	uncertainty factor
US EPA	=	US Environmental Protection Agency
US FDA	=	US Food and Drug Administration
UV	=	ultra violet light
WCRF	=	World Cancer Research Fund
WHO	=	World Health Organization

13 Notations

p	=	the probability of tumor formation (unitless)
d	=	the dose of the agent under test (mg/kg-bw-d)
q	=	the exponential coefficient (units are inverse of associated term)
ER(d)	=	the excess, over background, lifetime cancer risk for a dose, d, where d is the lifetime average daily dose (unitless)
q_1^*	=	the upper bound (95-percent confidence limit) cancer slope factor (CSF), also referred to as the cancer potency factor $(mg/kg\text{-}bw\text{-}d)^{-1}$
TDI	=	tolerable daily intake or toxicological reference value (mg/kg-bw-d)
BW	=	body weight (as mass in kg)
AF	=	allocation factor, a policy-driven factor to estimate the proportion of total exposure that occurs from drinking water consumption (unitless)
CR	=	consumption rate (L/d)

14 About the Author

Steve E. Hrudey pursued graduate training in public health engineering at the Imperial College of Science, Technology & Medicine, London, UK, in 1970 and retired from the University of Alberta in 2008 after 33 years. He now serves as a professor emeritus in the Faculty of Medicine and Dentistry and has also served on 30 expert panels addressing public health and environmental risks, including the Research Advisory Panel to the Walkerton Inquiry (2000 to 2002), the Expert Panel on Safe Drinking Water for First Nations (2006), and the Council of Canadian Academies Expert Panel on Sustainable Management of Groundwater in Canada (2009).

Dr. Hrudey has chaired the international expert panels on assessment of health risks related to trihalomethanes in drinking water for Health Canada (2002 to 2003), on environmental and public health impacts of Canada's oil sands industry for the Royal Society of Canada (RSC, 2010), on managing uncertainty in the provision of safe drinking water for the Canadian Water Network (2012), on evidence for causation of bladder cancer by chlorination disinfection by-products (2014 to 2015) for the Water Research Foundation, for the review of new national safe drinking-water regulations for New Zealand (2021), and on wastewater surveillance for SARS-CoV-2 in Canada for the RSC (2022).

Dr. Hrudey's research has produced over 200 refereed journal publications, 12 books, and 30 book chapters focusing on public health, environmental risk, and ensuring safe drinking water. Dr. Hrudey was awarded the top research (A. P. Black) award of the American Water Works Association (2012), elected as a Fellow of the Royal Society of Canada (2006), the Society for Risk Analysis (2008), the International Water Association (2010), and the Canadian Academy of Engineering (2014). He was elected to the Alberta Order of Excellence in 2017 and became a Member of the Order of Canada in 2020.

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