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Principles of risk decision-making

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ABSTRACT

Risk management decisions in public health require consideration of a number of complex, often conflicting factors. The aim of this review was to propose a set of 10 fundamental principles to guide risk decision-making. Although each of these principles is sound in its own right, the guidance provided by different principles might lead the decision-maker in different directions. For example, where the precautionary principle advocates for preemptive risk management action under situations of scientific uncertainty and potentially catastrophic consequences, the principle of risk-based decision-making encourages decision-makers to focus on established and modifiable risks, where a return on the investment in risk management is all but guaranteed in the near term. To evaluate the applicability of the 10 principles in practice, one needs to consider 10 diverse risk issues of broad concern and explore which of these principles are most appropriate in different contexts. The 10 principles presented here afford substantive insight into the process of risk management decision-making, although decision-makers will ultimately need to exercise judgment in reaching appropriate risk decisions, accounting for all of the scientific and extra-scientific factors relevant to the risk decision at hand.

KEYWORDS
Risk science; risk management; decision theory; risk decision-making; risk context

Introduction

Over the last three decades, risk science has evolved into a well-established transdisciplinary field, with strong theoretical and applied foundations. Following the publication of the 'Red Book' by the U.S. National Research Council in 1983 (NRC: National Research Council 1983), which described a structured approach to risk assessment and risk management, subsequent advances have brought increasing sophistication into the field (Krewski et al. 2007; NRC: National Research Council 1994), including the U.S. Environmental Protection Agency's recent NexGen framework for the next generation of risk science (Krewski et al. 2014).

Although scientific approaches to characterization of public health risks including epidemiological, toxicological, clinical and surveillance approaches have been well-described, principles of risk management decision-making are less well-articulated. The present review sought to introduce and test a set of decision-making principles, describing 10 such principles denoted *P1* through *P10* for ease of reference throughout this article, which might collectively provide useful guidance to decision-makers. The list of 10 principles was developed from the lived experience of these authors and comprises their combined opinions as being deemed the most appropriate. The principles are presented as a basis for widespread discussion, debate, and future evolution.

To evaluate the utility of these principles in practice, the application in 10 different risk decision contexts, labeled *RC1* through *RC10*, was examined which represents a diverse set of risk management issues of current national and international concerns. The objectives of this paper are three-fold: to (1) articulate fundamental decision-making principles that provide guidance in risk decision-making; (2) explore their relevance and application

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in real-world risk decisions; and (3) identify the characteristics of different risk contexts that render each of these principles most relevant.

In practice, several valid yet potentially contradictory principles are relevant to most risk contexts. Indeed, the conditions under which each principle is most relevant are important. It is worthwhile noting that while each of the principles offers valuable guidance for decision-making in its own right, various principles might lead the decision-maker in different directions. Risk decision-makers therefore need to exercise judgment in balancing the guidance provided by these principles to reach an appropriate risk management decision.

This review commences with a description of the 10 principles, along with an explanation of the motivation for their use in risk management decision-making. To appreciate their utilization in practice, one subsequently needs to explore the application of the 10 principles across 10 risk decision contexts, highlighting the principles that are most relevant to each context. Attributes of risk decisions that might favor the employment of certain risk decision principles are then discussed, based upon these same 10 examples. Other related risk decision principles are discussed in the **Supplementary Material**. The concluding section of this article emphasizes the use of the 10 risk decision principles presented here as a guide to making critical risk decisions, concurrently acknowledging the importance of judgment and experience in decision-making, along with consideration of context-specific socio-political considerations.

Table 1. Principles of Risk Decision-making

Principle	Description
P1.Risk-based decision-making	Risk management resources should be allocated in proportion to the magnitude of established risks that are amenable to mitigation.
P2.Precautionary principle	Where the potential consequences are great, uncertainty should not prevent risk management actions.
P3. Balancing risks and benefits	Where appropriate, risks may be taken in light of offsetting benefits.
P4. Cost-effectiveness	Risk reduction actions should be taken in a cost-effective manner, in order to achieve the maximum return on investment of risk management resources.
P5. Risk tolerance	Efforts should be made to reduce risks to the point where they are considered tolerable.
P6. Zero risk	In most cases, the ultimate goal of zero risk will not be attainable.
P7. Risk equity	Unavoidable risks should be shared in an equitable manner, and not disproportionately borne by specific groups or individuals.
P8.Stakeholder engagement	All stakeholders should be afforded an opportunity to participate in the process of risk management decision-making.
P9.Openness and transparency	Risk management decisions should be taken in an open and transparent manner, with the basis for the decision clearly and explicitly stated.
P10. Flexibility	Risk management decisions should be flexible, and subject to review as new information becomes available.

Principles of risk decision-making

Risk management decisions can be highly complex, requiring consideration of a wide range of scientific and extra-scientific factors. Guidance on risk decision-making, however, is provided by a number of well-established principles that have evolved over time, as well as structured, yet flexible, frameworks for risk assessment and management (Jardine et al. 2003). Although outside the scope of the present paper, an important aspect of any risk issue is problem formulation. Clearly defining the ultimate risk management objective can provide clarity on the most appropriate methods and data required for risk assessment, as well as risk management approaches and strategies (Paoli et al. 2022). Recently investigators determined the value of information (VOI) analysis by Price et al. (2021) and Hagiwara et al. (2022) which support problem formulation by examining whether additional information that might be collected to fill important data gaps might help to address ultimate risk management objectives.

In this review, 10 fundamental principles that decision-makers might apply when confronted with difficult risk decisions were consolidated. These principles are summarized in Table 1 and elaborated upon below. It is acknowledged that this collection of principles is not exhaustive and a summary of additional principles relevant to risk decision-making was included in the **Supplementary Material**, where it is argued that many of these additional principles may be subsumed or made redundant by those outlined below.

P1. Risk-based decision-making

The principle of risk-based decision-making (RBDM) focuses on risks about which there is relatively little uncertainty and which may be modified in a cost-effective manner (Macesker et al. 2002). RBDM seeks to allocate finite resources in a manner that optimizes the return on investment in risk management. According to Custer and Janssen (2015, pp. 2040), "assessing risk, and the costs and benefits of mitigating risk, should go hand in hand and serve as complementary evidence in RBDM". Applications of the RBDM principle in food, agricultural, environmental and medical risk issues have recently been discussed by Morgan, Crawford, and Kowalcyk (2021).

Evidence-based toxicology is a movement that complements RBDM by (1) identifying the best use of scientific evidence for toxicological interpretation, (2) maximizing the quality of results and thus (3) facilitating the RBDM process. This movement is closely associated with that of evidence-based medicine (Hoffmann and Hartung 2006): evidence-based risk assessment has been successful, as demonstrated by management of some forms of environmental pollution (See *RC1*: ambient air pollution). Krewski et al. (2022) recently proposed a framework for evidence-based risk assessment, taking into account multiple evidence streams, including human, animal and mechanistic evidence: looking to the future, new approach methodologies (Krewski et al. 2010, 2019) developed for chemical risk assessment might provide new types of evidence that might be utilized to further strengthen the evidence base on which risk decisions may be made.

Fundamental to the principle of risk-based decision-making is consideration of the weight of evidence (WoE) supporting a causal relationship between exposure and outcome. Rhomberg et al. (2013) provide a comprehensive review of over 50 WoE frameworks that have been proposed in the literature. More recently, the International Agency for Research on Cancer (IARC) updated its Preamble to the IARC Monographs (Baan and Straif 2022), which includes detailed guidance on integrating evidence from multiple evidence streams in identifying agents that induce cancer in humans (Samet et al. 2020).

P2. Precautionary principle

The precautionary principle (PP) reflects a "better safe than sorry" conceptualization of risk management and is widely cited in risk management and policy debates (Government of Canada 2003; Grandjean 2004). Although currently more than 18 definitions of PP exist, the guidance provided by these iterations is generally rooted in Principle 15 of the 1992 Rio Declaration on Environment and Development (United Nations 1992, 3):

> 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.

This is the version proposed to be used here. The most important aspect of this and many other versions of the principle is that, unlike RBDM, scientific uncertainty should not preclude risk management interventions for risks that may have serious, even catastrophic, consequences if left unattended. Similar to RBDM, however, PP also recognizes that risk management resources are finite and that expenditures on a risk that may not materialize consume resources that could otherwise be applied toward the reduction of more certain risks. Thus, PP also emphasizes the importance of cost-effective risk management action (Jardine et al. 2003). Given this, it would be incorrect to suggest that risk management action motivated by PP cannot *also* be risk-based. Rather, invoking PP avoids complete inaction in risk contexts where scientific uncertainty may be inherent or unavoidable, as long as cost-effective options are available.

P3. Balancing of benefits and risks

Trade-offs in life are inevitable, and many risks also carry significant benefits. The personal automobile, which is responsible for an estimated 50,000 annual deaths due to roadway accidents in North America (OECD/ITF 2015) as well as many other serious risks such as ambient air pollution, also carries significant benefits, including both economic benefits accruing to the automobile industry and lifestyle benefits to the driver and passengers. Economists have developed sophisticated methods that assign economic values to both risks and benefits, which are then used to calculate a benefit-risk ratio. If this ratio is greater than one, the benefits exceed the risks resulting in greater good than harm being done overall. Challenges in operationalizing benefit-risk analyses (BRA) arise as a result of the requirement to place a monetary value on non-marketable goods, such as (1) health gain or loss, (2) environmental damage or loss, and (3) quality-of-life concerns. The observed inconsistencies in such valuations underlie the difficulties with adopting such an approach (Agapova et al. 2014). Such approaches were also criticized for demoting ecosystem or human health from the realm of specially valued things to mere commodities (Kelman 1981) and for distinguishing between benefits to the environment and human health rather than shared well-being (Rea and Munns 2017).

The benefit-cost ratio may be employed to inform risk management decision-making, wherein risk management action is warranted when the ratio is greater than one, as the societal benefits outweigh the risks of that action (Braathen, Lindhjem, and Navrud 2009). In reality, BRA is viewed as a decision-support tool, which although helpful in comparing risks and benefits on a common (usually monetary) scale, fails to account for relevant socio-political considerations (see *P5* on risk tolerance) and distribution of benefits and risks among individuals and groups (see *P7* on equity). Further, the benefit-risk approach assumes an unconstrained risk management budget, a notion inconsistent with finite budgetary resources.

P4. Cost-effectiveness

Invoking the principle of cost-effectiveness (CE) directs the risk manager to consider both allocative and technical efficiency, seeking to invest available resources for risk management with the aim of reaching a specific social objective such as minimizing expected risk. Although economic efficiency in risk management is clearly a desirable goal, strict application of the CE principle would ignore other principles, such as the precautionary (*P2*) and zero-risk (*P6*) principles.

It has been argued that application of cost-effectiveness as the sole principle might result in all available risk management resources being applied toward that risk with the lowest CE ratio (cost divided by the specified reduction in risk), to the exclusion of other risks with less favorable CE ratios that also warrant attention (Weinstein and Stason 1977). However this is a highly unlikely scenario, given that diminishing marginal returns might occur with respect to investing in efforts to address a specific risk.

P5. Risk tolerance

Since the complete elimination of risk will not be feasible in most risk decision contexts, some level of risk will remain even after appropriate risk management interventions have been implemented (Hunter and Lorna 2001), a reality underscored by Lowrance and Klerer (1976) in their pioneering text on *Of Acceptable Risk*. Certain U.S. regulatory statutes suggest a target level of risk, typically in the range of 10^{-5} to 10^{-7} over the course of a lifetime that might be considered *de minimus* and not warranting further often highly cost-ineffective risk reduction (Castorina and Woodruff 2003).[1] This does not imply that such residual risks are necessarily ‘acceptable’; rather, these are benchmarks for what constitutes a reasonable level of risk beyond which it is difficult to justify further remedial action from a societal perspective. At the same time, such statutes do not discourage the pursuit of the ultimate goal of zero risk (next), should this be practically achievable in a cost-effective manner (Hsu and Stedeford 2011). It is also important to note that, while thresholds for acceptable risk will vary among risk contexts, with offsetting benefits often increasing risk tolerance, *perceptions* of risk levels and potential benefits may also vary based upon the attributes of that risk scenario (Fischhoff, Slovic, and Lichtenstein 1979).

Another practical approach to determining risk tolerance is provided by risk assessment matrices, which combines information on probability and severity to identify risks of lower or higher concern, typically expressed in the form of a two-dimensional matrix representing various combinations of probability and severity (Bao et al. 2017; Jensen and Hansen 2020). A priority risk issue, of both high probability and severe impact, needs to be addressed with more urgency than other issues represented in the matrix.

P6. Zero risk

The principle of zero risk sets the complete elimination of risk as the risk management objective. Indeed, surveys of societal attitudes toward risk management have consistently shown that a significant proportion of the Canadian public (40–60%) believes that a risk-free environment is an attainable goal (Krewski et al. 2008), despite such a goal being attainable only in limited circumstances. Despite the desirability of zero risk, the complete elimination of risk is generally not possible. Nonetheless, the zero-risk principle is useful in several respects. First, in some cases such as the banning of a risky consumer or therapeutic product it is possible to eliminate risk. Second, even when risk cannot be eliminated, the ultimate goal of zero risk provides an ideal to strive for over the long term, even if it is never fully achieved. Third, the quest for zero risk can be technology-forcing, leading to innovative and cost-effective incremental reductions in risk (Berthoud 2014). Although the zero risk principle P6 can be viewed as a special case of P5 in which risk tolerance is set to zero, the concept of zero risk is presented as a separate principle for these reasons.

P7. Risk equity

Risk decisions should be fair and equitable, without disproportionately affecting population subgroups (Adler 2008); ideally, both risks and benefits of risk management actions need to be shared in an equitable manner (Benn, Dunphy, and Martin 2009; Viscusi 2000). Farrow (2010) argues that distributional aspects of risk decisions warrant more attention, including decisions motivated by benefit-cost analysis which may be used in balancing risks and benefits under P3. Focusing on risk management actions that will do the greatest good for most individuals will maximize societal benefit, and avoid expenditure of limited risk management resources on unimportant risks (Zeckhauser and Viscusi 1996).

Risk decisions should reflect social, cultural, environmental, economic, legal and other values, which may raise concerns over whether such decision processes and/or decisions favor certain individuals or groups over others (Keller and Sarin 1988). This principle therefore implies that risk decisions need to incorporate elements of procedural and distributive fairness to all concerned.

The environmental justice movement that started in the 1960′s, partially driven by increasing awareness of environmental inequity of minority and low-income populations, provides useful context for the principle of risk equity. The term ‘environmental racism’ was used to point out that these groups were being exposed to higher levels of pollutants and toxins, increasing their risk burden compared to the general population. In 1994, President Clinton signed the executive order named, “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations,” which legislated environmental protection for all communities (Bowen et al. 1995; Ewall 2012). The U.S. EPA: Environmental Protection Agency (2017) defines environmental justice as:

“. . . the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies. EPA has this goal for all communities and persons across this Nation. It will be achieved when everyone enjoys the same degree of protection from environmental and health hazards and equal access to the decision-making process to have a healthy environment in which to live, learn, and work.”

While disadvantaged groups often face increased barriers to participation, a “double jeopardy” is faced with evidence that disadvantaged groups often face higher adverse exposures while also being more susceptible to these exposures because these individuals face, among other things, a myriad of other risks due to higher workplace exposures, greater levels of psychosocial stress, and enhanced prevalence of chronic diseases (Institute of Medicine 1999).

In considering this principle, it follows that disadvantaged individuals or groups need not bear a disproportionate burden of risk, nor a disproportionate share of the cost of risk reduction. Invoking the principle of risk equity in the management of risk might involve balancing considerations of individual and collective ethics in striving to achieve an equitable distribution of risks and benefits through fair and effective risk management choices.

P8. Stakeholder engagement

Democratic societies will immediately recognize the importance of stakeholder engagement in risk decisions. Effective stakeholder engagement in risk management requires subject matter competence in addition to more generalist abilities; and the process needs to be formal, open, and well managed. Appropriate stakeholder engagement may vary for each risk context, with best practices identified and promoted by scholars and practitioners alike (IAP2: International Association for Public Participation 2021; Webler and Tuler 2021).

Stakeholder involvement might also serve to identify novel approaches to risk management, which may not otherwise have been considered. Involvement of interested and affected parties might build support for (and acceptance of) the ultimate risk management interventions. Considered best practice, a list of stakeholders might include internal, external, community, practitioner, industry, multi-levels of government, and international regulatory bodies. Many risk assessment and management frameworks specify stakeholder involvement throughout the process: examples of this are illustrated in many of the published risk assessment and management frameworks, such as the 2009 Science and Decisions framework NRC: National Research Council 2009) the 2007 NRC vision for a new toxicity testing framework (NRC: National Research Council 2007), toxicity testing in the 21st century (Krewski et al. 2010) the 2014 EPA NexGen framework (Krewski et al. 2014), and the International Risk Governance Council (IRGC) Risk Governance Framework (IRGC: International Risk Governance Council 2017).

P9. Openness and transparency

With information becoming freely available almost as quickly as it is generated, the public has become increasingly-sophisticated in its efforts to understand the process of risk assessment and management, and more willing to question the underlying basis for risk decisions. Being aware of the importance of modern communications and legitimate demands by public interest groups for more information on risk issues of concern, government agencies responsible for risk management are expected to operate in a more open and transparent manner than ever before. With an emphasis on both ease of access and the fullest possible disclosure, stakeholder engagement with open and transparent processes are key to developing overall trust, credibility and support for decision-making. Many democratic countries have official websites documenting decision-making for government agency rules including proposed rules, public notices and invitations for public comment, including the Federal Register (https://www.federalregister.gov/) in the United States and the Canada Gazette (http://www.gazette.gc.ca/gazette/home-accueil-eng.php) in Canada.

P10. Flexibility

The accelerated pace of knowledge development including scientific evidence on the wide range of risks faced in our daily lives resulted in a need for flexibility in risk decision-making as new risk information becomes available; this often requires enhanced stakeholder engagement. The accumulation of new scientific knowledge might lead to adjustments in, and possibly even reversal of, previous risk decisions. An example of the latter outcome is the saccharin case discussed in *RC2*. Although research demonstrated that saccharin usage was safe in humans following its ban as an artificial sweetener in 1977, it has proven difficult to reinstate the use of a previously-banned product because of lingering adverse publicity (Harrison and Hoberg 1994). In contrast, the teratogen thalidomide, originally used for the treatment of morning sickness during pregnancy in the 1950s and

1960s, and then banned because of disabilities in babies born to mothers taking the drug, is currently indicated as a treatment for leprosy and chemotherapy-induced nausea and vomiting (Mayo Clinic 2022). However, its efficacy and safety continue to be evaluated (Wang et al. 2020).

A risk management approach or framework needs to be flexible and responsive to changing dynamics and risk levels, but this may be challenging in practice. For example, Saunders-Hastings and colleagues (2018) noted that a weakness of the Canadian response to the 2009 influenza pandemic was the inability to scale the intensity of the risk management response up and down in line with transmission patterns. With the outbreak of COVID-19 in 2019, intense efforts to develop and deploy an effective vaccine against the SARS-Cov2 virus (Ball 2020) were instrumental in reducing the number of serious (including fatal) cases (Watson et al. 2022).

Other principles

A review of the literature on risk decision-making identified a number of principles beyond the 10 major principles listed above. For example, the ALARA principle (as low as reasonably achievable) is widely used in radiation protection to limit human exposure to ionizing radiation: ALARA is closely related to the risk tolerance principle (*P5*) discussed above. BATEA (best available technology economically achievable) is similarly employed to encourage the use of advanced technology for risk reduction, with consideration of costs; the guidance provided by this principle is similar to the cost-effective (*P4*) and zero-risk (*P6*) principles discussed above. These and other more focused decision-making principles are discussed further in the **Supplementary Material**.

Application in different risk decision contexts

Different principles might legitimately suggest different risk management trajectories. In this section, it was of interest to determine which principles of risk management would be most relevant and appropriate in different risk decision contexts. Ten risk contexts, *RC1* through *RC10*, are discussed in detail below. These examples were selected to represent a diverse range of complex real-world challenges, including environmental pollution, food additives, therapeutic products, genetic modification, resurgent and emerging pathogens, and natural disasters. These examples will be used to illustrate the application of the 10 risk decision principles introduced above and to explore attributes of risk decisions that may favor the application of some principles over others.

The final three principles (*P8*, *P9*, *P10*) are somewhat universal and as elements of functioning democracies apply in most risk contexts. Active stakeholder engagement (*P8*) is important to ensure that the views of all segments of society are represented. Openness and transparency of the decision-making process (*P9*) is needed to foster informed decision-making by individuals and stakeholder groups. Finally, risk decisions need to be flexible (*P10*), adapting to new evidence as it becomes available (Jardine et al. 2003). Although the final 3 principles are expected to apply in virtually all risk contexts, there may be exceptions such as the need for discretion in addressing bioterrorism risks in which these principles may not be evoked.

RC1: Ambient air pollution (P1, P3-P5, P7, P8-P10)

Epidemiological and toxicological studies implicated ambient air pollution as an important cause of adverse health effects in the population (Costa et al. 2014; WHO 2021), reducing life expectancy by an average of 9 months in the European Union (EU). The effects of particulate matter (PM) are well documented (Chen, Chen, and Yang 2019; Eze et al. 2015; Schraufnagel et al. 2019; Tsai et al. 2022; Zhou et al. 2021). It has been estimated that the global fraction of adult mortality attributable to the anthropogenic component of $PM_{2.5}$ is 8% (95% CI: 5.3–10.5) for cardiopulmonary disease, 12.8% (5.9–18.5) for lung cancer, and 9.4% (6.6–11.8) for ischemic heart disease (Evans et al. 2013). More recently, Burnett et al. (2018) estimated that more than 8 million annual deaths are attributable to particulate air pollution worldwide.

In this context, the principle of risk-based decision-making (*P1*) is relevant, as there is a well-documented and well-quantified public health risk that needs to be addressed. The precautionary principle (*P2*) is not particularly relevant, as there is relatively little uncertainty regarding the health risks of particulate air pollution. Balancing of benefits and risks (*P3*) is relevant, as the benefit-cost ratio of 4:1, driven largely by an economic valuation of $7.4 M USD (EPA: Environmental Protection Agency 2011) for the loss of a single human life, indicates a highly-favorable return on pollution abatement investment Because of the large costs of pollution abatement, it is particularly important to seek efficient (cost-effective) interventions (*P4*) (WHO: World Health Organization 2016). The zero-risk principle (*P6*) is not particularly relevant in this context, as the complete elimination of ambient air pollution is unachievable, even at an infinite cost. Even if one was able to eliminate all anthropogenic sources of pollution, natural sources such as dust from the Sahara Desert, which is transported worldwide, would remain. Recognizing this, some level of risk needs to be tolerated (*P5*) as one moves toward but never achieves the idealized goal of zero risk. Risk mitigation efforts might also need to respect the principle of equity among different segments of society (*P7*), avoiding situations where the benefits accrue to one segment of the population at the expense of another.

The dominant principles in this risk context are likely to be *P1* (risk-based), *P3* (balancing benefits and risks) and *P4* (cost-effective), leading to reduced air pollution levels globally over time in a rational and efficient manner.

RC2: Artificial sweeteners (P6)

Artificial sweeteners have been used to reduce the caloric content of food for over a century. When saccharin was found to produce malignant urinary bladder tumors in a series of two-generation studies involving Sprague-Dawley rats fed up to 7.5% saccharin in their diets, the U.S. Food & Drug Administration (FDA) quickly moved to ban the use of saccharin as a direct food additive in 1977. The ban was subsequently superseded by a series of moratoriums imposed by the U.S. Congress, which has permitted the limited use of saccharin through to the present. This action was consistent with the 1958 Delaney Amendment to the U.S. Food, Drug & Cosmetic Act, which bans the use of carcinogenic food additives such as certain artificial sweeteners or food colors. This amendment overrides the principle of balancing benefits and risks, on the grounds that no organoleptic benefits of direct food additives might offset a cancer risk (FDA: United States Food and Drug Administration 2014). In this case, banning a food additive that does not occur naturally in the food supply achieved the ideal goal of zero risk (*P6*).

Even after the modification of the saccharin ban, the debate over the safety of saccharin has continued. While evidence of an association between saccharin and bladder cancer in humans was found in subsequent epidemiological studies, the results were inconsistent (IARC: International Agency for Research on Cancer 1999). The highest doses used in the animal studies (equivalent to consuming several hundreds of bottles of artificially sweetened soft drinks per day) challenged the conclusion that these outcomes reflected human risks. This debate was ultimately resolved when it was demonstrated that the urinary bladder neoplasms in rats exposed to high doses of saccharin were due to the formation of microcrystals in their urine, an effect that would not occur at lower human exposure levels (Cohen 1986). Although *P10* (flexibility in decision-making) would suggest that the ban on saccharin might be reversed in light of this evidence of safety, there is reluctance to lift the ban on a product that was previously considered to be dangerous.

The saccharin case also illustrates the issue of assessing the risks of substitutes (NRC: National Research Council 2014). Saccharin was largely replaced by the approval of aspartame as an artificial sweetener in 1981 (Murray 2002). Despite extensive pre-market safety testing, there still remain concerns regarding possible brain cancer risks associated with the consumption of aspartame (Weihrauch and Diehl 2004).

RC3: Climate change (P2, P4, P7, P8-P10)

In 1957, oceanographer Roger Revelle and chemist Hans Suess (1957) published what has been called the most famous sentence in the literature on global warming: “Human beings are now carrying out a large scale geophysical experiment of a kind that could not have happened in the past nor be reproduced in the future." The risk factor in this 'experiment' is known as positive radiative forcing, measured in units of watts per square meter, which is the difference between the amount of energy in sunlight striking the earth's surface less the amount that is re-radiated back into space. The composition of the earth's atmosphere, in particular the gases methane, carbon dioxide, and nitrous oxide, traps some of this energy, leading to the so-called 'greenhouse effect.' The concentrations of those gases in the atmosphere are considered to be the primary driver of the recent rise in global average temperatures.

Since this statement by Revelle and Suess, there has been increasing consensus on the contribution of human activity to global change. The Intergovernmental Panel on Climate Change (IPCC) reiterated in their Fifth Assessment Report that the effects of increases in anthropogenic greenhouse gases (GHGs) since the pre-industrial era, "together with those of other anthropogenic drivers, have been detected throughout the climate system and are extremely likely to have been the dominant cause of the observed warming since the mid-20th century" (IPCC 2014a, pp. 151). The Fifth Assessment Report also states: "About half of the cumulative anthropogenic CO_2 emissions between 1750 and 2011 have occurred in the last 40 years (high confidence)" (IPCC: Intergovernmental Panel on Climate Change 2013, 1535). This recognition has resulted in several targeted efforts and policy directives aiming to curb anthropogenic influence, including the United Nations Framework Convention on Climate Change (UNFCCC) Kyoto Protocol (which came into force in 2005) and the UNFCCC Paris Agreement (which came into force in 2016).

The chief policy goals in addressing climate change are first to stabilize concentrations of GHGs in the atmosphere (that is, ending the annual increases), and then to achieve a steady decrease in those concentrations. The Paris Agreement objectives are to limit the increase in global average temperature (relative to pre-industrial levels) to no more than 2°C, and preferably no more than 1.5°C, through the period of this century. The main adverse effects which the climate change policy goals seek to avoid or mitigate include: sea-level rise, temperature increases, ocean acidification and increasing storm severity, which would lead to impacts on agriculture, forests and marine life, including droughts, flooding, and storm damage. Since a large percentage of the human population currently lives at or near present sea levels, failure to prevent or mitigate these adverse effects could have profound consequences. Recent literature has begun to sharply reduce the timelines within which GHG emissions reductions must commence to avoid surpassing these thresholds (Goodwin et al. 2018a, 2018b). Further, because of inertia built into the climate and carbon cycle, "increased atmospheric concentration due to past emissions will persist long after emissions are ceased," and "much of the warming would persist for centuries after greenhouse gas emissions have stopped" (IPCC: Intergovernmental Panel on Climate Change 2014b).

The IPCC Sixth Assessment Report (2022) describes global and regional risks for increasing levels of global warming: "*Near-term actions [through 2040] that limit global warming to close to 1.5°C would substantially reduce projected losses and damages related to climate change in human systems and ecosystems, compared to higher warming levels, but cannot eliminate them all (very high confidence)*" (IPCC: Intergovernmental Panel on Climate Change 2022, pg. 15). For the medium and long term (2041–2100), *"The magnitude and rate of climate change and associated risks depend strongly on near-term mitigation and adaptation actions, and projected adverse impacts and related losses and damages escalate with every increment of global warming (very high confidence)"* (IPCC: Intergovernmental Panel on Climate Change 2022, pg.16).

The challenge to realizing policy goals include, above all, the willingness of individual nations, particularly the major emitters of GHGs (China and the United States), to adopt and enforce firm, consistent targets for ceilings and reductions on GHG emissions *over the long term*, and for the global community of nations to cooperate in this venture. Leiss et al. (2020) examined the gap between science based GHG emission reduction targets and inadequate results of multi-decade international treaty negotiations. Current nationally determined contributions under the Paris

Agreement remain shy of the 2030 emissions reductions target and the longer history of 'action' on climate change indicates that a considerable period will elapse until the challenges are addressed. In the meantime, global emissions continue to rise, and the inertia of excessive radiative forcing is still pushing the achievement of the chief policy goals far into the future. This situation has prompted some to advocate for geoengineering solutions such as the long-term dispersal of sulfate aerosols into the upper atmosphere, mimicking the effects of volcanic eruptions though this strategy has important uncertainties associated with it, with carbon sequestration, solar radiation management and the removal of carbon dioxide from the atmosphere often viewed as preferable alternatives (Keith et al. 2016).

Whether or not global cooperation to reduce greenhouse gas emissions is successful, it is likely that climate change impacts will pose serious and varied threats to public health. Worsening air pollution, extreme weather and reduced crop productivity have already been observed and are likely to continue. The potentially catastrophic implications of climate change suggest that a precautionary, risk-averse approach to management is urgently required (*P2*), even in the presence of scientific debate regarding the scale and severity of consequences. It is likely, however, that the most successful and sustainable risk management strategies will be those that are cost-effective and anchored in current economic realities (*P4*); those that are not may be viewed as environmentally-necessary but may be socially or politically unacceptable. In addition, as it is well-understood that vulnerable groups are often the most susceptible and least able to adapt to the consequences of climate change, considerations of where the health burden lies and how resources might be most equitably distributed are essential in risk management efforts (*P7*). Lastly, the complex, long-term and geographically-variable nature of climate change and its impacts suggests that principles of stakeholder engagement (P8) and transparency (P9) are necessary to design risk management strategies which are globally meaningful, locally relevant, effective and acceptable. As a point of no return is rapidly approaching in mitigating climate change (Leiss et al. 2020), it is unclear the extent to which one has the luxury of flexibility (*P10*) in addressing this global risk issue.

RC4: Nanotechnology (P1, P2, P3, P8-P9)

Nanotechnology is concerned with the design, synthesis, and characterization of materials and devices that are at the nanometer scale (a nanometer is one billionth of a meter). Nanotechnology promises a plethora of benefits to society with the potential to greatly enhance population health through applications of the technology (Kermanizadeh et al. 2016; EPA: United States Environmental Protection Agency 2005).

Nanomaterials (NM) are a diverse group of chemical compounds that include carbon nanotubes, carbon nanoparticles, inorganic and organic dendrimers, nanoparticles (NP) conjugated with various metals or other materials (antibodies, deoxyribonucleic acid), nano-size polymers (termed dendrimers), and composite materials (NP combined with larger materials). The ability to engineer self-assembling (i.e., self-organizing) substrates at the nanoscale produces macroscopic physical and/or chemical properties that their bulk material counterparts do not possess (Silva 2005). These NP may demonstrate new physico-chemical properties and show markedly different toxicities due to quantum effects.

Roco (2004; 2006) outlined four generations of nanotechnology development. The current, first generation is comprised of passive nanostructures or NM designed to carry out a single function. It includes NM incorporated into paints, coatings, emulsions, cosmetics and lubricants. The NP are designed to increase or alter specific physical properties such as hardness, durability, anti-oxidation capability, tribological characteristics including reducing friction, decreasing wear, and anti-corrosion, thermal properties, and conductivity.

The second generation of active nanostructures will introduce multi-step reactions at the nanoscale with NP that combine a limited number of chemical steps or reactions. For example, multistep drug delivery devices and multistep sensors. The third-generation nanotechnology will feature more complex, active nanosystems with several interacting reactions creating higher order complexity. The fourth generation of active nanotechnology is predicted to have hierarchical nanosystems functioning and rivaling that of living cells in their complexity.

Research has established that some types of NM may be highly toxic to living systems, thereby adversely impacting both human health and the environment. Other types of NM are seemingly inert. Concerns about the toxicity of NP in the environment include assumed persistence, high bioavailability of certain NM, and bioaccumulation in plants, insects, animals and humans. There is uncertainty regarding the ability of various NP to chemically interact with common compounds already present in the environment that might, in theory, alter the toxicity of either interacting component.

The toxicity of anthropogenic NP is exacerbated by the types and amounts now being manufactured which may lead to increased potential for risk (Moore 2006; Mouneyrac, Syberg, and Selck 2015). For first generation nanotechnology, adverse health and environmental effects of man-made NP in the environment have already been substantiated. Specifically, research with some types of dispersed nanosized particles demonstrated that these are highly toxic to fish in aquatic environments and to animals when ingested, inhaled or via dermal contact under certain conditions (Abbas 2021; Cazenave et al. 2019; Egbuna et al. 2021; Kermanizadeh, Powell, and Stone 2020; Oberdörster, Oberdörster, and Oberdörster 2005; Senel 2021). The toxicity depends upon some properties of the NP including the nature and size, surface area, shape, aspect ratio, surface coating, crystallinity, dissolution, and agglomeration (Egbuna et al. 2021).

New NM present challenges to toxicity testing that may not be easily addressed with existing risk management approaches (Institutes of Medicine, 2005). Nanoparticle pathways and entry exposure routes into the body requires further research to inform policy makers and regulatory organizations regarding the toxicological potential of certain NM (Elsaesser and Howard 2012; Kermanizadeh, Powell, and Stone 2020). Further, the potential for deleterious effects from NM has led to calls for more research on the toxicology of NP by the public, scientific community, and other stakeholders (Colvin 2003; Kamali, Khodaparast, and Seifi 2013; Service 2005; Zhang et al. 2021). To address the potential risks current chemical and particulate material regulations, and regulatory frameworks, need to be modified to encompass the uniqueness presented by NM exposure hazards (Tyshenko and Krewski 2008).

As nanotechnology develops through successive generations it is expected to undergo vigorous development with applicability to a myriad number of sectors. However, in view of the potential risks presented by nanotechnology's uncertain advancement, potential synergistic exposures to NP and ubiquity in the environment, it is important to balance economic interests against societal concerns as the technology develops (*P3*) (Hutchison 2008; Sparrow 2009). The risks associated with the products of nanotechnology and the trajectory of nanotechnology's development need to be carefully managed with inclusion of the engagement of stakeholders *(P1, P8)* (Tyshenko and Krewski 2008).

The safest option for nanotechnology's anticipated future development through the various increasingly complex generations would be the adoption of a precautionary approach that is both inclusive and transparent *(P2, P8-P9)* (Tyshenko et al. 2010). There are two main reasons to consider using a precautionary approach for NM. First, the enormous number of NP each with their different properties such as shape, size, material, functionalities, processes of manufacture, and applications makes it difficult to standardize and adopt a universal measurement method for toxicity (Ramanathan 2019). Secondly, uncertainty of active nanotechnology application development going forward in time suggest an increasingly precautionary approach is concomitantly needed at each successive generation of nanotechnology for effective risk management (*P2*) (Tyshenko et al. 2010).

The United Kingdom Royal Society report recommended a precautionary approach with regards to NP: exposure to certain types of NP needs to be avoided or limited with occupational precautions until more is known regarding the environmental and health impacts (UK Royal Society and the Royal Academy of Engineering 2004). Risk assessment and management frameworks and strategic plans for NP oversight were proposed (IRGC: International Risk Governance Council 2007; Tyshenko and Krewski 2008; EFSA Scientific Committee 2021a; 2021b; U.S. National Science and Technology Council, 2021). Additional nanotoxicity research may help to inform efforts to establish standardized regulatory frameworks with the goal of fully exploiting the potential of nanotechnology while minimizing harm to humans (*P3*). As our understanding of the risks and benefits of this technology matures, greater emphasis may be placed on other risk decision principles, including risk-based decision making (*P1*) and balancing of risks and benefits (*P3*).

RC5: Chemotherapeutic agents (P3, P4, P5, P9)

Chemotherapeutic agents used to treat a range of cancers are potent drugs designed to destroy malignant cells. Although such agents target abnormal cells involved in malignant transformation, many chemotherapeutic agents are genotoxic and present a risk of secondary cancers (Sak 2012). Estrogen-targeted therapies employed to treat breast cancer may also enhance the risk of serious cardiovascular complications, including heart failure and myocardial infarction (Valachis and Nilsson 2015). A decision to take a potentially life-saving drug that might result in serious or even fatal side effects involves a balancing of risks and benefits (*P3*) taken by the patient in consultation with his or her physician and a tolerance for a certain level of risk (*P5*). Benefit-risk considerations are particularly appropriate here, as the risks and benefits are borne by the patient and might be made with personal values of the patient as key decision criteria. Further, given the increasing role that consideration of cost-effectiveness plays in terms of reimbursement decisions in relation to health technologies for most publicly-funded health care systems, the principle of cost-effectiveness (*P4*) is also relevant to this context.

Stakeholder engagement (*P8*) has not been identified as relevant to *RC5*, since the patient is essentially the sole stakeholder. The requirement for informed patient consent corresponds more closely to the principle of openness and transparency (*P9*). Although changes in therapeutic regimen may be viewed as demonstrating flexibility, *P10* has not been invoked in this risk context since it pertains more to flexibility in clinical practice than it does to the choice of risk management strategy.

Other medical interventions, notably vaccines, may also involve benefit-risk considerations at the societal as well as the individual level (*P3*). This is due in large part to 'herd immunity,' wherein changes in individual immunity status might have important implications for pathogen transmission dynamics and human health outcomes at the population level (Metcalf et al. 2015). Vaccine hesitancy, a behavior manifested among a minority of the population, may reflect a personal view that the risks of vaccination outweigh the personal benefits, in conflict with public health recommendations for standard vaccination protocols for children for diseases such as measles and polio (WHO: World Health Organization 2016).

RC6: Natural disaster (extreme weather events) (P2, P4, P7, P8-P10)

Global climate change is expected to increase the frequency and severity of extreme weather events. These weather events have a range of direct and indirect health effects. A well-known and extreme example is the 2005 occurrence of Hurricane Katrina, which caused over 1,100 deaths in Louisiana (Jonkman et al. 2009). Severe health consequences have also been associated with ice storms such as the 1998 storm in Eastern Canada (Hartling, Pickett, and Brison 1999), tornados (Bourque et al. 2007) and extreme precipitation and flooding (Erickson et al. 2019; Jagai et al. 2015). Other examples include the damage produced by the 2017 Hurricane Maria in Puerto Rico Zorrilla 2017) and the cholera outbreak produced by the 2019 Cyclone Idai in Mozambique (Gruenbaum 2019). More recently, mental and physical health impacts associated with the 2021 British Columbia heat dome are beginning to be identified (Bratu et al. 2022). In each case, a large proportion of health consequences are the result of indirect or secondary impacts on infrastructure and human behavior, presenting important intervention points for risk reduction (Hales, Edwards, and Kovats 2003).

Despite improvements in early warning weather systems, a high degree of uncertainty still exists regarding the timing, location, severity and impacts of extreme weather events. The overall burden will be context-dependent, with consequences being exacerbated by weak health systems and response capacity (Austin et al. 2015). In addition, there is uncertainty in projections for future climate change (Klima and Jerolleman 2014). Considering the potential for a public health emergency to result from an extreme weather event, the precautionary principle (*P2*) will have relevance to natural disaster risk reduction efforts when there is insufficient evidence to invoke risk-based decision-making (*P1*).

A review of the health effects of extreme weather events found that much of the associated health burden is linked to five secondary impacts on infrastructure and human behavior (Toronto Public Health 2016), specifically: (1) loss of power, (2) essential service disruption, (3) evacuation, (4) improper use of fuel-burning equipment and (5) unsafe cleanup activities (Arrieta et al. 2009; Goldman et al. 2014; Johnson-Arbor, Quental, and Li 2014). Data suggest that a small number of causal nodes drive a substantial proportion of the associated health impact, presenting a pathway for cost-effective policy intervention. An effective strategy for dealing with the inherent uncertainty in climate resilience decision-making is to pursue "no regrets" strategies, which deliver a range of co-benefits beyond climate resilience which encourages the most effective and impactful use of resources (Hay and Mimura 2010). The key risk management principle underlying this strategy is that of cost-effectiveness (*P4*). In the case of extreme weather resilience, promotion of risk management focusing on the five identified causal nodes might form the foundation of an effective strategy.

Certain population groups are particularly vulnerable to experiencing a disproportionate health burden during and immediately following an extreme weather event; these include infants and children, women, the elderly, those with preexisting conditions, low-income or homeless individuals, minorities, Indigenous Peoples and recent immigrants (Clean Air Partnership 2009; Health Canada 2005, 2008). As such, equity (*P7*) is an important component in developing effective extreme weather resilience and response strategies. That the most vulnerable groups tend to be similar across event types suggests that a focus on these populations will promote all-hazard preparedness and response capacity.

The finding that much of the indirect health burden associated with extreme weather events is associated with maladaptive human behavior suggests a strong need for improved engagement (*P8*) of the local population to improve adaptive capacity. Locally-relevant educational and advisory material, alongside the active engagement of community leaders, is essential to promoting individual and community disaster resilience (Cutter et al. 2008). Open and transparent communication (*P9*) is necessary to foster public trust, with flexibility (*P10*) needed to ensure a response proportional to the severity of the weather event.

In sum, uncertainty in the timing, location and severity of an extreme weather event points to the relevance of the precautionary principle (*P2*), while the commonality of causal nodes and vulnerable groups across weather events supports a strategic emphasis on cost-effective (*P4*) and equitable (*P7*) risk management policy.

RC7: Prion diseases (P1, P2, P8-P9)

Prion diseases are caused by a misfolded form of the prion protein, which leads to neurodegeneration through propagation of the misfolded form within neural tissue. Fatal prion diseases have been described in multiple species, including scrapie in sheep, bovine spongiform encephalopathy (BSE) or 'mad cow disease' in cattle, chronic wasting disease (CWD) in deer and elk, and variant Creutzfeldt-Jacob disease (vCJD) in humans. Prion diseases may be transmissible between species: for example, BSE is thought to have originated from the inclusion of sheep offal in the diets of cattle in the United Kingdom, with consumption of beef containing the BSE agent leading to the development of vCJD in humans. The outbreak of the BSE epidemic in the UK in 1986 spread to other countries, and enormous negative socioeconomic impacts in BSE-affected countries (Leiss et al. 2010). Human prion disease may be transmitted by blood transfusion. Infectious prion proteins were detected in fertility drugs from human urine, presumably arising from donors with asymptomatic vCJD (Van Dorsselaer et al. 2011). There remain concerns regarding species transmission of CWD from deer and elk to other cervid species, including caribou (Haley and Hoover 2015). There is also increasing evidence that propagated protein misfolding plays a role in other neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Herms and Dorostkar 2016). At present, there are no effective medical interventions for prion diseases, although a promising vaccine against CWD is currently under development (Goñi *et al.* 2015).

A precautionary approach to prion disease risk management (*P2*) may be warranted to protect against the emergence of new prion diseases, including those generated through inter- and intra-species transmission. This concern is reinforced by the recent detection of a prion protein genotype (albeit one that reduced susceptibility to chronic wasting disease) among caribou populations in Alberta, Canada (Cheng et al. 2017).

For well-established prion diseases, however, the principle of risk-based decision-making (*P1*) is directly applicable, such as for BSE, CWD, and vCJD whose etiologies are now well-understood. This has been adopted internationally, through a geographically-based risk designation of countries as 'controlled risk' or 'negligible risk' by the World Organization for Animal Health.

Case studies of the management of BSE in different countries revealed varying degrees of stakeholder engagement (*P8*) and transparency (*P9*) by government officials, with Canada acting swiftly to disseminate all available information following the detection of the first domestic case in 2003, whereas Germany was slower to acknowledge the problem following the occurrence of BSE in 2000 (Leiss et al. 2010). Because of the significant health, environmental, and socioeconomic implications of prion disease outbreaks, there is limited flexibility (*P10*) in the application of stringent disease control measures.

RC8: Hydraulic fracturing (P1, P3, P4, P5, P7, P8–P10)

Unconventional tight reservoir formations in the sub-surface, including shales, mudstones, and tight sands, are a growing source of oil, natural gas liquids (NGLs), and natural gas. Further, the commercial extraction and increased use of natural gas, a fossil fuel that emits lower carbon dioxide quantities than oil or coal for equivalent energy delivery, is often viewed as an important transitional component of climate change mitigation through 2050, as the energy supply shifts toward renewable sources. This is deemed a critical period to advance the world's energy supply to no or lower GHG-emitting energy sources.

Hydraulic fracturing (HF) has become the fastest-growing technological process to develop unconventional resources. Three countries extract unconventional gas resources, with the United States being by far the largest global producer of shale gas, tight gas, and coalbed methane (600 billion cubic meters (BCM)), and Canada then China ranking second and third (95 and 31 BCM, respectively) (IEA: International Energy Agency 2018). The principal countries currently extracting crude oil from tight formations (shale oil) with HF are the United States, producing approximately 6.5 million barrels/day (mb/d) (EIA: Energy Information Administration 2019) and Canada, producing approximately 350,000 b/d (National Energy Board 2018).

Risk management for HF is therefore positioned within a complex spatial framework where "governance (both the substance of the laws and the activities of entities that implement and influence these) is challenged by perceived regional or even global benefits of the technological process, compared with local adverse impacts that can be the purview of several layers of government" (Larkin et al. 2018). The broad categories of direct and indirect risks concern (1) land development and infrastructure to gain access to sites and for deliveries of materials; (2) geoscience of the formation; (3) use and disposal of water and spent fracturing fluids; (4) air emissions, with local and global implications; (5) prevailing social and economic cycles in the region, including cumulative effects; and (6) resident and worker health and well-being (Dusseault and Jackson 2014).

The years of experience in oil and gas development and ongoing enhancements to regulatory approval processes for HF projects in some jurisdictions (e.g., British Columbia and Alberta) (Larkin et al. 2018) point to risk-based decision making (*P1*) as the dominant risk management approach. HF is not a case for the zero-risk principle (*P6*); working in the sub-surface, in areas with unknown or abandoned wells, rejects the potential to reach this threshold.

During this decade, growing concerns for international energy security could be juxtaposed with stated greenhouse gas emissions reductions targets and goals to reach net zero emissions by 2050. This might affect risk tolerance (*P5*) for HF in terms of broad acceptance as opposed to a quantitative risk estimate. To date this appears to be dependent on the jurisdiction. For example, where HF is permitted in Canada, provincial energy policy includes a strategic role for natural gas development (Alberta Government 2008; Government of British Columbia 2007) and, in the case of British Columbia, also with a goal for LNG plant development for export to the Asian market (Government of British Columbia 2013) although progress to date on these initiatives has been limited. These overarching goals may affect whether or not regulators can achieve local social acceptance through risk management interventions in the sense that projects will be approved, regardless of the level of risk. The same is true in the United States, where individual landowners own the sub-surface rights and may therefore choose to permit HF activities even though a neighborhood or community may be opposed.

Other jurisdictions, meanwhile, have determined through public and expert consultation processes that *P5* is unattainable (that is, that HF could not be implemented with a level of tolerable risk (Wheeler et al. 2015)). The inherent geoscientific complexity and uncertainty of this technology, combined with increased population density, has resulted in moratoriums (e.g., Nova Scotia, New Brunswick, Newfoundland, New York). Further, in the province of Quebec, ongoing uncertainty is evident in a changing position for HF indicating that the precautionary principle (*P2*) is also at play. For example, the province of Quebec lifted a 5-year moratorium for HF with the 2016 *Act to implement the 2030 Energy Policy* (National Assembly 2016). Then, a 2018 amendment to the Act proposed to ban HF, a proposal that died when a provincial election was called (Canada Energy Regulator 2021).

The principle of equity (*P7*) is applicable to HF, given the range of hazards and potential effects, both at the local and global scales. The activities, by definition, may unfairly impact some individuals or groups, particularly those living in proximity to the extraction operations, with benefits accruing to others. In addition, there is limited local or Indigenous authority to manage the risks of HF. As with the other risk contexts, the risk management principles related to democratization, stakeholder engagement (*P8*) and openness and transparency (*P9*), are applied but could yet be improved (Larkin et al. 2018).

In the case of HF, the balancing of benefits and risks (*P3*), social acceptance of tolerable risk (*P5*) and equity (*P7*), may not be achievable. The risks are to the local populations and the benefits are largely to others. This is because HF is based on numerous large multi-well pad developments, creating environmental and human health hazards for some, but mostly without major social or economic benefit. Providing compensation directly to local communities has been discussed (IRGC: International Risk Governance Council 2014).

The principles of cost-effective risk mitigation (*P4*) and flexibility (*P10*) are also relevant. While unconventional oil and gas have been extracted for several decades, HF is classified as an emerging technology precisely because new risk management options continue to be developed (Larkin et al. 2018), and the technology is novel to many jurisdictions. The proponents and regulators in active jurisdictions are attempting to mitigate environmental and human health risks of HF such that the above-noted concerns for risk tolerance, equity, and balance in benefits and risks, as well as stakeholder engagement and transparency, may continue to be alleviated.

RC9: Pandemic outbreak (P2, P3, P4, P5, P7, P8-10)

A global infectious disease outbreak, such as the recent COVID-19 pandemic caused by the SARS-CoV-2 virus, may exert enormous public health impact: as of this writing, the World Health Organization (2022) estimates there have been over 545 million cases of COVID-19, and over 6 million deaths worldwide. Such outbreaks emerged as a result of an antigenic shift, wherein genetic components of viruses re-assort to produce a novel viral strain to which humans possess no appreciable immunity (Zambon 1999). If the disease can be transmitted easily between humans and manifest in diseases, a global pandemic may thus occur. Over the past one hundred years, the combined global burden of the 1918 Spanish flu, 1957 Asian flu, 1968 Hong Kong flu, and 2009 swine flu has amounted to tens of millions of infections, hospitalizations, and deaths, as well as billions of dollars in associated health and socioeconomic costs (Saunders-Hastings and Krewski 2016).

While the timing and characteristics of a global pandemic, particularly with respect to transmissibility and clinical severity, cannot be known in advance of emergence, the occurrence of the future pandemics are a virtual certainty. Because of the high uncertainty and high impact of global pandemics, preparedness efforts tend to favor the precautionary principle (*P2*) over risk-based decision-making (*P1*). The expectation of little lead time between emergence and local seeding of an outbreak indicates that interventions need to be implemented even in the absence of reliable epidemiological data charting the future course of the outbreak.

A pandemic has the potential to develop into a public health emergency where treatment resources become scarce. As such, there is a need to allocate resources in a manner that maximizes benefits and minimizes risks (*P3*) in a cost-effective (*P4*) way. However, ensuring an equitable distribution of these risks (*P7*) is crucial to an ethical pandemic response that fosters public trust, even where this may obstruct a maximally cost-effective strategy (Verweij 2009). Pandemic plans tend to emphasize the primary goal of saving lives (PHAC: Public Health Agency of Canada 2015), the most cost-effective approach to which tends to involve vaccination and other preventive efforts (Appleby 2020; Saunders-Hastings et al. 2016). While cost-effective prevention efforts are necessary components of pandemic preparedness, these should not be conducted at the expense of investment in treatment. Similarly, hospital triage protocols should promote the diversion of care to those in severe need that are most likely to recover, such as through restricting intensive care admission to those requiring mechanical ventilation, and potentially making resource-allocation decisions based upon likelihood of survival (Christian et al. 2006). However, this needs to be implemented in an open and transparent (*P9*) way alongside efforts to minimize service disruption altogether.

During the course of a pandemic, 'zero risk' (*P6*) is unlikely to be an attainable goal on a national, regional, or individual level. While protection from less transmissible and more clinically visible pathogens might be possible through border control and travel restriction measures, little evidence supports these control measures as being effective against influenza (Cowling et al. 2010; Yu et al. 2012), in part because individuals become infectious before they are symptomatic. Although travel restrictions were also implemented by many countries following the outbreak of COVID-19, simple public health measures, including handwashing, masking and social distancing, were seen to be effective in reducing the spread of COVID-19 (Talic et al. 2021). Challenges encountered in developing effective public health messaging in support of such measures, and in addressing vaccine hesitancy/refusal, underscore the need for effective public health communication to encourage uptake of good public health practices (Fullerton et al. 2022). A tolerable level of risk (*P5*) was being sought at public and organizational levels. Levels of tolerable risk are unclear and disputed, however, when taken in conjunction with the uncertain severity of future pandemics. This has important implications for trigger thresholds for emergency measures such as school and work closure. It might also impact levels of worker absenteeism, especially in essential, high-risk positions related to healthcare provision (Mitchell et al. 2012). Open and transparent (*P7*) stakeholder engagement (*P8*), combined with flexible response strategies that are agile to emerging data (*P10*), will be crucial to supporting a practical level of tolerated risk.

Risk management approaches to a pandemic outbreak tend to promote a utilitarian view that emphasizes benefit-risk considerations (*P3*). Massive government spending related to the COVID-19 pandemic also highlight the need for cost-effectiveness interventions (*P4*). While these are important components, it is necessary to consider the equitable distribution of risks and benefits (*P7*). A social gradient of risk was reported for influenza and should provide insight for targeted preparedness and response efforts (O'Sullivan and Bourgoin 2010). Most importantly, a lack of certainty should not prevent the implementation of intervention strategies to mitigate the potentially severe consequences of a pandemic outbreak (*P2*).

In the years ahead, research findings related to risk management of COVID-19 will attempt to shed light on a myriad of responses at the individual, public and organizational levels. New mRNA-based vaccines against COVID-19 developed in record time within a year of the outbreak of the pandemic in December, 2019 also raises questions of evaluating the risks of adverse effects of such vaccines (Alami et al. 2022) (*P5*), and of balancing the risks of vaccination against those of not being vaccinated (*P3*) (Wagner et al. 2021). Equity considerations (*P7*) also arise in ensuring vaccine access at the global, regional and local levels (Acharya, Ghimire, and Subramanya 2021; NASEM: National Academy of Sciences, Engineering and Medicine 2020).

RC10: Genetically modified foods (P1, P3–P5, P8–P10)

Genetically modified (GM) foods constitute a particularly controversial risk issue. GM foods include products "derived from crops bioengineered by recombinant deoxyribonucleic acid (rDNA) techniques" (Chao and Krewski 2008a, 208), reflecting products that have undergone changes to their DNA through a process called genetic engineering.

Concern likely arises from differential perception, understanding and acceptance of risks associated with GM foods. While Tsatsakis et al. (2017) found that the risk of the environmental impacts of GM plants exerted damaging effects on crop pervasiveness and biodiversity, the risk scenario presented herein focuses on the human health hazards associated with GM foods. Whereas some potential health risks attributable to GM foods remain controversial, targeted safety evaluations of specific crops such as blight-protected potatoes (Habig et al. 2018) and herbicide-resistant soybeans (Herman et al. 2018) demonstrated that GM foods introduced no additional risks. Similarly, Chao and Krewski (2008a; 2008b; 2008c) developed a risk-based classification scheme for GM foods, testing the framework using a panel of 20 food products reflecting a range of characteristics. No products were found to be associated with a high risk of adverse human health outcomes.

In 2013, the European Food Safety Authority (EFSA) conducted a systematic review of the scientific literature and national risk assessment frameworks relevant to GM food safety (EFSA: European Food Safety Authority 2013). This review found a degree of harmonization in risk assessment practices that is indicative of the underlying risk management principles relevant to GM foods. A common theme that emerged from this in-depth examination of 92 papers and 7 national approaches to GM risk assessment was an approach that relied upon identifying unintended health effects via comparison to the most genetically-similar, conventional (non-GM) food comparator. This comparative assessment of differences between GM foods and their conventional analogues reflects the principle of 'substantial equivalence' (see **Supplementary Material**) and underlies an approach based upon risk-based decision-making (*P1*) (Chao and Krewski 2008a; Kok and Kuiper 2003). However, there is a need for further consideration of when and how the precautionary principle (*P2*) needs to be integrated into risk assessment and profiling, particularly where a history of safe use cannot be established (Ladics et al. 2015).

The principle of balancing risks and benefits (*P3*) is also of notable relevance, with a benefit–risk analysis that considers the potential risks alongside the potential benefits in terms of both quality and quantity of nutrient-rich crops that reduce nutritional deficiencies (Chassy et al. 2007; Farrell et al. 2022). Similarly, the principle of cost-effectiveness (*P4*), particularly as it relates to the efficient use of time and resources to reduce regulatory bottlenecks, is highly relevant to GM food risk assessment. Strategies advocate for a flexible, tiered, trait-based approach that prioritizes foods of higher concern and reduces regulatory processing time for low-risk categories (Chao and Krewski 2008a; Deng et al. 2008).

While GM foods would be more appropriately considered in terms of 'tolerable' risk (*P5*) than 'zero' risk, it is understood that there is a very low risk tolerance in this sector (Lucht 2015). This is characteristic of risk scenarios involving technological engineering, which are often subject to public and political hesitation and stringent regulatory processes. It is less clear, however, what constitutes the appropriate regulatory threshold in light of the public's evolving risk tolerance. Risk assessment approaches including national regulatory strategies in Canada and the UK seek to either establish a 'history of safe use' for GM foods, or compare them to conventional products with a history of safe use, as noted above (EFSA: European Food Safety Authority 2013). This approach is meant to inform risk assessment data needs by building upon previous exposure in large populations. However, the concept of a 'history of safe use' is vaguely defined and may vary by jurisdiction, with the most widely applied risk acceptability threshold being that of "no observed adverse effect" (EFSA 2013).

While considerations of equity were not reported in any of the national regulatory frameworks, the principles of stakeholder engagement (*P8*), transparency (*P9*) and flexibility (*P10*) were recognized as being of importance. This was largely due to the public uncertainty surrounding GM foods (EFSA: European Food Safety Authority 2013) and the gap in risk acceptance among farmers, regulatory agencies and consumers (Lucht 2015). Publication of risk assessments and invited consultations in advance of regulatory decision-making in conjunction with a flexible risk assessment approach that considers data needs within the context of risk levels could support these efforts (Kuzma 2019).

Attributes of risk decision contexts

The 10 risk contexts analyzed above demonstrate that application of the 10 risk decision principles presented here are context-specific. Each of these contexts has certain attributes that favor the application of specific principles, as illustrated in Figure 1. Understanding the key attributes of different risk contexts that favor the application of specific principles might help to generalize the present discussion to a much broader suite of risk contexts.

Modifiable risks that are subject to low uncertainty constitute the domain of risk-based decision making (*P1*). As discussed in our explanation of P1 above, risk-based decision-making includes the

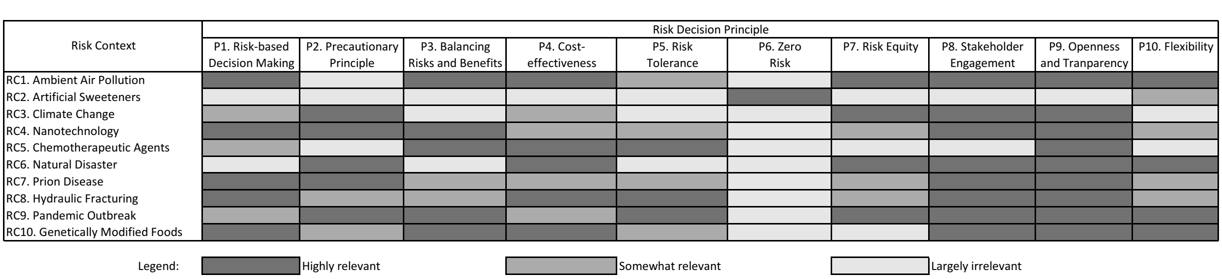

Figure 1. Application of risk-decision principles in different risk decision contexts.

careful use of "weight-of-evidence" wherein the total evidentiary record is integrated and assessed in order to the most accurate conclusions. An important practical consideration is the cost of risk mitigation; if the goal is to reduce the overall risk to society by the greatest possible amount, risk managers need to focus on the most cost-effective approaches to diminish risk. The principle of cost-effectiveness (*P4*) thus represents an important adjunct to the principle of risk-based decision-making.

The literature on the well-known precautionary principle (*P2*) concludes that a precautionary approach might be most appropriate when the potential consequences are quite serious, yet the realization of such consequences is highly uncertain. That is, the WoE in support of specific action(s) emerging from a risk-based process (*P1*) is inadequate in itself to justify specific action or inaction to the satisfaction of the decision-maker. The risk of inaction in such cases may be sufficiently great that some action is seen as essential to avoid possible future harm of significant proportions, even in the face of high uncertainty. The precautionary principle does have its limits, however; the definition includes the term "cost-effective" which provides a sense of what is reasonable. **High consequences** and **high uncertainty** thus represent two key attributes of risk decisions that favor the application of the precautionary principle. The downside of the precautionary approach is that the allocation of scarce risk management resources to risk issues that do not materialize results in an opportunity cost, had those same resources been re-allocated to more certain risk issues where a decrease in risk might have been achieved. It follows that indiscriminate application of the precautionary principle is inconsistent with the optimal allocation of available risk management resources.

Although balancing of risks and benefits (*P3*) seems intuitively reasonable when risk cannot be effectively eliminated or there are offsetting benefits, the **nature of the benefits** and **to whom the benefits accrue** have important implications when invoking this principle. For example, health risks may be offset by either health, social or economic benefits. Individuals might be more likely to accept health risks in exchange for health benefits, as exemplified by the case of a patient with a serious disease who is offered a possible cure in the form of a therapeutic intervention that itself carries the risk of serious side effects. Equally challenging is the case in which economic benefits accrue to individuals other than those incurring the risk, which can run counter to the principle of equity (*P7*).

The principle of cost-effectiveness (*P4*) seeks to achieve the greatest reduction in risk for a fixed investment of risk management resources. This principle can only be applied to risks that are **modifiable** and requires that risks be well-characterized, ideally with **low uncertainty**. However, too narrow a focus on cost-effective opportunities for risk reduction might lead to an imbalance in the burden of risk within society: cost-effective risk reduction that favors certain population subgroups over others may need to be considered in concert with the principle of equity and environmental justice (*P7*) in order to achieve an **equitable distribution of risks and benefits** in the general population.

The principle of risk tolerance (*P5*) is included among the 10 risk decision principles considered here in light of the fact that **most risks one faces in life cannot be completely eliminated**. Unfortunately, the concept of a 'tolerable' level of risk is an elusive one, with many authors having explored different concepts within the rubric of 'acceptable,' 'tolerable,' 'negligible,' or '*de minimus*' risk (Gross et al. 2010; Hrudey and Krewski 1995; Mumpower 1986; Peterson 2002). A key consideration here is the fact that concepts of 'tolerable' risk invariably invoke societal values, which may differ markedly both within and among societies. Nonetheless, some regulatory guidelines suggested ranges of risk on the order 1 in 100,000 to 1 in 10,000,000 that might be broadly 'tolerable', depending in part on whether exposure may occur in the occupational or general environments (Castorina and Woodruff 2003; Peterson 2002), although in other circumstances humanity elected to live with far higher risks such traffic accidents, smoking/recreational drug use or cosmetic surgeries. In some instances involving involuntary risks such as managing ambient air pollution (RC1), society lives with risks far higher than 1 in 100,000. The concept of 'virtual elimination' embodied in the Canadian Environmental Protection Act represents a more qualitative version of this principle, wherein a staged risk management action plan is implemented over a period of time to achieve incremental risk reduction, ultimately resulting in very small, but non-zero, levels of environmental contamination (CEPA 1999).

The zero-risk principle (*P6*) has been included among the 10 risk-decision principles primarily to serve as an idealized, yet largely-unattainable, goal for risks that cannot be completely eliminated. This principle has been operationalized in a number of contexts including the establishment of drinking water quality objectives under the Canadian Environmental Protection Act and the Toxic Substances Control Act that are unlikely to be achieved due to practical limitations in water quality treatment technologies (CEPA 1999; EPA 1976). In fact, should water treatment technology advance to the point where such idealized objectives are in fact achieved, it is likely that the objectives would be further reduced in a continual, technology-forcing effort to achieve even greater assurances of safety and equity.

The second dimension of the zero-risk principle applies in cases where the risks associated with a particular product or substance can be completely eliminated by banning the production or use of that agent. The Delaney Amendment to the U.S. Food & Drug Act, which precludes the addition of substances to the food supply with carcinogenic potential, would be such an example (NRC: National Research Council 1982). In contrast, prescription drugs that may confer great benefits to certain patients may be subject only to certain market restrictions in the presence of serious side effects.

Equity in risk-decision making (*P7*) is an inarguable goal in all its dimensions, including the related concept of environmental justice. However, the resolution of inequities related to risk management is a long-term goal and is often challenging and expensive if not logistically-impossible to achieve. This is the case when socioeconomic inequities are addressed through economic, cultural and political change. Regardless of the underlying forces responsible for inequity in risks and the extent to which inequities can be resolved, the balancing of risk and benefit across society remains a goal consistent with fundamental human rights.

Although the remaining three principles *P8*, *P9*, and *P10* are almost universally applicable, openness, transparency and stakeholder engagement might compromise the management of risk issues such as anti-terrorist initiatives and national security. However, setting such exceptions aside, openness and transparency are consistent with fundamental principles of democracy, while stakeholder engagement further serves to promote consideration of diverse perspectives on risk and engender public support for risk decisions. Most risk decisions need to include an element of flexibility, allowing for a review of past decisions in the light of relevant new information. Nonetheless, inflexibility may be appropriate in some contexts, such as the strict application of the Delaney Amendment for carcinogenic food additives, regardless of their organoleptic, preservative, nutrient or other qualities of the additive. Looking to the future, there may be merit in formulating an additional principle targeting risk ethics (ethical considerations arise both with respect to risk assessment, as in attributes of methodologies, engagement, and disclosure of uncertainties; and in risk management, as in ensuring an equitable distribution of both risks and benefits across society (Hansson 2018); Koivisto and Douglas 2015; Rozell 2018). In earlier work, Ersdal and Aven (2008) explored ethical considerations in the application of cost-effectiveness (*P4*) and the precautionary principle (*P2*), as well as the subsidiary ALARA principle discussed in Supplementary Material.

Conclusions

While societies throughout the history of mankind have confronted a wide array of health, environmental and other risks, systematic approaches to risk assessment and risk management have only begun to emerge within recent decades. Although increasingly sophisticated methods in risk science have greatly expanded our ability to assess risks in scientific terms, risk management decisions are often complex in the presence of different considerations regarding how the best risk decisions need to be made.

This article proposes 10 fundamental principles of risk management decision-making that are intended to encourage discussion and provide guidance to decision-makers confronted with complex risk decisions. In most real-world decision contexts, more than one principle will be relevant. Although each principle has merit in its own right, not all principles are equally-applicable in different risk decision contexts.

In some cases, there may be a dominant principle that is more relevant than others. For example, with climate change risk reduction, the precautionary principle is generally recognized as being the dominant risk decision principle. Conversely, in considering air quality management, the principles of risk-based decision-making and cost-effectiveness might be viewed as being equally applicable.

Since different principles may lead the decision-maker to different decisions, it is important to appreciate the nature of the risk decision context and to identify those principles that are most relevant in that context. By analyzing 10 different scenarios spanning a wide range of risk issues, which decision-making principles may be most appropriate were explored in different risk contexts and the practical applicability of the principles proposed demonstrated. Since more than one decision-making principle might be relevant in most risk contexts, judgment is required in arriving at an appropriate strategy or strategies to manage specific risks.

While we have stopped short of prescribing which types of principles will be most relevant based upon common attributes of a group of risk scenarios, this might be investigated further in future research involving a larger number of risk decision contexts possibly with the use of multivariate data analytic methods to associate principles with attributes of risk decisions. In the interim, the principles articulated here and the illustrations of their application in diverse risk decision contexts might assist risk managers charged with making critical risk decisions on behalf of society. In making such decisions, the importance of experience and judgment is again emphasized in reaching the right balance among the 10 principles presented, as well as the reality of recognizing the socio-political context in which all risk decisions are ultimately made.

Notes

1. The lifetime tolerable benchmark risks of 10^{-5} to 10^{-7} have been proposed primarily for risks associated with toxic chemicals in the environment, and do not necessarily apply to other risk contexts.

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