NEXTGEN DECISION-MAKING
FOR HEALTH AND ENVIRONMENTAL RISKS

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PREFACE

Approvals obtained to conduct the research

The research described in Chapter 4 (article 2) received ethical approval from the University of Ottawa's Office of Research Ethics and Integrity (#H-11-23-9868), Ottawa, Canada. Ethics approval was not required for the other chapters included in this thesis.

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ABSTRACT

Risk decision-making has evolved from specifying the main steps involved in risk assessment and how this links to the overall analysis and governance of risks, to complex and fully integrated risk science frameworks. With the advancement in science and technology, there has also been a significant change in the types of evidence available for identifying and characterizing hazards, determining potential exposure profiles, and evaluating the probability of health and environmental risks. These efforts have resulted in several publications focused on providing precision on specific areas within the risk assessment-management process and new approaches for undertaking risk assessments. There has also been a transition to more complex and holistic risk science frameworks, methodologies, and guidelines. The term next generation risk decision-making is used to capture these contemporary approaches. Further, while there is specific guidance for a particular approach, limited attention has been paid to the underlying considerations for developing these contemporary and more complex and holistic approaches to risk decision-making.

In this thesis, we address this knowledge gap through an embedded research model designed to determine the ongoing modernization efforts and approaches to next generation risk decision-making within both the Canadian and international regulatory context (national and federal level). The embedded research model is coupled with an independent knowledge mobilization and transfer strategy that relies on the engagement and collaboration, with diverse experts and thought leaders, to determine fundamental risk and ethical principles for risk decision-making. Further, a scoping review provides a mechanism to visualize the evolution in risk science over the last fifty years, and characterize best practices and ten key attributes for risk decision-making. To help integrate our findings, we rely on a realist paradigm to generate an *a priori* theoretical construct and *kaleidoscope model*, which translates the principles, best practices, and attributes into key considerations for developing an approach to next generation risk decision-making. Our findings are widely applicable to any organization or governmental body interested in learning about next generation risk decision-making, including adapting or developing their own approach to risk decision-making, informed by the results presented in this thesis. The embedded research model, knowledge mobilization and transfer strategy, realist paradigm, and publication in open science, peer-reviewed journals ensures that our findings are available for the broader community interested in next generation risk decision-making.

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> "What we learned in the past and what we're struggling with today might be the basis for something wonderful in the future." Jennifer Hollington, Public Sector Senior Executive (Ret.), Health Canada

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LIST OF ABBREVIATIONS

ALARP	As Low as Reasonably Practicable
AMR	Antimicrobial Resistance
APCRA	Accelerating the Pace of Chemical Risk Assessment
APVMA	Australian Pesticides and Veterinary Medicines Authority
AOPs	Adverse Outcome Pathways
ATPs	Advanced Therapeutic Products
BroadCAST-3Cs	Core, Audience, Spokesperson, Timely – Context, Clarity, Concise
CAAT	Center for Alternatives to Animal Testing
CaCVAM	Canadian Centre for the Validation of Alternative Methods
CARE	Collective benefit, Authority to control, Responsibility, and Ethics
CCA	Council of Canadian Academies
CCAAM	Canadian Centre for Alternatives to Animal Methods
CEPA	Canadian Environmental Protection Act
CF	Cystic Fibrosis
CIHR	Canadian Institutes of Health Research
COMc	Context, Mechanism, Outcome configuration
CMP	Chemicals Management Plan
DMF	Decision-Making Framework
DSL	Domestic Substance List
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EP	Ethical Principles

EU	European Union
FAIR	Findable, Accessible, Interoperable, and Reusable
FAO	Food and Agriculture Organization
GAP	Global Action Plan
HC	Health Canada
HEADLAMP	Health and Environmental Analysis for Decision-Making Project
HECSB	Healthy Environments and Consumer Safety Branch
HESI	Health and Environmental Sciences Institute
HTA	Health Technology Assessment
IATA	Integrated Approaches to Testing and Assessment
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IVIVE	In Vitro to In Vivo Extrapolation
IRGC	International Risk Governance Council
IST	In Silico Toxicology
LSCA	Frank R. Lautenberg Chemical Safety for the 21st Century Act (or new TSCA)
MAUT	Multi-attribute Utility Theory
NAFTA TWG	North American Free Trade Agreement Technical Working Group
NAMs	New Approach Methodologies
NAPs	National Action Plans
NGRA	Next Generation Risk Assessment
NGRDM	Next Generation or NextGen Risk Decision-Making

OCAP®	Ownership, Control, Access, and Possession
OECD	Organisation for Economic Co-operation and Development
OH	One Health
OSF	Open Science Framework
PCCRARM	The Presidential/Congressional Commission on Risk Assessment and Risk Management
PCPA	Pest Control Products Act
PHAC	Public Health Agency of Canada
PMRA	Pest Management Regulatory Agency
PODs	Point of Departures
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
PSCI	PETA Science Consortium International
QSAR	Quantitative-structure activity relationship
QUAL	Qualitative
QUAN	Quantitative
RCC	Regulatory Cooperation Council
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REB	Research Ethics Board
SWOT	Strengths, Weaknesses, Opportunities, and Threats
TEA	Transforming the Evaluation of Agrochemicals
TSCA	Toxic Substances Control Act
US EPA	United States Environmental Protection Agency
US FDA	United States Food & Drug Administration
UX	User Experience

WC	World Congress
WHO	World Health Organization
WoE	Weight of Evidence

CHAPTER 1: INTRODUCTION

1.1 Rationale

Every day, decisions are made regarding potential health and environmental risks. These risk issues include possible exposures to hazardous substances and the likelihood of such events resulting in adverse health consequences along with weighing the benefits and risks from intentional exposures to therapeutic products. Institutions, such as regulatory authorities, are also responsible for effectively communicating risk management strategies so that interested and affected parties can make informed decisions.

The risk decision-making process is part of a robust and well-defined approach designed to identify the risk issue of concern and context, evaluate the available facts, provide strategies to manage health and environmental risks, and communicate the information in an efficient and timely manner. To ensure an open, consistent, systematic, and transparent decision-making process, several national and international organizations have public-facing risk decision-making frameworks. These documents have continued to expand from foundational elements, such as the internationally recognized steps to risk assessment, to incorporating additional factors that further define the risk decision-making context (Bhuller et al., 2025b).

The evolution and transformation of available frameworks also relies on advances in aspects such as science and technology, public and political interest, and regulatory applications. A better understanding of the diverse factors for risk decision-making has resulted in more complex approaches to risk decision-making, including more recent holistic frameworks. The term next generation risk decision-making (NGRDM) is used to capture these contemporary strategies. The complex and fully integrated ONE Health approach to risk assessment, which explores the interactions between human, environment, and animal health, is one example of NGRDM (Johnson & Degeling, 2019; National Academies of Sciences Engineering and Medicine, 2023; Public Health Agency of Canada, 2024). Ongoing research and development initiatives also continue to provide opportunities to modernize existing strategies by considering the advances in the current state of science, knowledge, and the decision-making context. Consequently, there has been a continuous flow of knowledge creation, mobilization, and dissemination using diverse regulatory and non-regulatory approaches.

While conventional and modern frameworks provide insights on foundational and more contemporary elements related to the risk assessment-management paradigm (Bhuller et al., 2025b), there is a lack in the availability of a consolidated listing of key considerations – attributes, best practices, and other scientific or extra-scientific factors - for developing approaches to NGRDM. In this thesis, I address this limitation by using an embedded research model (Vindrola-Padros et al., 2017) coupled with an independent knowledge mobilization and translation strategy (Canadian Institutes of Health Research, 2012; Health Canada, 2017).

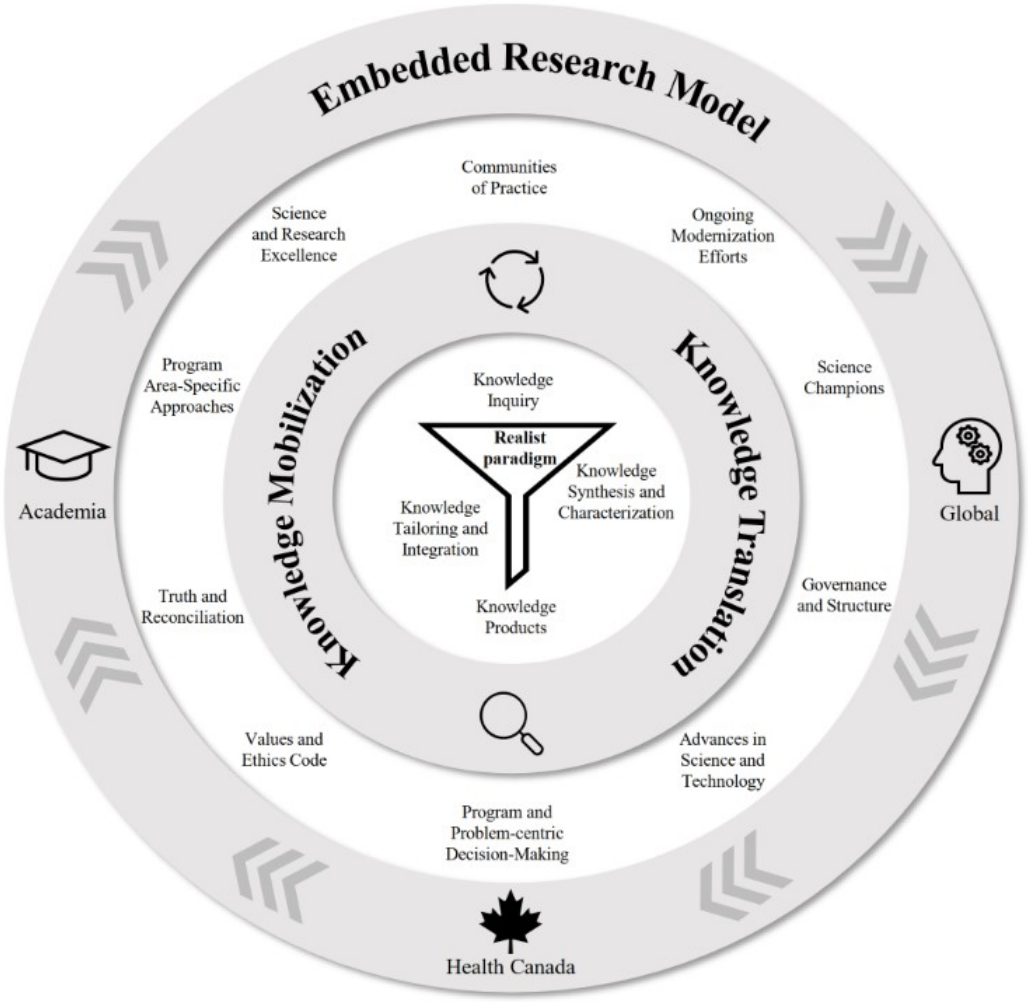

Figure 1 – Conceptual framework for developing considerations for next generation approaches to risk decision-making.

The embedded research model creates the space for engaging experts - Health Canada, global, and academia - on a discourse based on their lived experiences related to risk decision-making. This includes the role of values and ethics, advances in science and technology, ongoing

modernizing efforts, and other elements identified in **Figure 1**. The insight gained from these discussions is coupled with the knowledge mobilization and translation steps (central core) thereby incorporating additional knowledge (e.g., from the published literature) on risk decision-making.

The central core also includes the "knowledge to action" funnel (Graham et al., 2006) where the review, synthesis, characterization, tailoring, and integration of data relies on a realist paradigm (Pawson et al., 2004; Pawson et al., 2005). The integration of the qualitative and quantitative data results in the creation of several, mixed methods-based knowledge products/articles. Consequently, this creates the overall design and conceptual framework to carefully explore the ongoing modernization efforts and strategies resulting in NGRDM within the Canadian and international regulatory and non-regulatory context (national/federal level). Further, it also provides the overarching process for engaging and collaborating with diverse leaders, global thinkers, and experts, and examining the evolution in risk decision-making principles, procedures and best practices as described in the published literature and other open source documents.

The final chapter (Chapter 10) includes a **Glossary** for the key terms relevant to this thesis, including this realist paradigm-based definition for NGRDM:

> NGRDM is an iterative process linking the intersections between the research, regulatory, and risk **contexts** and an institutional mindset and culture, which, as an underlying **mechanism**, integrates a population health approach by maximizing upstream and downstream attributes for risk decision-making and uses a ONE Health lens to attain the **outcome** of promoting and protecting the health of humans, animals, and the environment.[1]

Chapter 6 includes additional details on how the realist-paradigm provides the worldview for developing and analyzing the derived context, mechanism, and outcome configuration (CMOc), which eventually creates the definition provided above. Chapter 2 provides additional insights on the research methodology and the use of the embedded research model, knowledge translation, and realist paradigm for the thesis-related activities.

[1]Within this context, upstream and downstream determinants includes risk decision-making attributes and best practices relevant for establishing the risk culture and a principle-based mindset. Further, a ONE health lens accounts for the multiple health determinants, dimensions, and interventions relevant for developing a NGRDM approach.

1.2 Objectives

This thesis examines the decision-making process for health and environmental risks. Its goal is to develop a theory-based, integrated model with key considerations for developing a NGRDM approach. It is hoped that the model and considerations will be of use to regulatory authorities and the broader science and risk-based communities who are interested in modernizing and strengthening risk decision-making processes. To achieve this overarching goal, this thesis specifically addresses the following objectives:

1) To critically examine and determine the key risk and ethical principles for health and environmental risk decision-making;
2) To explore the evolution in risk analysis and science (see **Glossary** for definitions), over the last fifty years, and use this knowledge to characterize key attributes for risk decision-making; and
3) To apply the realist paradigm to generate an *a priori* theoretical construct and model, which translates the principles, best practices, and risk decision-making attributes into considerations for developing an approach to NGRDM.

1.3 Thesis organization

This is an article-based thesis and is organized as follows:

Chapter 2 provides background information on the following key concepts: (i) rationale for using an embedded research model, knowledge translation approach, and realist paradigm (and when applicable, review/synthesis) as the overarching conceptual framework supporting the underlying research methodology for this thesis; (ii) importance of building awareness and understanding of risk decision-making using existing approaches and theories; and (iii) development of the underling research questions using an iterative approach, which includes relying on expert input and recommendations.

Chapters 3 and *4* addresses the first research objective stated above. The first article uses the embedded research model by engaging Health Canada staff who are interested in further exploring the key principles for risk decision-making (Bhuller et al., 2024). Building from a realist review/synthesis of established risk principles, a realist paradigm is used to generate an *a priori* hypothesis which is tested through this original research. The knowledge product from this

work is the identification and characterization of risk principles into distinct categories, which is further visualized using the *Systems Iceberg Model* (Sheffield et al., 2012). The second article engages experts from diverse sectors and uses the knowledge translation approach to create the *projector model* for ethical principles and considerations relevant for risk decision-making (Bhuller et al., 2025a).

Chapter 5 is a scoping review of risk assessment, management, and decision-making frameworks spanning over fifty years, which addresses the second research objective. This review analyzes thirty-nine publications to help visualize the evolution and transformation in risk decision-making over this period. Further, the analysis also results in the identification and characterization of best practices and ten attributes for risk decision-making (Bhuller et al., 2025b).

Chapter 6 adapts the knowledge synthesized from the previous chapters to address the final objective. Using a realist paradigm-derived CMOc, a further tailoring and integration of the risk decision-making principles, best practices, and attributes results in the creation of a *kaleidoscope model*. This model builds awareness and understanding of NGRDM by providing key considerations to help characterize the context, mechanism (underlying risk culture and behaviour), and desired outcome for NGRDM. The *a priori* hypothesis resulting in the model and CMOc is further explored by analyzing top-down, bottom-up, and risk science approaches to NGRDM (Bhuller, 2025c).

Chapter 7 is an overall discussion which synthesizes the key results from the four papers, explains how this work contributes to the advancement of population health, and lays out the next steps in advancing NGRDM.

Chapter 8 is an appendix containing a high-level summary of three supplementary articles, included in this chapter and prepared during the course of writing this thesis.

Chapter 9 is the glossary of key terms used in this thesis.

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CHAPTER 2: BACKGROUND

Chapter overview

As introduced in Chapter 1, this thesis generates various knowledge products to support the construction of the *kaleidoscope model* and key considerations for developing approaches to next generation risk decision-making (NGRDM). This chapter provides background information on the process used to establish the various methods and research activities required to assemble the knowledge for creating this model and considerations. This includes the following key concepts: (i) the rationale for using an embedded research model linked with the knowledge translation steps and reliance on a realist paradigm for testing *a priori* hypothesis and reviewing/synthesizing available evidence and knowledge mobilized from various research activities; (ii) the importance of key risk decision-making principles, theories, best practices, and frameworks in developing the considerations for NGRDM; and (iii) the key research questions for addressing the objectives identified in the first chapter of this thesis.

2.1 Research methodology

2.1.1 Embedded research model

This thesis relies on a conceptual framework (**Figure 1**, **Chapter 1**) which supports the methodological approach for co-producing and mobilizing knowledge by engaging diverse experts using a collaborative process. An embedded research model (Vindrola-Padros et al., 2017) was selected as it provided an ideal mechanism to build this type of culture of collaboration and partnership between the principal researcher (Yadvinder Bhuller; YB) and the diverse experts/participants. Further, this type of research model provided an opportunity for YB to be "embedded" within the risk science community, primarily at Health Canada, and assume an observer-participant role thereby enabling the research approach and results to be shaped by the ethnographic and lived experiences of all participants (Mills & Birks, 2014).

To create a bridge between the regulatory and academic world, the Deputy Minister and the Executive Committee members of Health Canada endorsed the embedded research model. These senior officials considered the model's strengths in supporting this independent research endeavour while providing a mechanism to observe and mobilize knowledge on the ongoing modernization efforts and advances in risk decision-making within this federal government

department. Further, they acknowledged how the Canadian Institutes of Health Research's strategy for better integrating of evidence into health decisions includes advancing the science and practice of knowledge mobilization (Canadian Institutes of Health Research, 2023). Consequently, several of the research activities incorporate active participation and co-authorship by Health Canada participants along with other national and global experts. There was also an internal steering committee with senior Health Canada officials who were nominated to provide input based on their expertise, regulatory perspective, and experience on various local, national, and international health and environmental issues.

The embedded research model's collaborative approach also supported engagement with experts from academia and the global stage (e.g., leaders of international organizations) throughout all phases of this thesis. For example, the scoping review's protocol (Chapter 5) was developed and refined in consultation with the University of Ottawa's Population Health research librarian. Prior to commencing the review, the study protocol was also published in the *Open Science Framework* (15 September, 2023), accessible at https://osf.io/gnyfk. Another example, was the use of a research study, participant-derived framework for establishing the *projector model* for ethical principles and considerations for risk decision-making (Chapter 4). The ability for the diverse experts to shape the various research activities was also well-aligned with the core requirement of participatory research (Abma et al., 2017; Baum et al., 2006) and was another consideration for selecting the embedded research model for the thesis-related activities.

2.1.2 Knowledge mobilization and translation

Several organizations see the value in integrating evidence, advancing science, and adapting best practices through embedded research models linked with knowledge mobilization and translation (Abma et al., 2017; Burger, 2022; Canadian Institutes of Health Research, 2012; Graham et al., 2006; Health Canada, 2017). This link is visualized through the icon of a funnel found in the core of the conceptual framework for this thesis (**Figure 1**, **Chapter 1**). Specifically, once new knowledge is mobilized using the various activities of the embedded research model (outer circle), which includes engagement and collaboration with diverse experts, the "knowledge to action" funnel (Graham et al., 2006) creates the direction and flow between the knowledge translation steps and products (i.e., the research articles).

The knowledge translation steps – knowledge inquiry, synthesis and characterization, and tailoring and integration – also guided the establishment of the key milestones and deliverables for this thesis. For example, the knowledge inquiry stage included a baseline, pre-thesis, research ethics board-approved (University of Ottawa and Health Canada) student study designed to establish the networks with the various communities of experts. This work also helped identify how Health Canada relies on a conventional, decision-making framework while modernizing their risk decision-making efforts using a top-down approach. The scoping review (Chapter 5) further verified this insight when analyzing the Canadian and other risk decision-making frameworks (Bhuller et al., 2025).

For this thesis, the knowledge synthesis and characterization steps included articles identifying and characterizing risk and ethical principles for decision-making (Chapters 3 and 4), best practices and attributes for risk decision-making (Chapter 5), and additional, supplementary work pertinent for this thesis (Chapter 8). Integration of this work resulted in the development of the final paper (Chapter 6) on the key considerations for NextGen risk decision-making (NGRA). Linking the embedded model with the knowledge translation steps also supported the use of mixed methods (quantitative and qualitative data) and a realist worldview for integrating and translating the mobilized knowledge into the final articles.

While not shown in **Figure 1**, the knowledge funnel also provided a staggered timeline for publishing each knowledge product/article. Each publication resulted in an opportunity for considering additional expert input based on the comments from the journal's review process. The published articles also helped create the underlying building blocks for the final knowledge product/paper provided in Chapter 6.

2.1.3 Realist paradigm

In considering the appropriate paradigm for this thesis, a key aspect was determining a worldview supporting the translation of the knowledge mobilized from experts and research participants along with relevant empirical, qualitative and quantitative data (e.g., from the published literature). Further, recognizing the existing wealth of information on this subject matter, it was important to analyze and build from established frameworks, guidance documents, and other reports relevant to risk decision-making. Consideration of existing material also provided a mechanism to acquire additional awareness and understanding of the complexities

and how several factors, including key principles and theories, are relevant for risk decision-making. Consequently, research paradigms such as realism (Blamey & Mackenzie, 2016; Flynn et al., 2019; Gilmore et al., 2019; Greenhalgh et al., 2015; Kazi, 2003; Pawson, 2017; Pawson et al., 2005; Pawson & Tilley, 2004; Porter & O'Halloran, 2012; Salter & Kothar, 2014; The RAMESES II Project, 2017; Wong et al., 2017) and pragmatism (Kaushik & Walsh, 2019) were considered as providing a suitable approach for incorporating qualitative and quantitative information.

Ultimately, the decision to rely on a realist approach was based on this paradigm's ability to support the integration of data using a realist review/synthesis of previously completed, mixed methods research activities (Creswell & Clark, 2018; O'Sullivan & Khan, 2020). Further, as a theory-driven approach, it provided a worldview for recognizing how actions (risk decision-making) are dependent on factors such as the context and an opportunity to develop and test *a priori* hypothesis (Blamey & Mackenzie, 2016; Kazi, 2003; Pawson, 2017; Pawson & Tilley, 2004; Porter & O'Halloran, 2012; Salter & Kothar, 2014). Therefore, a realist review/synthesis of established risk principles was selected for the principles paper (Chapter 3) as it also provided a mechanism to develop and test a realist paradigm-based *a priori* hypothesis. Similarly, the final paper also relied on a realist paradigm-derived context, mechanism, and outcome configuration (CMOc) to develop and test an *a priori* hypothesis for key considerations relevant to NGRDM (Chapter 6).

2.2 Risk decision-making principles, theories, and frameworks

The identification of the three initial articles of this thesis – relevance and feasibility of risk principles (Chapter 3), ethical considerations and principles for risk decision-making (Chapter 4), and the scoping review providing the evolution, best practices, and ten attributes of risk decision-making (Chapter 5) – is based on the recommendation of several experts who were consulted during the knowledge inquiry phase. These experts noted how these areas would serve as important building blocks for developing the final and fourth paper on the considerations for NGRDM (Chapter 6). Several of these experts also highlighted how risk decision-making is a function of additional and diverse factors including institutional values, public perception, paradigm shifts (e.g., towards non-animal testing solutions), and structures ranging from simple to complex and integrated approaches to risk assessment and management.

The importance of considering fundamental risk principles and the need to further identify and characterize ethical principles for risk assessment and management were also identified by Krewski and colleagues in the seminal publication *Principles of risk decision- making* (Krewski et al., 2022). This work also made reference to "decision theory" when listing the keywords for the article and the ten guiding principles built from previous work related to establishing integrated frameworks for risk management and population health and next generation risk science (Krewski et al., 2007; Krewski et al., 2014; Westphal et al., 2017).

Recognizing the intersections between risk decision-making principles and the multitude of factors affecting real-world decision-making, it was also considered important for this thesis to identify pertinent theories when reviewing the published information on risk decision-making. This included analyzing theories such as the *Public Administration - Decision Theory* (Frederickson et al., 2012), which incorporates Herbert A. Simon's insights on *Administrative Behavior, Administrative Theory*, and *Bounded Rationality* (Schwarz et al., 2022; Simon, 1980, 1997a, 1997b), to help understand elements such as the risk culture and behaviour relevant to NGRDM.

When developing the protocol for the scoping review (https://osf.io/gnyfk), the measured variables incorporated the expert input and recommendations for considering a diverse range of factors for data extraction including the core values and principles in risk decision-making, structures, and underlying theories. This input also played a key role in establishing the research questions for this thesis.

2.3 Research questions

The objectives for this thesis included the development of the *kaleidoscope model* with the key considerations for developing a NGRDM approach. This model and the other objectives (Chapter 1) were addressed through activities and articles aimed at addressing the following research questions:

1) What are the decision-making principles, for health and environmental risks, recommended by experts and considered to be important and feasible by front-line staff from Health Canada (e.g., risk assessors)?
2) What are the key ethical considerations and principles involved in the assessment and management of health and environmental risks?

3) What are the attributes of a comprehensive health and environmental risk assessment and management decision-making framework?
4) What are the considerations for NGRDM and how are these proposed elements of an integrated framework practical for contemporary and next-generation decision-making of health and environmental risks?

The subsequent chapters of this thesis provide the articles in chronological order; i.e., Chapter 3, article 1 addresses research question 1, Chapter 4, article 2 addresses research question 2, Chapter 5, article 3 addresses research question 3, and Chapter 6, article 4 addresses research question 4.

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CHAPTER 3: ARTICLE 1. Relevance and feasibility of principles for health and environmental risk decision-making

Chapter Overview

This chapter addresses the first research objective (Chapter 1) and question (Chapter 2) through an original research article based on a realist review/synthesis of relevant risk principles, as identified by experts, followed by a workshop with front-line staff from Health Canada (e.g., risk assessors). The workshop's aim was to determine the pragmatic application of the expert-derived decision-making principles for health and environmental risks. The paper goes further by classifying the principles into distinct categories (e.g., universal principles) and by applying them to global health and environmental issues.

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3.1 Abstract

Globally, national regulatory authorities are both responsible and accountable for health and environmental decisions related to diverse products and risk decision contexts. These authorities provided regulatory oversight and expedited market authorizations of vaccines and other therapeutic products during the COVID-19 pandemic. Regulatory decisions regarding such products and situations depend upon well-established risk assessment and management steps.

The underlying processes supporting such decisions were outlined in frameworks describing the complex interactions between factors including risk assessment and management steps as well as principles which help guide risk decision- making. In 2022, experts in risk science proposed a set of 10 guiding principles, further examining the intersection and utility of these principles using 10 diverse risk contexts, and inviting a broader discourse on the application of these principles in risk decision-making. To add to this information, Canadian regulatory practitioners responsible for evaluating health and environmental risks and establishing policies convened at a Health Canada workshop on *Principles for Risk Decision-Making*. This review reports the results derived from this interactive engagement and provides a first pragmatic analysis of the relevance, importance, and feasibility of such principles for health and environmental risk decision-making within the Canadian regulatory context.

Keywords: Risk decision-making; risk principles; regulatory context; risk science; concept mapping

3.2 Introduction

Regulatory risk decision-making is a complex process requiring careful consideration of multiple factors related to the underlying hazard, exposure pathways, regulatory and public health context, and understanding of the issue and potential adverse health or environmental risks. Several national authorities have published risk assessment guidance documents (APVMA 2019; EFSA 2024; Government of Canada, 2020; United States Environmental Protection Agency (EPA) 2014; United States Food & Drug Administration (FDA) 2024) and overarching risk management frameworks (Health Canada 2000; Pest Management Regulatory Agency 2021) describing the risk evaluation and decision-making processes. Some of these frameworks, such as Health Canada's decision-making framework established over two decades ago, include key principles which are relevant for health and environmental risk decision-making (Health Canada 2000).

With advances in several areas of science and technology, including risk science, there has been a steady growth in the publication of scientific articles focusing on how to incorporate such developments into the regulatory risk assessment process. A recent example is new approach methodologies (NAMs) (Clippinger et al. 2021, 2022; Hilton et al. 2022; Sewell et al. 2021; Stucki et al. 2022) and frameworks to help integrate NAMs (Krewski, Saunders-Hastings, Baan,

et al. 2022a).[1] Other examples include the need for greater regulatory use of modern science (Council of Canadian Academies 2012; Fentem 2023; Fentem et al. 2021; Zuang et al. 2023) along with considering next gen- eration risk assessment (NGRA) frameworks (Bhuller et al. 2021; Bury et al. 2021; Cote et al. 2012; Gilmour et al. 2022; Goodman et al. 2014; Krewski et al. 2014, 2020; Parish et al. 2020; Tannenbaum 2012). Experts advocating the use of NAMs and NGRA frameworks emphasize the importance of building confidence with these methods (ICCVAM 2018; van der Zalm et al. 2022) and articulating the underpinning principles for conducting modern risk assessments for cosmetic ingredients using NAMs (Dent et al. 2018).

Krewski and colleagues (2022b) noted the manner in which scientific approaches employed for characterizing health and environmental risks are described in the literature; however, the fundamental principles of risk decision-making are less well articulated. To address this limitation, Krewski et al. (2022b) relied upon their collective lived experience to create and define 10 guiding principles of risk decision-making. The practical application of these key risk decision-making principles was further described and assessed using 10 different risk decision contexts. These investigators also selected and characterized several risk contexts which provided a diverse range of complex, contemporary, and real-world examples involving environmental pollution, food safety, therapeutic products, emerging pathogens, new technologies, and natural disasters. The qualitative analysis undertaken by these individuals identified how an understanding of the key attributes of the risk decision contexts might favor the application of certain principles most relevant for specific risk decisions. To further evaluate and understand the fundamental principles underlying important risk decisions, additional discussion, analysis, and debate were also encouraged by these experts.

From a regulatory perspective, an embedded research and knowledge mobilization model (Canadian Institutes of Health Research 2012; Vindrola-Padros et al. 2017) provided an opportunity for engagement of Health Canada experts in regulatory science through workshops on risk decision-making and communication. One of the results of this engagement was the generation visually of an integrated risk decision-making process, which included a number of risk decision-making principles suggested by these experts (Bhuller and Trevithick-Sutton 2024). Another outcome of these discussions was a more comprehensive appreciation of how specific

[1]NAMs is term broadly used to encompass non-animal methods, alternatives, and technologies that reduce reliance on traditional animal toxicology data while focusing efforts on more humane and human-relevant science.

principles may be embedded in legislative statutes; although federal statutes in Canada generally do not include all the principles on which risk decisions should be made, some statutes do allude to what are essentially decision-making principles. For example, the *Pest Control Products Act* (PCPA) (Government of Canada 2024a) and the *Strengthening Environmental Protection for a Healthier Canada Act* (Environment and Climate Change Canada 2023a; Government of Canada 2024b) include specific requirements related to the precautionary principle. The PCPA also requires all pest control products to have acceptable health and environmental risks and value when utilizing these products in accordance to any proposed or final conditions of registration. The assessment of value includes product efficacy, intended effect on host organisms, and contribution toward the health, safety, and environmental benefits in addition to social and economic impacts of pest control products, thereby considering both risks and benefits. Regardless of the extent to which decision-making principles are codified in federal legislation, Health Canada's decision-making framework, established in the year 2000, provides a consolidated listing of 10 principles. These have been followed by a more recent and contemporary list of another 10 fundamental risk decision-making principles articulated by Krewski and colleagues (2022b).

The aim of this review is to expand on previous findings through a mixed methods study with regulatory practitioners from Health Canada. These front- line staff are responsible for conducting health and environmental risk assessments and establishing risk management policies and strategies. The underlying objectives of this paper are 3-fold to: (1) quantitatively characterize the relevance of health and environmental risk decision-making principles using the same 10 risk decision contexts discussed by Krewski and colleagues (2022b); (2) further evaluate the principles by separating relevance into two factors, namely importance and feasibility where one would anticipate some degree of correlation. It is noteworthy that the interaction between these two factors is relied upon to indirectly assess the relevance of risk decision-making principles; and (3) propose additional types of health and environmental risk decision-making principles which includes those that are independent of the risk decision context (i.e., universal principles). Through this analysis it is intended to enhance our understanding of how regulatory practitioners and frontline staff perceive, understand, and apply health and environmental risk decision-making principles in real-world decision-making scenarios.

3.3 Risk-based regulators as a foundational principle

Regulatory decision-making regarding health and environmental risks requires regulatory practitioners to consider several factors including advances in science, technology, policy, the political and international landscape, and public perception of risk (Health Canada staff, pers. comm., February 17, 2022). Prior to further discussing potential risk decision-making principles, it is therefore important to first determine the type of regulatory approach that best suits the underlying processes to support such decisions.

In *Fundamentals of Regulatory Design*, Dr. Malcom K. Sparrow describes several factors and models on which to establish a connection between modern regulators and "risk-based regulators" (Sparrow 2020). Sparrow (2020) explains how legal (regulatory approaches aimed at addressing illegal situations) and expert (regulatory strategies to reduce or prevent harm) models play important roles in regulatory decision- making processes designed for addressing risk (hazard and exposure); however, his findings demonstrate how, over time, regulatory authorities are shifting toward the use of an expert model. Further, while program-centric approaches continue to be pertinent for addressing contemporary issues, Sparrow (2020) justifies the utility of a more holistic strategy by incorporating problem-centric approaches. This investigator also describes the importance of considering all available regulatory tools needed to address a harmful situation, which he refers to as "regulatory craftsmanship."

Risk-based regulators typically rely on program- and problem-centric approaches, expert models, and regulatory craftsmanship and stewardship to reduce or prevent harm from an underlying hazard, such as toxic substances and exposure to hazardous situations. The risk decision-making context and processes used by Health Canada align well with this definition of a risk-based regulator and reflects the approach described in this federal department's framework for decision-making (Health Canada 2000). While there are well-established, program-area specific frameworks at Health Canada, problem-centric approaches are also applied (Health Canada staff, pers. comm., February 17, 2022). The COVID-19 pandemic is a good example of how Health Canada applied a program and problem-centric approach to address the risk from the 2019 novel coronavirus (SARS-CoV-2). Several program areas within Health Canada collaborated closely with sister organizations from the Health Portfolio - notably the Public Health Agency of Canada - to address this global population health crisis. Problem-centric approaches helped develop and guide public health measures, such as masking and common messaging regarding social

distancing and other preventive measures. Program-centric approaches ensured the accountability of areas responsible for the market authorizations of several product types including mRNA vaccines that proved to be highly effective in reducing the risk of serious clinical outcomes, such as hospitalizations and deaths (Chuenkitmongkol et al. 2022; Government of Canada 2022a, 2022b). The aim of this review was to explore the utility of using principles to guide the risk decision-making process within the context of program and problem-centric risk issues. A principle-based mindset is also relevant to the communication of risks (Bhuller and Trevithick-Sutton 2024). Further, as noted in Health Canada's decision-making framework, the application of such principles " . . . may be limited in certain instances due to legislative or other requirements or restrictions" (Health Canada 2000). This limitation is examined by considering the feasibility of applying decision-making principles to diverse risk contexts. With this understanding of Health Canada and, by extension, the workshop participants as being current and risk-based regulators who rely on both problem- and program-centric approaches, the theoretical and methodological approaches of the workshop are described and how this information relates to the formulation of principles for risk decision-making.

3.4 Theoretical approach

Our study relied upon a realist review which also provided the theoretical foundation for establishing an *a priori* hypothesis based upon this context, mechanism, and outcome configuration (CMOc):

> The ten risk decision contexts provide diverse and suitable scenarios **(C)** for discussing and evaluating the relevance, importance, and feasibility **(M)** of key risk decision-making principles for health and environ- mental risks **(O)**.

Within the context of this work, feasibility implies minimal limitations or restrictions impacting the ability to incorporate a particular principle in risk decision-making. These limitations might be due to the regulatory context within which the decision is being made, as well as the overarching laws and regulations, available resources, and other requirements or restrictions. Importance is defined as displaying significant value for the decision-maker and decision process; while relevance denotes how a specific principle is pertinent for the risk context of interest.

A realist review is a theory-driven approach for systematically gathering evidence and using this information to evaluate underlying assumptions. It does not seek "generalizable lessons" or "universal truths;" rather, it recognizes and addresses how actions are dependent on

factors such as the context in which the action is taken. The aim for a realist review and synthesis is explanatory: unlike systematic reviews, it follows a more heterogenous and iterative process (Pawson and Tilley 2004; Pawson et al. 2004). Consequently, a realist review and synthesis was considered appropriate as it provided the paradigm for assessing the CMOc by enquiring how regulatory practitioners view key risk decision-making principles in specific risk contexts.

A realist approach also supports the use of qualitative and quantitative data (mixed methods) analysis (Greenhalgh et al. 2015; Pawson 2017; Pawson et al. 2005). Our evaluation commenced by peer-reviewing the expert-generated risk decision principles and con- texts introduced by Krewski and colleagues (2022b) and then expanding on the qualitative description of relevance through a quantitative analysis. Further, our assessment also analyzed relevance indirectly and in more depth by separation into importance and feasibility of using these 10 principles across diverse risk decision contexts. As this process started from an existing, qualitative expert assessment using a mixed methods approach, our initial study design and analysis were framed as explanatory (Creswell and Clark 2018; Patton 2002).

3.5 Methodological approach

The CMOc and these underlying research questions guided the format and design of this investigation, as well as data required to address the three objectives as identified in parentheses:

1) What are the key principles for identifying, assessing, and managing health and environmental risks? For present purposes, key principles are notions reflecting contemporary risk management decision-making philosophy as identified by experts in risk and regulatory sciences.
2) How relevant are these principles for diverse health and environmental risk decisions? (Objective 1)
3) Using various risk decision contexts, how important and feasible are the relevant principles for health and environmental risk decision-making? (Objective 2)
4) Which of the key principles are broadly applicable to most risk contexts (i.e., universal principles)? (Objective 3)

By employing a realist approach, it was possible to determine "what risk decision-making principles work, for whom, and under what circumstances." The focused review synthesized principles from Krewski et al. (2022b), Health Canada's decision- making framework (Health Canada 2000), and input previously sought from Health Canada experts (Health Canada staff, pers. comm., February 17, 2022). This synthesis addressed the first research question while validating the regulatory use of the principles recommended by Krewski and colleagues (2022b), **Table 1** provides a crosswalk illustrating the relationship between all three reference sources, the identified principles, and links to various steps in risk decision-making. A consolidated (qualitative) listing of key principles is subsequently provided in **Table 2**.

Table 1: Crosswalk between Ten Risk Decision Principles and Decision-making Steps

Principles (Krewski and colleagues)	**Description (Krewski and colleagues)**	**Health Canada decision-making framework: Principle (P) or Step (S)**
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	P7 (use a "precautionary" approach)
P3: Balancing risks and benefits	Where appropriate, risks may be taken in light of offsetting benefits	S2 (assess risks and 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.	P2 (involve interested and affected parties)
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 (strive to make the process transparent)

P10: Flexibility	Risk management decisions should be flexible, and subject to review as new information becomes available.	P8 (tailor the process to the issue and its context)

Quantitative, secondary analysis of the 10 principles (Krewski, Saunders-Hastings, Larkin, et al. 2022b), using a 4-point Likert scale to further characterize relevance, provided additional insights for the second question.[2] The results from this initial, quantitative analysis (**Figure 1**) along with the consolidated listing of the key principles (**Table 2**) served as the starting point for our workshop with frontline staff. Details on data collection and ana- lysis are provided below.

Table 2: Consolidated Listing of Risk Decision-making Principles

Krewski and colleagues:*	**Health Canada's Decision-Making Framework:**
P1. Risk-based decision making	P11: Maintaining and improving health is the primary objective
P2. Precautionary principle	P12: Communicate in an effective way
P3: Balancing risks and benefits	P13: Use a broad perspective
P4: Cost-effectiveness	P14: Use a collaborative and integrated approach
P5: Risk tolerance	P15: Make effective use of sound science advice
P6: Zero risk	P16: Clearly define roles, responsibilities, & accountabilities
P7: Risk equity	
P8: Stakeholder engagement	**Personal Communication with Health Canada staff:**
P9: Openness and transparency	P17: Weave Indigenous Knowledge and Science
P10: Flexibility	P18: Respect Ethics and Values** (includes AI)
	P19: Apply FAIR Data Principles***
	P20: Reduce, Replace, and Refine Animal Studies (3Rs)

*These experts provide an additional eighteen (18) principles in a supplementary document, but note how the ten principles provided in the main paper "… are the most important overarching guiding principles to support modern decision-making." (Krewski et al., 2022b)

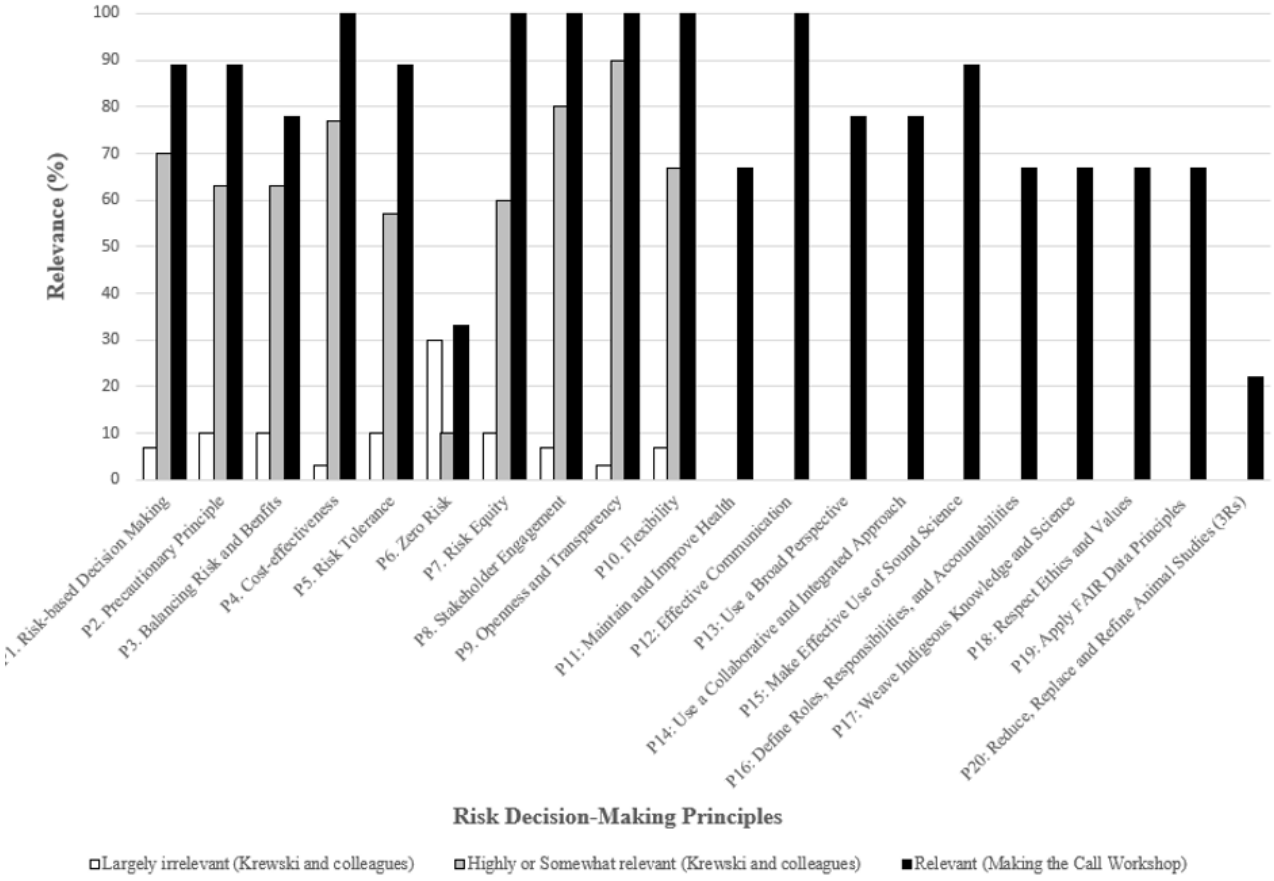
**Values are within the context of organizational behaviour and culture and the corresponding role for judgement in risk management, decision-making.

***FAIR: stands for Findable, Accessible, Interoperable, and Reusable.

Figure 1: Relevance of Risk Decision-making Principles across Diverse Risk Contexts

The relevance of Principles P1 to P10 (Krewski and colleagues), P11 to P16 (Health Canada's decision-making framework), and P17 to P20 (input from Health Canada staff) is provided as a percentage and reveals potential groups of principles which warrant further analysis.

[2]Likert scale (4-point): 3, 2, 1, and 0 for highly feasible/ important, somewhat feasible/important, largely not feasible/important, and left blank or no response, respectively.



3.5.1 Workshop on risk decision-making principles

In February 2023, frontline staff from Health Canada, participated in a workshop where they evaluated the proposed CMOc. This in-person and interactive workshop occurred during the annual Health Canada Science Forum for staff. Health Canada personnel were made aware of the workshop through the Department's internal broadcast news announcements and information published on the intranet. Further, all participants who attended the forum had access to booklets providing information on this workshop.

Twenty participants self-volunteered to participate in the workshop where these individuals shared their insights on the applicability of the principles in different risk decision contexts based upon their lived regulatory experiences with risk assessments, policy development, and compliance and enforcement activities. These participants were regulatory practitioners responsible for evaluating health and environmental risks and establishing policies across various programs within Health Canada. The workshop followed an exploratory, sequential, qualitative-quantitative (QUAL→ QUAN) design where the qualitative and quantitative data carry equal

weight (O'Sullivan and Khan 2020; Palinkas et al. 2011). The exploratory nature builds from the existing literature and initial analysis of relevance, which was further examined and expanded upon during the workshop by evaluating the importance and feasibility of risk decision- making principles. During the workshop, participants incorporated the QUAL→QUAN mixed methods approach as these individuals worked through the following three phases, each lasting 30 min[3]:

Phase I – Introduction and instructions. This phase included a description of how the interactive workshop relied upon a knowledge mobilization and transfer strategy employing an embedded research model (Vindrola-Padros et al. 2017). The knowledge planning and translation approach involved an investigator sharing regulatory and academic insights related to this research endeavor (Health Canada 2017). All participants viewed a 20-min video in which another investigator shared his views on the top 10 considerations for risk decision-making (Personal communication). Examples of the risk decision contexts and the corresponding, relevant principles (**Table 3**) were also shared with participants, along with instructions related to all phases of the workshop. Prior to the start of phase II, participants were instructed to relocate from where they were sitting to self-selected stations corresponding to each of the 10 risk decision contexts considered by Krewski et al. (2022b).

Table 3: Relevance of Principles P1 through P10 in Ten Risk Decision Contexts* (relevant principles**)

1. Ambient air pollution (P1, P3-5, P7-10)	6. Natural disasters (P2, P4, P7-10)
2. Artificial sweeteners (P6, P10)	7. Prion diseases (P1-5, P7-10)
3. Climate change (P1-2, P4, P7-9)	8. Hydraulic fracturing (P1-5, P7-10)
4. Nanotechnology (P1-5, P7-10)	9. Pandemic outbreak (P1-5, P7-10)
5. Chemotherapeutic agents (P1, P3-5, P9)	10. Genetically modified foods (P1-5, P8-10)

*A detailed description of the 10 risk contexts and principles is provided in Krewski et al. (2022b) article.
**Based on the "highly" and "somewhat relevant" categories for principles identified in Figure 1 of Krewski and colleagues (2022b).

Phase II – Linking the relevant principles with each risk decision context. Based upon their lived regulatory experience, participants used a science fair style scoring grid to cross-out principles considered irrelevant and recorded any comments on their rationale for taking this action. The science fair style scoring grid was made using a tri-fold display board (see picture in

[3]The University of Ottawa and Health Canada's Research Ethic Boards confirmed that ethics approval or informed consent was not required for this workshop.

Supplementary Material). The first panel included the section number and instructions on how to rank feasibility and importance for each principle. The middle and final panels provided the scoring grid and risk context, respectively. When designing this data extraction tool, the venue (in this case, a science forum) and opportunity to create a portable and interactive tool served as the key reasons for developing this style of scoring grid.

As participants had digital and hard copy access to the article by Krewski and colleagues (2022b) and the summary provided in Table 3, these individuals were fully informed of how these experts identified the relevant principles for each risk con- text. Each station accommodated 2–4 participants, had copies of Table 2, one copy of the article, a printout of the text describing the assigned risk decision context, and the science fair style workbook/scoring grid. All stations accommodated two participants except for the risk decision context 3 (climate change) which had 4. Due to time constraints, none of the participants had the opportunity to work on risk decision context 4 (nanotechnology).

Phase III – Determining the practical application of the relevant principles. In the final segment of the workshop, participants used the workbook/scoring grid to discuss and rank the consolidated principles from a feasibility and importance perspective, as it related to the specific risk decision context (**Table 3**) using the same 4-point Likert scale. Following the workshop, this information was ranked using a modified approach to concept mapping and multivariate data analysis. These results addressed the final research question and provided insights regarding areas warranting more attention.

3.5.2 Data collection and analysis

The completed workbooks were the primary data source for this study. Microsoft Excel was utilized for data entry and IBM SPSS Statistics 25 for data analysis which includes a hierarchical cluster ana- lysis and generation of a dendrogram. Raw data collected from this workshop are provided in the Supplementary Material.

The main analytical approaches used in this study are concept mapping and multivariate data analysis (Allen et al. 2015; Trochim 1989; Trochim et al. 2006). Concept mapping typically consists of the following steps: (1) preparation of statements; (2) selection of participants; (3) collection of data; (4) sorting and scaling according to a study-relevant scale; (5) mapping

statements on a 2-dimensional scale; and (6) labeling concepts and comparing aver- age ratings with previous outcomes.

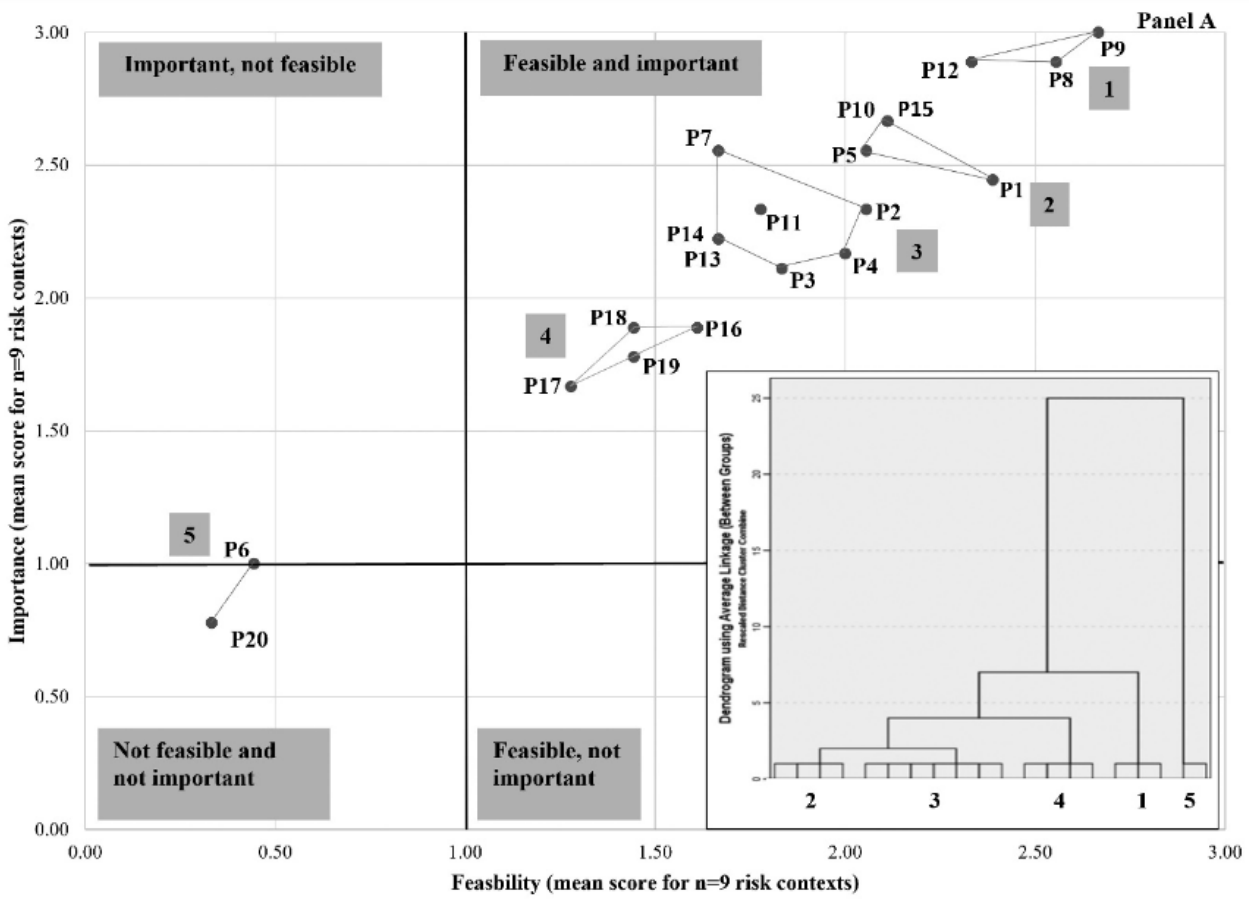
For step 1, the statements (i.e., the 20 principles) were developed through consultation with experts from Health Canada and incorporation of the fundamental principles recommended by Krewski et al. (2022b). The pragmatic application of these principles was assessed through an open invitation to any Health Canada participant who was attending the forum and was interested in this study. This approach for selecting participants (step 2) resulted in a heterogeneous population of staff who were well-informed of the various risk decision contexts and therefore, able to discuss and rank the principles based upon their lived regulatory and public health experience.

The rankings of the principles and any comments provided on the science fair style scoring grid - comprising both quantitative and qualitative data were collected in step 3. A 4-point Likert scale was utilized for sorting and scaling data in step 4. Step 5 of the concept mapping approach provided a mechanism to visualize the mean values for flexibility and importance by mapping them using a scatter plot (see **Figure 2(a)**).

For purposes of this study, sorting (step 4) was not required because the statements (i.e., key principles) were selected from previous findings. Further, only relevance was compared to previous outcomes from Krewski et al. (2022b) report, since this is the first investigation exploring the use of concept mapping to evaluate feasibility of implementing relevant risk decision-making principles and their importance for health and environmental risks (questions #2 and 3).

Figure 2. Association between Feasibility and Importance of Risk Decision-Making.

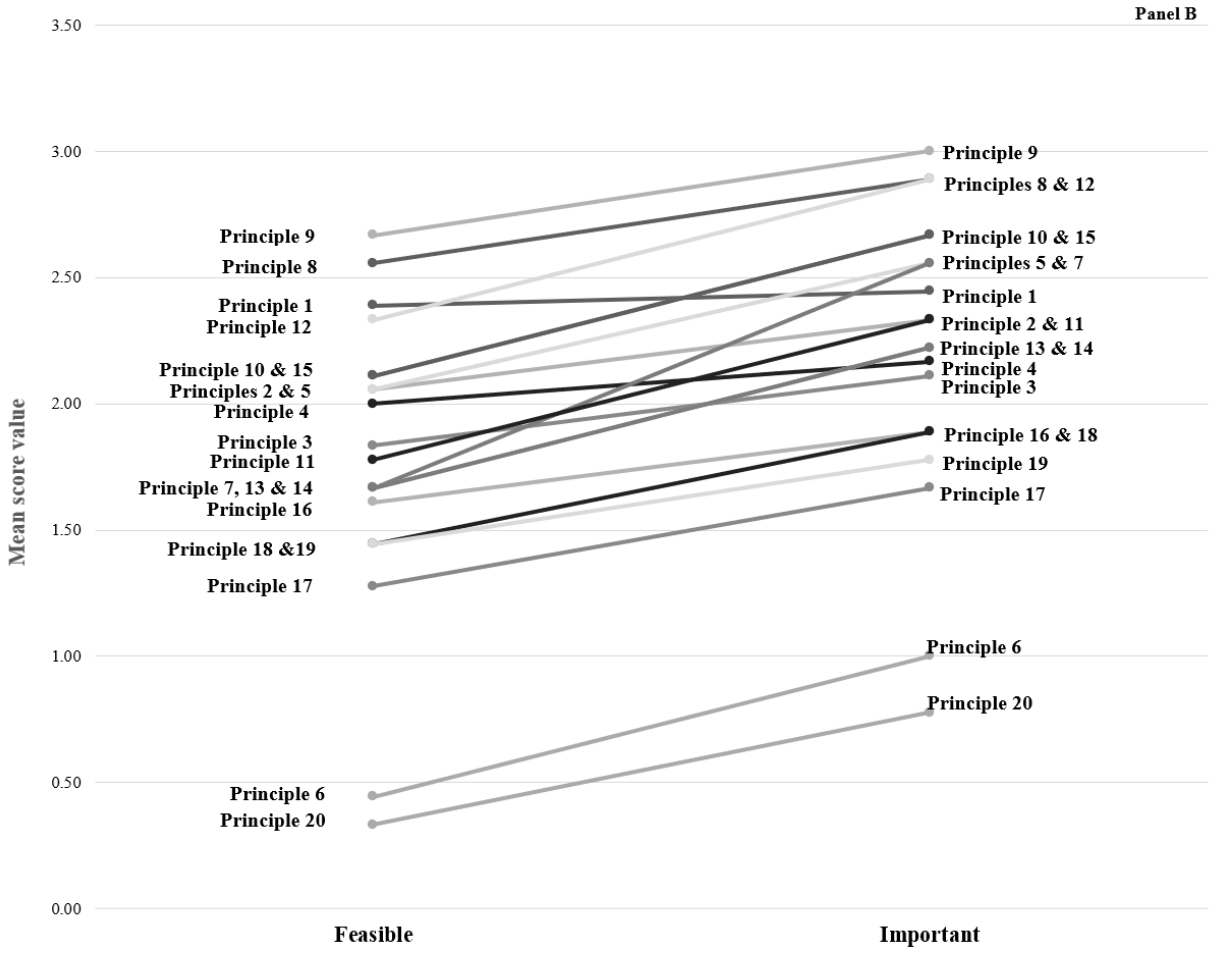
Panel A shows that the 20 decision-making principles fall into one of five clusters. **Cluster 1** includes universal decision-making principles which are mostly risk context-independent and apply to several health and environmental risk decision-making contexts. **Clusters 2** and **3** are key for health and environmental risk decision-making, but their application is risk context-specific. **Cluster 4** includes principles reflecting contemporary public administrative values, are context-specific, and can help guide the risk decision-making process. **Cluster 5** includes principles outside the Go-zone and consequently are not considered as decision-making principles



Principles

- **P1: Risk-based decision-making**
- **P2: Precautionary principle**
- **P3: Balancing risk and benefits**
- **P4: Cost-effectiveness**
- **P5: Risk tolerance**
- **P6: Zero risk**
- **P7: Risk equity**
- **P8: Stakeholder engagement**
- **P9: Openness and transparency**
- **P10: Flexibility**
- **P11: Maintain and Improve Health**
- **P12: Effective Communication**
- **P13: Use a Broad Perspective**
- **P14: Use a Collaborative and Integrated Approach**
- **P15: Make Effective Use of Sound Science**
- **P16: Define Roles, Responsibilities and Accountabilities**
- **P17: Weave Indigenous Knowledge & Science**
- **P18: Respect Ethics and Values**
- **P19: Apply FAIR Data Principles**
- **P20: Reduce, Replace, and Refine Animal Studies (3Rs)**

Panel B shows the linear relationship between the two factors, feasibility and importance, for each of the twenty principles. In all cases, importance is ranked higher than feasibility for the same principle.



The labeling of concepts in step 6 relied upon a hierarchical clustering of values and generation of a dendrogram. As noted in the inset image of **Figure 2(a),** clusters 2 and 3 are more closely related in comparison to clusters 1 and 4. Further, clusters 1 to 4 are part of the same main branch when compared to cluster 5 (far right) for principles 6 and 20. The scatterplot clearly illustrates this by noting how clusters 1 to 4 are in the area referred as "Go-zone" (Allen et al. 2015). This is the area where one finds principles with high scores for feasibility and importance. For this study, it is also an important tool for assessing and validating the principles recommended by the experts in risk and regulatory sciences (i.e., several of the principles should appear in the Go-zone).

Figure 2 is a scatter plot (panel A) and a match plot (panel B) of all 20 principles that were further evaluated according to the importance and feasibility of each principle for the nine risk decision- making contexts examined during the workshop. Participants ranked feasibility using the 4-point Likert scale followed by ranking importance utilizing the same scale. A value of 0

was used for each crossed out principle or those that were considered irrelevant for the particular risk decision-making context. In cases where participants provided their response as a range rather than a single value, the mean value was used for further analysis (e.g., 2.5 for a reported range of 2–3). The overall mean value of each principle across the 10 risk contexts for both categories (see **Supplementary Material: Tables 2 and 3**) resulted in the x-coordinate (feasibility) and y-coordinate (importance) for the scatter plot. These values also helped determine the linkage between the various groups or clusters of principles (see inset image of the Dendrogram in **Figure 2(a)**). Similarly, the match plot also relied upon the mean values for feasibility and importance of each principle; regression analysis helped confirm the statistical relevance of the positive and correlative relationship between these two factors.

3.6 Results

3.6.1 Evaluating the proposed CMOc

During the first phase of the workshop, participants discussed and evaluated the *a priori* hypothesis of the proposed CMOc and how the 10 risk decision contexts provided appropriate scenarios suitable for discussing the relevance, importance, and feasibility of risk decision-making principles. There was unanimous agreement and support for using these previously published risk decision contexts, as these provided sufficient familiarity (several participants were well-informed regarding these risk issues) and diversity for discussing and evaluating the relevance, feasibility, and importance of key decision-making principles for health and environmental risks. These risk contexts also helped initiate the dialogue between participants who then added additional comments based upon their own experiences. For example, participants who collaborated on risk context 6 (natural disasters, extreme weather events) wrote regarding how several of the principles linked with "emergency preparedness, prevention of climate change, Aboriginal communities defined by geography, public health agencies (federal, provincial, municipal), first responders, and NGOs (e.g., Red Cross)." Given the time allocated for this part of the workshop, the strategy of using risk contexts previously developed by experts in risk science was also appreciated by all participants as it provided a tool to help keep them on track and seamlessly transition to the next phase of the workshop. Consequently, the feedback from the participants confirmed how the a priori hypothesis and the proposed CMOc were appropriate for this type of workshop.

3.6.2 Determining relevance of risk decision-making principles

In assessing the relevance of all 20 principles across the diverse risk contexts, participants crossed out the principles considered to be irrelevant and/or did not include a value when ranking feasibility and importance for the assigned risk context. **Figure 1** provides a ranking for relevance: the values employed for this ranking are based upon assigning a score of "1" for principles identified as being relevant by the participants and "0" for irrelevant ones. The raw scores were then converted to % values in order to compare results with the weighted % values recommended by Krewski et al. (2022b) (see Supplementary Material for more details). The first 10 principles include % for relevant principles as determined by the input from the work- shop participants. These values appear alongside the weighted % for the same 10 principles articulated by Krewski and colleagues (2022b). The additional 10 principles (i.e., principles P11 through P20) and the corresponding % values are derived only from the participants in the Health Canada workshop.

As the discussion by Krewski et al. (2022b) previously demonstrated how the risk decision-making principles are relevant for most of the risk contexts, workshop participants did not rank relevance using the Likert scale. With the exception of the zero-risk principle, the weighted % values for all 10 principles scored greater than 50% for being either "highly relevant" or "somewhat relevant" as determined by these experts. Consequently, using a quantitative scale provided no additional value for ranking purposes, which was further confirmed by comparing the values noted by the participants. The workshop participants' ranking (see **Figure 1**) resulted in all principles scoring well above 50% except P6 (zero risk) and P20 (3Rs: reduce, replace, and refine animal studies).

The overall result for both groups confirms that most of the principles (P6 and P20 being the exceptions) are relevant for risk decision-making. Quantitative analysis with weighted scores from the experts also revealed the highest % value (90%) for principle P9 (openness and transparency) followed by principles P8 (stakeholder engagement, 80%), P4 (cost effectiveness, 77%), and P1 (risk- based decision-making, 70%). These experts previously reported how principles P8, P9, and P10 (flexibility) " . . . are almost universally applicable" (Krewski, Saunders-Hastings, Larkin, et al. 2022b).

The results from the workshop participants demonstrated the highest % values (100%) for principles P4 (cost-effectiveness), P7 (risk equity), P8 (stakeholder engagement), P9 (openness and transparency), P10 (flexibility) and P12 (communicate in an effective way). Further analysis of these principles might aid in determining if these are also universal principles. Principle P6 (zero risk) demonstrated comparable % values between experts and workshop participants; however, this principle is somewhat of an outlier as both scores are well below 50%. This conclusion aligns with the experts who explain how this principle is " . . . primarily to serve as an idealized, yet largely-unattainable, goal for risks that cannot be completely eliminated" (Krewski, Saunders-Hastings, Larkin, et al. 2022b). Principle P20 (3Rs: reduce, replace, and refine animal studies) does not appear to be a risk decision-making principle based on a low % value (22%) and these comments from the work- book for risk context 1 (ambient air pollution): "evidence std. [standard] not DM [decision-making] principle."

3.6.3 Using feasibility and importance to group risk decision-making principles

The mixed methods analysis of the relevant principles demonstrates how contemporary risk decision-making principles, as recommended by experts in risk science and regulatory risk management, are pertinent for frontline regulatory staff. Further, the grouping of certain principles with similar % value sets the stage for additional analysis of these risk decision-making principles. Krewski et al. (2022b) discussed attributes of different risk contexts and how these characteristics might support a better understanding of the relevance of the risk decision-making principles within specific risk contexts. Our analysis subsequently explores the views of front-line staff and how these individuals consider the practical application of these principles by evaluating and ranking their feasibility of implementation and importance. This analysis provides an alternative and indirect mechanism for considering composite views, contrasting feasibility versus importance (in lieu of relevance), for attaining additional insights on the pragmatic application of these principles in regulatory risk decision-making. The discourse during the workshop further confirmed how the participants preferred the use of these two terms, as these were more familiar with their application within a regulatory environment.

3.6.4 Scatter plot and clustering of risk decision-making principles

The scatter plot in **Figure 2(a)** (top panel) shows how most of the principles (n = 18 of 20, or 90%) cluster in the top right quadrant, where principles are judged to be both feasible and

important. This area is referred to as the "Go-zone" (Allen et al. 2015) and represent the space where key principles for risk decision-making need to appear. For example, except principle P6 (zero risk), the remaining 9 guiding principles identified by Krewski et al. (2022b) appear in the Go-zone. None of the principles appear in the bottom, right quadrant (feasible, not important) and the only principle P20 (reduce, replace, and refine animal studies (3Rs)) is in the bottom left quadrant (not feasible and not important). As noted previously, a potential explanation for principle P20 being rated low in terms of feasibility and importance is that this principle constitutes an evidence standard and not a decision-making principle. Principle P6 (zero risk) is on borderline between upper and lower quadrants for importance, but not in feasible zone (important, not feasible). In agreement with the views of Krewski et al. (2022b), several the work- shop participants noted that " . . . in most cases, the ultimate goal of zero risk will not be attainable . . . not attaining this level was also considered as irrelevant by the experts as it is more of a vision to aspire to."

When focusing on individual clusters in the Go-zone, the first group of principles comprised of P9 (openness and transparency), P8 (stakeholder engagement), and P12 (communicate in an effective way) have an average rating range of 2.33 to 2.67 for feasibility and 2.89 to 3 for importance. Their position in the Go-Zone along with the % values regarding relevance demonstrates the inclusiveness of these principles toward all risk decision contexts evaluated by the participants. This quantitative information supports the qualitative expert recommendation of how these three principles might be considered as universal principles applicable for most of the health and environmental risk decision-making contexts and are thus, not context dependent. Further, these process-centric principles might also help guide analytical approaches including those that may not fit established, regulatory decision-making pathways. Exceptions limiting the application of these principles may include risk decision-making activities related to events where there is a strong reason to not apply these principles, such as the reduced desirability of openness and transparency when dealing with bioterrorism (Krewski, Saunders-Hastings, Larkin, et al. 2022b).

The next two clusters include the contemporary and well-established principles recommended by experts in risk science and/or derived from Health Canada's decision-making framework (clusters 2 and 3 include principles P1, P5, P10, and P15 and principles P2 to P4, P7, P11, P13 to P14, respectively). These principles exhibited average ratings greater than 2 for importance and

greater than 1.5 for feasibility. As such, the overall mixed methods result for these principles and their clustering in the Go-Zone supports their utility as fundamental risk decision-making principles for consideration for a broad spectrum, but not necessarily all, health and environmental risk decision-making contexts. For example, while P3 requires one to balance risk and benefits, in Canada, the PCPA does not include a provision for a risk-benefit analysis. Consequently, the application of P3 for this regulatory risk context might involve an independent evaluation of value (including the performance and benefits (e.g., efficacy) of the pest control product), health, and environmental risks (Pest Management Regulatory Agency 2021). It is also important to note that principle P11 (maintaining and improving health is the primary objective) is included in Health Canada's mandate/mission and vision statements for this organization (Government of Canada 2014; Health Canada 2011).

The last cluster (4) in this quadrant (i.e., principles P16 to P19) includes risk decision-making principles that are more reflective of corporate values and behaviors from administrative organizations, such as Health Canada (e.g., reconciliation and the importance for weaving Indigenous Knowledge and Science) (Health Canada Senior Officials, pers. comm., June 9, 2023). Consequently, these principles are identified as guiding principles which are specific to the risk context and their application may inform one or all phases of the risk decision-making process. For example, guiding principles for ethics and values are important in an evidence-based process, as these might help guide the decision-maker toward bias-free and objective facts relevant for risk decision-making (Simon 1997). The importance of ethics in risk decision-making aligns with this recommendation from Krewski and colleagues (2022b): " . . . there may be merit in formulating an additional principle targeting risk ethics."

Cluster 4 possesses a mean rating range of 1.28 to 1.66 for feasibility and 1.67 to 1.89 for importance. These principles were also not identified by the experts in risk science as guiding risk decision-making principles (Krewski, Saunders-Hastings, Larkin, et al. 2022b). For example, while principle P16 (clearly define roles, responsibilities, and accountabilities) is from Health Canada's decision- making framework (Health Canada 2000), it is more pertinent for clarifying organizational and collaborative processes (e.g., to guide the identification of the decision-maker). This is consistent with the manner in which Krewski and colleagues (2022b) identified the principle of accountability in the supplemental information of their paper. Further, these experts also noted how this principle " . . . asserts that those in charge of decision-making

take responsibility and be answerable for their decisions" and they viewed it " . . . as an essential component of openness and transparency." The position of these principles in the Go-zone, however, supports ongoing knowledge mobilization and transfer efforts aimed at providing additional guidance to staff on the application of these elements at Health Canada (Health Canada Senior Officials, pers. comm., June 9, 2023).

P6 (zero risk) and P20 (3Rs) are part of cluster 5 according to the dendrogram and do not appear in the Go-zone. Both experts and workshop participants recognized the importance of P6 as some- thing to aspire to; however, the feasibility results clearly show how challenging this may be for regulatory risk decision-making. P20 also appears to be important when considering the evidence standards for evaluating health and environmental risks, but less for risk decision-making purposes.

3.6.5 Ranking feasibility and importance using match plots

The bottom panel in **Figure 2(b)** presents feasibility and importance using a match plot. The left-side provides the individual mean rankings for feasibility, starting at the top with principle P9 (openness and transparency) and ending with principle P20 (3Rs). The right-side includes the values for importance and ranks principle P9 and P20 as displaying the highest and lowest average values, respectively. When comparing the individual and mean rankings for the same principles between the two categories, importance is ranked higher than feasibility for all 20 principles.

While one might anticipate some level of correlation between feasibility and importance, the interaction of these two factors was employed to indirectly assess the relevance of risk decision-making principles. This was further supported by discourse during the workshop and the familiarity that participants had with these two factors within the context of regulatory risk decision-making. The results also quantify and help visualize how a principle may be indirectly determined to be relevant, even if the participants considered the implementation of a specific principle to be challenging. In other words, the mean importance value for the same principle still received a higher score than the corresponding mean value for feasibility. As demonstrated using the guiding principles P17 to P19, even though these are not considered as fundamental risk decision-making principles, front-line staff noted these were relevant and the mean rating of

important was greater than 1.5; however, these individuals ranked them lower when it came to implementing these principles with an average rating <1.5 for feasibility.

An important aspect of this analysis is the utility of the independent variables, feasibility and importance, and how these factors provide compositive views to further characterize and categorize the practical application of relevant risk decision- making principles across diverse risk contexts. When utilizing only relevance, results for the work- shop participants suggest that principles P4 (cost-effectiveness), P7 (risk equity), P8 (stakeholder engagement), P9 (openness and transparency), P10 (flexibility), and P12 (communicate in an effective way) are all universal as these parameters attained a 100% value; however, ranking and mapping the mean values of feasibility and importance resulted in only three universal principles (P8, P9, and P12).

From a regulatory and public health risk decision-making context, the overall trend or best-fit line (not drawn in **Figure 2(a)** (top panel)) illustrates a correlation between these two variables. Further, for all 20 principles (**Figure 2(b)** (bottom panel)), the relationship is positive and the correlation between these two variables is statistically significant with an r^2 value close to 1 ($r^2 = 0.9$; $p < 0.05$). This analysis, therefore, provides another useful strategy for considering the feasibility of implementing such risk principles as a tool to help determine the most relevant and (by extension) most important risk decision-making principles warranting attention within a regulatory and public health decision-making context. It may also help in further understanding the complex nature of the risk context and provide an opportunity to help prioritize limited risk management resources. This strategy is further examined by considering three global health and environmental risk issues and how these relate to the risk decision-making principles identified from our data.

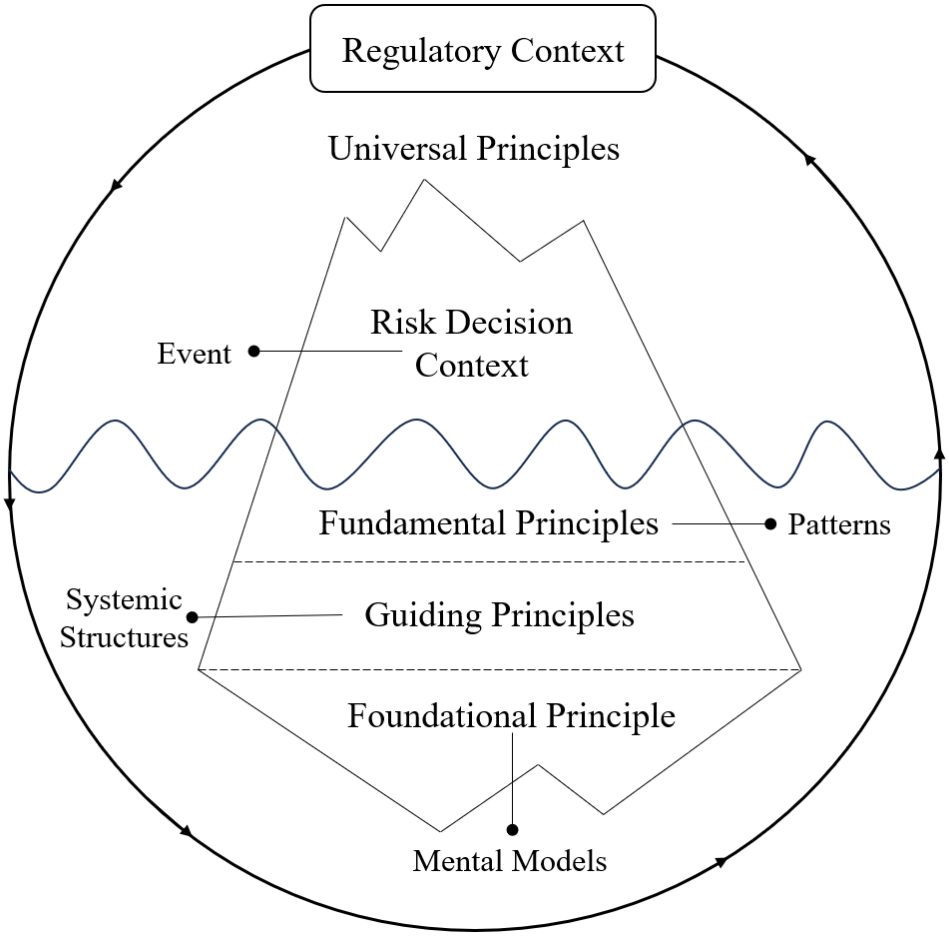
3.7 Application of results to global health and environmental issues

In applying the various categories of principles to global issues, a systems thinking approach is well-suited for complex risk contexts such as antimicrobial resistance (Peters 2014; Sheffield, Sankaran, and Haslett 2012). While such an approach is not required for all risk issues, a systems thinking lens (Bhuller and Trevithick-Sutton 2024) and tools such as The *Systems Iceberg model* (Sheffield, Sankaran, and Haslett 2012) provide mechanisms to better understand the risk decision-making context and what is required to address the risk issue of concern. The analogy of an iceberg helps illustrate a 4-level model where most of the constructs are not visible. **Figure**

3 includes these constructs (events, patterns, systemic structures, and mental models) and how these relate to the risk decision context and principles identified in our investigation.

Figure 3: Schematic Representation of Different Types of Risk Decision-Making Principles within the Regulatory Context

The risk decision context and principles are described using the constructs of *The Systems Iceberg model* (event, patterns, systemic structures, and mental models) proposed by Sheffield and colleagues (Sheffield et al., 2012). The risk decision context and universal principles are shown to be well above the wave (visible spectrum) while the fundamental, guiding, and foundational principles are shown to be below the wave (invisible spectrum). The regulatory context encapsulates everything thereby demonstrating the importance of considering, for example, legislative requirements when relying on the adaptation of this model for risk decision-making.



Our analysis relies upon the foundational principle to help establish the institutional values and attribute influences of governance and management of risky decision-making. These examples also include organizations which are considered modern and risk-based regulators. This layer (mental models) is the most comprehensive and most difficult area of the model and typically requires transformational changes including new regulatory statutes or amendments to existing legislation. The model's remaining invisible layers, including systematic structures and patterns, are represented by guiding and fundamental principles, respectively. Our focus is primarily on these areas as these provide insights on patterns (e.g., which principles are used more frequently) and any underlying organizational elements, such as guiding principles reflecting contemporary values relevant to the visible layer of the iceberg (global risk decision context).

3.7.1 Addressing antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) has been referred to as a global public health concern, crisis, and silent pandemic (Adebisi 2023; Tamhankar and Diwan 2022). In 2019, an estimated 4.95 million deaths were associated with bacterial AMR (World Health Organization 2023). It is noteworthy that invasive fungal infections are also increasing globally (World Health Organization 2023). AMR is an acceleration of a normal, evolutionary process which renders microorganisms resistant and no longer susceptible to antibiotics that previously inhibited their growth (Chandra et al. 2021; Lobie et al. 2021). The drivers for AMR are diverse and involve misuse, abuse, or overuse of antimicrobials. This includes antibiotics and antifungals in agricultural, clinical, and public settings (Lobie et al. 2021). The public health measures of using antibiotic-based sanitizers and COVID-19 treatment provides an example of misuse and overuse of existing antimicrobial agents, which contributed to the spread of AMR during and beyond the recent COVID-19 pandemic (Antimicrobial Resistance Collaborators 2022; Khouja et al. 2022; Lobie et al. 2021; Pelfrene, Botgros, and Cavaleri 2021; Sulis, Pai, and Gandra 2022).

In May 2015, the World Health Organization (WHO) endorsed a Global Action Plan (GAP) to address antimicrobial resistance at the 68th World Health Assembly. This plan included 5 strategic objectives and guidelines for countries to develop AMR national action plans (NAPs) (Willemsen, Reid, and Assefa 2022; World Health Organization 2015). Tejpar et al., (2022) presented a detailed time- line of key GAP events spanning the period 2015 through 2021 and how frequently each of the 5 objectives appeared in subsequent resolutions or declarations (Tejpar et al. 2022). Similarly, several investigators provided insights on country-specific NAP

and challenges such as limited funding and not having AMR on the policy-agenda, which continue to create barriers for implementing AMR (Anderson et al. 2019; Berman et al. 2023; Essack et al. 2017; Honda et al. 2023; Iwu and Patrick 2021; Kakkar et al. 2018; Kariuki, Wairimu, and Mbae 2021; Munkholm and Rubin 2020; Ohemu 2022; Orubu et al. 2020; Shabangu, Essack, and Duma 2023; Willemsen, Reid, and Assefa 2022; World Health Organization 2019).

A common and universal principle across all GAP and country-specific NAP is the need to address AMR using an approach referred to as One Health. This approach considers AMR's broad impact across various sectors of society and consequently a need for multisectoral and multi-institutional cooperation as well as partnerships across the interfaces amongst human, animal, and ecosystem health risks. One Health requires strong and collaborative governance structures to help prevent gaps in capacities and to facilitate continuous detection and response to emerging and persisting AMR-related threats (Balkhy et al. 2018; Lammie and Hughes 2016; Nunn et al. 2002; Ogyu et al. 2020; Phelan and Gostin 2017; Ramon Pardo, Sati, and Galas 2018; Wang, Lin, and Lu 2018; World Health Organization 2015, 2019).

The One Health requirements of a multisectoral, multi-institutional and collaborative approach aligned with all the universal principles: (1) stakeholder engagement (P8), (2) openness and transparency (P9), and (3) communicating in an effective way (P12). This alignment is reflected in the guidance provided in the WHO's GAP and country-specific NAPs. Further, apart from the precautionary principle (P2), all fundamental principles are applicable for such an approach. As noted by Krewski and colleagues (2022b), the precautionary principle is relevant to risk contexts where there is scientific uncertainty and threats are serious or may result in irreversible damage. While the threats of AMR are serious and not managing those threats might lead to death, there is scientific certainty regarding many aspects of AMR and consensus on the need for effective action plans. Bearing this in mind, this does not preclude the application of the precautionary principle or approach especially if it is a policy or regulatory requirement. Consequently, AMR risk management strategies, in both GAP and NAPs, require careful consideration of risks and benefits of using antimicrobials along with a multi-pronged approach for addressing this global health concern. As an example of a NAP, Canada's Pan-Canadian Action Plan on Antimicrobial Resistance for the years 2023 to 2027 embodies the guiding principles P16 through P19 by recognizing the value of Indigenous health practices, clearly defining the roles and

responsibilities for all levels of government and partnerships, and emphasizes the importance for collecting and sharing data. The Canadian NAP also includes the principle of One Health along with equity, collaboration (domestic and international), and momentum which is in agreement with P7 (risk equity) and the universal principles P8, P9, and P12 (Public Health Agency of Canada 2023).

The comparison between the One Health principle and risk decision-making principles demonstrates the complexity of taking such an approach. All three universal and 4 guiding principles, and most of the 10 fundamental principles are relevant and important for successful implementation of One Health. However, the challenge is around the feasibility of implementing all these principles as this typically requires extensive resources, time, and other factors including strong collaboration and governance. Consequently, viewing these principles from a feasibility lens provides additional insights on the breadth and depth of taking such an approach. Further, it should not be surprising that several countries are finding it challenging to implement country- specific NAPs. Therefore, this analysis of AMR provides an approach for applying relevant and important risk decision-making principles and then considering their feasibility for this type of interdisciplinary work. The application of these principles might aid decision-makers to determine where to focus resources and funds. For example, in lieu of focusing on all principles, other countries might take a similar approach as the Canadian NAP by focusing on risk equity (P7) and universal principles (P8, P9, and P12). This also serves as a mechanism for considering which principles are most applicable when creating or updating a country-specific NAP.

3.7.2 Strengthening regulations around chemicals management

van der Vegt et al. (2022) presented a comprehensive overview of how one of the oldest regulations for toxic substances, the 1976 United States *Toxic Substances Control Act* (TSCA), compares with the equivalent 1988/1999 *Canadian Environmental Protection Act* (CEPA) and Europe's 2007 enacted toxic chemicals legislation known as *Registration, Evaluation, Authorisation and Restriction of Chemicals* (REACH). There are similarities when comparing all three regulatory approaches such as the need to: (1) regulate existing and new substances, (2) communicate risks, and (3) include restrictions on chemical use; however, there are also significant differences. For example, unlike REACH, TSCA and CEPA rely upon a risk-based screening process, do not contain a minimum safety-related data requirement, and these

regulatory acts assume a chemical is safe until proven unsafe. REACH applies a stronger precautionary approach by assuming the opposite (i.e., chemicals are unsafe until proven safe). Further, the burden of proof required to demonstrate the health and environmental risks of a chemical relies heavily on the United States and Canadian governments, whereas REACH places this burden largely on the chemical industry (Foth and Hayes 2008; Sauer 2004a, 2004b; Silbergeld, Mandrioli, and Cranor 2015; van der Vegt et al. 2022).

In June 2016, the United States made amendments to TSCA under the *Frank R. Lautenberg Chemical Safety for the 21st Century Act* (LSCA or the new TSCA). At the federal level, these amendments should provide the United States Environmental Protection Agency with more regulatory authority and flexibility (Trevisan 2011). Further, these changes account for how " . . . existing US regulations have not kept pace with scientific advances" (Gross and Birnbaum 2017) and the need for a paradigm shift toward modernizing legal frameworks (Hilton et al. 2023). Another example of a "regulatory relic" is the Delany Clause and how it does not account for scientific advances and under- standing of cancer risk. It is now known how certain chemicals exhibit a dose-response or threshold for cancer and there are types of cancers in animals which are not relevant to humans (Krishan et al. 2021; Lam et al. 2012). The artificial sweetener, saccharin, provides an example of how high doses used in animal studies resulted in urinary bladder neoplasms from microcrystals which do not form in humans (Krewski, Saunders-Hastings, Larkin, et al. 2022b). In Canada, the Strengthening Environmental Protection for a Healthier Canada Act received Royal Assent in June 2023. These amendments provided the " . . . first set of comprehensive amendments to CEPA in over 20 years" and includes advancing Indigenous reconciliation while promoting the development and implementation of scientifically justified alternative testing methods which reduce reliance on vertebrate animal testing (Environment and Climate Change Canada 2023b).

Collectively, REACH and its amendments to TSCA and CEPA are intended to strengthen the regulations around chemicals management in Europe, the United States, and Canada, and foster global trade in chemicals and chemical products among these jurisdictions. REACH has also influenced the policy of chemical management in other countries such as China, Turkey, Japan, Taiwan, and South Korea (Silbergeld, Mandrioli, and Cranor 2015). These three regulatory directives also account for several of the risk decision- making principles identified in this review. Specifically, the initial enactment and subsequent amendments required adherence to all

three of the universal principles: stakeholder engagement (P8), openness and transparency (P9), and communication in an effective way (P12). The same applies for all 11 of the fundamental risk decision making principles, which includes a specific emphasis to the precautionary principle (P2) and risk assessment under uncertainty (Rogers 2003), maintaining and improving health as a primary objective (P11), using a collaborative an integrated approach (P15), making effective use of sound science and advice (P15). For TSCA and CEPA, all the risk-based decision-making principles are also relevant (e.g., P1 (risk-based decision-making), P3 (balancing risks and benefits), P5 (risk tolerance), and P7 (risk equity)). Amendments to CEPA also explicitly refer to Indigenous reconciliation, which ties in with the guiding risk decision-making principle for weaving Indigenous Knowledge and Science (P17). Further, these amendments link directly with the risk principles for ethics and values (P18) since decisions under CEPA are required to respect the right to a healthy environment, environmental justice, intergenerational equity, and protection of vulnerable populations (Environment and Climate Change Canada 2023a).

3.7.3 Transforming the agrochemical space for pest control products: Going beyond the 3Rs

Transforming the health and environmental risk decision-making process for pesticides (specifically, the active ingredient) and pest control products (formulated end-use product) used in agriculture settings including farms, greenhouses, and high tunnels reflects the application of advances in science in development of more modern risk management policies, regulatory approaches, and strategic plans. Herrmann et al. (2019) identified a paradox where toxicity testing (e.g., for pest control products) accounts for less than 10% of animal use when compared to the high number of animals used for biomedical research; however, much of the attention on the application of The Principles of Humane Experimental Technique (Herrmann, Pistollato, and Stephens 2019) and the 3Rs framework for replacement, reduction, and refinement for animal studies is focused in this area. Herrmann et al (2019) also reported the reasons for this attention are due to: " . . . limited number of targets for replacement in this field, public concern over this type of animal testing, and the possibility to gain government approval for developed replacement tests."

Our findings describe how Canadian regulatory practitioners identified P20 (the 3Rs: reduce, replace, and refine animal studies) as not being a risk decision-making principle, but rather an evidence-based standard for identifying hazards and assessing risks. This description of the 3Rs

is in agreement with gradual development and implementation of alternative test methods within programs responsible for regulating industrial chemicals (Clippinger et al. 2022; Environment and Climate Change Canada 2023a.) and pest control products (Bhuller et al. 2021). It also reflects how experts in this area are actively developing NGRAs to help incorporate non-animal approaches to toxicity testing (Cote et al. 2012, 2016; Fentem 2023; Fentem et al. 2021; Krewski et al. 2014, 2020; Pallocca et al. 2022; Tannenbaum 2012) and pro- vide approaches designed to build confidence with using NAMs as evidence-based standards for regulatory purposes (ICCVAM. 2018; van der Zalm et al. 2022; Zuang et al. 2023). Several experts in this area note this " . . . paradigm shift in toxicology will take place through incremental steps rather than by revolution" (Stucki et al. 2022).

In 2020, the Health and Environmental Sciences Institute assembled a technical committee with a goal to develop an approach for evaluating agrochemicals that went beyond one-to-one replacement strategies, such as NAMs, anchored in the 3Rs. The project proposal aimed to initiate a change in mind-set and paradigm shift by developing a landscape map for Transforming the Evaluation of Agrochemicals (TEA) and the underlying health and environmental risk decision- making process. The goal for the TEA initiative is to incorporate and build a conceptual based upon the most reliable available science from the existing literature (e.g., NGRA frameworks). This frame- work intends to be a fit-for-purpose, safety evaluation approach for agrochemicals supported by three foundational pillars: scientific gradualism, mindset innovation, and transformation innovation (Wolf et al. 2022).

When viewing the TEA initiative using the risk decision-making principles, all three universal principles apply. This multi-year initiative requires extensive and multi-stakeholder engagement (P8), needs to be open and transparent (P9) as this is also key to building scientific, regulatory, and public confidence with a novel approach, and communication needs to be undertaken in an effective manner (P12). Wolf et al. (2022) also noted how certain regulatory authorities, and their underlying foundational legislations, have sufficient flexibility (P10) to " . . . amend their [risk decision-making] approach and adapt advances to science." TEA also needs to incorporate several of the other principles described in this investigation. For example, making effective use of reliable science and advice (P15), utilizing a collaborative and integrated approach (P14), employing a broad perspective (P13), as well as applying the TEA approach to hazard and risk-based decision-making (P1). Therefore, the number of risk decision-making principles for this

transformative initiative and the feasibility for implementing them supports the Wolf et al. (2022) conclusion of how the TEA project will take time, especially in countries where regulatory requirements are enshrined in law.

3.8 Conclusions

The workshop conducted with Health Canada regulatory practitioners provided an opportunity to evaluate the a priori CMOc used to generate data for classifying 20 risk decision-making principles into four distinct categories: foundational (are you a risk-based regulator?), universal (risk context independent), fundamental (risk context dependent), and guiding principles (contemporary and process-based). The workshop created the space that enabled one to assess the CMOc using a knowledge mobilization and transfer strategy. The sharing of published, expert information with front-line staff helped facilitate the subsequent dialogue, which included a better understanding of the vocabulary and definitions of the risk decision- making principles. The observations also demonstrated how the workshop participants appreciated the realist approach used to develop the CMOc. Further, the realist paradigm was in agreement with the use of mixed methods, exploratory, sequential, QUAL→QUAN study design (O'Sullivan and Khan 2020; Palinkas et al. 2011). Overall, the proposed CMOc was determined as being appropriate for this type of workshop, audience, and analysis.

The expert-generated, qualitative attributes of different risk decisions (Krewski, Saunders-Hastings, Larkin, et al. 2022b) provided one approach to further characterize the relevance of using risk decision-making principles for various risk contexts. Our quantitative analysis, using a 4-point Likert scale for the two indicators (feasibility of implementing the risk decision-making principle and their importance), provided an alternative approach for understanding the inherent attributes of different risk decisions. Our findings also showed how both approaches result in similar trends for identifying relevant risk decision-making principles, which culminated in recommending the same universal principles. However, further analyzing the data and visualizing it using a concept map provided a mechanism to assign additional categories for each of the principles based upon their position in the Go-zone. These data also suggest how some frontline staff, who may not have the same level and depth of experience as the experts in risk science, might use their lived experience and understanding of feasibility in considering and selecting the most relevant and important principles for a particular risk context.

During the workshop, Health Canada participants were not able to evaluate risk context 4 (nanotechnology) due to time constraints; however, given the harmony of our overall findings, this is not considered to be a significant limitation as the remaining contexts provide a balanced and diverse range of risk contexts. It is also acknowledged that our intention was not to create an exhaustive listing of all potential risk decision-making principles. However, an attempt was made to ensure a sufficient sample of principles was available to undertake the mixed methods analysis. Further, while the participants of risk context 2 (artificial sweeteners) noted how certain principles might be grouped together (e.g., principles P13 (use a broad perspective) and P7 (risk equity)), only how the principles might be grouped based upon functions (e.g., risk and process) was reported. We also determined why P20 (3Rs: reduce, replace, and refine animal studies) is better positioned as an evidence-based standard instead of a risk decision-making principle. Further exploring this principle in ongoing studies aimed at evaluating ethical principles for risk management purposes is planned.

Our analysis revealed that all three process-based principles are universal risk decision-making principles. Further, in agreement with Krewski et al (2022b) our results, in most instances, demonstrated these principles as being independent of the risk context. The 11 fundamental and 4 guiding principles; however, were found to be risk-context dependent. These fundamental and guiding principles included risk, ethical, and process-based considerations along with contemporary elements reflecting the current values of the organization such as Health Canada's commitment toward reconciliation. Our plan is to focus our efforts on further understanding the attributes of key ethical considerations in a subsequent analysis of health and environmental risk decision-making principles.

The application of diverse risk decision-making principles to broader, global health and environmental issues shows how a principle-based approach/mindset might be used for planning and amending strategic plans such as AMR global and national action plans. This exercise also demonstrated how the application of such principles might aid in realizing the complexity of risk issues, such as management of new and existing chemicals. While the application of these principles was not assessed when developing plans for evaluating the performance of proposed or implemented risk management options, there might be value in taking such an approach. For example, evaluation plans and key performance indicators might be based upon identifying and selecting relevant, important, and feasible risk decision-making principles. Therefore, it is hoped

that our findings provide insights on how to use *The Systems Iceberg* to understand patterns, systemic structures, and mental models using a principle-based approach. An invitation for others to apply the principles discussed in this review to other risk decision-making contexts is welcomed as this might further contribute to the collective expansion in our understanding of risk decision-making principles.

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Supplementary material: Research data

Relevance and Feasibility of Principles for Health and Environmental Risk Decision-making

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The tables below (S1 to S6) include the raw data extracted from the participants' science fair style scoring grid (see Figure S1) along with descriptive statistics, such as the mean value, when applicable.

Table S1 provides the ranking for relevance of all twenty principles. The values used for this ranking are based on assigning a score of '1' for principles identified as being relevant by the participants and '0' for irrelevant ones. The percent values were used to generate the bar graphs in Figure 1.

Table S1: Relevance of Principles P1 through P20 in Ten Risk Contexts (1 = yes, 0 = no)

Risk Context[1]	Principles																			
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20
RC1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
RC2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
RC3	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
RC5	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1
RC6	0	1	0	1	0	0	1	1	1	1	0	1	1	0	1	0	1	0	0	0
RC7	1	0	1	1	1	0	1	1	1	1	0	1	0	1	1	1	0	0	1	0
RC8	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0
RC9	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
RC10	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	0	0
%	**89**	**89**	**78**	**100**	**89**	**33**	**100**	**100**	**100**	**100**	**67**	**100**	**78**	**78**	**89**	**67**	**67**	**67**	**67**	**22**

[1]Risk decision context (RC) 4 (nanotechnology) does not appear in any of the tables as participants were not able to work on this context due to time constraints.

Tables S2 and S3 include the raw values assigned by the participant for each principle, for the nine risk contexts evaluated during the workshop, along with the mean value used to create the scatter plot (Figure 2(a)) and match plot (Figure 2(b)).

Table S2: Feasibility of Principles P1 through P20 in Ten Risk Contexts* (3 = Highly feasible, 2 = Somewhat feasible, 1 = Largely infeasible, 0 = Left blank/no response)

Risk Context	Principles																			
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20
RC1	3	3	2.5	2	2.5	1	1	3	3	2	2	3	2	3	2	2.5	1.5	3	2	0
RC2	2.5	1.5	3	2	3	1	3	2	2	3	2	1	3	0	0	0	0	0	0	0
RC3	2	3	0	2	3	1	1	3	3	3	2	2	2	2	2	2	2	2	2	0
RC5	3	2	3	2	2	0	2	3	3	2	3	3	3	2	2	3	0	3	3	2
RC6	0	3	0	2	0	0	3	2	2	2	0	2	2	0	3	0	3	0	0	0
RC7	3	0	1	1	3	1	1	2	3	1	2	3	0	2	3	2	0	0	2	0
RC8	3	2	2	3	1	0	1	2	2	1	0	2	1	1	2	2	2	1	2	0
RC9	2	2	2	1	1	0	1	3	3	3	2	2	2	2	2	3	2	1	2	1
RC10	3	2	3	3	3	0	2	3	3	2	3	3	0	3	3	0	1	3	0	0
Mean	**2.39**	**2.06**	**1.83**	**2.00**	**2.06**	**0.44**	**1.67**	**2.56**	**2.67**	**2.11**	**1.78**	**2.33**	**1.67**	**1.67**	**2.11**	**1.61**	**1.28**	**1.44**	**1.44**	**0.33**

*Values of 2.5 or 1.5 are recorded when the participants recorded a range of 2-3 or 1-2, respectively.

Table S3: Importance of Principles P1 through P20 in Ten Risk Contexts * (3 = Highly important, 2 = Somewhat important, 1 = Largely unimportant, 0 = Left blank/no response)

Risk Context	Principles																			
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20
RC1	3	3	3	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
RC2	3	2	1	2.5	3	1	3	3	3	2	3	3	3	0	0	0	0	0	0	0
RC3	3	3	0	3	3	2	3	3	3	3	3	3	3	3	3	3	3	3	3	0
RC5	3	3	3	2	3	0	3	3	3	3	3	3	3	3	3	3	0	3	2	2
RC6	0	3	0	3	0	0	3	3	3	3	0	3	3	0	3	0	3	0	0	0
RC7	3	0	3	2	3	3	1	3	3	2	3	3	0	3	3	3	0	0	2	0
RC8	3	2	3	2	2	0	3	2	3	3	0	2	2	2	3	2	3	2	3	0
RC9	1	3	3	1	3	0	2	3	3	3	3	3	3	3	3	3	2	3	3	2
RC10	3	2	3	2	3	0	2	3	3	2	3	3	0	3	3	0	1	3	0	0
Mean	**2.44**	**2.33**	**2.11**	**2.17**	**2.56**	**1.00**	**2.56**	**2.89**	**3.00**	**2.67**	**2.33**	**2.89**	**2.22**	**2.22**	**2.67**	**1.89**	**1.67**	**1.89**	**1.78**	**0.78**

*2.5 is recorded when participants provided a range of 2-3 for the principle-risk context combination.

Tables S4 and S5 include the ranking for relevance as determined by Krewski et al., (2022). Table 4 provides the qualitative values (e.g., 'HR' for Highly relevant) while Table 5 converts them into quantitative scores using the three categories of the Likert scale: 3, 2, or 1 for HR, SR (somewhat relevant), or LI (largely irrelevant), respectively.

Table S4: Relevance of Principles P1 through P10 to Ten Risk Contexts (as determined by Krewski et al. (2022)))

Risk Context	Principles									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
RC1	HR	LI	HR	HR	SR	LI	HR	HR	HR	HR
RC2	LI	LI	LI	LI	LI	HR	LI	LI	LI	SR
RC3	SR	HR	LI	SR	LI	LI	HR	HR	HR	LI
RC4	HR	HR	HR	SR	SR	LI	SR	HR	HR	SR
RC5	SR	LI	HR	HR	HR	LI	LI	LI	HR	LI
RC6	LI	HR	LI	HR	LI	LI	HR	HR	HR	HR
RC7	HR	HR	SR	SR	SR	LI	SR	HR	HR	SR
RC8	HR	SR	SR	HR	HR	LI	SR	HR	HR	SR
RC9	SR	HR	HR	SR	HR	LI	HR	HR	HR	HR
RC10	HR	SR	HR	HR	SR	LI	LI	HR	HR	HR

*HR = Highly relevant, SR = Somewhat relevant, LR = Largely irrelevant

Table S5: Relevance Scores for Principles P1 through P10 Across Ten Risk Contexts

Risk Context	Principles									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
RC1	3	1	3	3	2	1	3	3	3	3
RC2	1	1	1	1	1	3	1	1	1	2
RC3	2	3	1	2	1	1	3	3	3	1
RC4	3	3	3	2	2	1	2	3	3	2
RC5	2	1	3	3	3	1	1	1	3	1
RC6	1	3	1	3	1	1	3	3	3	3
RC7	3	3	2	2	2	1	2	3	3	2
RC8	3	2	2	3	3	1	2	3	3	2
RC9	2	3	3	2	3	1	3	3	3	3
RC10	3	2	3	3	2	1	1	3	3	3

*Based on scores of 3, 2, or 1 for HR, SR, or LR, in Table 4, respectively

Table S6 provides the data and calculation for generating the weighted percent values for each principle by summing the individual weighted scores/category (e.g., Σ of all values with 3 for P1) and dividing it by the highest attainable score of 30.

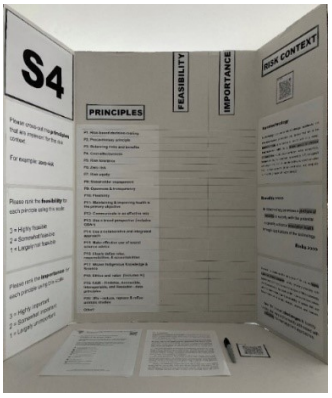
Table S6: Calculation of Weighted Relevance Score for Principles P1 through P10 Across Ten Risk Contexts

Risk Context	Principles									
Sum	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**
ΣHR	15	15	15	15	9	3	12	24	27	12
ΣSR	6	4	4	8	8	0	6	0	0	8
ΣLI	2	3	3	1	3	9	2	2	1	2
Percentage	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**
%HR	50	50	50	50	30	10	40	80	90	40
%SR	20	13	13	27	27	0	20	0	0	27
%HR or SR	**70**	**63**	**63**	**77**	**57**	**10**	**60**	**80**	**90**	**67**
%LI	**7**	**10**	**10**	**3**	**10**	**30**	**10**	**7**	**3**	**7**

*Weighted categories: HR = 3, SR = 2, LI = 1
% = ((sum of individual weighted values (e.g., ΣHR)/maximum total value of 30**) x100)
**Maximum value of 30 would occur for a principle receiving HR=3 for all ten risk contexts (ΣHR = 30).

Figure S1 is an example of the tri-fold display board used to create the science fair style scoring grid for risk context scenario 4 (or S4). The first panel includes the section number and instructions on how to rank feasibility and importance for each principle. The middle and final panels provide the scoring grid and risk context, respectively. The items in front of the board (left to right) include a hard copy of the Krewski et al., (2022) paper, a description of the risk context, a black marker for entering the data in the middle panel, and a QR code for the digital copy of the paper by Krewski and colleagues. Each risk context had the same set-up thereby allowing the participants to have access to the information they required to complete the activity.

Figure S1: Science Fair Style Scoring grid



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CHAPTER 4: ARTICLE 2. Ethical principles for regulatory risk decision-making

Chapter overview

This chapter addresses the first research objective (Chapter 1) and second question (Chapter 2) through an original research article which relies on knowledge mobilization and translation to determine ethical principles and considerations for risk decision-making. Experts and global thinkers in risk, health, regulatory, and animal sciences were convened to share their lived experiences in relation to the intersection between risk science and analysis, regulatory science, and public health. Through a participatory and knowledge translation approach, an integrated risk decision-making *projector model*, with ethical principles and considerations, was developed and applied using diverse, contemporary risk decision-making and regulatory contexts. The article was accepted for publication in the journal *Regulatory Toxicology and Pharmacology*.

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Data availability

The data used for the research described in this article is provided in the supplementary material.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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4.1 Abstract

Risk assessors, managers, and decision-makers are responsible for evaluating diverse human, environmental, and animal health risks. Although the critical elements of risk assessment and management are well-described in national and international documents, the ethical issues involved in risk decision-making have received comparatively little attention to date. To address this aspect, this article elaborates fundamental ethical principles designed to support fair, balanced, and equitable risk-based decision-making practices. Experts and global thinkers in risk, health, regulatory, and animal sciences were convened to share their lived experiences in relation to the intersection between risk science and analysis, regulatory science, and public health. Through a participatory and knowledge translation approach, an integrated risk decision-making model, with ethical principles and considerations, was developed and applied using diverse, contemporary risk decision-making and regulatory contexts. The ten principles - autonomy, minimize harm, maintain respect and trust, adaptability, reduce disparities, holistic, fair and just, open and transparent, stakeholder engagement, and One Health lens - demonstrate how public sector values and moral norms (i.e., ethics) are relevant to risk decision-making. We also hope these principles and considerations stimulate further discussion, debate, and an increased awareness of the application of ethics in identifying, assessing, and managing health risks.

Keywords: Ethical principles, regulatory context, risk decision-making, ONE Health lens, projector model

4.2 Introduction

The complex nature of regulatory risk decision-making is, in part, a consequence of the requirement for adhering to processes and activities grounded in regulations. This includes the generation of data for regulatory purposes, the application of the scientific method, and requiring regulatory evaluation prior to market authorization (Institute of Medicine, 2012; Saner, 2010). Further, risk decision-making encompasses risk assessors, managers, and other staff (including the decision-makers) responsible for evaluating human, environmental, and animal health risks within a federal regulatory context. These diverse, fit-for-purpose endeavours must align with regulatory directives, policies, and guidance documents along with requirements of national and international standard-setting bodies. Risk science is continually evolving, with multi-

stakeholder initiatives as well as tools advancing new approach methodologies. Modern risk science is ushering in a new paradigm with next generation risk assessments and science-policy frameworks aimed at modernizing some of these policies and guidelines (Bhuller et al., 2021; Clippinger et al., 2022; Cote et al., 2012; Cote et al., 2016; Kim and Choi, 2023; Krewski et al., 2020; Krewski et al., 2014; Stucki et al., 2022; United States Environmental Protection Agency, 2014).

Health risk assessments (human, environmental, and animal) conducted for regulatory purposes reflect internationally recognized and accepted practices for problem formulation, identifying and characterizing hazards, determining the sources of exposure, and evaluating exposure-response relationships. These risk assessments typically consider and quantify the risk context or scenario, the probability or likelihood that the scenario will occur, and the consequence of the occurrence of that scenario (Aven, 2020b). The risk assessment process includes integrating the evidence, addressing uncertainty, and considering the input from evaluators along with other sources of information. The inherent uncertainty implies that each risk assessment has only a probability of being correct, calling for a probabilistic risk assessment (Maertens et al., 2022, 2024) to make this transparent and in part quantifiable. Depending on the risk context, the evidence integration phase brings together the underlying scientific data along with other contextual factors such as societal costs and benefits (Krewski et al., 2022a). The risk management step then considers the outcome of the risk assessment, relevant contextual factors, and other elements pertinent to the overall risk decision-making process such as proposed mitigation measures and how best to communicate the risks (Amalberti, 2013; Bhuller and Trevithick-Sutton, 2024; Health Canada, 2000; Krewski et al., 2011, 2019).

For certain product types, (e.g., pharmaceuticals), the regulatory risk assessment phase includes considering the potential benefits from being exposed to the medicine or treatment regime (Colopy et al., 2015; Ghabri, 2023; Mussen, 2017; Verhagen et al., 2012). Ethical requirements, such as approval from a Research Ethics Board, may also be prescribed in law, regulatory directives, or risk management policies. For example, in Canada there is a regulatory requirement for an independent ethics approval along with regulatory authorization prior to commencing Phase I to III clinical trials for pharmaceuticals and biologics (Health Canada, 2022). To further explore and incorporate the ethical aspects of risks decision-making, interdisciplinary teams addressing a risk issue can also include bioethicists, environmental

ethicists, experts in animal welfare, and social scientists who collaborate with the risk assessors, managers, and decision-makers.

While the risk assessment is a science and evidence-based process, there is also a role for knowledge in terms of justified beliefs derived from observations, reasoning, and dialogue (Aven, 2018; Hartung, 2017), moral values (Hansson, 2012), and risk assessment policy - a term used to differentiate judgments and choices from the broader social and economic policy issues pertinent to risk management decisions (National Research Council, 1983). For example, aspiring to manage risks with an understanding that achieving zero risks is unattainable in most cases. Consequently, there is a level of risk that is *de facto* considered as being acceptable or tolerable under the specified conditions of use of the product under evaluation (Bouder et al., 2007). There are also established principles for setting risk acceptance criteria, such as the ALARP (as low as reasonably practicable) principle, some of which are justifiable from an ethical perspective (Vanem, 2012). Similarly, Krewski and colleagues also reflected on how risk assessments and the subsequent management and communication of risks rely not only on scientific evidence but also on other contextual factors including ethical principles and considerations (Bhuller et al., 2024a; Krewski et al., 2022b), which is the scope of this paper.

Scholarly literature has focused on the importance of adhering to ethical principles in relation to human rights (Hunt, 2004), animal rights and welfare (Herrmann et al., 2019; Paton et al., 2023; Singer and Harari, 2023), data sovereignty (Carroll et al., 2021), and ecological concerns (MacLean, 2012). There are also documents providing ethical principles for risk decision-making, such as the Public Health Agency of Canada's (PHAC's) *Framework for Ethical Deliberation and Decision-Making in Public Health* (Public Health Agency of Canada, 2017), *Ethics & Principles for Science & Society Policy-Making: The Brussels Declaration* (SciCom – Making Sense of Science, 2017), the in-depth review of risk management frameworks by Jardine and colleagues (Jardine et al., 2003), and articles describing how to integrate ethics in health technology assessments (Hofmann et al., 2015; Vanem, 2012). Nonetheless, there does not appear to be a more recent enumeration of key ethical principles and considerations for contemporary regulatory risk decision-making, which includes two central concepts in applied ethics: *societal values* (what is considered "good") and *moral norms* (standards on how one should act in society, along with duties and rights). Further, these "norms and values" extend to institutions where they guide the attitudes, character, and actions of risk assessors, managers, and

decision-makers throughout the evidence integration, assessment, and management phases of the decision-making process (Vanem, 2012). Therefore, this is a critical time for evaluating such principles as advances in science and technology, lessons learned from the COVID-19 pandemic (Cauchemez et al., 2024; Mihelj et al., 2022; Vickery et al., 2022; Wills and Shields, 2023), and other national and global health and environmental risks of concern have raised new fundamental questions about ethics in risk decision-making. Given such a landscape, the purpose of this paper is to present a framework for creating a model with ten ethical principles and considerations. These principles are built from existing literature relevant to risk decision-making for health (human, animal, and the environment). Consequently, while all the principles build from these two central concepts in applied ethics, they all do not belong exclusively to the field of ethics, and may overlap in part with other principles of risk science. The utility of these principles is then demonstrated using the application of the model to diverse and contemporary real-world risk contexts.

4.3 Methodological approach

For this study, the well-established phases of knowledge translation – knowledge inquiry, synthesis and characterization, and tailoring and integration (Graham et al., 2006; Health Canada, 2017) - were used to build from an initial set of proposed ethical principles to eventually develop the knowledge product (i.e., ethical principles relevant for risk decision-making and a visual referred to as the projector model). Thought leaders and knowledge users in risk, health, and animal sciences were convened to share their lived experiences in relation to the intersection between risk analysis, regulatory science, and public health.[1] All eight experts initially reviewed and provided comments on a discussion document, which incorporated the information provided in the **Supplementary Material** (e.g., detailed insights on ethical theories (**Table S1**) and principles (**Table S2**) relevant for risk decision-making). This was an important step as all involved started the knowledge-to-action process from a common starting point, which included insights from experts in the area of ethics. Further, the first set of ethical principles and proposed models shown in the **Supplementary Material** were also based on earlier research including reviews of risk decision-making principles (Bhuller et al., 2024a; Krewski et al., 2014) and existing ethical principles and considerations relevant to this initiative.

[1]The University of Ottawa's Research Ethics Board (REB) approved the study (Ethics file number: H-11-23-9868).

4.4 Designing a model for ethical principles

The U.S. National Research Council has previously acknowledged how risk assessment and risk management activities are separate but also interact and form key components of risk decision-making (National Research Council, 1994, 2009). Similarly, the overall mandate of regulatory bodies typically creates an intersection between risk decision-making regarding the specific risk issue at hand and the broader public health mandate for protecting and promoting health. Consequently, several of the experts supported the notion of creating ethical principles and considerations using a framework and providing overarching principles to help guide the risk decision-making process. Accordingly, instead of creating specific principles for risk assessment and management (**Figs. S1** and **S2**, **Supplementary Material**), a systems thinking lens (Bhuller et al., 2024a; Bhuller and Trevithick-Sutton, 2024) guided the creation of a more integrated approach.

During the first expert discussion, the initial speaker shared a conceptual approach for this initiative. **Fig. 1** is an adaptation of this approach resulting in an overarching framework with three constructs: (i) framing, (ii) directionality, and (iii) fluidity.

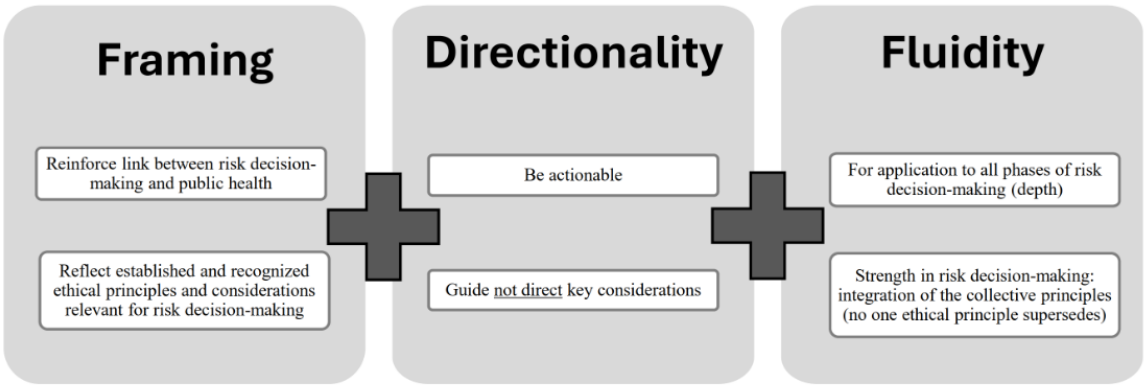

Fig 1. Constructs for developing ethical principles for regulatory risk decision-making.

The first construct - framing - intends to reinforce how risk assessment and management is fundamentally relevant to public health. This implies that ethical principles and considerations for risk decision-making could also reflect core principles for public health. The other aspect of this construct is to build from existing work, which includes the references provided in **Table S2**, **Supplementary Material** along with considering ethical principles developed for public health (Childress et al., 2002; Government of Canada, 2022b; Public Health Leadership Society, 2002). The second construct - directionality - requires that these principles are actionable in a manner

such that they guide ethical considerations (as opposed to prescribing how they are to be implemented). For example, engaging the perspectives of stakeholders and developing a risk management plan would be guiding. Directing includes a statement where all interested stakeholders, in all aspects of all activities, are identified for developing a risk management plan. The final construct - fluidity - prevents the principles from being ranked or placed in discrete categories such as risk assessment. In other words, independent of where the ethical principles and considerations are placed, they can be applied in all phases of risk decision-making.

To develop an integrated model, the experts also recognized the value of enunciating how the ethical principles "would promote good ethics." For example, is it unethical to withhold information by not being open and transparent? In the current regulatory climate, several authorities continue to support both open government and science and not being open and transparent would be in contradiction with contemporary institutional values. Further, a lack of transparency would also prevent stakeholders from making informed choices and decisions (thereby limiting autonomy), which could result in harm (compromising beneficence/non-maleficence). While there can be risk contexts where governments must withhold information (e.g., bioterrorism), for most regulatory risk-decision contexts, withholding information by not being open and transparent, would not be promoting "good ethics."

4.5 Towards an integrated risk and ethical decision-making model

As ethical issues can arise throughout the risk decision-making process, the initial models for this initiative (**Fig. S2**; **Supplementary Material**) required considerable modification to better reflect a broader and more holistic approach. For example, while the first set of proposed principles used two categories: risk assessment and management, the final model (**Fig. 2**) transitioned from two categories to a more holistic application of these principles and considerations within a broader and integrated regulatory worldview and context.

The projector model is developed using the framing and fluidity constructs and **Table 1** provides the descriptors for each ethical principle (based on these two key components: public sector values and moral norms), thereby addressing the last construct (i.e., directionality). The model depicts the interaction among the following three domains: (i) the broader regulatory worldview "reel"; (ii) the internal, foundational elements (three-legged tripod); and (iii) the projector for the decision-making process which is linked to the ethical and risk context reels. The two bands of

"film" going from the ethical context reel to the other, risk context reel has bi-directional arrows to note how aspects of the risk context inform the ethical context and *vice versa*. The regulatory worldview is also connected with the inner dimensions through the data ecosystem, and this creates the "data-information" bridge with the ethics and risk context reels. The projector's One Health "lens" eventually creates the mechanism to relay the "film" (knowledge) required for the public (depending on the context, this could be the entire population, population subgroups, or individuals) to make an autonomous and informed risk decision regarding the risk issue of concern.

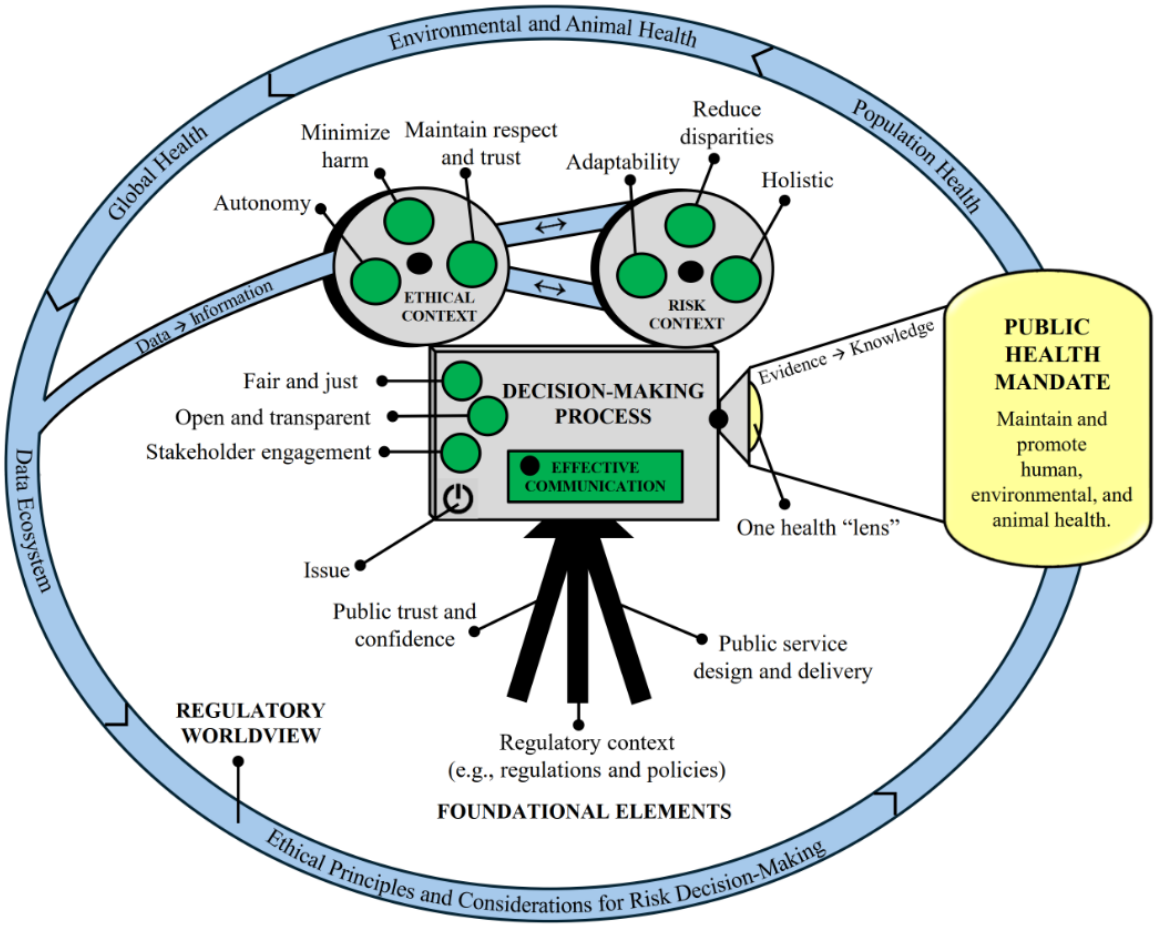

Fig 2. The projector model.

A One Health approach accounts for the interconnectedness of human, animal, plant, and ecosystem health, embodying a holistic perspective to risk decision-making. This approach also emphasizes an ethical obligation to consider the well-being of all species; acknowledges the interdependencies between human, animal, and environmental health; and recognizes that actions taken in one area can have significant and often unintended effects on others (Public Health

Agency of Canada, 2024). While such an approach is not necessary for all risk contexts, the projector model's incorporation of a One Health "lens" serves as a reminder of the juxtaposition between the risk and ethical contexts intertwined in the risk decision-making process (**Fig. 2**). Further, a One Health lens draws on foundational elements of ethics, particularly principles such as fairness, respect for all species, and the duty to minimize harm. These principles guide the transdisciplinary risk decision-making process, which values adaptability and collaboration across different sectors, ensuring that decisions are evidence-based, ethically defensible, and aligned with broader societal values. Consequently, the projector model shows how holism brings the One Health lens together with the field of ethics, as they both involve a shared responsibility to consider the moral obligations across multiple domains - human, animal, environmental, and ecological - while accounting for both immediate and long-term risk and ethical implications. This integrated approach also underscores the importance of ethical reflection in health risk decision-making, ensuring that interventions are not only scientifically sound but also ethically responsible.

The projected image also shows how the regulatory risk decision is grounded in pillars deeply rooted in public service and health factors and the regulatory context (foundational elements) while linking back to the underlying public health mandate of maintaining and promoting human, environmental, and animal health. As the knowledge generated (e.g., proposed and final regulatory risk assessment decisions) is typically for the public and other interested and affected parties (or a specific subpopulation within this audience), the projection is shown to occur within the broader worldview, which includes other aspects such as the link to global health.

The model shows the start of the process as an "on" symbol and the words "issue". Triggering of an issue - either planned or spontaneous - requires risk assessors, managers, and other members of the risk decision-making team to formulate and characterize the problem within the risk, ethical, and regulatory contexts. This includes determining the data/information "reel" to eventually generate the evidence for risk decision-making, along with a thorough understanding of the foundational elements supporting the decision-making process. For example, several regulatory authorities have values and ethic codes for public sector organizations which provide the foundational elements and pillars for all decision-making contexts for these institutions (OECD, 2000). This includes the role of Federal Public Servants and Ministers in upholding public trust and confidence along with statement of values (e.g., respect for people and

democracy), expected behaviours, and links to pertinent laws, such as the Canadian *Constitution Act,* relevant to the design and delivery of the public service (Government of Canada, 2011, 2023). Therefore, it is important to be well informed of these foundational elements and how the three pillars (public trust and confidence, regulatory context, and public service design and delivery) support and interact with risk decision-making. This includes being objective, responsible, and accountable for the regulatory risk decision. For example, unreasonably negative ("the sky is falling") or contradictory ("crying wolf") risk assessments can undermine the credibility of the regulator and defeat the purpose of subsequent risk communications. The model also shows how being uninformed of these elements could significantly and pejoratively impact the decision-making for all risk issues; the foundational elements not only support the projector (decision-making process) and reels (ethical and risk context), but it also allows for these internal elements to be linked to the broader factors within the regulatory worldview.

While the foundational elements relate to the general conduct of regulators, there are additional considerations specific to health risk assessments in a regulatory environment. Such considerations include how the available evidence is integrated, whether an estimated risk or level of precaution is judged as acceptable, or whether a health effect associated with a certain substance is also of global concern (e.g., a pandemic). Consequently, the data/information is viewed both from a broader, regulatory worldview perspective along with considering the ethical and risk contexts/reels prior to being integrated and subject to additional principles in the decision-making process. Further, it is also ideal to incorporate a broader worldview perspective, at an early stage of the process, while considering other factors relevant to the risk issue and context (e.g., data requirements). This guidance considers how health risk decision-making is complex and involves considering multiple factors, including science and ethics and the interactions between the risk assessment (science) phase, risk management (science-policy) phase, and broader (policy-political-publics) space (Bhuller and Trevithick-Sutton, 2024). Such an approach also provides an opportunity to link the risk issue with the institutional mandate along with the broader health context (population, environmental, animal, and global health), the data ecosystem, and eventually, the data/information required to address the issue.

In the projector model, effective communication (black circle) is identified as being relevant in all the components of this model. However, the same holds for all the principles, in that they are all relevant from the point where they are identified and then throughout the decision-making

process. For example, “maintain respect and trust” is identified within the ethical context reel; however, this principle is relevant during the risk context, decision-making process, and the link back to the regulatory worldview.

The projector’s One Health “lens” requires that the knowledge shared from the decision-making process connects with the institution’s public health mandate for maintaining and promoting human, environmental, and animal health. Further, when considering human health, the worldview requires all those involved in the risk decision-making process to make the connections with population, environmental, animal, and global health. For example, population health includes considering risk management strategies that account for high-risk subpopulations, upstream solutions for promoting health and well-being, and incorporates data, such as sex and gender-based analysis plus and other information related to the underlying social and structural determinants of health (Canadian Institutes of Health Research, 2011; Cohen et al., 2014; Frohlich et al., 2004; Government of Canada, 2013b; Greenwood et al., 2018).

The inclusion of environmental and animal health reflects the importance of going beyond accounting only for the welfare of humans. Further, global health accounts for how health risk issues have no boundaries and thus, it is important to determine how other jurisdictions are managing the issue. This is particularly relevant when foreign action (or inaction) by other actors and decision-makers can affect the risk decision-making at the national and even local level. The overall, regulatory worldview also brings both the ethical principles and considerations back to the data ecosystem used in the decision-making process. This worldview illustrates the interconnectedness and application of all of the ethical principles and considerations throughout the process. For example, when considering the type of data required for addressing an issue, the ethical principles of adaptability and respect are well aligned with approaches, such as value of information, which guide the determination towards only requiring the data/information truly needed for the specific context (Hagiwara et al., 2022). It also supports the need to view the risk decision-making from a One Health lens perspective.

Table 1: Ethical principles, guiding descriptors, and considerations

Domain[a]	Guiding descriptors and considerations for risk decision-makers
Ethical principles (EP1 to 3) flowing from the ethical to the risk context and	**EP1 - Autonomy:** Foster informed decision-making for all interested and affected parties by recognizing the capacity of choice to: (i) participate in decisions, (ii) provide information on the issue, assessment, and outcome, and (iii) where and when possible, support individuals and communities to act independently on the issue, based on their choices and interests.

decision-making process.	"Autonomy can [also] be violated when scientific information is represented in a way to support the interests of the information holder. Misrepresentation of scientific information precludes informed choices by actors, stakeholders, or consumers. Limiting information access also affects autonomy" (Kuzma and Besley, 2008). **EP2 - Minimize harm:** As achieving zero risks will be unattainable for most issues, aspire to manage health risks with an understanding to do more good than harm (beneficence, non-maleficence). Regulatory science aims to identify and characterize the hazard, sources of exposure, and the dose that can result in risks to human and animal health, and the environment. Consequently, health risk decisions seek to either prevent or minimize harm by providing specific conditions on use (e.g., on product labels of authorized products). For pharmaceuticals and other therapeutic products, another objective is to maximize the potential benefits (while minimizing risks) from exposure to the medicine or treatment regime (Colopy et al., 2015; Kuzma and Besley, 2008; Mt-Isa et al., 2014; Verhagen et al., 2012; Walker et al., 2015) **EP3 - Maintain respect and trust:** When dealing with risk and uncertainty, all individuals who are part of the decision-making process shall strive to deliver all risk decision-making activities and actions in a considerate and reliable manner. This includes being inclusive and upholding all the elements of the other principles. As an all-encompassing principle, maintain respect extends to other principles, such as respect for people and democracy, which are part of the foundational element and other ethical principles woven throughout all the risk decision-making domains. It also includes adhering with the requirements of existing data principles such as FAIR (findable, accessible, interoperable, and reusable) for science data management and stewardship along with CARE (collective benefit, authority to control, responsibility, and ethics) and OCAP® (ownership, control, access, and possession) which extend to respecting the data sovereignty for Indigenous science and knowledge (Carroll et al., 2021; First Nations Information Governance Centre, 2024). Further, respect also accounts for the welfare of animals as we continue to have a paradigm shift towards non-animal testing approaches for regulatory purposes (Bhuller et al., 2024b; Hilton et al., 2023a; Hilton et al., 2023b).
Ethical principles (EP4 to 6) relevant to the risk context.	**EP4 - Adaptability:** The data and information for identifying, assessing, characterizing, and managing risks is fit for purpose, reflects the best available science and evidence, and adheres to the other data principles (see EP3 - Maintain respect and trust). Flexibility is not just an important risk management principle (Bhuller et al., 2024a; Krewski et al., 2022b), it is also critical as an ethical principle. Several institutions value mechanisms which keep pace with emerging knowledge and technology generated from moral approaches respecting the welfare and rights of humans, the environment, and animals. Being adaptable, fit-for-purpose, and efficient is also important for the timely application of protection standards while maintaining procedural fairness (e.g., approaches resulting in evergreen risk

	assessment without imposing or creating unnecessary constraints on the regulatory risk decision-making process, procedural unfairness, or unnecessary burden on regulated parties) **EP5 - Reduce disparities:** Work towards ensuring that unavoidable risks are shared in an equitable manner and not disproportionately borne by specific groups, subpopulations, or individuals. Reducing disparities extends to sharing both risks and benefits in an equitable manner. Consequently, this ethical principle is aligned with the previously established risk principle, risk equity. Further, risk equity-based decisions reflect the social, environmental, economic, cultural, legal, and other values (Krewski et al., 2022b). This reflection and application of the risk equity/reduce disparities also includes managing risks through effective risk communication. For example, by delivering the message based on how the target audience will receive and act on the information (Bhuller and Trevithick-Sutton, 2024) and communicating in a culturally and linguistically appropriate manner. **EP6 - Holistic:** Embrace the interconnectedness and multi/inter/transdisciplinary nature of risk science by supporting the inclusion and incorporation of all relevant data generated from various evidence streams and incorporated by integrating this data/information to generate the best knowledge for determining the nature, probability, and severity of the health risk. Modern evidence integration and data interpretation practices seek to ensure that all relevant evidence is included in the health risk assessment (Krewski et al., 2022a). This includes using appropriate quality assessment and weight of evidence approaches to arrive at an objective conclusion consistent with the cumulative body of evidence available at the time of the assessment (World Health Organization, 2021).
Ethical principles (EP7 to 10) relevant to the risk decision-making process.	**EP7 - Fair and just:** Promote a decision-making process that is impartial, unbiased, and rationale (Aschner et al., 2021). The risk decision-making process and outcome entails treating the interested and impacted groups, subpopulations, and individuals with equal concern and respect. This includes addressing distributional issues that are unique to the risk context and considering the ethical dimensions of risk (e.g., social and structural determinants of health) from an individual and societal perspective (Greenwood et al., 2018; Jardine et al., 2003; MacLean, 2012; Public Health Agency of Canada, 2017). Further, ethical considerations also dictate that the available evidence is evaluated in an objective manner, with all efforts being made to ensure that potential biases are avoided or minimized (Kitson et al., 1998; Krewski et al., 2022a; World Health Organization, 2021) **EP8 - Open and transparent:** Build and maintain public respect and trust (EP3), and confidence through clarity, honesty, truthfulness, and visibility in the decision-making process, effectively communicating, and making accessible the information so that all interested and affected parties can make autonomous (EP1) and informed choices and decisions.

	PHAC's *Framework for Ethical Deliberation and Decision-Making in Public Health* notes the link between trust and the "success of public health initiatives" and how this relationship requires processes that are open and transparent (Public Health Agency of Canada, 2017). By being open and transparent, regulatory institutions can make documents accessible (open data and science) while clarifying, preserving, and respecting their legal obligations to protect the confidentiality of business and personal information (Jardine et al., 2003; Public Health Leadership Society, 2002). Open and transparent was also previously determined as being a universal risk principle relevant to a vast majority of risk contexts (Bhuller et al., 2024a). **EP9 - Stakeholder engagement:** Promote engagement and collaboration with all interested and affected parties, to the extent possible, by creating an institutional culture and decision-making processes supporting this type of discourse. Engagement with the public, private sector, and non-governmental organizations creates a dialogue between the regulatory authority and stakeholders. This requires the regulatory authority to create ethical spaces for discourse (Adams, 2021; Ermine, 2007) along with the time for building and maintaining mutual trust and respect (SciCom –Making Sense of Science, 2017). Another key aspect of stakeholder engagement is to provide actionable information where applicable. This includes guidance on risks versus benefits such as continuing consumption or treatment with a product, availability of alternatives and who to consult (e.g., physician or pharmacist), and proper disposal of products deemed too risky for continued use. Further, engagement, effective communication, and collaboration are also essential attributes of a high-performing organization and a key component of the statement of values for the Canadian public sector (Government of Canada, 2011; Treasury Board of Canada Secretariat, 2003).Similar to open and transparent (EP8), stakeholder engagement was also previously determined as a universal risk principle relevant to a majority of risk contexts (Bhuller et al., 2024a) **EP10 - One Health lens:** Recognize how the final decision will be projected into the broader worldview - for the public and all interested parties - and use this understanding to view the issue and the context from the human, environmental, and animal health perspective while considering other ethical principles and pertinent factors for risk decision-making. The core feature of policies such as One Health and Health in All Policies is the importance of partnership, shared decision-making, and collaborative governance (Green et al., 2021; Herriot and Valentine, 2018; World Health Organization, 2015). Consequently, these policies are complex and broad by design and thus, appropriate for risk issues and contexts that are just as complex. Examples include the Pan-Canadian strategies for health data and antimicrobial resistance (Government of Canada, 2022a; Public Health Agency of Canada, 2023), and other "wicked problems" (Auspos and Cabaj, 2014). While partnership, shared decision-making, and collaborative governance is not necessary for all risk issues, the application of a One Health lens provides an opportunity to view these issues from a broader perspective thereby providing additional insights towards more informative decision-making. For example, the intersections between these domains are important in understanding the paradigm shift towards non-animal testing strategies especially when they provide the best

	science for evaluating health risks while reducing negative impacts on animals and the environment (Bhuller et al., 2024c)

[a]While not all of the ethical principles are exclusively from the field of ethics, they all build from these two central concepts in applied ethics: public sector values and moral norms.

4.6 Applying the projector model to contemporary health risk issues

The corresponding domains and decision-making principles of the projector model build from existing ethical principles and these two central concepts in applied ethics: values and norms. What is unique to the projector model, however, is the integration and presentation of these domains and principles within the risk and ethical context relevant for regulatory risk decision-making (human, animal, and environmental issues). Consequently, the projector model helps visualize how the ethical context continues to flow into the risk context and the decision-making process. This means that the risk and decision-making components include principles which also build from the two central ethical concepts and thus, have additional, ethical considerations thereby differentiating them from more technical and perhaps process-based risk principles (e.g., addressing technical bias during the risk assessment phase of the decision-making process). Having said that, the bidirectional and continuous flow also implies that not all of the ethical principles belong exclusively to the field of ethics. For example, while open and transparent and stakeholder engagement have previously been identified as universal risk principles applicable to a majority of risk contexts (Bhuller et al., 2024a), these principles also have important ethical aspects as shown in the present work. The application of this model is further examined by considering three contemporary risk issues and how they relate to the ethical principles, grounded in institutional values and moral norms, and identified in this model. All three examples require a One Health lens, consideration of the broad worldview factors, and are from various perspectives including a regulatory one. Consequently, the foundational elements are not further discussed in detail as they are assumed to be relevant and required for these issues.

4.6.1 Enzyme replacement therapy for managing cystic fibrosis

Cystic fibrosis (CF) is an inherited, fatal, multi-organ, genetic disease involving primarily the lungs and digestive system of young children. As a pediatric disease, it creates a thick sticky mucus which clogs the lungs, makes it difficult to breathe, and can result in a risk of life-threatening lung infections. CF also affects the pancreas and pancreatic duct where the thick secretions prevent the release into the small intestine of digestive enzymes responsible for

breaking down food. Consequently, CF patients find it hard to digest and absorb nutrients and must rely on oral enzymatic interventions designed to help with the treatment of pancreatic insufficiency attributed to CF (Davies et al., 2007; Petruzziello-Pellegrini et al., 2018). Pancreatic enzyme replacement therapy relies on the use of encapsulated tablets that enable the enzyme preparation to withstand the acidic environment of the stomach. Following ingestion, these tablets go past the stomach and into the small intestine where the active enzyme is released (Keller et al., 2009). The enteric coating on some of these encapsulated products is made from phthalates, a substance widely used in several consumer products, medications, and industrial products. In 2009, Keller and colleagues also reported the presence of exceedingly high concentrations of phthalate metabolites in the urine of CF-patients using enteric-coated pancreatic enzymes. Organizations, such as the Cystic Fibrosis Foundation, published notices informing the CF community of the benefits to using phthalates in these tablets - they slow the release of the medicine making it more effective - while clarifying how there is no medical evidence showing concerns for toxic effects in CF patients using these medications over long periods of time (Cystic Fibrosis Foundation, 2012).

In analyzing this issue from a regulatory and ethical perspective, the principles of autonomy (EP1; informed decision-making regarding the presence of phthalates), reduce disparities (EP5; unavoidable risks of phthalates not being disproportionately born by a specific subgroup of CF patients), and maintain respect and trust (EP3; dealing with the potential risks and uncertainty regarding such exposure in a respectful manner) apply for this risk issue and context. Further, regulatory authorities were also committed to finding an alternative solution with more equitable access to tablets with phthalate-free enteric coating. This required viewing the issue from the broader regulatory worldview perspective (population and global health) and engaging all interested stakeholders (EP9; regulated community, CF organizations in Canada and the US, experts in CF, and other regulatory authorities) using effective communication and a fair, equitable, open, and transparent approach (EP 7 and 8).

> *"We [regulators] had to look at the risk of the phthalates, which we know have a variety of adverse effects. They are endocrine disruptors, estrogenic, developmental, hepatotoxic, nephrotoxic, cardiotoxic, and have cancer risk increasing effects. But on the other hand, if children with cystic fibrosis don't get these enzymes, they suffer very serious malabsorption effects, which could be potentially fatal." (Speaker 4, February 9, 2024))*

The regulatory authority's worldview also extended to include the data ecosystem for this risk issue. Specifically, the need for data to support a phthalate-free enteric coating tablet for CF thereby eliminating potential risks of concern associated with chronic exposure to phthalates, which includes impacts on the endocrine, respiratory, and digestive systems of children (Wang and Qian, 2021). In taking this approach, the Canadian regulatory authority and representatives from the pharmaceutical industry used an adaptable (EP4) and holistic (EP6) approach where the underlying objective continued to be the collective goal of minimizing harm (EP2) for the CF-patient.

> *"We [regulators] worked with the industry to say, you know, this coating, this enteric coating is a problem. So, can you come up with an alternative solution. Industry said: "Yes, we can do that." To provide a greater level of regulatory oversight, we moved the high dose products for children from a natural health product to a biologic drug, which would be prescription only and require a high level of regulatory oversight. The company came up with a new coating which didn't contain phthalates. It got a very prompt pre-market review and it is now on the market." (Speaker 4, February 9, 2024)*

It is important to point out that while the above example focuses primarily from the regulatory perspective, the ultimate success of a fair and just (EP7) and holistic approach (EP6) to addressing the issue for this risk context relied on the engagement (EP9), contribution, and understanding of the parents, caregivers, patients, and advocacy groups.

4.6.2 The ethics regarding the best available science

A fundamental ethical issue in characterizing risks, for regulatory decision-making purposes, is in relation to the data ecosystem. For example, how can the risk assessment community ensure that the human data are generated and collected in an ethical manner? Globally, while there continues to be ethical debates around specific aspects of clinical trials (e.g., inclusion of pregnant women), a standard practice of randomized clinical trials investigating the benefits and risks of therapeutic products is for the protocol to be reviewed and approved by institutional review boards before the trial begins. The ethical review ensures, amongst other things, that the clinical trial participants are not subject to undue harm and are well informed of the risks and benefits associated with being part of the trial. The knowledge acquired from human clinical trials is a valuable source of data regarding the safety, efficacy, and quality of therapeutic products used for clinical purposes (Health Canada, 2022). In reality, however, humans can also

be exposed to other product types such as pest control products. Consequently, policies, such as the *Restricted Use of Human Studies with Pesticides for Regulatory Purposes*, provide clear instructions, including when to attain ethics approval, on the rare cases where human studies with pest control products can occur for regulatory purposes (Pest Management Regulatory Agency, 2016).

Ethical issues related to animal welfare and rights also occur when using animal data for the purposes of health risk assessments (Balls et al., 2024; Herrmann et al., 2019; Paton et al., 2023; Singer and Harari, 2023). Several multi-stakeholder initiatives are serving as catalysts for a global paradigm shift towards addressing these concerns by focusing efforts grounded in the reduction and replacement of animals used in testing (Hilton et al., 2023a). Progress towards this goal is being supported by the development and advances in science and technology in the area of *in vitro*, *in silico* and other novel, non-animal test methods (Bean et al., 2023; Bhuller et al., 2021; Clippinger et al., 2022; Hartung et al., 2024; Schmeisser et al., 2023; Stucki et al., 2022; Varshavsky et al., 2023). Regulatory authorities in Europe, the United States, and Canada have already taken action by making the use of toxicological studies on animals as a last resort for cosmetic products (Bury et al., 2021; Dent et al., 2018; Dent et al., 2021; Fentem et al., 2021; Government of Canada, 2013a).

> *"When I came into science, as I said 35 years ago, the knowledge of science doubled every 15 years. Around 2000, it was already doubling every seven years. And now, it is calculated to be doubling every 2 to 3 years in scientific knowledge. Imagine how much more we know now compared to the time when we introduced our toolbox. I think we have a very strong need to adopt technical progress and better the situation." (Speaker 3, February 9, 2024)*

The use of non-animal strategies and the corresponding discourse has also transitioned from one-to-one replacement including refining or replacing a conventional animal assay with a non-animal solution, on a case-by-case basis, towards the creation of several new approach methodologies incorporating advances in science and technology (e.g., organ-on-a-chip), and complex next generation risk assessment strategies designed to use the best available science and regulatory approach for assessing risks (Bury et al., 2021; Cote et al., 2016; Kim and Choi, 2023; Krewski et al., 2020; Krewski et al., 2014; Otto et al., 2022; Pallocca et al., 2022; Schmeisser et al., 2023; Tannenbaum, 2012; United States Environmental Protection Agency, 2014; Wolf et al., 2022). Further, a recent dialogue with leaders in the area of non-animal strategies, animal welfare and rights, and next generation risk assessors included a recommendation to go beyond

recommending non-animal testing methods as cost-effective and human relevant solutions to including the environmental and ethical (humane) perspectives (Bhuller et al., 2024c). For example, some of these leaders questioned if certain new approach methods provided human relevant data which is "as good" or "better than the conventional animal studies" (Clippinger et al., 2021; Gilmour et al., 2022; OECD, 2023), what are the ethical implications (and risks) for continuing to use the traditional animal studies as opposed to transitioning to these new approaches representing the best available science? A similar question was raised by some of the experts from this initiative.

> *"It is ethically important that we are acknowledging the imperfection of the tools we are working with. I very much believe that we have to move to something which is much more accepting. This includes the uncertainty with which we are working and the weakness of existing tools. I think this is a call for a truthful and effectful evaluation of what we are doing as we are trying to pursue more non-animal approaches." (Speaker 3, February 9, 2024)*

In applying the projector model as a tool to further understand the ethical implications of not considering the best science, the slow uptake of non-animal strategies for regulatory purposes could be due to the risk and ethical contexts. Specifically, the challenges in adapting (EP4) the data ecosystem which now contains new science or taking a broad and holistic approach (EP6) which respects and trusts (EP3) how non-animal strategies are designed to meet the goals of reducing disparities (EP5) and minimizing harm (EP2). Data requirements prescribed within laws can create barriers prolonging the uptake of new approach methods, and thereby requiring regulatory authorities to consider other regulatory tools, such as policies (Hilton et al., 2023a; Wolf et al., 2022). Another reason could be that the discourse about new approach methods may not reach the entire scientific community (EP1: autonomy, EP8: open and transparent, and EP9: stakeholder engagement), resulting in a reduced ability to build confidence in these non-animal approaches and, ultimately, public respect and trust (EP3). To help address this issue, experts and thought leaders advancing non-animal strategies recommend a continued broadening of the 'NAM-community' through open and transparent (EP8), respectful and trustful (EP3) engagement (EP9) with all interested parties and stakeholders (Bhuller et al., 2024c).

For regulatory authorities who are already committed to receiving new approach methods as an alternate to animal tests, this decision aligns with the One Health lens (EP10) and the broader, regulatory worldview as it accounts for a movement with links to human, environmental, animal, and global health. This includes institutions that are also considering strategies to help define the

type of data truly required for addressing an issue. For example, the ethical principle of adaptability (EP4) is well aligned with methodologies, such as value of information, which provide insights into determining the data/information truly needed for the specific context (Hagiwara et al., 2022).The challenge in the lack of mutual acceptance of such non-animal methods, by all regulatory institutions, is the impact on the data ecosystem: animal studies will continue to be conducted and this data/information will loop back into the ethical and risk context-reels for regulatory decision-making (with or without the non-animal-equivalent study).

4.6.3 The precautionary principle: Is too much caution unethical?

Krewski et al. (2022b) and Bhuller and colleagues (2024a) have previously proposed several fundamental principles of risk decision-making with implications for ethical decision-making practices (Bhuller et al., 2024a; Krewski et al., 2022b). One such principle is the balancing of benefits and risks to ensure that the greatest good is done for most people. This principle recognizes the benefits and risks of agents such as therapeutic products which people are exposed to, and how balancing of potential risks against the desired benefits needs to be done in a fair and equitable manner. The CF example demonstrated the relevance of ethical principles when considering the risk and benefits of taking phthalate-based enteric coated tablets. In this work, we can now see how this principle has ethical underpinnings as this example demonstrates a morally right decision-making approach (i.e., ethical theory of utilitarianism).

The precautionary principle is another example that encourages risk management actions to be taken in the presence of threats which can result in serious or irreversible harm even though there is substantial uncertainty about the risks thereby also raising ethical considerations (Ahteensuu and Sandin, 2012; Carolan, 2016; European Risk Forum, 2011; Krewski et al., 2022b; Lokke, 2006; Rogers, 2003; Saltelli and Funtowicz, 2005). In viewing the precautionary principle from an ethical perspective, the projector model provides a mechanism for considering how the risk and ethical contexts intersect with foundational elements such as the regulatory context. Lichtenberg (2010) describes how setting regulations to achieve reasonable certainty through a quantitative evaluation of risks is consistent with cost-effective approaches to regulation. However, he also notes how “precautionary regulation … can have perverse effects, even when that regulation is firmly grounded in rational decision making based on quantitative risk assessments” (Lichtenberg, 2010). For example, precautionary decisions to ban transgenic crops or no longer chlorinate drinking water may be taken based on a poor understanding of the

scientific evidence. However, they can also be ethically questionable when dealing with potential food shortages or a disproportional, increased risk of waterborne disease due to lack of chlorination. Another example, from Lichtenberg's earlier work, is the analysis of introducing new drugs and how this can result in an increase in the ability to work and contribute to both self and societal well-being (Lichtenberg, 2005). The ethical perspective in this case is taking an overly cautious approach thereby significantly delaying the approval of new drugs or not approving them at all (e.g., based on their hazard profile).

> *"As a toxicologist, I've strongly believed in the precautionary principle as a very important ethical principle, but I have also started changing the argumentation a bit more towards the economic aspects of what we are doing. To challenge a little bit of this, sure we want to save, we don't want to poison anyone, but we should also be aware that our attrition of substances is killing people. I was very much surprised when I read somewhere, by Lichtenberg, around 2005, who showed very convincingly how the introduction of a new entity, a new type of drug, in the respective area, is prolonging the life of the entire population, not just the people who get it, the entire population by about two weeks. Now, imagine how many substances never made it into clinical trials because an Ames test, to not even take an animal test here, was positive. These precautionary measures very often take out possibilities to do something good." (Speaker 3, February 9, 2024)*

Precaution in the interest of risk avoidance is certainly prudent, particularly with potentially catastrophic risks such as those associated with global health concerns (e.g., COVID-19, antimicrobial resistance, and food safety/security). The Lichtenberg examples, however, demonstrate how extreme precaution, in the face of uncertainty, can result in the manifestation and eventual increase in other health risks. For example, not approving new drugs or other products can increase disparities (opposite of EP5: reduce disparities) concerns in subpopulations who require access to these novel interventions. It also raises the question of whether the risk context, for these types of scenarios, is sufficiently adaptable (EP4), relies on a broad and holistic (EP6) approach, and meets the requirement for minimizing harm (EP2). The ethical challenge is to find the right balance between being overly cautious and considering the precautionary principle within the portfolio of risk issues confronting risk managers. The underlying intent should also be to strive for achieving reasonable certainty through the evaluation of risks while considering the ethical principles and how they relate to the broader worldview (Aven, 2020a). In doing so, risk-based decision-making can continue to be fair and just (EP7) and open and transparent (EP8) while maintaining respect and trust (EP3) and aspiring to do more good than

harm (EP5). In doing so, risk-based decision-making can continue to be fair and just (EP7) and open and transparent (EP8) while maintaining respect and trust (EP3) and aspiring to do more good than harm (EP5).

4.7 Discussion

In this paper, we build from the existing material by offering an alternative and pragmatic approach for considering ethical principles using the projector model. We rely on the foundational elements of this model as pillars supporting all regulatory decision-making. These elements, along with the One Health lens, projects all risk decisions in the broader worldview while serving as a reminder of linking these decisions back to the core public health mandate. The circular and integrated nature of this model serves as another reminder of the interconnectedness of all the elements within the health risk decision-making process. Consequently, while the principles and considerations are listed within the ethical and risk context along with the decision-making process, respectively, their application occurs throughout the entire process. Further, the ten principles and considerations are also linked, when applicable, with other principles while taking into consideration how ethics - values and moral norms - "underlie the need to take appropriate action even in the face of some scientific uncertainty" (Coughlin, 2008).

Risk is an integral part of life. People are constantly confronted with making personal decisions about risk which require balancing risks and benefits: even everyday activities such as commuting back and forth for work carry both benefits associated with employment and risks associated with an accident en route. Similarly, government agencies responsible for making human, environmental, and animal health decisions, on behalf of the populations they serve, are faced with balancing risks and benefits at the societal level. This includes contemplating the underlying ethical principles and considerations, relevant for risk decision-making, which can aid in achieving this balance. For example, ensuring the benefits and risks are not disproportionately distributed among population groups and that one group does not realize benefits at the expense of another group.

The regulatory health risk decision-making process is complex because of all the intersections between the various components including the risk assessment and management phases, and other factors such as the links between science and ethics, governance structures, and how best to

communicate risks (Bhuller and Trevithick-Sutton, 2024). The overlap between risk and ethical principles is another complexity that can be visualized using *The Systems Iceberg* Model (Bhuller et al., 2024a). Specifically, this model shows how the visible spectrum has universal 'risk' principles, such as openness and transparency (EP8) and stakeholder engagement (EP9), and effective communication, which are mostly independent of the risk context. These risk principles are now shown to be relevant from an ethical perspective. Fig. 2 also shows a similar overlap between risk-ethical principles for the risk context reel and decision-making process. For example, these previously established and deeply rooted 'risk' principles (Bhuller et al., 2024a; Krewski et al., 2022b) are now reported as also having an ethical aspect relevant for risk decision-making: (i) zero risk (captured under minimize harm (EP2); (ii) respect ethics and values, apply FAIR data principles, and reduce, replace, and refine animal studies are relevant to EP3 (maintain respect and trust); (iii) flexibility (incorporated under adaptability; EP4); (iv) risk equity (described as reduce disparities; EP5); and (v) weave Indigenous knowledge and science, apply a broad perspective, and use a collaborative and integrated approach (captured under holistic; EP6).

4.8 Conclusion

The framework for creating the projector model and the underlying ethical principles and considerations was developed using an iterative, participatory, and collaborative approach which incorporated the lived experiences of leaders, knowledge users, and thinkers in risk, regulatory, animal, and life sciences. A limitation of this work, perhaps, is the lack of formal inclusion of an expert in ethics; however, as the methodology for this initiative builds from existing work by such experts, this is not considered to be a significant limitation. Further, a balanced and diverse range of perspectives is provided to support the development of the projector model. As the principles are used to analyze three diverse risk decision-making contexts, this does strengthen the model's utility while providing a narrative to explain the risk issue from an ethical perspective. However, lack of additional examples or scenarios (e.g., addressing conflicts arising in the application of specific principles) is another limitation. Therefore, it is hoped that our findings and the development of the projector model for ethical principles relevant to regulatory health risk decision-making are insightful and serve as a starting point for more discourse on this subject matter. Consequently, we invite others to consider the application of the projector model

to other risk decision-making contexts as a mechanism to further contribute to the collective expansion of our understanding of ethical principles for risk decision-making.

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Supplementary material 1: Certificate of ethics approval

05/12/2023

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-11-23-9868
Titre du projet / Project Title	Ethical principles and considerations in risk decision-making workshop.
Type de projet / Project Type	Thèse de doctorat / Doctoral thesis
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	05/12/2023
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	04/12/2024

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
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Conditions spéciales ou commentaires / Special conditions or comments

Supplementary material 2: Informed Consent Form

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Faculty of Health Sciences

Université d'Ottawa
Faculté des sciences de la santé

École interdisciplinaire des sciences de la santé

University of Ottawa
Faculty of Health Sciences

Interdisciplinary School of Health Sciences

Ethical principles and considerations in risk decision-making armchair discussion/learning event and workshop - Consent Form

I, the undersigned *[name]*_____, voluntarily agree to participate in this study as described in the information letter. The objective of this study is to generate a list of key ethical principles and considerations for health and environmental risk decision-making.

I have received and carefully read the information/email and I understand that I will participate as an expert in a virtual armchair discussion/learning event and workshop with other experts. I also understand that there will be participants from Health Canada who will also attend the learning event and this event, along with the workshop with experts only, will be recorded.

The risks and discomfort associated with these tasks have been explained to me. I have asked all questions that I had in regard to this matter and I am satisfied with the answers that were provided. I understand that I have the right to withdraw from this study at any time without any repercussions as noted in the information letter. Should I choose to withdraw, all my input will be removed and not used unless the principal investigator has my permission to use my data. The only exception to this is the group data as it will not be possible to remove my data given the collective nature of the group discussion.

I have received a copy of the information email and consent form.

Name: _____

Signature: _____

Organization: _____

Date: _____

SPACE RESERVED FOR THE PROJECT COORDINATOR

I have described the study to the appropriate person and insured that he/she understands the consequences involved.

Name: _____

Signature: _____

Date: _____

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Supplementary material 3: Research material

Ethical principles for regulatory risk decision-making

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The first section of this document provides an overview of the interplay and intersections between risk science and ethics along with a listing of prominent ethical theories relevant for risk decision-making. This information is particularly useful for those who are less familiar with the interactions between ethics and risk science.

The second section provides details on the knowledge translation methodology and the use of an online tool/survey (Survey Monkey; https://www.surveymonkey.com/) for evaluating the initial set of principles proposed for this initiative.

Section three provides the survey results (raw and aggregated) followed by the initial two models proposed for this research endeavour. This information and the discussion around the two models served as a catalyst for shifting the focus of the research, as discussed in the main paper, towards the development of a framework which guided a broader and more holistic model for ten ethical principles and considerations relevant for risk decision-making.

Section 1

1.1 Risk science, ethics, and moral agents

Risk decision-making involves identifying, assessing, and managing risks, and how this relates to other factors such as risk communication, governance, and policy (Bhuller & Trevithick-Sutton, 2024). The assessment of risks could also inform risk management policy and serve as a mechanism to generate "Type A" risk science-knowledge (outcomes from a specific assessment and management of a particular risk of concern). "Type B" risk science-knowledge encompasses the mobilization of knowledge on broader concepts such as frameworks, theories, and principles to help improve the current approaches used in risk analysis (Aven, 2018a; Aven, 2020; Bhuller et al., 2024b). As the focus of the present initiative is on risk decision-making for regulatory purposes, the main paper relies on the term risk science "… to encompass both the scientific enterprise of risk assessment and, in analogy to management science, risk management actions taken to reduce risk" (Krewski et al., 2014). Further, an underlying goal of the main paper is to broaden the collective understanding of Type B risk science-knowledge while providing overarching ethical principles. Consequently, while initial attempts are made to identify specific

ethical principles for risk assessment and management, the final model is an overarching and integrated approach which brings together the risk and ethical contexts, and the risk decision-making process.

Experts in risk science have asserted that "risk is a truly interdisciplinary, if not transdisciplinary, phenomena" (Aven & Renn, 2010). This understanding extends to the approach and governance of scientific risk assessments, evaluation of safety, and regulatory reviews (Saner, 2005; Saner, 2010). For example, hazard characterization, exposure assessment, and subsequent steps in the risk decision-making process typically involve a team with diverse expertise (including toxicology, epidemiology, chemistry, biology, biostatistics, medicine, and regulatory science) in understanding, managing, and communicating risk. Team members are often dealing with a range of risk issues, including "black swans" defined as issues manifesting as unpredictable and catastrophic events (Aven, 2015). Those contributing to the risk decision-making process also need to remain cognizant of the heterogeneity in the target audience, their perceptions, and how they will respond to the outcomes of the risk assessment. Therefore, to support effective risk communication (internal and external), these individuals often engage with other experts in communication and behavioural sciences (Bhuller & Trevithick-Sutton, 2024).

Ethics is a branch of philosophy centered around human conduct and, more specifically, the behaviour of individuals in society. Ethics studies what is morally right and wrong and is relevant to administrative institutions such as the public sector and national or federal regulatory authorities responsible for making public health decisions (Public Health Agency of Canada, 2017). There are two central concepts in applied ethics: societal values (what is considered "good") and moral norms (standards on how one should act in society, along with duties and rights). A moral agent is "… a person or a competent person that can have moral duties towards others and that can be held accountable for their actions and decisions" (Vanem, 2012). By analogy and given the public service role of federal staff, moral agents includes risk assessors, managers, and decision-makers.

1.2 Intersection between risk science and ethics

As described in the Handbook of Risk Theory, ethically justifiable risk decisions cannot simply replace "ethical deliberation, reasoning, and argument, by techniques that measure and aggregate individual preferences. Those techniques also need to be ethically justified" (MacLean, 2012). In other words, risk decisions need to account for how established moral norms, such as beneficence, govern intrinsic behaviours and fundamental beliefs embedded in societal values. These "norms and values" extend to institutions where they guide the attitudes, character, and actions of risk assessors, managers, and decision-makers throughout the evidence integration, assessment, and management phases of the decision-making process (Vanem, 2012). For example, the 2023 Deputy Ministers' Task Team on Values and Ethics Report to the Clerk of the Privy Council provides a renewed, post- COVID-19 pandemic conversation on the Government of Canada's values and ethics code for the federal public service. This includes the enduring importance of democracy and public trust as a core value of respect for democracy applicable to all decisions made by public servants, including those related to health risks (Government of Canada, 2023). The importance of improving the ethical conduct in the public service is not just specific to Canada, as noted in the OECD publication Trust in government - Ethics Measures in

OECD Countries (OECD, 2000). Consequently, other regulatory authorities, such as the United Kingdom Government (HM Treasury, 2023), have also updated their respective guidance documents for public sector organizations.

Understanding the genesis of moral norms and values for regulatory authorities can also aid in knowing how these intrinsic elements lead to the development of extrinsic, objective, fundamental, and impersonal rules or principles. For example, risk assessors and risk managers may take guidance from foundational values and ethics codes for all federal servants along with a set of risk decision-making principles relevant to addressing diverse risk contexts (Bhuller et al., 2024a; Krewski et al., 2022). Collectively, this creates a mindset required to guide the decision-making approach while relying on input from others who are part or collaborating with the process. Within this mindset, the institutional moral norms, values and principles, and available evidence create the knowledge and understanding required for a collaborative approach to the evaluation of health and environmental risks (Aven, 2018a). It also provides opportunities to weigh facts, values relating to the acceptability of risks (Sexton & Linder, 2014), consider general principles (Sexton, 2013), and other considerations such as public perception of risk relevant for decision-making.

The link between values/moral norms (right or wrong) and risk decision-making (best risk management strategy based on the evidence at that time) is still relatively new (Hansson, 2012; Hansson, 2013). Non-utilitarian writings, such as the Kantian framework proposed by Immanuel Kant (moral absolutism), do not explicitly discuss risks before the 1970s (MacLean, 2012). When considering more recent evaluations, Dejean and colleagues (2009) describe how health technology assessments (HTAs) are inherently "ethical"; however, it is exceedingly difficult to define what "ethics" means in the context of HTAs (DeJean et al., 2009). Similarly, Johnson and Degeling (2019) discuss whether ethical principles relevant to the One Health (OH) approach should be "value neutral/free tools", and thus compatible with existing ethical frameworks or whether OH should embody specific values thereby requiring an OH-specific ethical framework (Johnson & Degeling, 2019). While the main paper focuses on the methodology used to develop the ethical principles and considerations for risk decision-making, the next section further explores the foundations of key ethical theories here as a means to demonstrate the intersections between ethical and risk decision-making principles using deontological (morally right or wrong) and teleological (depends on the consequence) decision-making constructs. This information is particularly useful for those who are less familiar with these theories.

1.3 Prominent ethical theories and risk decision-making

Decision-theory provides a conceptual framework to support rational decision-making (Borgonovo et al., 2018; Frederickson et al., 2012; Howard, 1966; Jensen, 2012; Roeser et al., 2012; Simon, 1997); however, institutional ethics (values and moral norms) are also important for regulatory risk decision-making. For example, ethical principles can guide risk assessors to be more aware of their own biases and boundaries and their impact on the risk decision-making process (Frederickson et al., 2012; Simon, 1997).

Contemporary research is also demonstrating how satisfaction, decision acceptance, and perceived decision-maker legitimacy are driven in part by ethical parameters such as perceptions

of fairness (Kuzma & Besley, 2008). Further, experts in risk science have emphasized the importance of integrating risk perceptions, judgements, and thinking which is automatic, instinctive, quick, and emotional (also known as System 1 type thinking) in the assessment and management of risks (Aven, 2018). Similarly, PHAC notes how "public health decision-making often involves making difficult choices among competing or conflicting ethical considerations, including values and principles" (Public Health Agency of Canada, 2017).

Table S1 provides a summary of prominent ethical theories, extracted from the published literature, and relevant to the goals of the present paper (Ferrie, 2006; Hofmann et al., 2015; Mantatov & Mantatova, 2015; Vanem, 2012). While this tabulation does not represent the entirety of such theories, it provides pertinent information supporting the inclusion of ethical principles and considerations of both a utilitarian and non-utilitarian nature. The justification for this approach is based on our previous understanding of how risk and risk decision-making in different contexts is both interdisciplinary and diverse. Consequently, a holistic approach incorporating a broad range of ethical consideration, not restricted to a single ethical theory, is advisable for identifying foundational ethical principles relevant for risk decision-making.

Table S1: Ethical theories relevant for risk decision-making (listed in alphabetical order)

Theory	Description
Aristotle's virtue ethics and ethics of care (character focus)	Not enough to just do the right thing; choosing how to act includes cultivating traits of excellence (virtues such as wisdom, compassion, and courage). Ethics of care also looks at a person's motivation and character, stresses the importance of human warmth and sensitivity, and is rooted in feminist thinking (sensitivity to unique situations).
Casuistry (case based)	Defending an action or developing and justifying moral judgements by relying on how cases were addressed previously (e.g., historical context) or by policy.
Consequentialism (results focus)	A teleological theory based on values relating to or involving the explanation of phenomena and where acts of "goodness" are judged solely on consequences. Universal consequentialism considers how the consequences will affect all parties involved. Utilitarianism is a form of universal consequentialism based on the principle of utility, i.e., the morally right decision is the one with the best overall consequence of the utility of all parties affected. This theory includes a comparison of different benefits and how each option relates to intensity, duration, proximity, purity, extent, and future benefits. The use of non-animal testing approaches (e.g., new approach methods and methodologies which are comparable or superior to traditional animal assays) is one example of utilitarianism. Using non-animal strategies addresses animal welfare provisions, can provide more human relevant data, is a more "humane" approach, and adheres to the principles of the 3Rs (replacement, reduction, or refinement) with a particular focus on reduction and replacement for the use of animals.
Discourse ethics	Bottom-up approach which relies on driving towards a consensus on certain norms.
Imperative of responsibility (responsibility ethics)	A philosophical approach to ethics, by Hans Jonas, highlighting how modern technology provides humans with unprecedented power and as a post-Kantian ethics, it extends the notion of duty to include future generations. Consequently, there is an extended and moral responsibility towards future generations and the

	environment through the use of "heuristics of fear" as a means to prevent the destruction of humanity. Adversaries of this theory argue that fear is not enough.
Moral absolutism (rule/duty focus)	A deontological theory based on moral norms that help distinguish "right versus wrong" based on rationally justified actions which are independent of the consequence (e.g., universal moral norms/laws such as do not steal or lie). Kantian absolutism (Immanuel Kant) relies on the principle of Categorical Imperative which can test the moral soundness of an intended action by considering the implications of everyone doing likewise.
Moral relativism	Considers "political correctness" and context (e.g., culture and contemporary societal values). Consequently, different rules apply in different situations. For example, the cancellation of certain medical procedures in hospitals to accommodate patients during the onset of the COVID-19 pandemic.
Principle theory	Reliance on key ethical principles in healthcare (respect for autonomy, beneficence, nonmaleficence, and justice) and not endorsing a particular ethical theory.
Wide reflective equilibrium	Used in a coordinated manner, wide reflective equilibrium is a method of moral argument which gathers existing judgments about an issue and identifies which moral principles are at stake.

While **Table S1** provides a general overview of ethical theories, experts, such as Dr. Sven Ove Hansson, note the need to discuss "the ethics of risk, rather than in general-purpose moral theories" which includes "attempts to apply general-purpose theories, most commonly utilitarianism and deontology, to the problem at hand" (Hansson, 2023). This is important as the ethics pertinent to risk decision-making inherently include "problems of risk and uncertainty" and thus, "moral theories have to be extended so that they cover actions whose outcomes are not determinable beforehand" (Hansson, 2003). Consequently, the main paper explores the application of ethical principles within a regulatory context by demonstrating how regulatory and public health risk science link with various institutional values and moral norms. These linkages also align with our previous work where we used the Systems Iceberg Model to show the connections between the regulatory and risk context, and risk decision-making principles. With this model, we demonstrated how the risk context is in the visible spectrum (peak of the iceberg) and is linked to a majority of principles identified as being part of the nonvisible spectrum (located below the surface/wave). The deeply rooted and difficult to view spectrum also included ethical principles relevant for risk decision-making purposes (Bhuller et al., 2024a).

1.4 Ethical principles for regulatory risk decision-making

Risk assessors, managers, and decision-makers operate objectively in the evaluation of health and environmental risks while considering other factors relevant to the regulatory review and decision-making process (e.g., cost-benefit). Within the regulatory-public health context, the actions of these moral agents are also shaped by institutional values and codes of ethics. Risk assessments are usually undertaken using utilitarian frameworks, as these provide a good fit with regulatory decision-making which also focuses on how best to manage the consequences of the risk assessment. When considering biotechnology and nanotechnology derived products, however, Kuzma and Besley (2008) demonstrated the interconnectivity between risk analysis, regulatory review, and ethical principles using utilitarian (e.g., risks, benefits, costs, and

beneficence) and non-utilitarian (e.g., justice/equity, integrity, consent/autonomy, and non-maleficence) principles (Kuzma & Besley, 2008). Here we provide examples of the application of ethical principles relevant to Canadian regulatory risk decision-making while noting how other countries have similar holistic approaches (**Table S2**).

Table S2: Ethical principles and considerations relevant for regulatory purposes*

Reference Document	Description
Health Canada risk assessment workshop (Health Canada officials, personal communication, October 31, 2018)	Fundamental principles of bioethics addressed during the conduct of a risk assessment include: (i) fostering informed decision making for all stakeholders (autonomy); (ii) doing more good than harm (beneficence); iii) inflicting the least harm possible to reach a beneficial outcome (non-maleficence); and (iv) ensuring a fair process of decision making (justice). Principles for ethical risk assessment practice include: (i) transparency; (ii) considering stakeholder groups; (iii) variability and uncertainty; and (iv) disclosure of limitations. Ethical considerations include: (i) technical bias adjustments and addressing non-technical bias based on a range of perspectives reflecting different stakeholder groups and value systems (societal values); (ii) balancing the protection of confidential data and private information while striving to be open and transparent (trust); (iii) ethical obligation not to overstate knowledge and acknowledge uncertainties when dealing with uncertainty and ambiguity, and to be clear on the risk assessment objective; and (iv) addressing sensitive populations; broader societal values should be considered such as not unfairly creating disadvantages for different groups.
PHAC Framework for Ethical Deliberation and Decision-Making in Public Health (Public Health Agency of Canada, 2017)	Ethical dimensions include: (i) respect for persons and communities (autonomy); (ii) welfare of others/utilitarian (beneficence); (iii) treat groups fairly and equitably (justice); (iv) avoid harm to others (non-maleficence); (v) and reciprocity, solidarity, openness, honesty, truthfulness in the relationship with the public and transparency in decision-making processes (trust). Procedural considerations include: (i) accountability; (ii) inclusiveness; (iii) responsibility; (iv) responsiveness; and (iv) transparency. Public Sector values include: (i) respect for democracy (rule of law), people (human dignity), and public interest (integrity); (ii) responsible use of resources (stewardship); and (iii) professional design and delivery (excellence) (Government of Canada, 2011, 2023; Treasury Board of Canada Secretariat, 2003).
Risk Management Frameworks for Human Health and Environmental Risks (Jardine et al., 2003)	As noted by the authors, these ten principles, based on fundamental ethical principles and values, are proposed to guide risk management decision-making: (i) foster informed risk decision making for all stakeholders (autonomy); (ii) do more good than harm (beneficence, non-maleficence); (iii) be cautious in the face of uncertainty ("better safe than sorry"); (iv) ensure an equitable distribution of risk (equity); (v) risk management processes must be flexible and evolutionary to be open to new knowledge and understanding (evolution, evaluation, iterative process); (vi) fair process of decision making (fairness, natural justice); (vii) impose no more risk than you would tolerate yourself (the Golden Rule); (viii) promise no

	more risk management than can be delivered (honesty); (ix) the complete elimination of risk is not possible (life is not risk free); and (x) seek optimal use of limited risk management resources (utility).
Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Canadian Institutes of Health Research et al., December 2022)	Respect for person (autonomy), concern for welfare (beneficence), and fair and equitable conduct and treatment (justice).

*Ethical principles are in parentheses and the references are listed in alphabetical order.

In discussing ethical principles for health impact assessments, while Dejean and colleagues identified challenges in defining ethics in the context of HTAs, Tannahill and Douglas (2014) rely on the decision-making triangle framework to help synchronize decisions with the evidence, theory, and the application of ten ethical principles: do good, do not harm, fairness, sustainability, respect, empowerment, social responsibility, participation, openness, and accountability (Tannahill & Douglas, 2014). Further, Bellemare and colleagues (2018) note how the most frequent reason cited for integrating ethics in HTAs is to inform policies based on "ethical principles aimed at improving general health and wellbeing of society." Ethical principles (e.g., autonomy) and considerations (e.g., empowering individuals and incorporating dimensions such as transparency and accountability) are also cited as being important for HTAs (Bellemare et al., 2018). In a similar vein, Hansson (2023) discusses applied ethics and how the development of new concepts and theories (e.g., healthcare ethics and the use of four "mid-level" principles: autonomy, beneficence, nonmaleficence, and justice) can be applied in other areas (Hansson, 2023).

There are existing risk and public health ethical frameworks, declarations, and models such as the "ETHICS" model (Winnipeg Regional Health Authority (WRHA) Ethics Services, 2015), which provide ethical insights and approaches for risk decision-making. Hypothetical retrospection, as another example of a framework, bridges the gap between moral philosophy or "actions known beforehand" and dealing with uncertainty and risks as "pervasive features of practical decision-making" (Hansson, 2007; Hansson, 2013). The basic concept for hypothetical retrospection is an understanding of how risk decision-making, unlike moral philosophy, is concerned with probabilities of what could occur in the future. Consequently, hypothetical retrospection refers to the decision one should have made based on the actual information available at the time of the decision and not the hypothetical information available at the time of retrospection. It aims to provide an approach to ensure that the decision made is morally acceptable from the perspective of actual retrospection.

The preceding discussion demonstrates the interconnectedness between risk and ethical principles relevant for risk decision-making. Following recent exploration of contemporary risk decision-making principles (Bhuller et al., 2024a; Krewski et al., 2022), it is timely to undertake a similar analysis focusing specifically on ethical principles and considerations within a health risk decision-making context. The main paper describes the methods used for undertaking such an analysis, within the scope of an independent research endeavour, with a diverse team of experts/study participants.

Section 2

2.1 Knowledge translation

The well-established phases of knowledge translation (Graham et al., 2006; Health Canada, 2017) were used to gain insights on the initial set of proposed ethical principles for risk assessment and management (survey questions 1 to 10). The survey allowed participants to rank the principles, update the proposed model (armchair discussions and virtual meetings with participants), and provide input towards a final knowledge product: a consolidated model with ethical principles and considerations relevant to risk decision-making in a regulatory context.

2.1.1 Phase I: Knowledge inquiry

This phase required all eight study participants to review the discussion document prior to ranking the proposed ethical principles and considerations using the survey provided in **Table S3** and a 3-point Likert scale: highly relevant (3), somewhat relevant (2), or largely irrelevant (1). The ranking occurred using an anonymous survey tool (Survey Monkey; https://www.surveymonkey.com/) where the results were only accessible to the lead author (YB). The survey also included sections where the participants provided additional comments in addition to other points noted in the discussion document or shared during the armchair discussions and team meetings.

Table S3: Let's talk ethics - Principles for risk assessment and management
Risk Assessment (1 to 5) and Risk Management (6 to 10)

1. Flexible, evergreen, comprehensive (use a broad perspective), and fit-for-purpose assessments

Description: Risk assessment should use a broad perspective while being flexible to deal with the complexity of real-life situations. The objectives should be clearly and explicitly stated using tools such as problem formulation and the underlying evidence should be fit-for-regulatory decision-making purpose. Risk assessments should remain current, and updated as new information becomes available.

☐ 3: Highly relevant ethical principle (risk assessment) ☐ 2: Somewhat relevant ethical principle (risk assessment) ☐ 1: Largely irrelevant ethical principle (risk assessment)

Comments:

2. Integrate evidence (multiple streams)

Description: Risk assessors should apply appropriate systematic search strategies to identify all relevant data from multiple evidence streams. Further, multiple evidence streams should be combined in an appropriate manner (both qualitatively and quantitatively) while considering and accounting for differences in data quality and approaches (e.g., weaving Indigenous knowledge and science).

☐ 3: Highly relevant ethical principle (risk assessment) ☐ 2: Somewhat relevant ethical principle (risk assessment) ☐ 1: Largely irrelevant ethical principle (risk assessment)

Comments:

3. Respect data

Description: The data integrity for studies used in risk assessment should be validated, reproducible, qualified, and mutually accepted by authorities. Risk assessors should respect the FAIR principles (Findable, Accessible, Interoperable, and Reusable) for science data management and stewardship along with the CARE (Collective benefit, Authority to control, Responsibility, and Ethics) and OCAP® principles (Ownership, Control, Access, and Possession) which extend to respecting the data sovereignty for Indigenous science and knowledge. Risk assessment data should be made available for evaluation and re-analysis by others. This includes being subject to an objective peer review, making effective use of sound science advice, use of appropriate qualitative and quantitative data analytic methodologies employed to ensure valid data inferences, and conducting autonomous and independent assessments.

☐ 3: Highly relevant ethical principle (risk assessment) ☐ 2: Somewhat relevant ethical principle (risk assessment) ☐ 1: Largely irrelevant ethical principle (risk assessment)

Comments:

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4. Minimize technical bias

Description: Risk assessors should be well-informed on how to recognize study designs and approaches to minimize or eliminate technical bias.

☐ 3: Highly relevant ethical principle (risk assessment) ☐ 2: Somewhat relevant ethical principle (risk assessment) ☐ 1: Largely irrelevant ethical principle (risk assessment)

Comments:

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5. Full disclosure

Description: Risk assessments should disclose data gaps/uncertainties in available data and be subject to objective peer review.

☐ 3: Highly relevant ethical principle (risk assessment) ☐ 2: Somewhat relevant ethical principle (risk assessment) ☐ 1: Largely irrelevant ethical principle (risk assessment)

Comments:

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6. **Stakeholder engagement**

Description: Involve interested and affected parties in the risk management decision-making process. This does not preclude relying on formal provisions for internal and external stakeholder involvement during all the others stages of the risk decision-making process.

☐ 3: Highly relevant ethical principle (risk management) ☐ 2: Somewhat relevant ethical principle (risk management) ☐ 1: Largely irrelevant ethical principle (risk management)

Comments:

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7. Acceptability of risk

Description: The criteria, principle (e.g., ALARP (as low as reasonably practicable)), limit, or threshold for determining the acceptable levels of risks should be clearly and explicitly stated.

☐ 3: Highly relevant ethical principle (risk management) ☐ 2: Somewhat relevant ethical principle (risk management) ☐ 1: Largely irrelevant ethical principle (risk management)

Comments:

8. Risk equity

Description: Risks should not be disproportionately distributed across population subgroups.

☐ 3: Highly relevant ethical principle (risk management) ☐ 2: Somewhat relevant ethical principle (risk management) ☐ 1: Largely irrelevant ethical principle (risk management)

Comments:

9. Open, transparent, timely, and effective communication

Description: The basis for risk management decisions should be accessible and explicitly disclosed, and the risk management decision should be rendered in the shortest possible time that is appropriate for the circumstances and situation. Communication of risks (and benefits) also need to be adjusted so that they account for the target audience.

☐ 3: Highly relevant ethical principle (risk management) ☐ 2: Somewhat relevant ethical principle (risk management) ☐ 1: Largely irrelevant ethical principle (risk management)

Comments:

10. Social responsibility

Description: Risk management decision should reflect contemporary societal values (see foundational "core" ethical principles in the *Discussion Document*).

☐ 3: Highly relevant ethical principle (risk management) ☐ 2: Somewhat relevant ethical principle (risk management) ☐ 1: Largely irrelevant ethical principle (risk management)

Comments:

11. Please provide any additional comments here (e.g., one or more ethical principles).

2.1.2 Phase II: Knowledge sharing and synthesis

For the first armchair discussion, five study participants had the opportunity to share their insights during the 2024 annual Health Canada Science Forum. The Forum is an annual event for all staff interested in learning about science and research related activities within and external to Health Canada. Through a virtual armchair discussion titled: Let's talk ethics: Considerations and principles for risk decision-making, several participants shared their area of expertise and provided a response to the following questions:

From your lived experience dealing with health or environmental risks, what are your top three ethical principles from the list provided by the lead author (YB)?

Are there any ethical principles or considerations missing from the proposed list?

For the second armchair discussion, conducted shortly after the Forum, the remaining three participants provided their input (i.e., answers to the two questions above). This discussion was then followed by an open session where all participants provided additional comments on further refining the proposed ethical principles and considerations.

2.1.3 Phase III: Knowledge product (Data collection and analysis)

The data collected from the iterative approach was evaluated using mixed methods. An exploratory, sequential, qualitative-quantitative (QUAL→QUAN) design guided the development of initial models and principles subsequently leading to the final, integrated model with ethical principles and considerations relevant to regulatory risk decision-making. In this design, the qualitative (armchair discussions, meetings, and comments provided in the discussion document) and quantitative data (survey results) carry equal weight (O'Sullivan & Khan, 2020; Palinkas et al., 2011).

The main source of the data included the comments provided in the discussion document, the online survey, which included the results from the ranking of the proposed ethical principles (see below), and the recordings of the virtual armchair discussions and notes from the team meetings. Microsoft Excel (v2406) was used for data entry, visualization, and descriptive data analysis.

After curating all the summary notes, a coding scheme allowed for the extraction and generation of themes using a reflexive, thematic analysis-based approach (Braun & Clarke, 2020; Saldana, 2016; Skjott Linneberg & Korsgaard, 2019). The extracted notes were initially coded using inductive and in vivo codes (i.e., the study participants' "own" words) followed by the application of deductive ones using the predetermined questions and NVivo (v14). The deductive application helped refine and further categorize the codes into themes.

Section 3

3.1 Survey results (raw data and descriptive statistics)

The table below provides the raw scores for each principle (P1 to P10) from the panelist members (A to G) using a 3-point Likert scale: highly relevant (3), somewhat relevant (2), and largely irrelevant (1). The results were submitted anonymously to the lead author (YB) using the online survey tool (Survey Monkey; https://www.surveymonkey.com/). Microsoft Excel was used for data entry and descriptive data analysis.

Principle (P)	Participant and ranking (3, 2, or 1)							Overall Mean:	Highly and somewhat relevant	Largely irrelevant
P1: Flexible	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.00	2.40	1.00
Highly relevant			3				3			
Somewhat relevant		2		2		2				
Largely irrelevant	1				1					
P2: Integrate Evidence	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.14	2.60	1.00
Highly relevant				3		3	3			
Somewhat relevant		2	2							
Largely irrelevant	1				1					
P3: Respect data	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.14	2.33	1.00
Highly relevant			3				3			
Somewhat relevant	2	2		2		2				
Largely irrelevant					1					
P4: Minimize Tech Bias	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.00	2.40	1.00
Highly relevant				3			3			
Somewhat relevant		2	2			2				

Principle (P)	Participant and ranking (3, 2, or 1)							Overall Mean:	Highly and somewhat relevant	Largely irrelevant
Largely irrelevant	1				1					
P5: Full Disclosure	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.14	2.33	1.00
Highly relevant				3			3			
Somewhat relevant	2	2	2			2				
Largely irrelevant					1					
P6: Stakeholder Eng	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.71	2.71	-
Highly relevant	3		3		3	3	3			
Somewhat relevant		2		2						
Largely irrelevant										
P7: Acceptable risk	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.43	2.67	1.00
Highly relevant			3	3	3		3			
Somewhat relevant		2				2				
Largely irrelevant	1									
P8: Risk equity	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.71	2.71	-
Highly relevant	3		3	3	3		3			
Somewhat relevant		2				2				
Largely irrelevant										
P9: Open & transparent	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.71	2.71	-
Highly relevant	3		3		3	3	3			
Somewhat relevant		2		2						
Largely irrelevant										
P10: Social Responsibility	**A**	**B**	**C**	**D**	**E**	**F**	**G**	2.29	2.50	1.00
Highly relevant			3	3			3			
Somewhat relevant		2			2	2				
Largely irrelevant	1									

3.2 Proposed ethical principles

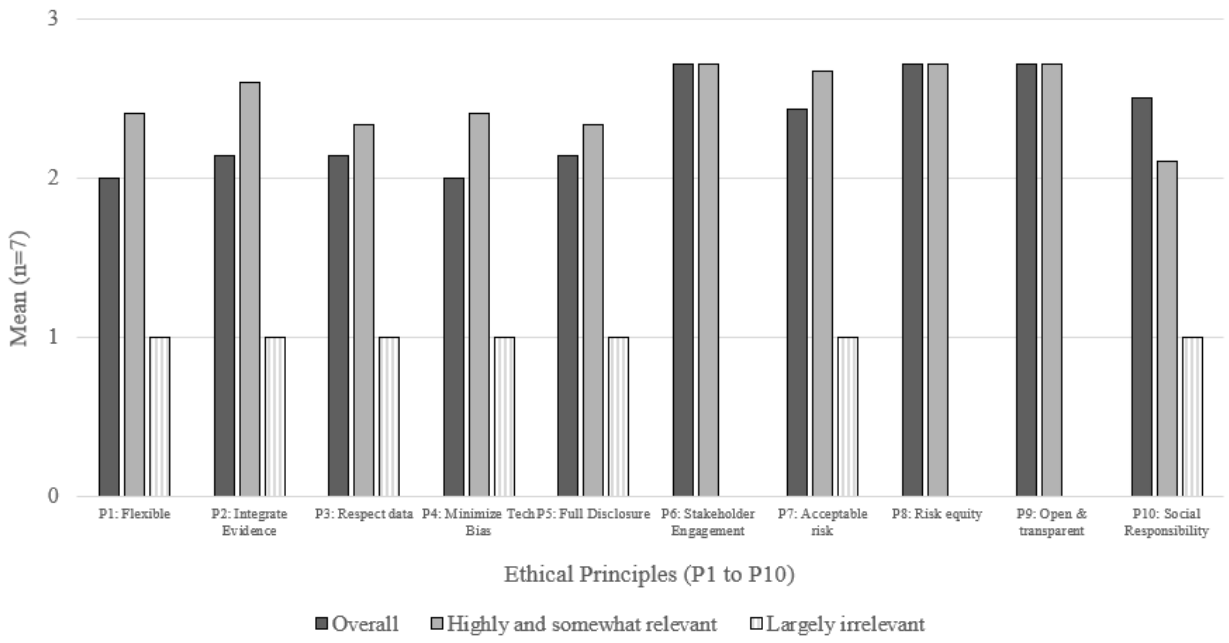
The survey was sent to all eight study participants, seven of whom were able to provide responses. The global results demonstrated how the participants found the proposed ten principles to be relevant for developing ethical principles and considerations for contemporary risk decision-making (**Figure S1**); the overall mean for all principles was greater than or equal to 2: highly and somewhat relevant. For principle 6 (P6: stakeholder engagement), principle 8 (P8: risk equity), and principle 9 (P9: open and transparent), none of the participants identified these as largely irrelevant. In fact, as all participants identified these principles as being largely and somewhat relevant, these principles were retained for further development in the subsequent discussions of ethical principles relevant to risk decision-making. P6 and P9 were also previously identified as universal risk principles which are mostly risk context-independent and apply to several health and environmental risk decision-making contexts (Bhuller et al., 2024a). Consequently, this further supported exploring these universal/risk context independent principles as they appeared to also be relevant from an ethical perspective.

Based on the overall survey results, armchair, and meeting discussions, the participants focused their efforts on further discussing relevant principles and establishing a framework for developing a model. Several comments on the initial principles and descriptors showed how

some of the principles are important "methodological" and "more process oriented" principles (as opposed to ethical principles grounded in institutional values and morals). For example, one of the panel members called the proposed risk assessment principles (P1 to P5) as "more of a principle of application and not a core principle." These sentiments were also shared during the armchair discussion where other study participants independently noted how some of the principles were more "procedural principles."

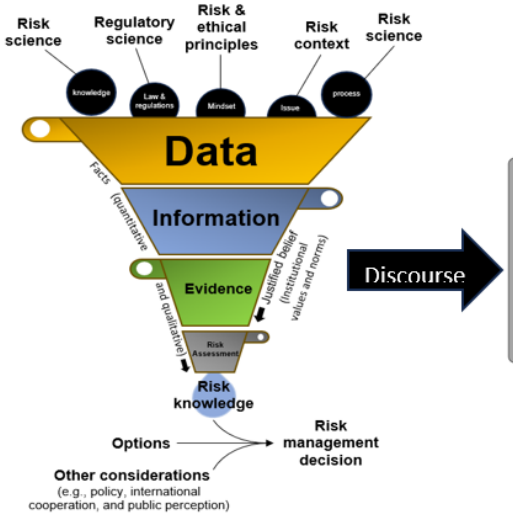
During the armchair discussions, study participants identified the principle of autonomy, timely facilitation of replacing testing on animals in risk assessment, and fit-for-purpose risk assessments as being relevant to this initiative. When discussing fit-for-purpose, the importance of being adaptable was described as an important mechanism for regulatory processes to keep pace with emerging science and technologies. This included the use of non-animal methods to support regulatory data needs (Hilton et al., 2023). Lack of adaptability was also noted as a concern when risk assessments do not keep pace with risk protection needs for marginalized communities exposed to various stressors. Further, outdated regulations and limited training or access to new and relevant science were also identified as factors creating risks of being outpaced by technologies and by default missing opportunities to improve risk management strategies.

Stakeholder engagement was identified as an "obvious ethical priority" because it creates opportunities for advocacy, transparency, and open communication, while providing a platform for collaboration. Open and transparent communication was noted as a basic need which can help foster other principles such as risk equity and social responsibility. These results were well-aligned with the quantitative findings from the anonymous survey and demonstrated the interconnectedness of these principles. Other key comments included the significance of building and maintaining public respect, trust, and confidence, the creation of "data ecosystems" to satisfy regulatory needs while accounting for animal rights and welfare, and looking at risk equity from a broader lens. That is, the application of risk equity includes humans and animals and from a utilitarianism perspective, consideration of the interests of all humanity and sentient beings (Bhuller et al., 2024). Further, for principle P3 (respect for data), one of the respondents noted that the "ethical angle is not just respect for data, but respect for people and places as sources of data and the impact it has on them to use (or not use) their data."

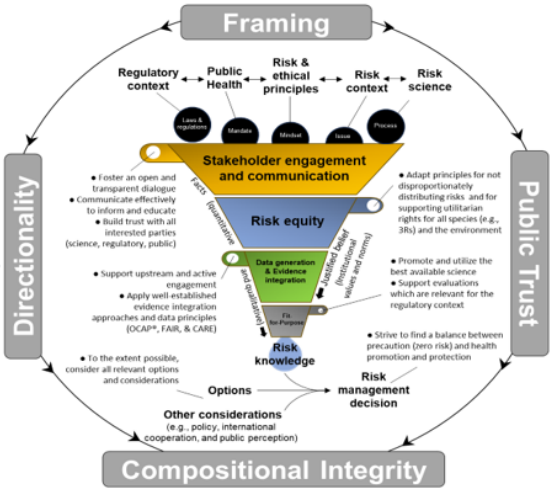


3.3 Proposed models for ethical principles for risk assessment and management

The following diagrams represent the initial and second version of the proposed conceptual model for this initiative (**Figure S2**). The first model was prepared in advance of the first meeting (and survey) with participants and reflects a bottom-up proposal from the lead author (YB) based on a regulatory risk assessment and management perspective. It shows how data eventually translates to evidence required for assessing risks, and how the knowledge acquired form this process is incorporated in the risk management decision. The key elements for this process (e.g., risk science knowledge and a mindset based on ethical principles for risk decision-making) are identified at the top of the knowledge transfer funnel.



The initial model developed using a bottom-up, regulatory risk assessment and management perspective.



Second version of the model based on the initial comments (survey and armchair discussion).

The changes in the second version are based on the comments on the discussion document (summary of relevant literature), survey results, and controlled feedback (completed armchair discussion). A major criticism of the initial model was the need to create a visual which goes beyond using the knowledge transfer funnel. This was deemed necessary as the model is required to better represent the broad and integrated aspect of these principles. It is important to emphasized that the intent of the framework is to guide the development of the model (without being incorporated in the model). Consequently, the final version of the model provided in the article includes a separate diagram for the framework.

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CHAPTER 5: ARTICLE 3. Key attributes of health and environmental risk decision-making: A Scoping Review

Chapter overview

This chapter addresses the second research objective (Chapter 1) and third question (Chapter 2) through an original research article based on a scoping review of the evolution in risk analysis and science (see **Glossary** for definitions), over the last fifty years. This review provides a visual representation of this evolution along with ten key attributes relevant for health and environmental risk decision-making. The supplementary material also provides the registered protocol and detailed information extracted from the final list of thirty-nine publications used for the analysis. In the final paper, the ten attributes are further transformed into considerations for developing an approach to NextGen risk decision-making. The article was accepted for publication in the journal *Risk Analysis*.

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Data availability statement

The data that support the findings of this study are available in the Supporting Information section of this article.

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5.1 Abstract

Government agencies, international institutions, and independent experts have published approaches for the assessment and management of health and environmental risks. This includes evidence-based strategies and publications supporting risk decision-making frameworks reflecting contemporary practices, the overarching context, and governance structures for addressing known and emerging risk issues. This scoping review surveys the literature, over the last five decades, to identify key attributes of health and environmental risk decision-making and how these inherent characteristics are related to the overarching regulatory decision-making

context. The findings provide insights on how these publications accounted for the circumstances and triggers at that time. This includes incorporating factors reflecting advances in science and technology, a better understanding of underlying values (e.g., societal), and an expansion in the scope and complexity required for conducting different evaluations relevant to health and environmental risks. Consequently, the evolution from linear to more expanded and holistic decision-making frameworks incorporates foundational elements, such as the well-established steps for assessing risks, while adding aspects reflecting transformative changes and paradigm shifts (e.g., the use of non-animal testing strategies for evaluating human safety). Our analysis also resulted in the generation of a consolidated listing of ten attributes: trigger/issue, regulatory context, regulatory factors, core values, risk decision-making principles, cross-cutting attributes, design (scope and steps), structure, decision-making pathway, and evidence-knowledge requirements for risk decision-making. A better understanding of this evolution in risk decision-making and the listing of key attributes will be used in future work aimed at developing considerations for next generation decision-making approaches for health and environmental risks.

Keywords: Risk decision-making, health, environmental, attributes, regulatory context

5.2 Introduction

National regulatory authorities are responsible for assessing health and environmental risks, making risk management decisions, and communicating risk information to help the public make informed choices for maintaining and improving their wellbeing. As an example, in Canada, the federal health and environmental risk decision-making responsibility resides with various departments, including Health Canada and, by extension, the specific program areas responsible for regulating diverse products (e.g., biologicals, pharmaceuticals, nutraceuticals, food, pesticides, industrial chemicals, and medical devices) (Government of Canada, 2014a). Health Canada's decision-making process for identifying, assessing, and managing health risks is described in a public-facing decision-making framework established over two decades ago (Health Canada, 2000). The United States, European, and other national regulatory authorities have similar public-facing documents (EFSA, 2013; OECD, 2010; United States Food & Drug Administration (FDA), 2017).

The risk decision-making process typically begins with identifying the risk issue and its context (i.e., what is the problem?). Once the problem is formulated, the hazard (the intrinsic ability of a substance to cause harm), risks (a measure of both the harm resulting from being exposed to a hazardous agent, together with the likelihood harm will occur), and benefits or value of the product (e.g., therapeutic properties) are assessed during the "science" or risk assessment phase of the risk decision-making process. Options for managing risk are then considered, followed by implementation, monitoring, and evaluating the outcome of the risk decision, with risk communication occurring throughout. Over the course of several decades, risk assessment, management, and communication have evolved into a well-defined discipline known as risk science (Aven, 2020; Krewski et al., 2014).

A landmark report establishing the scientific basis for this discipline is the 1983 National Research Council (NRC) "Red Book" (National Research Council, 1983; Whittaker, 2004). In 2007, the US NRC published another pivotal report, Toxicity Testing in the 21st Century, which provided a long-term strategy for incorporating new tools and technologies to improve toxicity testing for identifying and characterizing hazards and establishing points of departure (reference dose or concentration) for risk assessment purposes (Krewski et al., 2020; National Research Council, 2007). The Council of Canadian Academies' report on Integrated Approaches to Testing and Assessment (Council of Canadian Academies, 2012) is another example of incorporating 21st century thinking into current approaches for health hazard evaluation and risk assessment.

A changing public health context also impacts how governments and their decision-making processes adapt with evolving societal interests. For example, advanced therapeutic products (ATPs) refer to products, such as personalized medications or medical devices, where the regulatory and evaluation process warrants a more agile and flexible approach (Health Canada, 2022). Although the regulatory submission and review of future medications and devices will continue under existing frameworks, ATP incorporates a unique approach to regulating certain novel, personalized, and complex products. Another example is the responsibility and accountability of public health leaders toward the Truth and Reconciliation Commission's Calls to Action (Government of Canada, 2023). This call to action recognizes the value of Indigenous practices, the deeply rooted impacts of colonization, and the role Indigenous Science and Knowledge play in addressing health and environmental issues (Greenwood et al., 2018).

Finally, other examples include local and global public health issues, such as the COVID-19 pandemic (Cauchemez et al., 2024; Chuenkitmongkol et al., 2022; Galang, 2021; Government of Canada, 2022a, 2022b; Perillat & Baigrie, 2021; Pettit, 2021), antimicrobial resistance (Antimicrobial Resistance Collaborators, 2022; Government of Canada, 2014b; Khouja et al., 2022; Lobie et al., 2021; Pelfrene et al., 2021), food safety and security (Government of Canada, 2015, 2019a, 2020, 2024a), water safety and quality (Government of Canada, 2019b), and climate change (Government of Canada, 2024b).

With an evolving context and advances in science and technology, several regulatory authorities have published guidance reflecting modern approaches to risk assessment. For example, the United States Environmental Protection Agency's report on Next Generation Risk Assessment: Incorporation of Recent Advances In Molecular, Computational, And Systems Biology (United States Environmental Protection Agency (EPA), 2014) and the Federal Drug Administration's Predictive Toxicology Roadmap (United States Food & Drug Administration (FDA), 2017) demonstrate how these national authorities plan to incorporate new approach methodologies (NAMs), a term used to capture more recently developed non-animal methods, into the scientific assessment phase of their decision-making processes. In Canada, the movement toward incorporating NAMs into risk decision-making processes for pest control products and industrial chemicals has prompted Canadian regulatory authorities to consider novel frameworks such as the Framework for the Next Generation of Risk Science (Bhuller et al., 2021; Krewski et al., 2014).

Although there continues to be a steady stream of publications focused on developing next-generation approaches for risk assessment (Bhuller et al., 2021; Bury et al., 2021; Clippinger et al., 2022; Cote et al., 2012; Dent et al., 2018; Goodman et al., 2014; Parish et al., 2020; Sewell et al., 2021; Stucki et al., 2022; Tannenbaum, 2012; United States Environmental Protection Agency (EPA), 2014; van der Zalm et al., 2022; Wolf et al., 2022) and frameworks for evidence-based (Krewski et al., 2022a) and evidence-informed (World Health Organization, 2021) decision-making, there are few published, analytical reviews on risk (assessment and management) decision-making frameworks for health and environmental risks (Jardine et al., 2003; Power & McCarty, 1998). Further, the existing reviews reflect the risk assessment tools, management processes, and context at historical points in time. Consequently, these reports do

not account for recent advances in science and technology and may not reflect the current regulatory milieu of risk decision-making.

This scoping review aims to enhance our understanding of the evolution of risk science and advances in the risk assessment–management paradigm by identifying and characterizing key attributes for health and environmental risk decision-making. To our knowledge, a broad, structured, and contemporaneous scoping review of the evolution of risk science has not been undertaken. Accordingly, this review seeks to expand the collective knowledge on this topic through a robust, systematic descriptive synthesis of relevant decision-making frameworks for health and environmental risks. Our intention is to address the following research question: What are the key attributes of health and environmental risk decision-making, and how are these inherent characteristics related to the federal regulatory decision-making context, processes, and governance structures?

5.3 Methods

The authors of the present scoping review followed the staged approach described by Arksey and O'Malley and the Joanna Briggs Institute (Arksey & O'Malley, 2005; Peters, Godfrey et al., 2020; Peters, Marine et al.,2020). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018) guided the required reporting requirements for this work. Prior to commencing the review, a study protocol was published in the Open Science Framework (September 15, 2023), accessible at *https://osf.io/gnyfk*.

5.3.1 Search strategy

The following electronic databases were searched for relevant publications: MEDLINE (Ovid), Embase (Ovid), Scopus, and Global Health (EBSCO). The search strategy included identifying the key terms, medical subject headings (MeSH), and major concepts (e.g., risk management, assessment, and mitigation along with decision-making and health). A preliminary search strategy, in MEDLINE (Ovid) and provided in the **Supporting Information** section accompanying this article, was developed using four seed articles (Bhuller et al., 2021; Jardine et al., 2003; Krewski et al., 2014; Wolf et al., 2022). The strategy was then refined in consultation with the University of Ottawa's Population Health research librarian. As the preliminary results (2438 articles) using the refined strategy included the four seed articles (and other relevant

reports recommended through snowball sampling), the search strategy was subsequently translated to query all the databases on September 19, 2023.

We also used the major concepts to identify relevant grey literature using Google, Google Scholar, and databases from authoritative organizations, including the World Health Organization (WHO), International Council for Harmonisation (ICH), Organisation for Economic Co-operation and Development (OECD) iLibrary, Food and Agriculture Organization (FAO), United States Federal Registry, European Union regulatory agencies, and Government of Canada departments and agencies. References provided from experts in risk science (**Supporting Information** section) were also considered during the screening and selection process.

5.3.2 Eligibility criteria

As the phenomena or concepts of interest are to identify key attributes of health and environmental risk decision-making and characterize how these inherent characteristics relate to the national/federal regulatory decision-making context, processes, and governance structures, the following eligibility criteria were applied in this scoping review.

5.3.2.1 Type, context, and summary of evidence sources

We included (i) all types of published and peer-reviewed articles analyzing existing risk (assessment and management) decision-making frameworks; (ii) proposals from independent experts on new approaches and frameworks for health and environmental risk assessments; (iii) government reports and frameworks on how to conduct risk assessments and management within a regulatory decision-making context; (iv) international reports including considerations of toolkits for conducting risk assessments; and (v) published literature, attained through purposeful snowball sampling, from sources describing an overall approach to risk decision-making.

Documents were excluded when they did not describe an overarching approach (e.g., framework, model, or roadmap), had a narrow focus on a single dimension (e.g., a particular condition such as Alzheimer's disease or a specific high-throughput assay), or were not relevant to health and environmental risk decision-making. To be included in this review, sources had to be published in English and French, and there were no limits on date of publication, research methods, or countries of origin.

Table1 provides a summary of the information extracted from each eligible record. The identified fields were developed using an iterative process with input from all authors.

Table 1: Summary of extracted information

Criteria	Description
Bibliographic information	Title, author(s), year of publication, and origin (e.g., North America).
Objective	Purpose or aim of the publication.
Type	Framework, guidance, report, or review (includes research studies).
Population and setting	Audience and area of application (international, national, or local).
Core values and principles	Vision, mission, or mandate and other underlying values (e.g., societal), and decision-making principles.
Design	Scope (e.g., risk assessment, risk management, or decision-making) and steps (number and heading (e.g., hazard identification)).
Structure	Fully integrated (e.g., dynamic or circular), partially integrated, or sequential (e.g., one-way logic model, checklist or decision-tree).
Evidence-knowledge	The publication includes the use of quantitative and/or qualitative data? yes/no
Regulatory factors	Used in a broad sense to capture elements and considerations for risk decision-making in a federal/national regulatory context, such as (i) practical factors that can create constraints/barriers; (ii) opportunities/ levers for tailoring a process to specific needs (e.g., fit-for-purpose strategies); (iii) policy and mandate factors to frame the decision; (iv) contextual factors that need to be balanced, traded-off, or compromised (e.g., ethics, distribution of risks and benefits, risk–benefit trade-offs, costs of alternative, costs to industry and other interested parties, and level of engagement with interested and affected parties); (v) other, extra-scientific factors in risk decision-making (e.g., public perception of risk, socio-economic factors, and political considerations); and (vi) broad factors such as international collaboration (formal and informal)
Underlying theory	Modern or classical theories relevant to risk decision-making.
Risk governance	Role and relationship of the various components for risk decision-making (e.g., risk assessment is embedded in the risk management process).
Notable feature	The main recommendations from the publication (e.g., maximizing utility of the risk assessment).

5.3.3 Study screening and selection process

The web-based platform, Covidence, was used to collate the search results from various databases and create the PRISMA flow diagram (Veritas Health Innovation, 2022). Duplicates were removed before screening and manually throughout the screening and selection process. The two reviewers, Xaand Bancroft (X.B.) and Yadvinder Bhuller (Y.B.), independently

screened the titles and abstracts and resolved all conflicts through discussion prior to proceeding to full-text review. During the first step of the full-text review, 15% of the articles were reviewed by both reviewers to confirm the process. Following this step, Y.B. proceeded with the full-text review. Conflicts not successfully resolved by the two primary reviewers were brought to the research team for discussion.

5.3.4 *Data charting, extraction, and analysis*

The categories for data collection and extraction (Table 1) were based on our experience with risk decision-making frameworks and insights on the structure, governance (roles and responsibilities), and processes of risk decision-making (Bhuller & Trevithick-Sutton, 2024; Krewski et al., 2020, 2007, 2022a; Krewski et al., 2014). These categories also considered published work comparing health and environmental risk management frameworks (Jardine et al., 2003; Power & McCarty, 1998) and elements from decision-making theories relevant for public administration and management. For example, the Public Administration—Decision Theory (Frederickson et al., 2012), which incorporates Herbert A. Simon's insights on Administrative Behavior, Administrative Theory, and Bounded Rationality (Schwarz et al., 2022; Simon, 1980, 1997a, 1997b).

The extraction of the data relied on an interactive and two-phased approach. In the first phase, the extraction tool/table (Table S1) was piloted by X.B. and Y.B., using three studies. This process provided another opportunity to ensure that the inclusion/exclusion criteria were being applied with the intended rigor and manner identified in the published protocol. This included adherence to the specified rules for inclusion and exclusion of the publications being considered for analysis. Following this exercise, the lead author (Y.B.) proceeded to extract the data from the remaining publications (second phase) and was also responsible for the subsequent data analysis. The charting exercise relied on an ongoing discourse between the two reviewers and was guided by the JBI Manual for Evidence Synthesis Data Charting Tool for Scoping Reviews (Peters, Godfrey et al., 2020; Peters, Marine et al., 2020) and recommendations from Pollock et al. (2023).

Our descriptive synthesis of the extracted content relied on a mixed-methods approach starting with quantitative frequency counts of the key findings (e.g., number of frameworks with fully integrated structures), followed by a qualitative analysis (Creswell & Clark, 2018; O'Sullivan &

Khan, 2020). The additional themes (e.g., evolution in terminology) were also identified using in vivo codes followed by an inductive thematic analysis of the extracted elements (Braun & Clarke, 2020; Saldana, 2016; Skjott Linneberg & Korsgaard, 2019). Further, the publications included in the synthesis were analyzed to identify the key attributes in risk decision-making. Each publication's notable feature was also used to classify the change into distinct categories reflecting their contribution toward the evolution in risk decision-making.

5.4 Results

The results begin with a brief overview of the included publications using quantitative data. This is followed by key terminology and a qualitative analysis of the outcomes describing the evolution of risk decision-making over time.

5.4.1 Summary of included studies

The literature search resulted in 27,656 unique English publications (no French articles were identified that met eligibility criteria) after deduplication (**Figure 1**). The title and abstract screening reduced the initial number of unique publications to 64. During full-text review, 39 publications were eligible for inclusion and subsequent analysis. The principal reasons for exclusion, following full-text evaluation, included “not being related to risk decision-making” (n= 12), followed by “not health or environmental risk decision-making” (n = 7).

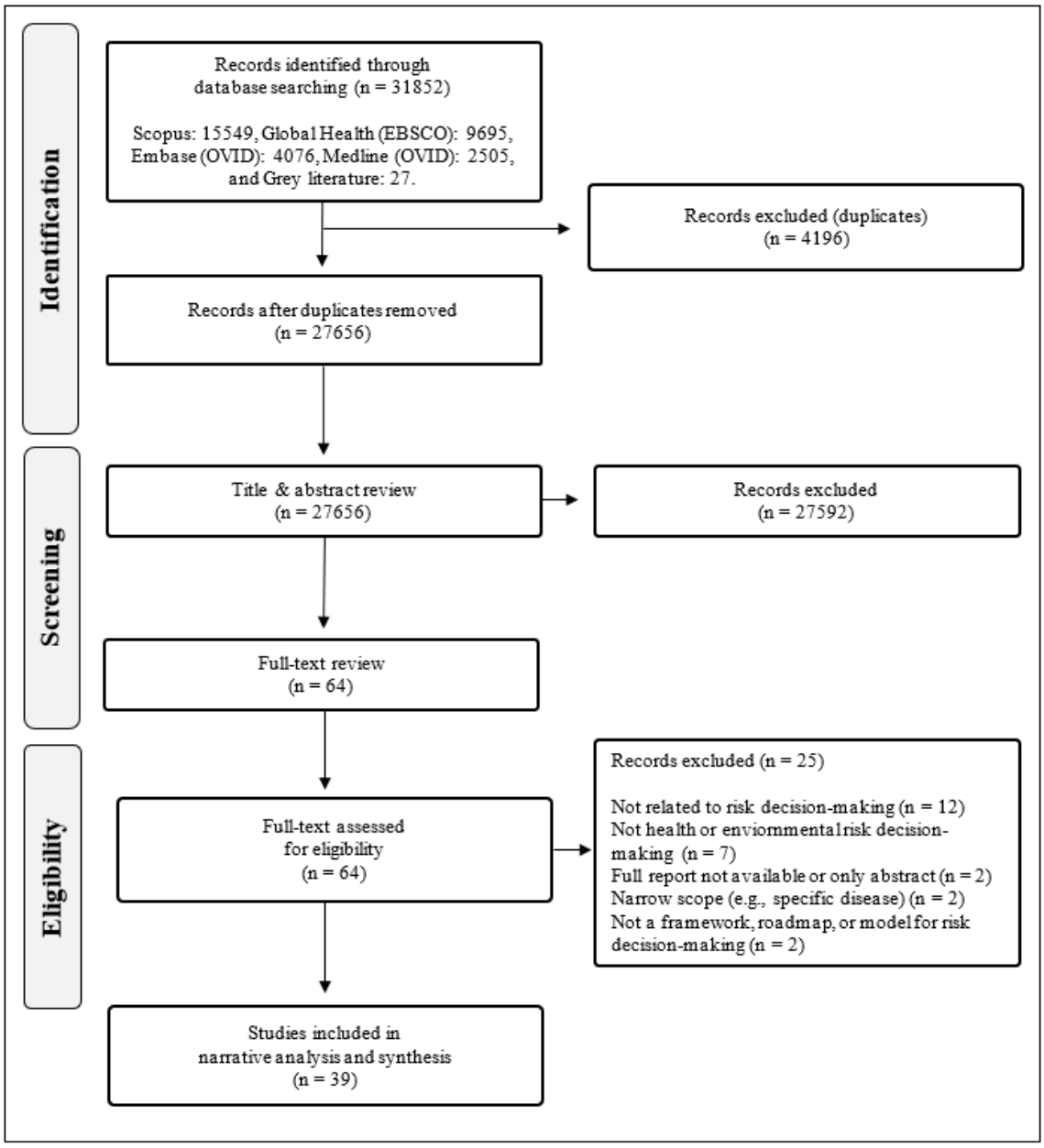

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart outlining the search strategy and the number of publications meeting the study inclusion criteria for analysis and synthesis.

In further analyzing the type of data published over time, more than half of the publications (64%) were published in North America, with 14 publications in Canada and 11 from the United States. European documents accounted for approximately 31% of the publications. There were two international publications (Corvalán et al., 2000; OECD, 2010) and another from a network of six not-for-profit blood operators with the secretariat located in Western Australia (Alliance of Blood Operators, 2014). The most frequent publication "type" was "framework" (41%), followed by reports (26%), reviews (23%), and guidance documents (10%). Only three

publications (8%) were applicable exclusively for an international setting, whereas 56% were identified as "national" documents. The remaining 36% of documents spanned jurisdictions and, thus, were classified into three categories: international, national, and local (15%); international and national (8%); or national and local (13%) setting.

When considering the "evidence-knowledge" criteria (**Table 1**), all publications (n = 39) referred to the use of quantitative and qualitative data for risk decision-making. Publications, such as the Risk Management Framework for Nano-Biomaterials Used in Medical Devices and Advanced Therapy Medicinal Products (Giubilato et al., 2020), also emphasized the importance of quantitative comparisons of nanoproducts to facilitate meta-analysis and in silico modeling. Other publications noted the value in incorporating historical data when evaluating pest control products (Nealis, 2015), which includes historical use of these products (Pest Management Regulatory Agency, 2021).[1]

More than half of the publications (60%) did not present an underlying theoretical construct. Decision theory was only reported in one publication (National Research Council, 2009), and another included decision theory under uncertainty (OECD, 2010). Other examples of theoretical constructs included multi-attribute utility theory (Food & Agriculture Organization of the United Nations, 2017), behavioral decision theory (Institute of Medicine, 2011), and Dempster–Shafer theory (evidence for combining evidence, applied in the context of computational toxicology) (Krewski et al., 2022a). Additional theories mentioned in other publications are included in **Table S1**.

Only four publications (10%) did not include an explicit reference to core values and principles. For the ones providing this information, the core values and principles were aligned with the description provided in **Table 1** for this criterion. For example, the Corvalán et al. (2000) publication, Decision-Making in Environmental Health: From Evidence to Action, included social values and three principles related to the Health and Environmental Analysis for Decision-Making Project (HEADLAMP) (Corvalán et al., 2000). The framework on the tolerability of risk described the systematic determination of the most appropriate approach for controlling risks, which includes the application of principles, such as ALARP which stands for as as low as reasonably practicable (Bouder et al., 2007).

[1]An underlying science-policy note for the Pest Management Regulatory Agency was updated in 2021, thereby resulting in this framework appearing as an outlier (black and grey circle, right, **Figure 2**).

Another framework designed to improve the quality of health, safety, and environment regulations (Aven et al., 2010) also incorporated the notion of how core values and norms are the morals guiding individual and collective action (e.g., through the application of the precautionary and other principles).

As most of the publications (90%) provided information on core values and principles and (97%) included implicit or explicit information on risk governance, this supported how these two criteria are important attributes for risk decision-making. Similarly, as all 39 publications included insights on design (scope and steps), structure, and regulatory factors, these criteria were also considered relevant attributes for risk decision-making.

5.4.2 Terminology

In the present work, we use "risk decision-making process" as an overarching and categorical term for describing different applications and more detailed evaluations for managing diverse types of risk. The underlying process also includes various phases and must encompass, when necessary, entire fields (e.g., considering environmental and health risks in the decision-making process). Risk decision-making is also applied in different regulatory contexts, and thus, there can be expectations for having different attributes. Consequently, although our analysis is primarily focused on the national/federal regulatory, risk decision-making context, it does not preclude the application of our work beyond this setting.

Our analysis also considered how the terminology for this process has evolved over time by tabulating definitions for risk analysis, assessment, governance, management, and science (**Table S2**). We note that the definition of "risk assessment" and the corresponding four steps have remained constant from when referenced in the first publication for this analysis, the US National Research Council's "Red Book" (National Research Council, 1983). The term "risk analysis" reflects the entire process of hazard identification, risk assessment, management, and communication (Dreyer & Renn, 2009; Food & Agriculture Organization of the United Nations, 2017; OECD, 2010) and problem formulation (Gormley-gallagher et al., 2011). When described, "risk governance" relates to the respective actors, rules, conventions, actions, processes, and mechanisms concerned with how relevant risk information is collected, analyzed, and communicated and how decisions are managed (Bouder et al., 2007; International Risk Governance Council (IRGC), 2017). "Risk management" typically describes the collective

events and considerations involved in addressing and communicating risks through various inter-related activities, factors, and considerations (Alliance of Blood Operators, 2014; Health Canada, 2000; Krewski et al., 2007). Some documents also refer to this step of the risk decision-making process as "risk control, estimation, and evaluation" (Canadian Standards Association, 1991) and "risk response" (Nealis, 2015). The term "risk science" reflects contributions from experts, including a more contemporary definition by Krewski et al. (2014), which encompasses both the scientific enterprise of risk assessment and the risk management actions taken to reduce risk (Jardine et al., 2003; Krewski et al., 2014; Westphal et al., 2017). Therefore, it is like risk analysis but also includes elements of risk governance by extending the definition of risk science to also include the scientific enterprise.

5.4.3 Evolution of risk decision-making

The studies included in the review were analyzed to determine the changes in the risk decision-making approach/process over a 53-year period (1970–2023). Initially, the intent was to identify the key attributes of risk decision-making and then determine a quantitative approach to measure the change in these factors over time. However, upon closer examination of the publications, several foundational elements (e.g., the well-established and internationally recognized steps to risk assessment) were preserved as one transitioned from a framework to another published in a subsequent year. Further, the evolution and enhanced approaches to decision-making were a result of several interrelated factors. Consequently, a qualitative approach was deemed more appropriate for considering the degree of integration from previous approaches. By identifying elements that were conserved over time and attributes determined as being a major change, thereby serving as the pivotal contribution for that publication (e.g., incorporation of population health in the risk assessment/management paradigm), we were able to map the chronological transformation in the degree of integration for risk decision-making over time (**Figure 2**).

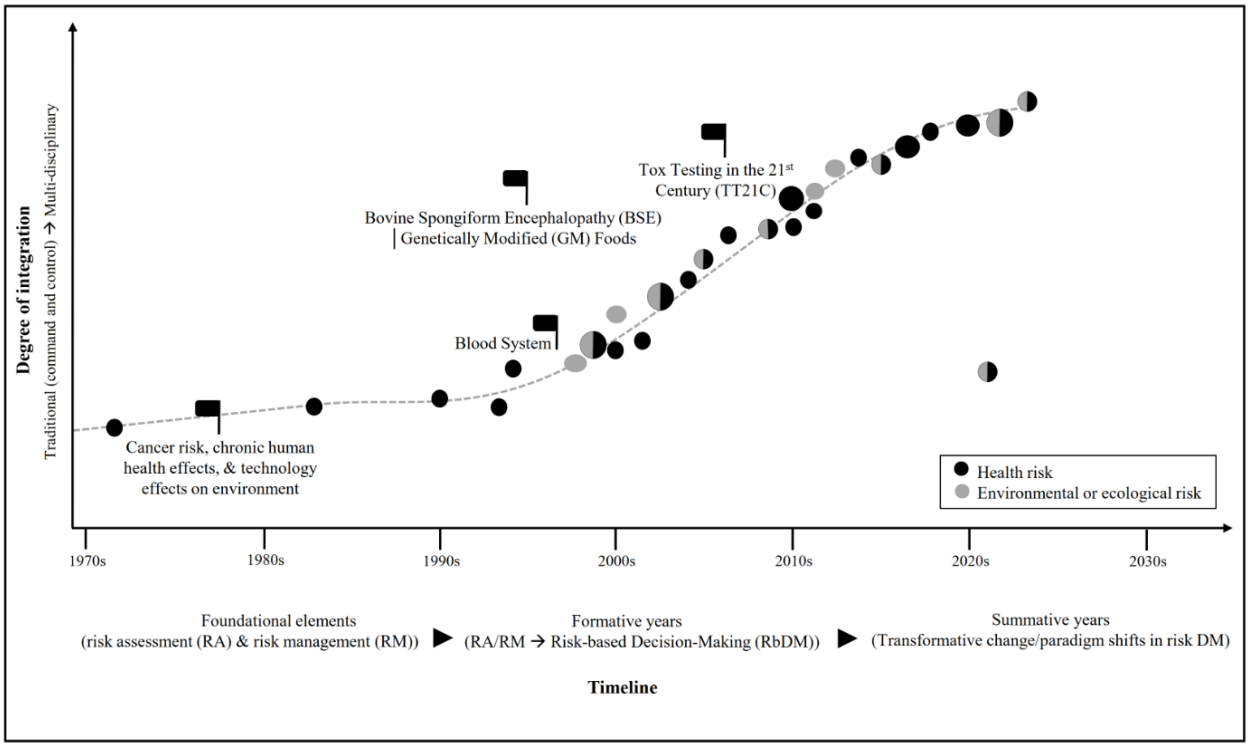

Figure 2. Evolution in health and environmental or ecological risk decision-making mapped by determining the degree of integration (change from traditional [foundational elements] to multi-disciplinary approaches) over time. Publications in the field of health risk science and environmental or ecological risk science are represented by black and gray circles, respectively, and those related to both health and environmental or ecological risk science are represented by joint, black and gray semi-circles.

The degrees of integration of the 39 publications included in this analysis are shown from the 1970s through to the present. In identifying the notable feature and mapping the pivotal changes from each publication over time, an inflection point occurs around the sixth shaded gray circle found below the flag for "Blood System." This is followed by acceleration in the availability of publications after the 1997 publication of *The Presidential/ Congressional Commission on Risk Assessment and Risk Management (PCCRARM): Framework for Environmental Health Risk Management* (Presidential Commission on Risk Assessment & Risk Management, 1997). Significant public concerns/risk issues reported in some of the publications are identified using "black flags." For example, in the 1970s, the public had a heightened concern toward cancer risk, chronic health concerns, and the effects of technology on the environment. Consequently, these issues are noted in the 1983 US National Research Council's Risk Assessment in the Federal Government: Managing the Process the Process (also known as the "Red Book") and resulted in the publication of several US guidance documents (National Research Council, 1983, 2009).

The six larger circles, presented in **Figure 2**, represent critical reviews occurring at specific time points. From left to right, the first one was on environmental risk assessment–management

frameworks (Power & McCarty, 1998), followed by health and environmental risk management frameworks (Jardine et al., 2003), the OECD review of risk-based regulations (OECD, 2010), the future of risk science (Westphal et al., 2017), a review of quantitative benefit–risk assessment frameworks (Kurzinger et al., 2020), and risk management frameworks for chemicals (Moore et al., 2022).

5.4.3.1 Pivotal contributions to risk decision-making

The pivotal contributions to risk decision-making were identified as being related to the following aspects: (i) an expansion in the scope of risk decision factors considered in the publication and a shift toward representing some of the governance and policy factors in a graphic representation; (ii) an increase in the number and type of evaluations conducted to address the expanded decision scope represented in the respective framework; (iii) significant advancement in methodologies of risk assessment; (iv) broadening of legitimate aspects relevant for risk decision-making (e.g., risk judgment); and (v) increased public and political expectations for consultation and transparency. Additional details are available in **Table S1**.

The gradual increase in the scope, factors, expectations, and number of distinct and parallel processes incorporated in the risk decision-making process (e.g., population health [Krewski et al., 2014; Westphal et al., 2017] or socio-economic and socio-behavioral aspects [Wilks et al., 2015]) results in an "S-shaped" or sigmoidal curve, as seen in **Figure 2**. Consequently, as one goes from left (1970s) to right, the publications evolve from simple approaches (linking research to risk assessment and management) to complex and multidisciplinary strategies. This also creates three overlapping periods, beginning with the establishment of the foundational elements for risk assessment and risk management. This is followed by the formative years (shifting from the risk assessment/management paradigm to risk-based decision-making) and then the summative years (transformative change/paradigm shifts in risk decision-making).

These three distinct periods are further explored below and additional details are also provided in **Table 2**, **Table S1**, and **Figure S1**. The use of the early, formative, and summative years, as a means to separate the changes and evolution in risk decision-making, is also aligned with the three periods previously identified by Dryer and Renn (2009): (i) technocratic (science → policy → risk communication), (ii) decisionist (risk assessment (scientific considerations) → risk evaluation (technical, economic, and social considerations) → risk management (technical,

economic & social considerations) → policy outcome and regulation)), and (iii) transparent model (social framing: socio-economic & political considerations → risk assessment ↔ risk evaluation → risk management → policy outcome and regulation) (Dreyer & Renn, 2009).

Table 2: Attributes of risk decision-making over time

Attributes (*a priori*)	**Early years** (1970/80s; 2 publications)	**Formative years** (starting in late 1990s; 30 publications)	**Summative years** (starting in early 2020s; 7 publications)
Structure	Sequential and logical frameworks designed for regulatory authorities to take action to protect public health.	Sequential to more iterative, comprehensive, and integrated frameworks. Several frameworks are circular diagrams representing the integrated and iterative nature of the decision-making process.	Holistic, fully integrated, and consideration of multi-disciplinary fields relevant to contemporary health and environmental risk decision-making.
Design (scope and risk decision-making steps)	Defining the risk assessment steps - hazard identification, dose-response assessment, exposure assessment, and risk characterization - and how they relate to risk management (National Research Council, 1983).	Advancing specific steps of the risk decision making process: More emphasis on pre-assessment or the planning phase (scoping and problem formulation[a]) (National Research Council, 2009) and maximizing the risk assessment. Broadening the utility of risk characterization as a distinct phase between risk assessment and management (Institute of Medicine, 2011; United States Environmental Protection Agency (EPA), 2014). Providing additional insights on cross-cutting elements such as stakeholder engagement, communication, and context (International Risk Governance Council (IRGC), 2017). Recognition and integration of other fields (e.g., population health determinants), diverse assessments (e.g., contextual) (Alliance of Blood Operators, 2014), and parallel processes (e.g., stakeholder engagement) (Suter II et al., 2005).	State-of-the-art, life-cycle, and adaptive approaches to risk assessment (Giubilato et al., 2020) and management (Moore et al., 2022). Integrated evidence to risk assessment (Krewski et al., 2022a) and evidence to decision-making frameworks (Stratil et al., 2020a). Algorithmic processes to benefit-risk assessments (Kurzinger et al., 2020). Transformative approaches to research and development. This includes participatory research, incorporating advances in data sciences, and continuous learning and improvement designed to meet future regulatory needs (One Environment-One Health) (National Academies of Sciences Engineering and Medicine, 2023).
Risk governance	Establishing and maintaining a clear "conceptual" distinction between	Risk assessment is part of an integrated risk decision-making process, which includes risk	Systems thinking and approaches such as One Environment-One Health which require collaborative

	risk assessment and risk management (National Research Council, 1983)	management (Jardine et al., 2003; Krewski et al., 2007) Role for leadership through modern management practices, extended enterprise (HM Treasury, 2004; Treasury Board of Canada Secretariat, 2001), and positioning the core risk governance process within broader factors including the organizational capacity, political and regulatory culture, and social climate (International Risk Governance Council (IRGC), 2017)	governance and participatory research during the research and development phase for future regulatory risk decision-making purposes (National Academies of Sciences Engineering & Medicine, 2023) Similar broad and holistic approaches are also being considered for specific chemicals such as the Transforming the Evaluation of Agrochemicals initiative (Wolf et al., 2022)
Regulatory factors	These 'broader' factors are relevant to all phases of the risk decision-making process (Bhuller & Trevithick-Sutton, 2024). They are diverse and include political, social, environmental, legislative, public, ethical, cultural, socioeconomic, technological, public acceptance and perception, transparency, dealing with uncertainty, leadership, consumer interests, globalisation, stakeholder fatigue, trade, regulatory impact, regulatory landscape, trade-offs, collaboration, multiple stakeholders, data quality, and weight of evidence. The United Kingdom's HM Treasury uses the PESTLE model, which incorporates political, economic, socio-cultural, technological, legal/regulatory, and environmental considerations (HM Treasury, 2004).		
Key notable features	Reform in organizational structures and processes: centralized risk assessment activities while keeping the assessment activities distinct from risk analysis, risk management options, and risk decision-making strategies (National Research Council, 1983).	More comprehensive approach to risk management with emphasis on iterations & discussions with stakeholders throughout the decision-making process. Problem formulation, broad context, and upfront consideration of diverse factors. Maximizing utility of risk characterization and modernization efforts.	Shift towards a collaborative risk governance and broader, systems thinking and public health approaches to risk decision-making. Development of evidence-to-decision frameworks to help prepare the regulatory authority for future decision-making and transformation/ paradigm shifts in current processes.

[a]Scoping is a deliberative process for decision-makers interested in defining a risk-related problem. Problem formulation is a technically oriented process used by assessors to operationally structure the risk assessment (National Research Council, 2009).

5.4.3.2 Key attributes for risk decision-making

Table 2 provides information on the key attributes and how they relate to the early, formative, and summative years of risk decision-making. The first transition - early to formative years - reflects two key publications: The Presidential/ Congressional Commission on Risk Assessment and Risk Management (PCCRARM): Framework for Environmental Health Risk Management (Presidential Commission on Risk Assessment and Risk Management, 1997) and Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks (Health Canada, 2000). Subsequent references to these two documents solidifies their importance in setting the foundation for the risk assessment/management paradigm and the pivot towards further enhancing the overall approach and process of risk decision-making during the formative years. Similarly, the movement from the formative to summative years accounts for publications focused on providing detailed guidance on evidence integration (Krewski et al., 2022a; Rehfuess et al., 2019; Stratil et al., 2020a; Stratil et al., 2020b) and more complex, systems thinking frameworks focused on further integrating health and environmental research for future regulatory purposes (National Academies of Sciences Engineering and Medicine, 2023).

Table 3 further consolidates the information provided in **Table 2** (and **Table S1**) by identifying a list of 10 attributes related to the structure, governance (roles and responsibilities), and processes of risk decision-making. The trigger/issue is the attribute that initiates the risk decision-making process. Cross-cutting attributes include factors that typically interact with other attributes, such as determining the best design (scope and steps) and evidence-knowledge required for addressing the specific trigger and issue. The regulatory context creates the overall boundary for decision-making and includes regulatory factors (e.g., legislative statutes), which can also be cross-cutting; that is, they can influence other attributes in the risk decision-making process such as the decision-making pathway. The core values and principles reflect the institutional values and moral norms, which can evolve based on changes in societal values (e.g., contemporary paradigm shifts toward non-animal testing strategies for cosmetic products [Dent et al., 2018, 2021]).

Table 3: Consolidated list of ten attributes of risk decision-making

Attribute	Guiding descriptor
Trigger/Issue	Defines the risk context and can be a known, emerging, or anticipated (e.g., determined using foresight and planning exercises) health and/or environmental risk.

Regulatory context	Creates the overall boundaries of risk decision-making thereby making it an overarching and cross-cutting attribute.
Regulatory factors	These are broad and diverse elements which are also considered when establishing the regulatory context. These factors include regulatory, economic, advisory, community-based, or the technological nature of risk management (i.e., REACT factors (Westphal et al., 2017)). Further, they can incorporate the political, economic, socio-cultural, technological, legal/regulatory, and environmental considerations (i.e., PESTLE factors (HM Treasury, 2004)).
Core values	Foundational elements which support risk and ethical decision-making principles and the risk decision-making process.
Risk decision-making principles	Extrinsic, objective, fundamental, and impersonal rules. These can also include ethical principles grounded in institutional values and moral norms.
Cross-cutting attributes	Stakeholder engagement, effective, open and transparent communication, and continuous learning and improvement are attributes which are relevant for a majority of risk contexts. The memory aid, BroadCAST-3Cs - where 'CAST' stands for core, audience, spokesperson, and timely and '3Cs' for context, clarity, and concise - can facilitate effective risk communication (Bhuller & Trevithick-Sutton, 2024).
Design (scope and steps)	The aim of the design is to maximize the utility of the following steps: - Planning and pre-assessment (scoping and problem-formulation); - Using a multi/transdisciplinary and integrated risk assessment (e.g., integration of Toxicity Testing in the 21st Century, next generation risk assessment (exposure-first and increased reliance on non-animal testing strategies), population health approaches, and concern assessment: socio-economic/behavioural and geopolitical considerations); - Ensuing risk characterization goes beyond simple ranking of risks; and - Supporting all the risk decision-making steps using strong risk governance, which includes internal and external leadership and collaboration.
Structure	Fully integrated and adaptable (fit-for-purpose) processes which adhere to and respect the institution's governance structure for risk decision-making.
Decision-making pathway	Adaptable and ranging from straightforward to complex decision-making pathways.
Evidence-knowledge	Quantitative and qualitative data relevant for risk decision-making. Value-of-information and how best to integrate the data are important considerations.

5.5 Discussion

By identifying and characterizing the key attributes for health and environmental risk decision-making, using guiding descriptors, this scoping review has addressed the research question: What are the key attributes of health and environmental risk decision-making, and how are these inherent characteristics related to the regulatory decision-making context, processes, and governance structures? Our contribution to the field of risk analysis and science also includes the identification of 10 attributes reflecting the best practices and recommendations from over 50 years of work dedicated to risk decision-making, its evolution, and ongoing transformation within a regulatory context (**Table 3**). We also demonstrate how the inherent characteristics of these attributes relate to the regulatory context, process, and underlying governance, which includes attributes, such as stakeholder engagement, which are cross-cutting.

Our analysis also validated our choice of several a priori criteria that eventually transitioned into risk decision-making attributes. The analyzed publications supported these elements while providing additional insights on other suitable attributes. Further, the evolution in risk decision-making was determined to build upon foundational elements, whereas the complexity in subsequent approaches and underlying processes was a result of expansion in the scope, number of evaluations, advances in methodologies, and aspects such as the relevance of risk judgment and public expectations. Consequently, it is reasonable to consider that an expansion of evaluations conducted would follow the expanded scope in risk decision-making frameworks to include, for example, processes for ethical considerations and risk tolerability evaluations. Similarly, our analysis aligns with publications demonstrating how changes in the assessment methodologies (e.g., consideration of non-animal testing approaches) and paradigm shifts in regulatory sciences (Hilton et al., 2023) are being driven by the need to conduct different evaluations relevant to health (and environmental) risk, as called for in expanded decision-making frameworks.

5.5.1 Strengths and limitations

As this is a scoping review, a critical appraisal of the quality of the synthesized evidence (i.e., summary measures, risk of bias, and certainty of the evidence) was not necessary. To minimize errors in study selection, analysis, and interpretation, two reviewers worked independently when screening the titles and abstracts. The process of resolving disagreements was decided in advance, and a study protocol was published prior to starting the review. The extraction tool was also piloted, using three studies, and revised accordingly through review team discussion and documentation of decisions. The research team included two bilingual reviewers, as both French and English publications were considered in the selection of potential studies.

Although the study relied on mixed methods to present the results, a limitation was the inability to use the quantitative data beyond descriptive purposes. However, this is not considered to be a major limitation, as the qualitative analysis and the use of the key notable features separating one approach from the next were deemed sufficient to map the changes over time (Figure 2).

We acknowledge that the publications excluded in our analysis could include references routinely used for health and environmental risk decision-making. Further, although our screening phase included 27,656 documents, we may not have accounted for all possible

publications. Having said that, there is a degree of confidence that the search strategy resulted in the inclusion of several pivotal and key publications. Prior to commencing the review process, experts in risk science identified 58 publications for consideration (Supporting Information section). When comparing the final list of publications used for data extraction and analysis, 24 (62%) were those that were also identified by these experts. Consequently, there is a good degree of overlap between the publications determined using the independent scoping review process and those identified by experts.

5.6 Conclusion

The first publication discussed in this scoping review, the US National Research Council's 'Red
The first publication discussed in this scoping review, the US National Research Council's "Red Book," provides a historical and foundational perspective on the link among research, risk assessment, and risk management (National Research Council, 1983). Forty years later, the last publication discussed comes full circle with recommendations for a more integrated, One Environment-One Health approach for future regulatory-research needs (National Academies of Sciences Engineering & Medicine, 2023). The ongoing transformation in the research area reflects continuous work in navigating the paradigm shift for updating ossified legislative statutes (Hilton et al., 2023), along with transforming the regulatory risk decision-making processes for industrial chemicals and pest control products (Bhuller et al., 2021; Wolf et al., 2022) and other product types (Angelis & Phillips, 2021). Similar changes are also occurring in the area of medical products where global authorities are aiming to advance benefit–risk assessment approaches to decision-making (Walker et al., 2015). As regulatory risk-based decisions must continue to be informed by the best available evidence from research and other sources (including big and open data), there is also a need to modernize current evidence integration approaches for decision-making. Consequently, it is not surprising to find more recent publications emphasizing ways of combining evidence from multiple streams to ensure completeness in evidence-based risk assessment (Krewski et al., 2022a; Norris et al., 2021; Rehfuess et al., 2019; Stratil et al., 2020a, 2020b; World Health Organization, 2021).

Although much has been accomplished in the field of risk analysis and science over the last five decades, the present synthesis of these advances provides a basis for further refinement of current paradigms for risk assessment and management. However, what seems to be lacking are the underlying considerations for integrated, modern, and even generic approaches to

contemporary and future risk decision-making. Our goal is to address this gap with our next endeavor. We are currently developing the key considerations for establishing a next generation risk decision-making approach that builds upon the information provided in this scoping review and recent work on risk communication (Bhuller & Trevithick-Sutton, 2024), risk principles (Bhuller et al., 2024; Krewski et al., 2022b), and discussions on ethical considerations and principles for risk decision-making.

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Supplementary material 1: PRISMA-P 2015 checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #; Line #s
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a scoping review	N/A; title in the OSF registry identifies the entry as a protocol for a scoping review.
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO; OPEN SCIENCE FRAMEWORK) and registration number	OSF registry: https://osf.io/gnyfk
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Contributors names included in the OSF registered protocol.
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Description and research question are included in the OSF registered protocol.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Provided in the OSF registered protocol.

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Provided in the OSF registered protocol.
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Drafted, but not a requirements for the OSF registered protocol.
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Provided in the OSF registered protocol.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Since this is a scoping review of documents, the concepts and contexts are described (Pages 5-10)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Provided in the OSF registered protocol.
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A - This is a scoping review of open text and opinion
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A - This is a scoping review of open text and opinion

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary material 2: OSF Registered protocol

Health and environmental risk decision-making attributes: A protocol for a scoping review of risk decision-making frameworks

This is an update to the original registration

This update was made on Sep 15, 2023

Reason for update:
Correcting the spacing errors found in the published protocol.

Contributors

Yadvinder Bhuller, Xaand Bancroft, Raywat Deonandan, Agnes Grudniewicz, Anne Wiles, and Daniel Krewski

Description

Government agencies, international institutions, and independent experts have published updated approaches for next generation risk assessments and evidence-based strategies to support health and environmental risk decision-making. This includes contemporary frameworks and models reflecting current risk assessment and management processes and when applicable, the overarching context and governance structures for addressing health and environmental issues. While there continues to be a focus on developing additional frameworks, models, and roadmaps on how to integrate modern approaches, the reviews comparing the available risk decision-making frameworks are limited. Further, the published comparisons may not incorporate recently developed approaches and scientific advances or reflect the current, federal/national regulatory context (e.g., use of non-animal strategies for evaluating human safety). Accordingly, this scoping review aims to survey the existing literature and provide a narrative analysis of the existing frameworks.

Registration type	Date registered	Date created
OSF Preregistration	September 15, 2023	September 15, 2023

Associated project	Internet Archive link
osf.io/u3fw2	https://archive.org/details/osf-registrations-gnyfk-v1

Registration DOI
https://doi.org/10.17605/OSF.IO/GNYFK

Subjects
Other Pharmacology, Toxicology and Environmental Health Life Sciences Medicine and Health Sciences Other Medicine and Health Sciences Pharmacology, Toxicology and Environmental Health Other Life Sciences Environmental Health Life Sciences

Citation
https://osf.io/gnyfk

Study Information

Hypotheses
This is a scoping review, therefore there is no hypothesis necessary for the study.

Design Plan

Study type
Other

Blinding
No blinding is involved in this study.

Is there any additional blinding in this study?
No response

Study design

The objectives of this scoping review are to survey, examine, summarize, and characterize existing literature on federal/national decision-making frameworks for health and environmental risks. The research question is: What are the key attributes of health and environmental risk decision-making and how are these inherent characteristics related to the federal regulatory decision-making context, processes, and governance structures?

No files selected

Randomization
No response

Sampling Plan

Existing Data
Registration prior to creation of data

Explanation of existing data

This is a scoping review, therefore the data exists in literature and we will be using a specific search strategy to collect the articles (please see details below).

Data collection procedures

The following electronic databases will be searched for relevant publications: MEDLINE (OVID), EMBASE (OVID), SCOPUS, and Global Health (EBSCO). Key terms include ‘risk management or assessment or evaluation and mitigation’, ‘decision-making’, and ‘health’. Google, Google Scholar, the World Health Organization (WHO), International Council for Harmonisation (ICH), Organisation for Economic Co-operation and Development (OECD) iLibrary, Food and Agriculture Organization (FAO), United States Federal Registry, European, and Government of Canada’s search engines or publication websites will be used to extract grey literature, books/chapters, and reports as well as references of relevant reviews. Reports shared using purposeful snowball sampling (i.e., reports shared by experts and references from the published and grey literature) will also be considered.

No files selected

Sample size

The number of studies to be included in the scoping review is unknown at this time. Once the review is complete, the Flow Diagram will outline details of how the studies were selected, screened and the criteria for them to be included.

Sample size rationale
Not applicable

Stopping rule

Based on established scoping review methodology, a search strategy (informed by a professional librarian) will be applied to relevant databases. Articles that meet the inclusion criteria will be retained and those that do not will be excluded. This is decided by two reviewers who will independently assess the article and make the decision to retain. Any conflicts will be resolved through discussion or a third reviewer.

Inclusion criteria: Documents providing an overarching approach (framework, roadmap, and/or model) relevant to health and environmental risk decision-making and for an entire domain (e.g., risk sciences: risk assessment and risk management) or class of products (e.g., next generation framework for chemicals management or new frameworks for pharmaceuticals and agrochemicals) will be included. This incorporates work from national/federal regulatory authorities, international organizations (e.g., World Health Organization), review articles (e.g., systematic, scoping, rapid, or literature review), and research work (e.g., conceptual reports describing or proposing a set of decision criteria, decision-making tool, or approach).

Exclusion criteria: Studies will be excluded if they did not present an overarching approach for human health and environmental risk decision-making or provides a narrow focus on a single dimension (e.g., a specific condition or assay such as Alzheimer's or skin sensitization, respectively, frameworks on nanotechnology, or action plans for combatting antimicrobial resistance), or focus on domains not relevant to health and environmental risk decision-making. Further languages other than English and French, and commentaries, opinion pieces, editorials, blogs, and conference abstracts will also be excluded.

Variables

Manipulated variables
Not applicable in this scoping review protocol.
No files selected

Measured variables Updated

Data to be extracted will include the following key information on each included study:

1. Authors
2. Title of publication
3. Year of publication

4. Origin, country of origin, geography
5. Aim/purpose/objective(s)
6. Type of text/publication (e.g., research paper, review, report, tool, guidance document, policy, framework)
7. Population represented (international, national, local)
8. Setting/context (international, national, local)
9. Methodology (quantitative, qualitative, mixed methods)
10. Key findings related to the scoping review question. The reference includes information on the following attributes related to health and environment risk management decision-making. Details corresponding to these attributes will be extracted and captured in a tabular summary: (a) Core values and principles in risk decision-making; (b) Risk decision-making steps; (c) Structures; (d) Facts (i.e., evidence and knowledge sources for risk decision-making); (e) Regulatory factors (practical, policy and mandate, and contextual); and (f) Underlying theory (e.g., logical models or reference to classical theories for decision-making) 11 Description of framework attributes (a) to (f)

No files selected

Indices
No response
No files selected

Analysis Plan

Statistical models

We will conduct simple frequency counts of the key findings will be conducted (e.g., how many frameworks use a dynamic or cyclic structure?). Additionally, a narrative analysis and summary will be used to synthesize the content. As there is a possibility for discovering additional attributes, in vivo codes will be used to help guide any subsequent inductive and further thematic analysis of these elements. Therefore, the main focus of the scoping review will be the narrative analysis of legacy/historical and more current frameworks along with summarizing the attributes from these documents and how they relate to the described risk decision-making process.

No files selected

Transformations
Not applicable

Inference criteria
Not applicable

Data exclusion
Not applicable

Missing data

If data is missing from an included study, the authors of that study will be contacted in an attempt to request the missing data. If the data cannot be obtained, then the study will be excluded and this will be noted in the scoping review analysis.

Exploratory analysis
Not applicable

Other

Other
No response

Supplementary material 3: Tables S1, S2, S3, S4 and Figure S1

The tables and figure in this document provide detailed information intended to supplement the information provided in the manuscript. **Table** includes additional insights on the key findings (e.g., notable features). **Table S2** - terminology - is a consolidated listing of definitions for risk analysis, assessment, governance, management, and science from the 39 extracted publications. These terms provide insights on how they were introduced and then further developed over the course of 40 years of risk-based decision-making. **Table S3** provides the preliminary search strategy. The 58 publications recommended for consideration by experts in risk science are included in **Table S4**, **Figure S1** identifies the name and key attribute(s) for each reference directly in the *Degree of Integration versus Timeline* graph, and the references start on the page after Figure S1.

Table S1: Key findings from the references (1983 to 2023 – shaded rows are reviews of frameworks)

Title (reference)	Year	Origin	Objective	Type Framework Guidance Report Review	Population & Setting International National Local	Key findings Core values & Principles	Risk decision-making (DM) steps	Structures Full integration (F) Partial integration (P) Sequential (S)	Evidence-Knowledge Quantitative Qualitative	Regulatory Factors	Underlying Theory	Risk Governance Explicit Implicit	Notable features
Risk Assessment in the Federal Government: Managing the Process (Red Book) (National Research Council, 1983)	1983	US; North America	Response to congressional request for uniform guidelines & insights on separating risk assessment (RA) activities from risk management (RM).	Report	National & local	Reform of organizational structures based on three interrelated principles (P) of RA activities (see key innovation).	4 steps (RA): hazard identification, dose-response assessment, exposure assessment, & risk characterization.	S: logical framework research → RA → RM	Quantitative & qualitative	✓ (e.g., authority for federal administrative agencies to act for protecting public health)	-	Implicit; Establish & maintain a clear conceptual distinction between RA & RM without separation.	● Reforms in organizational structures & procedures: RA activities centralized (P1) but separate from risk analysis & RM options & DM strategies (P2) & recommendations on the composition of expert panels (P3). ● Strengthen reliability & objectivity of scientific assessment for regulatory purposes.
Risk Analysis Requirements and Guidelines (CAN /CSA-Q634-91) (Canadian Standards Association, 1991)	1991	Canada; North America	Provide guidelines & requirements for the application of a quality process in risk analysis.	Guidance (standard)	National & local	-	3 steps (risk analysis): scope definition, hazard identification, & risk estimation.	S: hierarchical & one-way, RM-DM process	Quantitative & qualitative	✓ (e.g., life cycle phase, type & consequence of hazards which includes public safety)	-	Implicit; RM framework has two main branches: RA → risk analysis & risk control → DM	● Focus is on risk analysis & promoting uniformity primarily for hazards. ● Role of risk analysis, its application in analyzing risks, & presenting risk information using a multidisciplinary approach, which includes documentation, verification, & updating the risk analysis.
The Presidential/ Congressional Commission on Risk Assessment and Risk Management (PCCRARM): Framework for Environmental Health Risk Management (Presidential Commission on Risk Assessment and Risk Management, 1997)	1997	US; North America	Policy implications & appropriate use of RA & RM for regulatory purposes subject to various Federal laws.	Report	National & local	Comprehensive approach to RM with 3 key principles: broad context, stakeholder consultations, & iterations.	6 circular steps (RM) starting with problem /context surrounding a central core - engage stakeholders. Integrated ecological RA framework.	P: integrated framework (circles) with unilateral flow (one-way) F: ecological RA (discussion among assessors, managers, & stakeholders: throughout process	Quantitative & qualitative	✓ (economic, social, cultural, ethical, legal, political implications, worker & community health, & ecological hazards)	Scientific & economic theory (measures of willingness to pay & opportunity cost)	Implicit; Risks analyzed with the problem in context prior to examining options for addressing risks & DM.	● More comprehensive approach to RM with emphasis on iterations & discussions with stakeholders throughout DM process ● Problem formulation, broad context, & consideration of diverse factors. ● Application of the framework to both health & ecological RA. ● The ecological RA (volume 2; PCCRARM) is from the US Environmental Protection Agency (EPA).
A comparative analysis of environmental risk assessment/risk management frameworks (Power & McCarty, 1998)	1998	Canada; North America	Analysis of 7 frameworks: Common themes, differences in approach, & conceptual innovations for addressing health &	Report	National	Several frameworks make explicit reference to values & principles.	Ranges from explicitly RM to implicitly management-oriented & RA embedded in RM.	Ranges from F (n=4) frameworks, P (between RA & RM; n=2) frameworks, or S: a linear with implicit feedback (n=1) framework.	Quantitative & qualitative	✓ (e.g., social, ethical, & economic values)	-	Implicit; Role of science is noted for estimating risks (n=4), RM DM (n=2), & RA, but not alone (n=1)	● Trend towards greater stakeholder involvement, decreased emphasis on quantitative characterization of risk & uncertainty, & development of iterative decision-based analysis cycles in frameworks. ● RA embedded within RM with more emphasis on RM. ● Formalize problem formulation, role of science, & inclusion of social, ethical, & economic values in risk analysis.

Title (reference)	Year	Origin	Objective	Type Framework Guidance Report Review	Population & Setting International National Local	Key findings Core values & Principles	Risk decision-making (DM) steps	Structures Full integration (F) Partial integration (P) Sequential (S)	Evidence-Knowledge Quantitative Qualitative	Regulatory Factors	Underlying Theory	Risk Governance Explicit Implicit	Notable features
			environmental risks.										
Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks (Health Canada, 2000)	2000	Canada; North America	Describe key challenges (e.g., Krever Commission of Inquiry on the Blood System in Canada) leading to the development of a revised & more modern RM-DM framework.	Framework	National	Core values include public, organizational, & cultural considerations. The underlying values also shape the 10 principles of the framework.	6 circular steps (RM) surrounding a central core - involve interested & affected parties.	F: Selection of a circle diagram (as opposed to a linear one) accounts for an integrated DM process, the corresponding steps, & their interrelationships.	Quantitative & qualitative	✓ (e.g., social, political, legal, ethical, cultural, international economic, environment, value-of-information, & level of resources)	Probability theory included in the definition of analysis.	Implicit; Assessing risk & benefits is part of the integrated RM-DM process.	● Similar structure to the PCCRARM framework. ● Maintaining & improving health (P1) is the primary objective & takes precedence over all other considerations. ● Overview guidance on environmental RA, socioeconomic analysis, risk communication, public involvement, integrating population health & RM DM, & developing health-based outcome measures.
Decision-Making in Environmental Health: From Evidence to Action (Corvalán et al., 2000)	2000	Switzerland; Europe	To provide a model & framework for environmental health DM on behalf of the World Health Organization.	Framework	International, National, & Local	Social values & 3 principles related to the Health & Environmental Analysis for DM Project (HEADLAMP) process.	3 steps (DM): Definition, assessment, & policy formulation.	F : The HEADLAMP process is a fully integrated circuit. The frameworks (see notable features) describe the pathway linking the source activities with the health effects.	Quantitative & qualitative	✓ (e.g., economic development, social practices, clean technologies, & education)	-	Implicit; The policy action (final step of HEADLAMP process) feeds directly back into the second step (& when applicable, the first step).	● HEADLAMP process deliberately takes an interdisciplinary & intersectoral approach based on scientifically established relationships between environmental exposure & health effects (P1); environmental indicators (P2); & using routinely collected data (P3). ● Environmental health hazard pathway framework & the driving forces, pressures, state, exposures, effects & actions (DPSEEA) framework.
Integrated Risk Management Framework (Treasury Board of Canada Secretariat, 2001)	2001	Canada; North America	To advance, strengthen, & integrate RM practices into strategic DM within the public service, workforce culture.	Framework	National	Focus is on citizen & public service values & ethics. A principle-based framework provides guidance on the precautionary approach.	9 steps (RM) within a continuous circle where the core is continuous learning & communication.	F: The core also notes that the practice of integrated RM occurs from corporate strategy & planning to front-line operations, which includes people & processes.	Quantitative & qualitative	✓ (e.g., legal considerations, empirical & public context, precautionary approach)	-	Implicit; assessing key risk areas (RA) & RM (selecting & implementing a strategy) are part of the fully integrated process.	● Aim to advance the development & implementation of modern management practices for public service employees. ● Ability to use the in conjunction with other approaches, such as risk management in public policy: a DM process (exhibit 2: link to Health Canada's Decision-Making Framework). ● A practical guide to assist public service employees, at all levels, in their DM.
Risk management frameworks for human health and environmental risks (Jardine et al., 2003)	2003	Canada; North America	A comprehensive analytical review of frameworks for RA, RM, & risk communication approaches at the national, provincial/ state, territorial, &	Framework	International, National, & Local	Public values, morals, & beliefs; 10 DM principles with corresponding ethical principles provided within brackets.	Ranges from explicitly RM to implicitly management-oriented & RA embedded in RM.	F, P, & S: Appendix B has a range of structures; several are logic model type structures while others are decision-trees or integrated circles (e.g., Health Canada's DM & US PCCRARM frameworks).	Quantitative & qualitative	✓ (e.g., laws, policies, population health, community interests, socioeconomic factors, perceptions, & ethical considerations).	-	Implicit; several frameworks describe how RA is embedded in the RM-DM process.	● 7 key elements for comprehensive human health, ecological, & occupational RA-RM: problem formulation stage, stakeholder involvement, quantitative RA components, iteration & flexibility, informed DM, & flexibility. ● Separating RA from RM could severely compromise the DM process. ● Review describes the differences, commonalities, strengths, & weaknesses of a range of frameworks. ● Problem formulation identified as most important step for RA & RM.

Title (reference)	Year	Origin	Objective	Type Framework Guidance Report Review	Population & Setting International National Local	Key findings Core values & Principles	Risk decision-making (DM) steps	Structures Full integration (F) Partial integration (P) Sequential (S)	Evidence-Knowledge Quantitative Qualitative	Regulatory Factors	Underlying Theory	Risk Governance Explicit Implicit	Notable features
			international level										
The Orange Book: Management of Risk - Principles and Concepts (HM Treasury, 2004)	2004	UK; Europe	To provide guidance to staff ranging from new recruits to senior leaders responsible for creating a RM culture.	Report	National	Principle-based approach where the values (2023 Orange Book) reflect modern civil service & the civil service code (e.g., being honest, innovative, & ambitious) (HM Treasury, 2023).	4 steps (RM): identify, assess, address, & review/report risks around a central core - communication & learning. The framework is surrounded by two layers: the extended enterprise & risk environment /context.	F: The 2004 & 2023 reflect a cyclic process where the RA is embedded within a broader element of factors reflecting the enterprise & risk environment/ context.	Quantitative & qualitative	✓ (PESTLE model: political, economic, socio- cultural, technological, legal/regulatory, & environmental)	-	Implicit; RA is part of the integrated & cyclical RM process, which includes the extended enterprise & risk context/ environment.	● The concept of risk appetite - justifiable & tolerability - provided using the simple risk/tolerability matrix. ● Hierarch of risk pyramid: uncertainty increases from operational (base) to strategic decision (apex). ● 2023 RM framework continues to have 4 steps: risk identification & assessment, treatment, monitoring, & reporting; however, the core is 'continual improvement'. Further, the outer layers include arrows showing the movement of information & insight across the outer (governance & leadership, integration, & collaboration) & inner compartments.
An Integrated Framework for Health and Ecological Risk Assessment (Suter II et al., 2005)	2005	US; North America	A World Health Organization's International Program on Chemical Safety (WHO/IPCS) framework developed to improve quality & efficiency of RA through exchange of information & better inputs for DM.	Review	International, National, & Local	-	3 steps for integrated RA: Problem formulation with hazard identification, analysis (exposure & dose-response assessment), & risk characterization.	F: The integrated RA steps run parallel with the RM & stakeholder participation processes.	Quantitative & qualitative	✓ (e.g., legal, economic, & technological constraints on management actions)	-	Implicit; integrated RA runs parallel with RM & stakeholder participation.	● Recognition of parallel processes (stakeholders & risk managers) which interact with the scientific RA process. ● Framework reflects collaborative efforts between WHO/IPCS & US EPA. ● Human health, human welfare, & ecosystems integration described using diverse models; previous work further expands on 'bottom-up' & 'top-down' approaches (Suter II, 2004).● US NRC Red Book played a key role in the development of ecological RA (Suter II et al., 2003). ● Evidence integration requires a weigh of evidence (WoE) approach, which requires judgement.
An Integrated Framework for Risk Management and Population Health. (Krewski et al., 2007)	2007	Canada; North America	The purpose of this article is to explore commonalities in RM & PH fields & use this knowledge to strengthen the ability to address PH risk issues.	Review	National	See Jardine et al. (2003) Common goal for risk science & PH is to improve health.	3 main components (RM): Interactions between biological, social, & environmental domains), health risk science & policy analysis, & multiple RM-PH interventions.	F: holistic & transdisciplinary RM-PH framework	Quantitative & qualitative	✓ (e.g., statutes & non-regulatory options such as economic incentives)	Citation includes a reference to empowerment theory for collaborative partnership.	Implicit; integrated health risk sciences & policy analysis prior to considering RM-PH.	● Integrating two separate concepts, RM & PH, by recognizing how they are intrinsically linked; RM attempts to avoid negative risk factors while PH seeks to promote positive health determinants. ● RM-PH REACT interventions (regulatory, economic, advisory, community action, or technological). ● Integration of health risk science (transdisciplinary field relying on population genetics, epidemiology, toxicology, clinical science & health surveillance) & health risk policy analysis (evidence-based policy).

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The Tolerability of Risk: A New Framework for Risk Management (Bouder et al., 2007)	2007	US; North America	To undertake an in-depth view of the concepts & practices related to tolerability of risk (ToR) based on the collective knowledge of leading experts & practitioners.	Framework	National	Judgement & societal values. The principles include ALARP (as low as reasonably practicable), good governance, transparency, effectiveness, efficiency, equity & fairness, accountability, strategic focus, sustainability, & respect for the rule of law.	4 steps (RM): Pre-assessment, risk appraisal, tolerability & judgement, & RM which circulate a central core - communication - & are situated within two spheres: management (decision on & implementation of actions) & assessment (generation of knowledge).	F: Knowledge flows from the assessment sphere to the management sphere & requires communication through out the process.	Quantitative & qualitative	✓ (e.g., political, legitimacy, ethical, social context, sustainability, incentives, taxation, public acceptance & perception)	Probability, classical decision, prospective, & cultural theory.	Explicit; The framework advocates the notion of inclusive risk governance which underlines the importance of stakeholders & public groups, particularly for global health & systemic risks	● Development of a ToR framework arose out of consideration of the ALARP principle. ● Framework developed under the direction of the International Risk Governance Council (IRGC; 2005). ● Traffic light model: Acceptable risk, tolerable risk, need of reduction, & intolerable risk (prohibition & substitution). ● The concept of risk governance comprises a broad picture of risk by including RM (or risk analysis) and the risk DM process (includes coordination & collaboration with all the actors involved) ● 4 types of risk problems: simple. (traditional/routine DM instruments), complex (risk-informed), uncertain (precaution-based & resilience-focused), & ambiguous (discourse-based).
Environmental Health Sciences Decision Making: Risk Management, Evidence, and Ethics - Workshop Summary (Institute of Medicine, 2009)	2009	US; North America	To provide a risk DM approach as a function of evaluating science & economics, & communication of the outcome to society.	Report	National & Local	Values (science, social, & policy). The workshop provided an overview of DM principles. The report focuses on the precautionary principle as a moral & political principle for action when dealing with scientific uncertainty.	A systems & holistic approach to DM where 3 outer spheres - science, society, & economic - intersect with a core sphere (risk analysis, & communication is pertinent to the entire DM process. RA, benefit assessment, & RM occurs withing each outer-inner sphere's intersection.	F: The integration occurs as each sphere interacts with the core (visualized as arrows moving from the inner risk analysis sphere to each respective outer sphere).	Quantitative & qualitative	✓ (e.g., conflict of interest, bias, ethics, legal & public health advocacy, transparency, stakeholder perspectives, & scientific issues - WoE, uncertainty, susceptible populations, & credibility of science)	-	Implicit; the risk DM approach is a function of evaluating the science & economic information along with effectively communicating the outcome to society.	● There is a need to shift from reductionist/traditional to systems & public health approaches to DM. ● A systems/holistic approach provides an opportunity to address a disconnect between environmental health science & DM for environmental health. ● A systems-public health approach further provides a DM process to go beyond precaution by considering 3 key factors: responsibility for all outcomes (good or bad), utilizing core public health functions, & linking the research agenda to data needs using right targets. It also provides insights on the implementation of the precautionary principle as it relates to the overall practice of public health. ● Risk analysis (core) & risk DM, therefore, involve balancing the needs of science, economics, & society while communicating effectively.
Science and Decisions: Advancing Risk Assessment (National Research Council, 2009)	2009	US; North America	To provide guidance to the EPA on how to improve the agency's risk-analysis approaches.	Report	National	Societal values (high level) & principles for addressing uncertainty & value-of-information.	Risk-based DM framework, 3 phases: Problem formulation & scoping, planning & conduct of RA, & RM. All phases allow for	F: The framework includes feedback loops/DM check-points at the second phase (RA) to increase the utility of this phase.	Quantitative & qualitative	✓ (e.g., institutional processes, statutory obligations, top-leadership /executive participation, &	Decision theory	Implicit; RA-RM continuum requires an effective system of governance & a process with these elements: clarity &	● RA design: shift in thinking/emphasis by deliberately paying more attention to the upfront, formative phases of problem formulation - a technically oriented process to assist assessors in operationally structuring the assessment - & scoping - a deliberative process to assist decision-makers in defining a risk-related problem.

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							internal & external stakeholder involvement.			stakeholder input)		accountability of roles and responsibilities, greater transparency of the process, documentation of the process, & oversight & periodic review.	● Inclusion of a distinct step in the second phase of the risk-based DM process to increase the utility of the RA. ● Advances in RA includes Tox Testing in the 21st Century (TT21C) tools ● RA is a method for evaluating the relative merits of RM options and not an end in itself. ● Call for technical improvements in uncertainty & variability analysis, & unified approach to dose-response assessment (cancer & non-cancer).
Food Safety Governance: Integrating Science, Precaution and Public Involvement (Dreyer & Renn, 2009)	2009	Germany; Europe	An ongoing contribution for development of food safety governance and the highest standards for all European citizens.	Review	National	Core values and principles are primarily linked back to the *General Food Law* (GFL) & good food safety.	The RM-DM stages include framing, assessment, evaluation, & management positioned around a core: participation & communication.	F: The general framework for the precautionary & inclusive governance of good safety builds around a logical structure founded on four consecutive stages which interact in a circular & integrated manner.	Quantitative & qualitative	✓ (e.g., legal, institutional, health triggers, socio-economic, political, uncertainty, ambiguity, consumer interests, public trust, stakeholder fatigue, globalisation, societal fragmentation, & trade liberalisation)	Game theory (mediation), risk as a sociological theory, & risk communication theory	Explicit; the 4-stage design creates the conceptual & functional distinction of RA (European Food Safety Authority (EFSA)) & RM (European Commission /member states) activities as specified in the GFL.	● Key risk triggers for developing the general framework: Bovine spongiform encephalopathy (BSE) & genetically modified (GM) foods. ● The framework's structure is aligned with other contemporary conceptions of risk governance & emerging broad frameworks (e.g., IRGC 2005). ● 4 RA/RM-DM approaches: presumption of prevention, precautionary assessment, concern assessment, & conventional risk assessment. ● RA policy requires upfront framing (subject to international activities). ● 3 models describing the evolution of RA-RM DM: *technocratic* (science → policy → risk communication), *decisionist* RA (scientific considerations) → risk evaluation (technical, economic, & social information) → RM (policy outcome & regulation), & *transparent* (social framing (socio-economic & political considerations)) → RA ←→ risk evaluation → RM. ● Dealing with incertitude: RA (firm basis for probabilities), ambiguity (complex factors represented by probabilities; concern assessment), uncertainty (no firm basis for probabilities; precautionary assessment), & ignorance (no firm basis for probabilities; precaution, resilience, flexibility, diversity).
A framework for decision support on HSE regulations (Aven et al., 2010)	2010	Norway; Europe	To improve the quality of decisions on health, safety, & environment	Framework	National	Core values & norms are the morals guiding daily action (individual & collective). The	The decision for the HSE regulations relies on 2 constructs (main concerns & decision	P: The 3 constructs interact in a unilateral flow. The main concerns & decision process include several,	Quantitative & qualitative	✓ (e.g., see additional principles)	Moral theory (relation to norms, values, & standards) & theory of justice	Implicit; the framing of the problem & subsequent steps leading to regulatory	● Additional principles: Proportionality (regulators intervene as required), accountability (regulators justify their decisions), consistency (rules & standards: joined up and fairly implemented), transparency (regulators should be open

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			(HSE) regulations.			principles include precautionary and other decision supporting ones (see notable features).	process on HSE regulation). A third construct (stakeholder input) feeds directly into main concerns & the decision process.	integrated processes.			(discourse ethics)	review & decision are fully integrated in the decision process on HSE regulation.	and regulations should be user-friendly and simple), & targeting (regulations should be focused on the problem while minimizing side effects). ● The decision process on HSE regulation starts with framing the problem definition & includes evaluations for effect & consequences prior to regulatory review, decision, implementation, & evaluation.
Risk and Regulatory Policy - Improving the Governance of Risk, OECD Reviews of Regulatory Reform (OECD, 2010)	2010	OECD; International	To assist OECD member countries in developing coherent frameworks for the governance of risk in regulatory policy.	Report	International & National	Normative, ideological, societal values along with guiding, policy, & principles of administrative law.	See IRGC framework - provided as a suitable example (Bouder et al., 2007)	See IRGC framework (Bouder et al., 2007)	Quantitative & qualitative	✓ (e.g., legal context, economics, ecological, trade, internet systems, policy impacts (ex ante (prospective) and ex post (retrospective)), transboundary & global risks).	Theory of DM under uncertainty (Chapter 3 & Annex 3.A.1)	Explicit; The IRGC framework.	● Role of government: regulatory, stewardship, & management. ● Focus on risk-based policy development for regulatory impact analysis (RIA) & compliance & enforcement activities. ● Clarifies risk-based approach and why RM frameworks are best suited for administrative organizations such as national regulatory authorities. ● DM under uncertainty provides a conceptual framework for considering uncertain events & their consequences (i.e., risks). A limitation of this theory, however, is its structuring for individual decision maker (same stakeholders & attitudes toward risk).
A Risk-Characterization Framework for Decision-Making at the Food and Drug Administration (FDA) (Institute of Medicine, 2011)	2011	US; North America	To present a framework for products regulated by the US FDA.	Report	National	-	DM steps (3): identify & define decision context, estimate or characterize public-health consequence using 6 risk characterization attributes, & use the outcome from the characterization to compare decision options.	P: structured, integrated, & broad view of DM which focuses on the importance of risk characterization as being important for DM & not just for ranking risks. DM also depends on input from social, political, & economic factors.	Quantitative & qualitative	✓ (Committee responsible for this report focused on public-health, scientific, & technologic while recognizing that DM involves other factors including legal & policy considerations)	Probability, multi-attribute utility theory, & behavioral decision theory	Implicit; FDA DM (core) receives input from the social, political, & economic factors along with the risk characterization framework.	● The framework is designed to be as general as possible while providing consistent information to support the wide variety of decisions faced by the FDA. ● Focus of this framework is on providing a more robust view & construction on risk characterization as it relates to DM. ● 6 attributes for risk characterization: exposed population, mortality, morbidity, personal controllability, ability to detect & mitigate adverse health effects. ● 3 types of decisions: mitigation-selection, targeting (priority setting), strategic investment (long-term). ● DM framework's 3 steps align well with the 3 phases of the US NRC (2009) report.
Green Leaves III: Guidelines for Environmental Risk Assessment and Management (Gormley-gallagher et al., 2011)	2011	UK; Europe	Build upon the previous guidance on RA & RM (year 2000) through case studies demonstrating best practices	Framework	National	Values includes monetary, cultural, societal and legal. The guideline focuses on generic principles (and	DM stages for RA-RM (4): Formulate problem, assess risk, appraise options, & address risk which circulate around a core:	F: Cyclical, iterative structure. The dashed lines between the formulate problem step and assess risk further demonstrate the strong interdependencies	Quantitative & qualitative	✓ (e.g., economic, technological, organisational capabilities, environmental security, & social issues)	Bayesian probability theory	Explicit: Assessing & addressing risk are on opposite sides of the cyclical framework for environmental risks.	● A cyclical framework for environmental risk management offers a less complex structure for the decision-maker. ● Not all risks require comprehensive & detailed assessments. ● Problem formulation clearly sets out the problem & the boundaries for DM. ● Participatory RA is a valuable method to support public engagement.

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			(e.g., increased focus on risk governance).			not domain-specific ones).	iterate, communicate, & learn.	between these two stages.					● RM strategies: Terminate, mitigate, transfer, exploit, & accept. Multi-criteria decision analysis (MCDA) provide a practical approach for comparing options.
Federal Contaminated Sites Action Plan (FCSAP): Decision-Making Framework (Environment Canada, 2013)	2013	Canada; North America	Provide a roadmap for specific activities & requirements for addressing federal contaminated sites in Canada.	Framework	National	Value includes 'land value'. Principles are provided in a 2006 document: *Recommended Principles on Contaminated Sites Liability*.	This DM framework is based on a 10-step federal approach /process for contaminated sites.	S: One-way, step-wise, DM process supported with a DM tree with checkpoints (yes/no).	Quantitative & qualitative	✓ (e.g., historical review, technical feasibility, engineering controls, institutional capacity)	Part 1, Appendix A: Theory - role of cost/benefit analysis, alternatives, potential evaluation criteria, etc.	Implicit; RM strategy requires an historical review along with an initial and detailed testing program.	● The DM steps: 1) Identify suspect site; 2) Historical review; 3) Initial testing program; 4) Classify site (optional); 5) Detailed testing program; 6) Re-classify site; 7) Develop remediation/RM strategy; 8) Implement remediation/RM strategy; 9) Confirmatory sampling and final reporting; and 10) Long-term monitoring (if required).
Risk-Based Decision-Making Framework for Blood Safety (Alliance of Blood Operators, 2014)	2014	Australia; Western Australia	To optimize the safety of the blood supply by proportional allocation of resources & analyze & account for a serious of contextual factors affecting DM of blood risks.	Framework	International, National, & Local	Values includes societal, ethical, legal, & market. The report also includes 7 RM principles along with 3 for health economic assessments.	4 risk-based DM steps: Issue identification & problem formulation, assessment, evaluation, & decision. These circulate a core: risk communications & stakeholder engagement.	P: cyclical DM process (one-way). Monitoring is included in the 4th step (decision). The risk-based DM sits above 4 RM policy foundations: risk tolerability, expectations for conduct of assessments, risk communication & stakeholder engagement, & RM principles.	Quantitative & qualitative	✓ (e.g., social, economic, ethical, risk tolerability, risk trade-offs (costs, social concerns, availability & effectiveness of tests) & legal)	-	Implicit; Assessment & evaluation feed into the DM step. The RA can also be used with other types of assessments (health economics, legal, technological, social & political).	● The Framework facilitates the gathering & consideration of information on health risk, economic factors, & broader societal factors in an integrated approach to decision making. ● It outlines policy foundations needed for risk-based DM, as well as procedural guidance on RA, health economics & outcomes, stakeholder engagement & consultation, risk communication & evaluation of risk tolerability. ● The 7 RM principles: Beneficence, fairness, transparency, consultation, practicality & proportionality, vigilance, & continuous improvement. ● 3 types of assessments: blood safety, health economics & outcomes, & contextual.
Framework for Human Health Risk Assessment to Inform Decision Making (United States Environmental Protection Agency (EPA), 2014)	2014	US; North America	To describe a process for conducting human health RAs responsive to EPA's DM needs	Framework	National	Consider societal needs (sustainability analysis). There are 8 general principles for Human Health RA along with 4 for risk characterization.	4 elements help inform decision for human health RAs: Initiation, planning & scoping, problem formulation (conceptual model & analysis plan), RA, which includes risk characterization. These elements are to be fit for purpose & incorporate public,	F: Integrated and cyclic structure.	Quantitative & qualitative	✓ (e.g., RA purpose, scope, regulatory requirements, community interests)	-	Implicit: RA → risk characterization → informs DM. Fit for purpose & public, stakeholder, & community involvement occur throughout the DM process.	● Framework is in response to NRC recommendations for advancing human health RA by maximizing the utility of the RA phase and placing a key emphasis on the concept of "fit for purpose". The utility of the RA phase is also enhanced by including the risk characterization step directly after the assessment thereby making this a deliberate element for DM. ● The RA process also integrates planning & scoping to clearly identify the boundaries for the RA. Scoping also serves as the foundational element for the problem formulation step. ● 4 principles for risk characterization: Transparency, clarity, consistency, & reasonableness (TCCR). Additional principles are found in the EPA2004e

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							stakeholder, & community involvement.						document: *Risk Assessment Principles and Practices and other documents* (e.g., principles for exposure assessment).
A Framework for the Next Generation of Risk Science (Krewski et al., 2014)	2014	Canada; North America	To create a NegGen framework to support DM using 3 cornerstones: new data on toxicity pathways, population health (PH) perspective, & new RA methodologies.	Review	National	Values includes social, economical, & political considerations along with value of information. The principles are the same 10 as provided in Jardine et al. (2003).	Risk-based DM has 3 stages: Objectives (problem formulation & Scoping), RA (health determinants & interactions & characterization of risk & uncertainty), & RM (risk-based decision-making). All stages rely on communication, stakeholder involvement, & transparency.	F: Integrated approach for Tox Testing in the 21st Century (TT21C), PH, & new approaches to RA	Quantitative & qualitative	✓ (e.g., PH-based, risk-based, regulatory, economic, advisory, community, & technological. These factors are also relevant as options during the RM phase of the risk-based DM process.	-	Implicit; RA phase accounts for PH & is embedded in the RM process for risk-based DM.	● U.S. EPA initiated the NexGen project (2011) to develop a new paradigm for the next generation of risk science. ● Advances in RA methodologies includes next generation risk assessment (NGRA) frameworks. ● The RA incorporates the PH approach by accounting for the multiple health determinants & how they interact with risk factors. ● Problem formulation & scoping accounts for the risk context, DM options, & value-of-information. ● Strong emphasis on problem formulation & upfront consideration of a broad array of RM options. This is deliberate as the intent is to ensure that the RA phase is designed to support rational choice of DM options for the particular risk context.
Integrated Assessment of Risk and Sustainability in the Context of Regulatory Decision Making (Sexton & Linder, 2014)	2014	US; North America	To describe sustainability both as a process & goal & how to combine it with risk for regulatory DM.	Review	National	Social norms & values along with principles of sustainability & those established by international standards.	- Conceptual model & analysis	P: Venn diagram showing where the overlap between risk & sustainability creates the integrated assessment.	Quantitative & qualitative	✓ (e.g., economic, social, equity, statutory requirements, susceptibility, & environmental)	-	Implicit; Risk & susceptibility are separate fields which can intersect.	● 4 important common areas between risk & sustainability: Sustainability is concerns related to the future (uncertainty), RM & sustainability are practical alternatives for addressing problems, lay people use holistic & intuitive approaches to RA, & both are subject to risk perception & social amplification. ● 4 ways to combine risk & sustainability for regulatory DM: independent assessments, incorporate sustainability into the RA-RM paradigm, incorporate risk into the sustainability paradigm, or an integrated analysis of risk & sustainability.
A Universal Framework for the Benefit-Risk Assessment of Medicines: Is This the Way Forward? (Walker et al., 2015)	2015	UK; Europe	To develop a universal framework for the evaluation of benefit-risk assessment of medicines.	Framework	International & National	Values trees for identifying benefits & risks. Review also includes guiding principles.	8 steps for the universal benefit-risk assessment framework: framing the decision.	S: Step-wise, logic, & structured approach.	Quantitative & qualitative	✓ (e.g., context of problem & decision, understanding of condition to be treated, & unmet medical need)	-	Implicit; Identification & assessment of benefits & risks feed into the interpretation & decision.	● Framework incorporates insights from other benefit-risk frameworks described in UMBRA (universal methodology for benefit-risk assessment). ● Examples: 6-step PhRMA BRAT (Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team), 8-step BRAIN (Benefit-Risk Assessment in New and Old Drugs), 7-step Centre for Innovation in Regulatory Science (CIRS), 8-step, EMA PrOACT-URL (problem, objectives, alternatives,

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													consequences, trade-offs, uncertainty, risk tolerance, linked decisions). ● Basis of most frameworks is MCDA (multicriteria decision analysis).
A risk analysis framework for forest pest management (Nealis, 2015)	2015	Canada; North America	To provide a risk analysis framework for evidence-based analysis, harmonized responses, & best practices.	Framework	National & Local	No principles, but paper identifies socio-economic values.	5-step risk analysis framework.	F: There are feedback loops in the interpretation step located between the assessment & response phases of the framework.	Quantitative & qualitative (includes historical and standards for evidence and uncertainty)	✓ (e.g., regulatory costs, roles & responsibilities, regulatory impact (e.g., from gypsy moth))	-	Implicit; The RA and response integrate evidence to characterize risk, interpret knowledge, & analyze options.	● 5 steps: Trigger, Scope (umbrella), & cylinder - assessment, interpretation, response - supported by communication, integrate & adapt, & debrief & report. ● Risk analysis: Multidisciplinary approach to inform policy decisions (context: threats - society & environment). ● Explicit estimation of uncertainty distinguishes risk analysis from most forest management plans, policies, & strategic documents.
White paper on the promotion of an integrated risk assessment concept in European regulatory frameworks for chemicals (Wilks et al., 2015)	2015	Switzerland; Europe	To propose a conceptual framework of an integrated (RA) with socio-economic analysis & social-behaviour considerations.	Framework	National	Societal values, beliefs, political systems, & cultural factors, behaviours. Principles include humane techniques, sustainability, & harmonization.	Integrated (RA) framework: Socioeconomic assessment and socio-behavioural component feed into the top & bottom components.	F: Inner component (problem formulation, evaluation, & risk characterization) are linked with the outer components to form a closed and bi-directional loop.	Quantitative & qualitative	✓ (e.g., risk factors, social needs, societal, policy, roadmap for short-, mid- & long-term efforts)	-	Implicit; integrated RA, RM, risk communication & socio-economic & socio-behavioural framework.	● More holistic approach to RA as a solution for addressing current scientific, societal, & policy needs. ● Mutual exploitation of environmental risk assessment (ERA) & human health risk assessment (HHRA) & vice versa ● Coherent & more efficient. characterization of overall risk to humans & the environment for better informing the risk analysis process.
Introduction to the IRGC Risk Governance Framework, revised version (International Risk Governance Council (IRGC), 2017)	2017	Switzerland; Europe	To provide a methodological orientation & empirical evidence approach to the use of risk governance concepts.	Framework	International	Societal values & interest. Risk governance applies from the principles of governance to identification, assessment, management, evaluation & communication of risks in the context of plural values and distributed authority.	4 interconnected elements for the risk governance path: strong pre-assessment, appraisal, characterisation & evaluation, & management. Cross-cutting aspects include communication, stakeholder engagement, & context.	F: Holistic, integrated, multidisciplinary, & multistakeholder approach to risk governance.	Quantitative & qualitative	✓ (e.g., regulatory systems, current laws, cultures (political and regulatory), trade-offs, organisational capacity, & social climate)	social, relational, & governance, theory	Explicit; The RA (& concern assessment) sits in the appraisal phase which feeds into the (knowledge) characterisation & (risk) evaluation phase. RA phases includes risk characterisation	● The principles include transparency, effectiveness & efficiency, accountability, strategic focus, sustainability, equity & fairness, respect for the rule of law, & the need for the chosen solution to be politically & legally feasible as well as ethically & publicly acceptable. These principles are well-aligned with the ISO principles. ● The overall governance is divided into two: understanding (generating & evaluating knowledge) & deciding (DM & management). ● Risks are complex, uncertain, & even ambiguous. Further, core risk governance process & context depends on other factors including organizational capacity.
Food Safety Risk Management Evidence: Informed Policies and Decisions, Considering Multiple Factors	2017	Italy; Europe	To help develop country capacities for improved food safety governance.	Guidance document	International, National, & Local	Values include monetary, community, & knowledge. The risk analysis principles are adopted by CAC	4-step, fully integrated, circular RM process: preliminary RM activities, identification &	P: 5-step process for multi-factor DM: define the decision problem, identify proposed alternatives, select decision factors &	Quantitative & qualitative	✓ (e.g., Consumer interests, food safety standards, RM regulatory actions (strong,	Multi-attribute utility theory (MAUT). The integration of multi-factor analysis into	Explicit; Leaders in the governance hierarchy along with champions or innovators, at all levels in	● This 'generic framework' is adapted from a version included in *Food Safety Risk Analysis – a guide for national food safety authorities* (FAO/ WHO 2006). ● Although food safety decision-making continues to evolve, the risk analysis paradigm remains the cornerstone.

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Food and Agriculture Organization (FAO) Guidance Material (Food and Agriculture Organization of the United Nations, 2017)						for science-based assessment of health risk (see Codex General Principles of Food Hygiene).	selection of RM options, implementation of RM decision, & monitoring & review.	criteria to assess alternatives, gather evidence & compare alternatives, & choose best alternative.		less stringent, non-regulatory), & existing requirements, standards, policies, & guidelines)	food safety decisions occurs at multiple levels of the RM-DM process.	an organisation, are relevant for carrying the information in the guidance forward.	● Food safety risk managers & policy-makers charged with protecting public health & safety are working in an ever more complex world. Further, the current DM environment presents a number of challenges. ● Faced with this complexity, risk managers & policy-makers need structured methods & guidance that applies multiple-factor DM schema.
Framework for Initiating and Conducting Risk Analysis Activities on Microbial Hazards in Food (Bureau of Microbial Hazards, 2017)	2017	Canada; North America	To describe the current risk analysis practices & future directions of the Bureau.	Framework	National	Values & principles reflect those provided in Health Canada's DM framework, CSA's *Risk Management: Guideline for Decision-Makers*, & the Codex Alimentarius Commission *Principles & Guidelines for the Conduct of Microbiological RM (MRM).*	10-step flowchart/DM tree	S: Top-down, one-way, flowchart and decision-tree	Quantitative & qualitative	✓ (e.g., Policy, operations, hazard-food combination; public health problem, food production/ processing/ distribution/ consumption/ current trade & regulatory considerations, & knowledge gaps)	-	Implicit; Risk analysis are validated & approved by both the risk analysis team and the risk management team. The final Health Canada management approval can include two additional steps - publication & communication strategy - when applicable.	● 10 stages/steps: Initiation, commissioning, data gathering, data analysis, data modelling/generation, drafting and review, validation & approval, peer-review, & process stops or Final HC Management Approval: Publication and communication strategy. ● The risk analysis activities are actions taken to enable development of risk management options (e.g., risk profile, a qualitative RA, or a quantitative RA). These activities could also be viewed broadly as representing the approaches for assessing public health risk. ● For qualitative RAs where the knowledge of the hazard & exposure is captured in narrative form.
Future directions in risk science (Westphal et al., 2017)	2017	Canada; North America	To discuss the strengths & contribution of the NextGen framework & how it emulates a fundamental change (Krewski et al., 2014).	Review	National	Societal values & behaviours, value-of-information, & value in problem formulation along with RA principles.	See Krewski et al., 2014	See Krewski et al., 2014	Quantitative & qualitative	✓ (e.g., fundamental RM principles, economic analysis, socio-political consideration & risk perception)	-	Implicit; The RA phases feeds into the RM phase & considers health determinants & interactions along with TT21C & new approaches to RA.	● Review builds from a historical perspective which includes pioneer texts such as *Acceptable Risk* & *An Anatomy of Risk*. ● NextGen framework merges: evidence-based approaches to RA as noted in the NRC vision framework for toxicity testing (TT21C), PH determinants & interactions, & NCR's *Science and Decisions: Advancing Risk Assessment* framework for the design & conduct of RA of environmental agents. ● RM interventions: REACT (regulatory, economic, advisory, community-based, or technological nature for RM).
CSA ISO 31000:18: Risk management - Guidelines (ISO 31000:2018, IDT) -	2018	Canada; North America	To provide guidelines on managing risk faced by organizations.	Guidance document (standard)	National & Local	The core principle is to value creation & protection.	One of the 3 clauses is the process (clause 6) for risk treatment. This	F: Cyclical process with 3 spheres/ clauses: The principles (clause 4) can trigger the other	Quantitative & qualitative	✓ (e.g., external & internal (section 5.4.1 of the standard);	-	Implicit; Integration of RM into an organisation's activities &	● A key shift between this standard & the 1991 standard is the establishment of core principles & the link with leadership & top management (framework). This connects the RA/risk treatment process

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A National Standard of Canada (Canadian Standards Association, 2018)			The standard was reaffirmed in 2023.				process has 3-steps: scope, content, criteria, RA, & risk treatment, which are supported by communication & consultation, recording & reporting, & monitoring & reviewing.	two clauses: framework (clause 5) & process. The framework and process are fully interconnected and thus, can go back-and-forth..		social, cultural, political, legal, regulatory, financial, technological, economic, environmental along with international, national, regional, & local)		functions requires leadership & a commitment (stakeholders & particularly from top management).	with governance, i.e., the underlying organizational structure & culture (internal and external). ● This is the second edition of the standard. This version adopts the identical 2018-02 one & supersedes the 2010 standard. ● The principles of RM are a key criteria for success along with leadership (top management) & integration of RM through an iterative process which streamlines content & places a greater focus on sustaining an 'open systems model' to accommodate multiple needs & contexts.
Risk Management Framework for Nano-Biomaterials Used in Medical Devices and Advanced Therapy Medicinal Products (Giubilato et al., 2020)	2020	Italy; Europe	To provide a scientific strategy to assess all risks emerging along the life cycles of nano-biomaterials (NBMs) used in medical devices (MD) & advanced therapy medicinal products (ATMP).	Framework	National	-	6 layers for RM.	F: RA & risk-benefit analysis RM framework (RMF)	Primarily quantitative but also qualitative. For IATA, this includes information from clinical studies (preferably), then human relevant *in vitro* & *in silico* data, & lastly animal in vivo data.	✓ (e.g., RMF builds upon REACH & relevant OECD guidelines including integrated approaches to testing & assessment (IATA) & adverse outcome pathway (AOP) approaches to RA.	-	Implicit; RA and RM steps are separate but connected elements of the overall framework. Further, the RA is linked to risk prevention, control, & monitoring while the risk-benefit analysis feeds into the risk control & RM strategies for medical devices.	● This framework is a result of a collaborative effort of a team of experts within the EU Project BIORIMA ((BIOmaterials RIsk MAnagement) & with relevant inputs from external stakeholders. ● The framework aligns with current regulatory requirements, provides a state-of-the-art, life-cycle approach to RA/RM. ● The collection & generation of data for NBMs safety assessment is also based on innovative & evidence integration using IATA. ● 6 layers: Product, lifecycle stages, exposure: unintentional (workers, environment) & intentional (patients), gather existing information, 2 pillars: risk assessment & risk-benefit analysis, & 2 pillars: risk prevention, control & monitoring & risk control or risk management. ● The RMF provides two pillars to structure the RA & RM process: one relevant to occupational &environmental risks associated with unintentional exposure (left side), one relevant to the risk-benefit analysis of patients (right side).
Development of the WHO-INTEGRATE evidence-to-decision framework: an overview of	2020	Germany, Europe	To provide a comprehensive overview of criteria used for proposing an integrated framework for	Review	International	The 7 substantive DM criteria are developed using a principle-based approach which relies on	There are 3 levels for the EtD framework: individual, population, & systems.	F: Circular & integrated at all levels of society. The WHO-INTEGRATE evidence to decision (EtD) framework is	Quantitative & qualitative	✓ (e.g., evidence considerations, cost, rights, societal, feasibility,	The framework relies on a theory-based categorization of a system comprising of three levels:	Implicit; EtD framework involves all levels of society: individual,	● The WHO Integrated (EtD) COVID-19 (WCID) framework version 1.0 - an adaptation for COVID-19 - has 11 + 1 criteria for the quality of evidence (Stratil et al., 2020). ● 7 substantive DM criteria: Health related balance of benefits & harms,

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systematic reviews of decision criteria for health decision-making. (Stratil et al., 2020a)			real-world DM processes, including guideline development, health technology assessment, & for resource allocation.			global values, concepts, & principles. Review also includes 45 sub-criteria & separate criteria for evidence considerations.	The are 7 substantive criteria along with 45 sub-substantive criteria & evidence considerations.	rooted in global health norms & values as reflected in key documents of the World Health Organization and the United Nations system.		health systems, & legislative)	criteria, sub-criteria, and decision aspects.	population, & systems.	human & individual rights, acceptability considerations, societal considerations, considerations of equity, equality, & fairness, cost & financial considerations, & feasibility & health systems considerations. ● Decision-making in public health & health policy is complex and relies on several approaches & tools, such as multi-criteria decision analysis, health technology assessments & evidence-to-decision (EtD) frameworks.
Structured benefit–risk evaluation for medicinal products: review of quantitative benefit–risk assessment findings in the literature (2020) (Kurzinger et al., 2020)	2020	France; Europe	To identify and review, for the first time, currently available, published, structured, quantitative benefit-risk assessments (BRAs).	Review	National	Product value, value-trees & value-adjusted number related to risk-benefit analysis & 3 x 3 principle of 3s (rheumatology).	3 decision steps; Starting point for a structured BRA & decision analysis & DM: descriptive framework. For more precise assessments: Semi-quantitative (step 2) or quantitative (step 3) methodologies (see notable features).	P: Structured, systematic, algorithmic, & decision-trees.	Quantitative & qualitative Knowledge & clinical experience, interaction with food, real world evidence, & use of multi-criteria decision analysis (for quantitative RA)	✓ (e.g., Patience-preference evidence, regulatory landscape & setting, collaboration, multiple stakeholders, regulatory science, trade-offs, risk tolerance, uncertainty, & knowledge gaps)	-	Not applicable as the review is focused on a specific type of assessment (i.e., benefit-risk assessment).	● Recommended methods to start with are FDA's PrOACT-URL (problem, objectives, alternatives, consequences, trade-off, uncertainly, risk tolerance, & linked decisions), BRAT (Benefit–risk Action Team), ITC/MTC (indirect treatment comparison/mixed treatment comparison), followed by collecting the data, classifying the evidence, identifying favorable & unfavorable. effects, & presenting data on key effects. ● If one alternative: Qualitative BRA is sufficient. If not: Recommended method: MCDA (Multi-criteria decision analysis) prior considering a semi-quantitative BRA. Alternatively, effects data is aggregated & if there is an explicit value judgement using a quantitative BRA. Recommended methods MCDA or wNCB (weighted net clinical benefit) when all endpoints are binary & there are only two alternatives. ● The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) framework is also used to further differentiate the various approaches into non-quantitative (descriptive/qualitative) & quantitative frameworks.
A Framework for Risk Assessment and Risk Management of Pest Control Products	2021	Canada; North America	To describe the framework that guides Health Canada's Pest Management Regulatory Agency (PMRA) in the assessment and	Guidance document	National	Mandate for health & environmental protection. The Agency also undertakes a value assessment &	4 DM steps with additional components for each step,	P: Structured, one-way, decision flow/process. The assessment of risk & value integrates the outcomes from these evaluations	Quantitative & qualitative	✓ (e.g., weight of evidence (WoE), compatibility, sustainability, existing alternative methods,	-	Implicit; The health and environmental risk & value are separate but connected assessments that feed into	● This framework supersedes the Agency's Science Policy Note SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*. ● 4 DM steps: Identification of issue & context (problem formulation), assessment of risk (health & environment) & value,

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(Pest Management Regulatory Agency, 2021)			management of risk & regulatory DM.			specifies maximum residue limit (MRL) values, when necessary.		during the intersection between RA/RM.		industrial practices, agricultural production systems, & regulatory requirements)		the RM-DM step.	management of risk, & monitoring & evaluation of results. ● Guidance documents help to comply with governing statutes & regulations (industry & stakeholders). They also aid on how mandates & objectives should be implemented in a fair, consistent & effective manner (staff).
Frameworks for screening and risk management of chemicals and advanced materials: A critical review (Moore et al., 2022)	2022	US; North America	To identify an adaptive RM framework based on process improvements using a review of 12 existing frameworks related to the evaluation of chemicals & management of chemical or material risk.	Review	International & national	Regulatory standards resulting from new science. Principles: FAIR, reference to guiding principles (e.g., in the proposed conceptual framework), OECD principles & key elements of WoE.	2 parts for adaptative management of emerging contaminants.	P: Iterative assessment & DM process with a decision-tree (yes.no) at the intersection between the iterative assessment & evaluation & RM-decision-making step on whether the data is sufficient for DM.	Quantitative & qualitative	✓ (e.g., regulatory programs, frameworks, structures, authorities, processes, status, response, requirements; industrial, regulatory, & social concerns; public concern, regulatory communication)	-	Implicit; Iterative assessment & evaluation feed into the RM. (RM) which loops back into the first phase through monitoring & adaptive management.	● 2 parts for adaptive RM: Iterative assessment & evaluation (Problem formulation, Tier 1: Screening Assessment, Tier 2: Quantitative RA) & RM decision: Unacceptable or acceptable risk. Acceptable risk loops back to the first part though monitoring & adaptive management. ● Proposed framework's elements: • Application of a WoE framework with guiding principles throughout the data evaluation process • Consideration of product life cycle, including possible downstream exposures • Consideration of socioeconomic issues • Provision for process flexibility through each iteration (e.g., may need to refine conceptual model following an initial evaluation and collect additional data) • Clear criteria for evaluating data sufficiency for decision-making • Promotion of transparency in data documentation, decision-making, and communication • Implementation of validated analytical procedures prior to substance release and distribution • Requirement for early monitoring & adaptive management to address any unanticipated issues.
Development of an Evidence-Based Risk Assessment Framework (Krewski et al., 2022)	2022	Canada; North America	To explore the development of an evidence-based RA framework.	Report	International	Regulatory values & principles from the European Food Safety Authority (EFSA), the International Agency for Research on Cancer (IARC) monographs, & GRADE guidance	6 steps for evidence-based RA: Define risk issue, identify evidence stream, assemble relevant data, Tiers: data poor, data limited, & data rich, qualitative synthesis, & quantitative synthesis.	P: Structured, decision-tree. The process can loop back to fill critical data gaps for Tier 1: Data poor using risk decision control, value of information, & new approach methodologies.	Qualitative & quantitative synthesis	✓ (e.g., Data quality, weight of evidence (WoE) criteria, analytical approach, default assumptions, & regulatory requirements)	Dempster-Shafer theory of evidence for combining evidence, applied in the context of computational toxicology.	Implicit; The outcome from the preliminary evidence-based RA framework (risk characterization or hazard determination) could feed into RM-DM.	● EFSA's prioritization of the principles of impartiality, methodological rigor, transparency, & public engagement ● The IARC Monographs are prepared according to principles of scientific rigor, impartial evaluation, transparency, & consistency. ● GRADE principles (systematic and expedited reviews) - While GRADE was originally developed in the context of randomized clinical trials (RCTs), its application has expanded to include risk of bias related to randomized & non-

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						(Grading of Recommendations, Assessment, Development, & Evaluations)..							randomized intervention & exposure studies.
Transforming EPA Science to Meet Today's and Tomorrow's Challenges (National Academies of Sciences Engineering and Medicine, 2023)	2023	US; North America	To provide the US EPA's Office of Research & Development (ORD) with strategic advice to better position its research & development enterprise with future research needs of the EPA.	Report	National	Public values: One environment-one health & systems thinking (collaborative governance, effective communication, & participatory research). Principles: ethical, standards, research codes, & Indigenous values (participatory research).	5-step, systems thinking, research & development strategy designed to produce fully integrated research to support future EPA DM.	F: An integrated approach, exposure-first, and a nested system which goes from the molecular to the ecosystem level. Strategic foresight & planning feeds into and out of the 5-steps. Extensive collaboration supports long-term research & innovation.	Quantitative & qualitative	✓ (e.g., Enhanced strategic planning , integrating innovation, strengthening collaboration, & effective communication) Appendices: biotechnology, big data, data science, machine learning, leadership & workforce.	Computing, social conditions, & theories related to citizen science.	Implicit: comprehensive, systems thinking (holistic) approach towards enhancing ORD's scientific capacity at all levels through collaborative governance with other agencies, scientific community, & stakeholders.	● One Environment-One Health is a systems thinking for enhancing research & scientific capability, at all levels, through complex interactions among environmental, social, & economic systems in support of EPA's mission. ● Challenges for such an approach: assessing ecological & human risk holistically, assessing cumulative risk & environmental justice, & accounting for global issues, such as climate change. These require a new level of integration of research planning, & a new level of embedding processes in the broader community of stakeholders (audience & research collaborators). ● 5 steps: identify multiple sources of stressors, model, assess exposure (organisms), measure doses or concentrations, & estimate human & ecosystem effects.

Table S2: Terminology: Definitions for risk analysis, assessment, governance, management, & science (shaded rows are reviews of frameworks)

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
Risk Assessment in the Federal Government: Managing the Process (Red Book) (US National Research Council (NRC), 1983)	-	The characterization of the potential adverse health effects of human exposures to environmental hazards. The term risk assessment is often given narrower and broader meanings. For some observers, the term is synonymous with quantitative risk assessment & emphasizes reliance on numerical results. This 'broader definition' includes quantification, but also includes qualitative expressions of risk. Four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate.	-	The process of evaluating alternative regulatory actions and selecting among them. Risk management, which is carried out by regulatory agencies under various legislative mandates, is an agency decision-making process that entails consideration of political, social, economic, and engineering information with risk-related information to develop, analyze, and compare regulatory options & to select the appropriate regulatory response to a potential chronic health hazard.	-
Risk Analysis Requirements and Guidelines (CAN /CSA-Q634-91) (Canadian Standards Association, 1991)	The use of available information to estimate the risk to individuals or population, property or the environment, from hazards. Risk analysis generally contain the following steps: scope definition, hazard identification, risk estimation.	Risk assessment - the process of risk analysis and risk evaluation.	-	The complete process of risk assessment & control. Synonyms: Risk control, risk estimation, & risk evaluation.	-
The Presidential/ Congressional Commission on Risk Assessment and Risk Management (PCCRARM): Framework for Environmental Health Risk Management (PCCRARM, 1997)	-	An organized process used to describe & estimate the likelihood of adverse health outcomes from environmental exposures to chemicals. The four steps are hazard identification, dose-response assessment, exposure assessment, & risk characterization.* *Risk characterization is defined as the process of organizing, evaluating, & communicating information about the nature, strength of evidence, & the likelihood of adverse health or ecological effects from particular exposures.	-	The process of analyzing, selecting, implementing, & evaluating actions to reduce risk. The goal of RM is scientifically sound, cost-effective, integrated actions that reduce or prevent risks while considering social, cultural, ethical, political, & legal considerations.	-
A comparative analysis of environmental risk assessment/risk management frameworks (Power & McCarty, 1998)	Not applicable as this is a review of frameworks. It does, however, include comments such as criticisms from the commission responsible for the US PCCRARM on the approach to RA & how it does not pay enough attention to the additional factors influencing the RM process (see goal for RM above)				
Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks (Health Canada, 2000)	-	A process that involves determining the likelihood that a specific adverse health effect will occur in an individual or population, following exposure to a hazardous agent.	-	A term used to collectively describe the activities & considerations involved in addressing and communicating information about health risks.	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
		Risk assessment includes four tasks: hazard identification, hazard characterization, exposure assessment, and risk characterization (a summary & integration of the previous tasks.		Risk management includes a number of inter-related activities: identifying & analysing options for addressing the risk, developing and implementing a strategy for managing the risk, monitoring & evaluating the effectiveness of the strategy, & communicating information both about the risk and about the decision-making process.	
Decision-Making in Environmental Health: From Evidence to Action (Corvalán et al., 2000)	Risk assessment & management are terms which are used in this document; however, there isn't a glossary of terms or definitions.				
Integrated Risk Management Framework (Treasury Board of Canada Secretariat, 2001)	A term used as the more comprehensive label, referring to an overall process for dealing with risk, including identification, assessment & implementation of measures. The use of management rather than analysis is intended to reflect the general applicability of the concepts to be developed, not only in technical or science-based sectors, but also in other public policy areas.	Terms is used in terms of assessing key risk areas, measuring likelihood & impact, & ranking risks	-	Risk management is a systematic approach to setting the best course of action under uncertainty by identifying, assessing, understanding, acting on & communicating risk issues. Integrated risk management is a continuous, proactive & systematic process to understand, manage & communicate risk from an organization-wide perspective. It is about making strategic decisions that contribute to the achievement of an organization's overall corporate objectives.	-
Risk management frameworks for human health and environmental risks (Jardine et al., 2003)	The term is used in the review; however, the terminology & definitions are restricted to risk assessment, management, & communication.	See (PCCRARM, 1997) For some of the frameworks, risk assessment involves risk analysis & risk evaluation.	-	See (PCCRARM, 1997)	The terms is used within the context of health risk science (e.g., Krewski and colleagues).
The Orange Book: Management of Risk - Principles and Concepts (HM Treasury, 2004)	-	The evaluation of risk with regard to the impact if the risk is realised & the likelihood of the risk being realised.	The term 'governance' is used with respect to good risk management & how this allows stakeholders to have increased confidence in the organisation's corporate governance & ability to deliver.	All the processes involved in identifying, assessing & judging risks, assigning ownership, taking actions to mitigate or anticipate them, & monitoring and reviewing progress.	-
An Integrated Framework for Health and Ecological Risk Assessment (Sutter II et al., 2005)	Risk assessment & management are terms which are used in this document; however, there isn't a glossary of terms or definitions.				
An Integrated Framework for Risk Management and Population Health. (Krewski et al., 2007)	The term is used within the review; however, it is not defined.	Characterization of the potential adverse health effects of human exposures to environmental hazards. Risk assessment involves four steps: hazard identification, dose-response assessment, exposure assessment, & risk characterization. Population health risk assessment is defined as a scientific process that involves characterizing risks to the health of a population.	-	Population health risk management is defined as a process that involves identifying & analyzing options for addressing a health risk, developing and implementing a strategy for managing the risk, monitoring & evaluating the effectiveness of the strategy, & communicating information both about the risk and about the decision-making process.	-
The Tolerability of Risk: A New Framework for Risk Management (Bouder et al., 2007)	-	The term is used in this document; however, it is not defined per se. The purpose of risk assessment is the generation of knowledge linking specific risk agents with uncertain but possible	Translates the substance & core principles of governance to the context of risk & risk-related decision-making. It includes the totality of actors, rules, conventions, processes & mechanisms concerned with how relevant risk information is collected,	The term is used in this document; however, it is not defined per se.	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
		consequences. The final product of risk assessment is an estimation of the risk in terms of a probability distribution of the modelled consequences.	analysed & communicated & management decisions are taken. On a national scale, governance describes structures and processes for collective decision making involving governmental & non-governmental actors. At the global level, governance embodies a horizontally organized structure of functional self-regulation encompassing state & non-state actors bringing about collectively binding decisions without superior authority.		
Environmental Health Sciences Decision Making: Risk Management, Evidence, and Ethics - Workshop Summary (Institute of Medicine, 2009)	The term is used within the document; however, it is not defined. For example, risk analysis & risk decision-making (DM) are described as balancing the needs of science, economics, & society. The proposed framework's core is risk analysis & it has the following steps: translation, evaluation, characterization, implementation & communication.	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Science and Decisions: Advancing Risk Assessment (National Research Council, 2009)	The term is used within the document; however, it is not defined.	Entails the evaluation of information on the hazardous properties of substances, on the extent of human exposure to them, & on the characterization of the resulting risk. Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing & analyzing scientific knowledge & information for potentially hazardous activities or for substances that might pose risks under specified conditions. Risk assessment can be divided into four steps: hazard identification, dose-response assessment, exposure assessment, & risk characterization	-	The process by which the results of risk assessment are integrated with other information - such as political, social, economic, & engineering considerations - to arrive at decisions about the need & methods for risk reduction.	-
Food Safety Governance: Integrating Science, Precaution and Public Involvement (Dreyer & Renn, 2009)	A term used (especially in the USA) to refer to the entire process of hazard identification, risk assessment, risk management & risk communication.	A range of assessment techniques involving systematic characterisation of likelihoods and outcomes (usually through the determination of probabilities) in order to inform the prioritising of different decision options.	The term is used extensively & is the focus of the document (e.g., in relation to the precautionary principle, advocating, & protecting human health); however, it is not defined.	While risk management does not appear in the glossary of terms, management is defined as a term used to refer to the process informed by assessment of DM, implementation of measures, & monitoring of how these measures perform in practice.	-
A framework for decision support on HSE regulations (Aven et al., 2010)	-	-	-	-	-
Risk and Regulatory Policy: Improving the Governance of Risk,	A process consisting of three interconnected components: risk	A scientifically based process consisting of four steps: hazard identification, hazard	The term is used extensively & is the focus of the document (e.g., risk governance	The process, distinct from risk assessment, of weighing policy alternatives in	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
OECD Reviews of Regulatory Reform (OECD, 2010)	assessment, risk management & risk communication.* *Regulation for the European Food Safety Authority, Articles 3(9)-(12).	characterisation, exposure assessment & risk characterisation.	frameworks can improve social welfare, by ensuring that regulatory approaches are efficient, effective, & account for risk/risk trade-offs across policy objectives); however, it is not defined.	consultation with interested parties, considering risk assessment & other legitimate factors, , if need & be, selecting appropriate prevention & control options.	
A Risk-Characterization Framework for Decision-Making at the Food and Drug Administration (FDA) (Institute of Medicine, 2011)	The term is used within the document; however, it is not defined.	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Green Leaves III: Guidelines for Environmental Risk Assessment and Management (Gormley-Gallagher et a., 2011)	The process of determining what decisions are appropriate to protect a system or environment from harm or adverse affects. This encompasses problem formulation, risk assessment, risk management, & risk communication.	The formal process of evaluating the consequence(s) of a hazard & their likelihoods/probabilities.	On a national scale, governance refers to the structure & processes for decision making that involve non-governmental and governmental actors. On a global scale, governance represents an organised structure of regulation encompassing state & non-state actors that bring combined decision making without the presence of one superior authority.	The process of appraising options for responding to risk & deciding which to implement	-
Federal Contaminated Sites Action Plan (FCSAP): Decision-Making Framework (Environment and Climate Change Canada, 2013)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Risk-Based Decision-Making Framework for Blood Safety (Alliance of Blood Operators, 2014)	-	A formal, systematic process for estimating the level of risk that considers both the consequences of exposure to a hazard & the probability or frequency of their occurrence. Risk assessments follow the methodology established by the discipline in which the assessment is conducted, although a core set of steps & quality expectations have been developed that apply to most processes.	-	A systematic approach to setting the best course of action under uncertainty by identifying, assessing, understanding, acting on & communicating risk. Risk management is the broader policy setting & decision-making function that is related to, but functionally separate from, risk assessment. Risk management & risk assessment functions must interact at several points in decision processes, particularly at the problem formulation stage when the scope, level of detail & urgency of an assessment are determined to ensure that the assessment provides the information needed for the risk management decision	-
Framework for Human Health Risk Assessment to Inform Decision Making (US EPA, 2014)	The term is used within the document (i.e., it provides relevant resources for risk analysis); however, it is not defined.	Two elements: • Exposure and effects assessment: Exposure assessment, a core component of a risk assessment, will reflect the considerations identified in problem formulation. The parallel core component, effects assessment, includes hazard identification & dose-response assessment. Susceptible or more highly exposed populations may be identified in these assessments, when relevant information is	-	The term is used within the document; however, it is not defined.	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
		available. • Risk characterization: This step of the risk assessment, in which the exposure & effects assessments are integrated, provides risk managers with risk estimates & a useful, synthesized set of conclusions about the risk. It is intended to adhere to four principles: transparency, clarity, consistency & reasonableness (TCCR).			
A Framework for the Next Generation of Risk Science (Krewski et al., 2014)	-	The four-stage risk assessment process (NRC 1983) - hazard identification, dose–response assessment, exposure assessment, & risk characterization - remains the current benchmark for risk assessment practice.	-	See (PCCRARM, 1997)	A term used to encompass both the scientific enterprise of risk assessment &, in analogy to management science, risk management actions taken to reduce risk. The NexGen framework for risk science is noted to include a pathway-based toxicity testing paradigm, a population health approach, & advanced approaches to risk assessment.
Integrated Assessment of Risk and Sustainability in the Context of Regulatory Decision Making (Sexton & Linder 2014)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
A Universal Framework for the Benefit-Risk Assessment of Medicines: Is This the Way Forward? (Walker et al., 2015)	-	The term is used within the document (e.g., benefit-risk assessment); however, it is not defined	-	The term is used within the document (e.g., benefit-risk management); however, it is not defined	-
A risk analysis framework for forest pest management (Nealis, 2015)	Risk analysis is a multidisciplinary approach to informing policy decisions in the context of threats to society & the environment at local to global scales. Although simple in concept, risk analysis can be complex in application. It nonetheless adheres to clear & consistent practices requiring accurate scoping of the problem, discovery of evidence, characterization of risk, estimation of uncertainty, identification of options, & communication with stakeholders. Risk analysis is relevant to governments as a working framework providing a broad and consistent approach, a clear link to provisions of legislation & evidence-	The overall process of hazard identification & risk estimation by explicit analysis of scientific & socioeconomic evidence to characterize, evaluate, and summarize risk in a way that addresses the specific needs of decision makers. The significance of the threat may depend on severity and cumulative impacts, temporal & spatial extent of these impacts, & whether or not these impacts are reversible.	-	Evaluates those risks that warrant intervention, identifies options for response, & determines the appropriate action to manage risk. Also referred to as risk response. The extent to which an action is appropriate will depend on its efficacy, feasibility, & consideration of whether the response introduces new risks or exacerbates existing ones. This requires a pest management plan, decision-making process, & provision for quality control and review in relation to statutory policies.	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
	based policy, implemented via transparent processes.				
White paper on the promotion of an integrated risk assessment concept in European regulatory frameworks for chemicals (Wilks et al., 2015)	The term is used within the document; (e.g., the framework's vision also proposed a more holistic approach to risk analysis); however, it is not defined.	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Introduction to the IRGC Risk Governance Framework, revised version (International Risk Governance Center (IRGC), 2017)	The term is used within the document; however, it is not defined.	The term is used within the document; however, it is not defined.	Governance refers to the actions, processes, traditions & institutions by which authority is exercised & collective decisions are taken & implemented. In turn, risk governance applies the principles of governance to the identification, assessment, management, evaluation & communication of risks in the context of plural values & distributed authority. Risk governance includes all important actors involved, considering their rules, conventions & processes. It is thus concerned with how relevant risk information is collected, analysed, understood & communicated, & how management decisions are taken & communicated. Risk governance mobilises both descriptive issues (how decisions are made) as well as normative concepts (how decisions should be made). In its application as a normative concept, it specifies the principles of good governance (e.g., transparency, effectiveness and efficiency, accountability, strategic focus, sustainability, equity & fairness, respect for the rule of law, & the need for the chosen solution to be politically & legally feasible as well as ethically & publicly acceptable).	The term is used within the document; however, it is not defined.	-
Food Safety Risk Management Evidence: Informed Policies and Decisions, Considering Multiple Factors Food and Agriculture Organization (FAO) Guidance Material (FAO, 2017)	A process consisting of three components: risk assessment, risk management, & risk communication.	A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, & (iv) risk characterization.	-	The process, distinct from risk assessment, of weighing policy alternatives in consultation with all interested parties, considering risk assessment & other factors relevant for the health protection of consumers & for the promotion of fair-trade practices, &, if needed, selecting appropriate prevention & control options.	-
Framework for Initiating and Conducting Risk Analysis Activities on Microbial Hazards in Food (Bureau of Microbial Hazards, Food Directorate, Health Canada, 2017)	The term is used extensively & is the focus of the framework; however, it is not defined per se. That is, the risk analysis process is noted to be based on the principles described in the Canadian Standards Association document, Risk Management: Guideline for Decision-Makers, as	The process of identifying & characterizing hazards in order to determine the probability of an event & the severity of its impact. The four elements of a risk assessment based on guidelines developed by the FAO/WHO Codex Alimentarius Commission are: Hazard	-	See (Health Canada, 2000)	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
	well as those principles described in the Codex Alimentarius Commission Principles & Guidelines for the Conduct of Microbiological Risk Management (MRM).	Identification, Exposure Assessment, Hazard Characterization & Risk Characterization. These steps can be completed in a qualitative, or a quantitative sense. When a risk assessment is done in a qualitative sense, the knowledge of the hazard & exposure can be captured in narrative form, and this approach is suitable for both describing the risk in relative terms and informing risk management decisions. For risk scenarios where there is enough data on relevant parameters related to the hazard and exposure, it is possible to provide a statistically based estimate of risk, reported as probability of illness per serving or per year, which could be in the form of a qualitative or quantitative risk assessment.			
Future directions in risk science (Westphal et al., 2017)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	The term is used within the document; however, it is not defined in previous work (see Krewski et al., 2014).
CSA ISO 31000:18: Risk management - Guidelines (ISO 31000:2018, IDT) - A National Standard of Canada Canadian Standards Association (CSA)	To comprehend the nature of risk & its characteristics including, where appropriate, the level of risk. It is a detailed consideration of uncertainties, risk sources, consequences, likelihood, events, scenarios, controls, & their effectiveness.	The overall process of risk identification, risk analysis, & risk evaluation. Risk assessment should be conducted systematically, iteratively, & collaboratively, drawing on the knowledge & views of stakeholders. It should use the best available information, supplemented by further enquiry, as necessary.	-	Coordinated activities to direct & control an organization with regard to risk. Managing risks is based on principles, framework, & a process, which includes the risk assessment which leads to risk treatment.	-
Risk Management Framework for Nano-Biomaterials Used in Medical Devices and Advanced Therapy Medicinal Products (Giubilato et al., 2020)	The term is used within the document (e.g., benefit-risk analysis); however, it is not defined.	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Development of the WHO-INTEGRATE evidence-to-decision framework: an overview of systematic reviews of decision criteria for health decision-making.(Stratil et al., 2020)	These terms are not used within this document, which is focused on evidence-to-decision-related systematic reviews.				
Structured benefit–risk evaluation for medicinal products: review of quantitative benefit–risk assessment findings in the literature (Kürzinger et al., 2020)	The term is used within the document (e.g., benefit-risk analysis); however, it is not defined.	The term is used within the document (e.g., benefit-risk assessment); however, it is not defined	-	The term is used within the document; however, it is not defined.	-
A Framework for Risk Assessment and Risk Management of Pest Control Products (Pest Management Regulatory Agency, 2021)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-
Frameworks for screening and risk management of chemicals and advanced	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	-

Title (reference)	Risk analysis	Risk assessment	Risk governance	Risk management	Risk science
materials: A critical review (Moore et al., 2022)					
Development of an Evidence-Based Risk Assessment Framework (Krewski et al., 2022)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	The term is used within the document; however, it is not defined.
Transforming EPA Science to Meet Today's and Tomorrow's Challenges (National Academies of Science & Medicine, 2023)	-	The term is used within the document; however, it is not defined.	-	The term is used within the document; however, it is not defined.	The term is used within the document; however, it is not defined.

Table S3: MEDLINE (OVID) preliminary search strategy (1946 to June 2, 2023)

1.	Risk Management/ or Risk Assessment/ or "Risk Evaluation and Mitigation"/
2.	(risk adj (assess* or benefit? or analy* or health or environmental or science?)).ti,ab,kw.
3.	((next gen* or nextgen*) adj10 (assess* or evaluat* or risk)).ti,ab,kw.
4.	(framework? or roadmap? or perspective?).ti,ab,kw.
5.	1 or 2 or 3
6.	4 and 5
7.	decision making, organizational/
8.	(decision making or decisionmaking or evidence based or science based or risk based or regulatory or integrated).ti,ab,kw.
9.	7 or 8
10.	6 and 9
11.	Health/
12.	(health or environment*).ti,ab,kw.
13.	11 or 12
14.	10 and 13

This strategy was appropriately translated to the other databases listed above. Preliminary results (2,438 hits) confirmed the inclusion of the four seed articles.

Table S4: Documents recommended by experts in risk science

Experts in risk science identified these publications for consideration, of which 24 (shaded rows) were included among the references used for data extraction and analysis.

1.	Alliance of Blood Operators. (2014). Risk-Based Decision-Making Framework for Blood Safety. https://www.allianceofbloodoperators.org/media/101766/ABO-Risk-based-decision-making-framework-for-blood-safety-for-consultation.pdf
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17.	Food and Agriculture Organization of the United Nations. (2017). Food safety management: Evidence-informed policies and decisions, considering multiple factors. https://www.fao.org/3/I8240EN/i8240en.pdf
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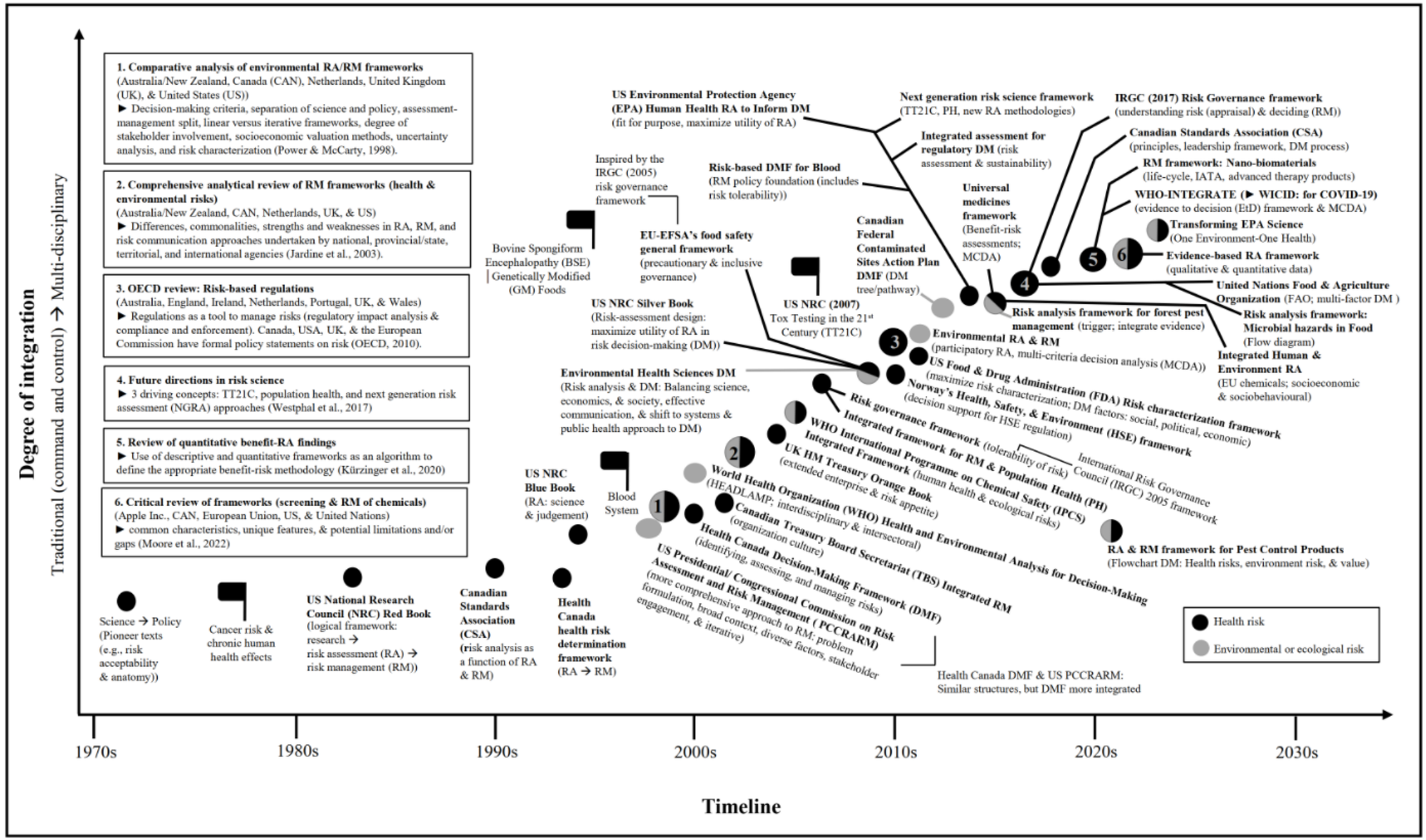
Figure S1: Evolution in Risk Decision-Making - Key Milestones & Attributes



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CHAPTER 6: ARTICLE 4. Key considerations for establishing a NextGen approach to risk decision-making

Chapter overview

This chapter addresses the final research objective (Chapter 1) and question (Chapter 2) through an original research article which applies a realist paradigm to generate an *a priori* theoretical construct and model. The *kaleidoscope model* translates the principles and attributes, from the previous papers, into considerations for developing an approach to NextGen risk decision-making (NGRDM). This model and the theoretical constructs are then applied to top-down, bottom-up, and risk science-based, NGRDM approaches and analyzed using a strengths, weaknesses, opportunities, and threats (SWOT) analysis. This chapter has also been prepared for publication in a peer-reviewed journal supporting open access articles.

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6.1 Abstract

Risk decision-making has evolved from linear processes linking risk assessment with management activities to more mature, dynamic, and integrated frameworks. Further understanding of complex decision-making approaches is provided by a series of milestone publications providing detailed insights and precision on specific areas, such as the importance of problem formulation, new strategies to risk characterization, principles of risk decision making, and effective risk communication. This has resulted in rapid growth in risk decision-making approaches, including next generation risk assessments, frameworks on the tolerability of risk, and recommendations for conducting risk-benefit assessments. Recent work has also focused on characterizing the intersections between fundamental ethical principles and risk decision-making. While efforts on how to integrate research activities most effectively into regulatory decision-making are continuing, the key considerations relevant to establishing next generation risk decision-making approaches are lacking. In this paper, we build on our understanding of this evolution in risk decision-making through the development of a realist paradigm-based context, mechanism, and outcome configuration. We then use this configuration to create the kaleidoscope model with these ten key considerations relevant for developing next generation approaches to decision-making: foresight and planning, research and development, regulatory context, risk context, upstream and downstream attributes, risk culture (behaviour and governance), a ONE Health lens, risk communication, risk management, and broader regulatory factors. We also present a strengths, weaknesses, opportunities, and threats analysis to help in evaluating the configuration and determining their impact on top-down, bottom-up, and risk science approaches to next generation risk decision-making.

Keywords: NextGen, risk decision-making, kaleidoscope model, risk science, realist paradigm

6.2 Introduction

Risk decision-making has transitioned from processes describing the foundational elements and links between risk assessment and management in landmark publications (National Research

Council, 1983; Whittaker, 2004) to complex and integrated decision-making approaches (Bhuller et al., 2024a). Diverse factors, including societal values, legislation, advances in science and technology, and political considerations, have played a key role in the evolution as chronicled in diverse frameworks, reports, reviews, and guidance documents (Bhuller et al., 2024a). An appreciation of the complexity of risk decision-making has also resulted in the development and publication of several documents providing detailed insights and precision on one or more dimensions of this process. This includes expert reports on elements such as problem formulation for scientific assessments (Paoli et al., 2022) and frameworks on the tolerability of risk (Bouder et al., 2007), risk characterization for decision-making (Institute of Medicine, 2011), and next generation approaches to risk science (Krewski et al., 2014).

Another important consideration in risk decision-making is risk governance and how this relates to underlying institutional values, principles, and moral norms (Bouder et al., 2007; Dreyer & Renn, 2009; International Risk Governance Council (IRGC), 2017). Fully integrated frameworks for risk management and population health (Krewski et al., 2007), health and ecological risk assessment (Suter II, 2004; Suter II et al., 2005), and One Environment-One Health transformative strategies for managing future risks (National Academies of Sciences Engineering and Medicine, 2023b) provide holistic strategies which link to and expand on these underlying elements. Further, while these frameworks incorporate additional perspectives pertinent to risk decision-making, they also require establishing and maintaining strong structures supporting collaborative governance and processes for engaging all interested and affected parties. This includes developing trust and respect by creating ethical spaces (Adams, 2021; Ermine, 2007) and adhering with established risk (Bhuller et al., 2024d; Krewski et al., 2022b) and ethical decision-making principles (Bhuller et al., 2024d).

Fully integrated approaches can include processes incorporating policies, such as *One Health* (Public Health Agency of Canada, 2024) and *Health in All Policies* (Green et al., 2021; Herriot & Valentine, 2018; Leppo et al., 2023)), which inherently require collaborative governance. Consequently, these integrated approaches also present the same challenge as what is seen when applying a broad, systems thinking strategy for addressing a health or environmental risk. Systems thinking is defined as "… seeing how things are connected to each other within some notion of a whole entity" (Peters, 2014). It provides a holistic strategy for decision-makers to consider multiple perspectives for addressing complex issues but also includes challenges, such

as successfully identifying and maintaining a common set of priorities, resources (human, technical, and financial), timelines, and governance structures, throughout the process (Boswell et al., 2021; Trochim et al., 2006). Other challenges in developing approaches to risk decision-making include contextual factors, such as ensuring effective communication, arising from the intersection between risk assessment (the 'science') and the broader political-publics space (the 'policy') (Bhuller & Trevithick-Sutton, 2024). As a result of all these challenges, the level of integration in risk decision-making can range from partial approaches targeting specific aspects of risk science to fully integrated frameworks (Bhuller et al., 2024a).

Collectively, our previous work related to risk decision-making has provided insights into the multitude of factors and challenges relevant for risk decision-making. For example, by analyzing the evolution of risk decision-making practices over the last fifty years, we identified and characterized these ten key attributes of health and environmental risk decision-making: trigger/issue, regulatory context, regulatory factors, core values, risk decision-making principles, cross-cutting attributes, design (scope and steps), structure, decision-making pathway, and evidence-knowledge requirements for risk decision-making (Bhuller et al., 2024a). Exploring diverse designs, processes, and structures, for contemporary and future risk science-related strategies to decision-making, also revealed that the current literature does not provide specific guidance on how to establish next generation/NextGen risk decision-making (NGRDM) approaches.

In this paper, we build from our knowledge and understanding of the evolution of risk decision-making by generating key considerations for developing NGRDM approaches. A realist paradigm-based context, mechanism, and outcome configuration (CMOc) provides the theoretical constructs for classifying pertinent risk decision-making attributes as considerations for NGRDM. The CMOc also creates a model – the *NGRDM kaleidoscope* – to help visualize the placement of these considerations and how the interact in the overall process. We then assess the CMOc by analyzing these considerations through an analysis where we explore the *strengths*, *weaknesses*, *opportunities*, and *threats* (SWOT) (Benzaghta et al., 2021; Teoli et al., 2024) of top-down, bottom-up, and risk science approaches to NGRDM.

6.3 Methodological and theoretical approach

The methodological and theoretical approach relies on the realist paradigm-based constructs for establishing the key considerations for NGRDM. This includes developing the *NGRDM kaleidoscope* to help visualize the interactions and continuous flow between the theoretical constructs and the ten considerations. The subsequent sections provide more details on the use of realist-paradigm in developing the approach for this research endeavour.

6.4 Realist paradigm

We previously relied on a realist paradigm to determine the relevance and feasibility of risk decision-making principles, and classified these principles into distinct categories - universal, fundamental, guiding, and foundational (Bhuller et al., 2024b). In this work, this worldview was also considered appropriate as it provided a theory-driven and exploratory approach for systematically gathering, synthesizing the available evidence, and evaluating underlying assumptions (Pawson et al., 2004; Pawson & Tilley, 2004).

As our goal was to determine what key considerations work for NGRDM, for whom, and under what circumstances, realism also provided the paradigm to develop and test an a priori hypothesis based on two constructs - the context [C] and mechanism [M] - and how these two elements relate with the final construct - the outcome [O] (Kazi, 2003). For this work, the a priori hypothesis is written using this context, mechanism, and outcome configuration (CMOc):

> *NextGen risk decision-making requires an understanding of the intersections between the research, regulatory, and risk contexts [C] using an institutional mindset and culture which integrates a population health approach to maximize upstream and downstream attributes for risk decision-making and a ONE Health lens [M] to promote and protect the health of humans, animals, and the environment [O].*

A realist approach also supported the use of mixed methods (Greenhalgh et al., 2015; Pawson, 2017; Pawson et al., 2005), which was pivotal in developing the a priori hypothesis along with the considerations and the kaleidoscope model for NGRDM. In other words, the underlying knowledge used to develop the CMOc, considerations, and model was based on expert input and data from previous research related to the: (i) identification, categorization, and visualization of key risk decision-making principles (Bhuller et al., 2024b; Krewski et al., 2022b); (ii) development of the projector model and key ethical principles and considerations for regulatory

risk decision-making (Bhuller et al., 2024d); (iii) evolution of risk decision-making approaches and best practices over the last fifty years (Bhuller et al., 2024a); (iv) use of design thinking to create a mindset towards new approach methodologies and next generation risk assessments (Bhuller et al., 2021); (v) link between risk science and new approach methodologies using an "astronaut's perspective" (Bhuller et al., 2024c); and (vi) tools for effective risk communication, which includes an understanding of how risk assessment and management fits within the broader set of risk decision-making factors (Bhuller & Trevithick-Sutton, 2024). The **Supplementary Material** provides a summary of these six articles and how the insights gained from this work helped in formulating the CMOc and the *NGRDM kaleidoscope*.

6.5 NGRDM kaleidoscope model

The model for visualizing the CMOc is based on the analogy of how a kaleidoscope, when appropriately positioned, brings together fragmented pieces to form a unique pattern. As shown in **Figure 1**, the CMOc provides the right orientation to view the four structured, contextual considerations, three fragmented and intersecting mechanism considerations, and the last three fully formed and established considerations of the outcome construct.

Figure 1: Kaleidoscope model for key considerations in Next Generation Risk Decision-making (NGRDM). The first and second constructs - context and mechanism - are surrounded by seven considerations found within irregular but connected shapes. The final construct, outcome, includes a more defined pattern of shapes as this reflects the well-established best practices for these considerations that are relevant for NGRDM.

Based on our analysis of thirty-nine publications over the last fifty years (Bhuller et al., 2024a), the considerations in the kaleidoscope model reflect the ten attributes we previously determined to be pertinent for risk decision-making. In this paper, we expand and build considerations for developing an approach to NGRDM by associating the relevant attributes with the CMOc constructs (**Table 1**).

Table 1: Ten key considerations for developing an approach to NGRDM

Construct	Descriptor	Considerations
Context	Provides insights on the circumstances relevant for NGRDM.	(C1) Foresight and planning, (C2) Research and development, (C3) Regulatory context, and (C4) Risk context
Mechanism	Establishes the mindset for those who are interested, responsible, or accountable for developing a NGRDM approach.	(C5) Upstream and downstream attributes, (C6) Risk culture, and (C7) ONE Health lens (human, environmental, and animal)
Outcome	Reflects the considerations required to project risk decisions, from a NGRDM approach, and how to manage the risks at an institutional and global level.	(C8) Broader regulatory factors (PESTLE: Political, Economic, Socio-cultural, Technological, Legal/regulatory, Environmental), (C9) "REACT: Regulatory, Economic, Advisory, Community-based, Technological" considerations for risk management, and (C10) Risk communication

The core of **Figure 1** has a circular icon with arrows reflecting the integrated nature of the constructs and their underlying considerations. For example, while regulatory considerations (C3) are part of the 'context' construct of the CMOc, when analyzing these considerations, one must also account for the broader regulatory "PESTLE" factors (C8), "REACT" considerations for risk management (C9), and risk communication requirements (C10) identified in the final construct (i.e., outcome). Visually, the *NGRDM kaleidoscope* shows this by raising the platform for the outcome construct so that it appears as having the potential to shift, move, rotate, and be considered during the phases occupied by the other two constructs. Further, as risk decisions are

projected from the institutional to the global level, several considerations adhere to best practices and established universal principles. As an example, effective communication is a universal risk and ethical principle (Bhuller et al., 2024b; Bhuller et al., 2024d; Krewski et al., 2022b) where the pragmatic application can be achieved using the mnemonic "BroadCAST-3Cs". **Broad** captures the range for effective communication and "CAST-3Cs" stands for: the **core** message, adjusting the message to meet the needs of the target **audience**, identifying the **spokesperson** responsible for delivering the message, relaying the message in a **timely** manner, and ensuring the message is **context**-specific, **clear**, and **concise** (Bhuller & Trevithick-Sutton, 2024).

6.6 Data analysis

Experts in risk science have evaluated the strengths, weaknesses, practical experience, and specific issues addressed when evaluating various risk management decision-making frameworks for health and environmental risks (Jardine et al., 2003). We take a similar approach in this paper by using a SWOT analysis to demonstrate how top-down, bottom-up, and risk science approaches to NGRDM incorporate the ten considerations of the CMOc identified in **Table 1**.

A SWOT analysis relies on the interactions between the internal (*strengths* and *weaknesses*) and external (*threats* and *opportunities*) elements of an organization or approach. Originating in the early 1950s, it is a useful tool for strategic planning with application to various fields including education, agriculture, and healthcare (Benzaghta et al., 2021). As with any tool, a SWOT analysis has its advantages and disadvantages. For example, it provides sufficient flexibility for incorporation with other frameworks including the PESTLE framework (Benzaghta et al., 2021). A SWOT analysis can also be used to evaluate and rank documents, such as national action plans for antimicrobial resistance (Willemsen et al., 2022). However, it is also criticized for providing a potentially biased, snapshot perspective limited to those undertaking the analysis. Consequently, this could result in a risk of misrepresentation as it may not reflect the changing environment (Teoli et al., 2024).

While we acknowledge these limitations in undertaking a SWOT analysis, our previous scoping review of risk decision-making frameworks demonstrated that we are no longer in a period of rapid and steep growth of these types of publications (Bhuller et al., 2024a). Further, the ten considerations (**Table 1**) used in the SWOT analysis builds on risk decision-making attributes

from over fifty years of analyses in this area. Therefore, the 'pairing' of the considerations with the SWOT analysis along with the subsequent review, by an interdisciplinary team of co-authors and reviewers, is also intended to address potential biases and risk of misrepresentation.

6.7 Describing the components of the CMOc

Prior to undertaking a SWOT analysis, the various components and considerations of the CMOc are described in this section. The detailed information reflects how these components and considerations appear in the NGRDM kaleidoscope (**Figure 1**). We start with providing insights for establishing the first construct from this configuration, **context**, and the four underlying considerations: foresight and planning (C1), research and development (C2), regulatory context (C3), and risk context (C4). We then move clockwise and provide information to understand and address three critical considerations - upstream/downstream attributes (C5), risk culture (C6), and ONE Health lens (C7) - for the **mechanism** construct of the CMOc. The final sub-section explores the last construct, **outcome**, and the three well-established considerations – broader regulatory "PESTLE" factors (C8), "REACT" considerations for risk management (C9), and risk communication (C10) - relevant for relaying the NGRDM decision from the institutional to the global level.

6.8 Establishing the context considerations for developing a NGRDM approach

Research and development (C2) play a key role in creating innovative opportunities for informing the regulatory and risk decision-making processes (National Academies of Sciences Engineering and Medicine, 2023b; National Research Council, 1983). Foresight and planning (C1) activities are also important as they can identify barriers and opportunities for bridging the gap between the research (C2), regulatory (C3), and risk (C4) contexts. Foresight involves a strategic discourse exploring possible, plausible, and alternative futures and how to act upon the insights, challenges, and opportunities now/in the present (Monteiro & Borgo, 2023; Public Horizons Canada, 2024). Planning entails the development of a strategy, the vision/mission statement, and resource requirements for addressing the risk issue. The final strategy is typically promulgated through the publication of a strategic plan relevant for a specified period (e.g., next 5 years). The ongoing collaborative efforts for advancing non-animal testing strategies serves as a contemporary example to further describe and understand the contextual considerations (C1-4) and how they connect with the other constructs of the NGRDM kaleidoscope.

6.8.1 Foresight and planning (C1): The role for agile and design thinking

The paradigm shift towards adapting non-animal testing strategies for regulatory purposes (Hilton et al., 2023a) builds from landmark reports including *The Principles of Humane Experimental Technique* (Russell & Burch, 1959), *Toxicity Testing in the 21st Century* (TT21C): *A Vision and a Strategy* (National Research Council, 2007), and *Integrating Emerging Technologies into Chemical Safety Assessment* (CCA (Council of Canadian Academies), 2012). While these documents may not explicitly use the term 'foresight', they set the stage (vision) for a plausible future embracing the 3Rs – replacement, reduction, and refinement of animal studies – advocated by Russell and Burch. The advancements in science and technology and innovation (ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods), 2018, 2023), along with legislative and ethical support towards more humane, human-relevant, and scientifically sound approaches (Balls et al., 2024; Herrmann et al., 2019; Singer & Harari, 2023), have also been key in planning and advancing new approach methodologies – "A term used to encompass non-animal methods, alternatives, and technologies that reduce reliance on traditional animal toxicology data while focusing efforts on more humane and human-relevant science" (Bhuller et al., 2024e).

Planning for the incorporation of non-animal strategies (e.g., by regulatory authorities) in risk science has been greatly facilitated through the publication of roadmaps (ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods), 2018; United States Food & Drug Administration (FDA), 2017), diverse frameworks (Ball et al., 2022; Magurany et al., 2023; Parish et al., 2020; van der Zalm et al., 2022), and specific guidance documents (Avila et al., 2020; Hilton et al., 2023b; OECD, 2023; Schmeisser et al., 2023; Stucki et al., 2022). A common element in foresight activities, subsequent planning, and advancing of such methodologies reflects a mindset that embraces the complexity and the need to address barriers through collaborative approaches and experimentation (Bhuller et al., 2024e; Bhuller et al., 2021; Hilton et al., 2023a).

The *Canadian Regulatory Perspective on Next Generation Risk Assessments for Pest Control Products and Industrial Chemicals* (Bhuller et al., 2021) provides an example of an agile and iterative approach for creating such a mindset. For pest control products, this included adapting the five stages of design thinking – empathize, define, ideate, prototype, and test - as a tool for forecasting, planning, developing, and visualizing the non-animal testing approach. Through a

top-down approach relying on the user experience of risk assessors, managers, and decision-makers, the design thinking stages helped in understanding, exploring, and materializing relevant guidelines through multi-stakeholder collaboration. For science-based organizations, elements of design thinking, such as building, experimenting, and testing, share similarities with the scientific process and thus, resonated with the individual leads and working group members. For industrial and environmental chemicals, foundational elements, adoption/adaptation, and key principles were pivotal in taking a similar approach towards the development of a proposed path for translating case study findings into applications. Subsequently, the desired outcome included successful materialization and application of several non-animal strategies into new or existing guidelines (Stucki et al., 2022).

While these two examples are specific to pest control products and industrial chemicals, it does not preclude the consideration of foresight and planning (C1) along with the application of agile strategies and design thinking to other product types and risk contexts. Further, this type of thinking creates an open mindset, which is important as one transitions to the subsequent considerations (C5-C10) of the NDGRDM kaleidoscope. Having an open mindset aids in understanding the vital role of continuous learning and improvement of risk science knowledge (Bhuller et al., 2024c) and the possibility for considering other approaches relevant to NGRDM.

6.8.2 Research and development (C2): Fit-for-regulatory (C3) purpose

For non-animal testing solutions, the success in the advancement of such strategies includes research endeavours (C2) which inform regulatory activities (e.g., policy and risk decision-making) as the research activities are designed to be fit-for-regulatory (C3) purpose. This is not a simple task as regulatory data requirements require strict adherence with protocols and guidelines (e.g., good laboratory and clinical practices) designed specifically for regulatory applications (Agerstrand et al., 2017; Allen et al., 2021; Berridge et al., 2023; Hilton et al., 2022; Jeong et al., 2022; OECD, 2018; Prior et al., 2020).

Global institutions, such as the Organisation for Economic Co-operation and Development (https://www.oecd.org/en.html), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (https://www.ich.org/), the World Health Organization's Chemical Risk Assessment Network (https://www.who.int/groups/chemical-risk-assessment-network), the Health and Environmental Sciences Institute (https://hesiglobal.org/),

PETA Science Consortium International e.V. (https://www.thepsci.eu/), and the Human Society International (https://www.hsi.org/), help bridge the gap between the research (C2) and regulatory landscapes (C3). This is accomplished through various working groups, communities of practice, and other types of engagement and collaborative initiatives. A major outcome of these endeavours is the creation of diverse, fit-for-regulatory (C3) purpose and mutually acceptable technical guidelines, reports, and other publications made available for adoption/adaptation at the global and institutional levels.

These international organizations also support multi-year collaborative efforts, amongst interested and affected parties, which provides an opportunity to also build trust, mutual respect, and confidence with the underlying research (C2), data, and approaches used to develop, standardize, and establish fit-for-regulatory purpose solutions (C3) by all interested and affected parties. For example, there are specific frameworks for building science, regulatory, and public confidence with non-animal methods (ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods), 2018, 2023; National Academies of Sciences Engineering and Medicine, 2023a; van der Zalm et al., 2022).

Engagement and collaboration amongst a diverse population of experts also provides an opportunity for a discourse and further understanding of various regulatory factors (e.g., legislation, policy, science, and technology) and the role they play when considering a NGRDM approach. **Figure 1** also shows how the regulatory factors (C3) are relevant to understanding the context for a NGRDM approach and the outcome considerations of the established, structured, and broader regulatory PESTLE factors (C8). The circular formation of the arrows, found in the centre of the *NGRDM kaleidoscope*, are intended to visualize this overlap and highlight the integration of all ten considerations throughout the process.

6.8.3 The risk context (C4): Determining the ideal risk-based approach

Risk is a measure of both the harm resulting from exposure to a hazardous agent together with the likelihood that the harm will occur (Bhuller et al., 2024c). Risk decision-making inherently includes “problems of risk and uncertainty” (Hansson, 2023). The inclusion of the term “likelihood” in the definition of risk and the intrinsic uncertainty implies that risk-based approaches only have a certain probability for correctly determining whether the harm will occur (Bhuller et al., 2024d). Consequently, some of the goals of a risk-based approach (C4) are to

address and reduce uncertainty (i.e., data gaps), integrate all the relevant evidence (Krewski et al., 2022a), and consider more refined, probabilistic risk assessments, when necessary (Maertens et al., 2024; Maertens et al., 2022).

As shown in **Figure 1**, the 'risk' consideration (C4) serves as the trigger (power or 'on/off' icon) for selecting the ideal risk-based approach for the issue. The listing of potential strategies includes 'NextGen', but this term appears at the end because it is important to consider contemporary and well-established approaches prior to developing an NGRDM strategy. Examples of established risk-based approaches include frameworks, roadmaps, and guidance for evaluating only hazards (e.g., the *International Agency for Research on Cancer Monographs on the Identification of Carcinogenic Hazards to Humans* (World Health Organization, 2019a)), benefit-risk evaluations and analysis (Colopy et al., 2015; Mt-Isa et al., 2014; Verhagen et al., 2012), and risk tolerability (Bouder et al., 2007), along with other frameworks for risk analysis and science (Bhuller et al., 2024a). A risk-based approach also includes activities such as scoping and prioritization (e.g., based on the risk profile of a substance), workflows for next generation risk assessments where exposure-first approaches are integrated with new approach methodologies (Wood et al., 2024), program and product-specific frameworks (e.g., Risk-Based Decision-Making Framework for Blood Safety (Alliance of Blood Operators, 2014)), and the traditional, 4-step approach to risk assessment which starts with identifying the hazard (National Research Council, 1983).

Potential triggers for developing a NGRDM approach include addressing gaps in current risk decision-making approaches or identifying a novel area requiring a NGRDM strategy to identify, assess, and manage risks. Modernizing efforts designed to advance the incorporation of non-animal strategies, by various regulatory authorities, is a good example of how these institutions are addressing an existing gap in regulatory risk-decision making processes for specific products (Environment and Climate Change Canada & Health Canada, 2024; United States Environmental Protection Agency (EPA), 2021; United States Food & Drug Administration (FDA), 2017; Zuang et al., 2023). These 'top-down' NGRDM approaches build from existing and overarching frameworks, typically rooted in legislative requirements, which are linked to program and product area-specific NGRDM approaches (e.g., next generation risk assessments using new approach methodologies). "Framing challenges and opportunities" for a novel area, such as gene-edited organisms for pest control (CCA (Council of Canadian Academies), 2023), is an example

of a complex, bottom-up approach to NGRDM for these products. Top-down and bottom-up approaches can range from partial to fully integrated and multidisciplinary approaches to NGRDM (National Academies of Sciences Engineering and Medicine, 2023b). The degree of complexity, however, increases as one transitions from partial to fully integrated and multidisciplinary approaches.

Table S1 (**Supplementary Material**) provides a consolidated list of questions for building awareness and understanding around the NGRDM approach. These questions are not designed to be a checklist per se, rather, they are intended to guide the user towards carefully judging each consideration as they use the NGRDM kaleidoscope to move through the CMOc. These questions were also used to develop the inputs for the SWOT analysis of NGRDM approaches.

6.9 Understanding the mechanism for developing a NGRDM approach

As shown in **Figure 1**, unlike the context construct of the CMOc, the mechanism and the next three considerations - upstream/downstream attributes (C5), risk culture (C6), and ONE Health lens (C7) - include elements that extend from the institutional to the global level. These mechanism-related considerations can be extremely challenging as they involve the intersection between distinct experts (e.g., risk assessors, managers, and decision-makers) and their institutions. Further, considerations, such as the risk culture of an organization, builds from several internal factors including foundational elements such as deeply rooted core values and principles (Bhuller et al., 2024b). These considerations also establish the underlying individual-institutional behaviour (and attitudes) for establishing the desired structure and decision-making pathway for the NGRDM approach. From the global level, when these elements are not fully understood, the internal, institutional-level processes and approaches are often viewed as a black box. The complex and multifaceted nature of the mechanism construct, which includes the interplay and intersections between individual ethics and the values and moral norms of an organization, can also make it difficult to adequately characterize this construct. Consequently, the shapes and considerations for this construct, in **Figure 1**, visually represent these characteristics by being more abstract and spread out when compared to the other two constructs.

6.9.1 Upstream and downstream attributes (C5): Navigating within established boundaries

To address the complexity of the mechanism construct, we rely on a population health approach as this provides a strategy to view the entire CMOc system of the *NGRDM kaleidoscope*, the

intersections within and between each construct, and the links as one navigates from a construct to the next one. Built from landmark reports, including the White Paper titled: *A New Perspective on the Health of Canadians* (Lalonde, 1974), several institutions now apply a population health approach as it provides a broad, systems view for focusing on interrelated conditions and factors influencing the health of populations. This includes accounting for both upstream (deeply rooted factors) and downstream determinants of health, which are relevant for promoting and protecting health (Canadian Institutes of Health Research, 2011; Cohen et al., 2014; Government of Canada, 2013).

Within the context of risk decision-making, Krewski and colleagues (2007) have also proposed frameworks which integrate population health with the management of risks (Krewski et al., 2007). In 2014, these experts also published *A Framework for the Next Generation of Risk Science* where the risk assessment phase incorporated a population health approach. Consequently, this accounted for the multiple determinants of health (e.g., biological and genetic, environmental and occupational, and social and behavioral determinants such as income, social status, and education) along with advanced approaches to risk assessment methodologies and new directions in toxicity testing (Krewski et al., 2014).

In terms of the kaleidoscope model, the application of a population health approach is designed to show how the mechanism construct includes upstream and deeply rooted risk decision-making determinants (core values and principles), downstream attributes (visible structure and decision-making pathway), and other determinants (e.g., cross-cutting attributes). Further, as a population health approach also uses systems thinking to view all the connections among health determinants, this approach becomes a tool to help see and navigate between various boundaries (Boswell et al., 2021; Peters, 2014; Trochim et al., 2006). In the mechanism construct, these boundaries encapsulate the upstream and downstream attributes, the internal behaviour and governance (i.e., risk culture), and eventually the "ONE Health lens" (Bhuller et al., 2024d; Bhuller & Trevithick-Sutton, 2024) required for creating an approach to NGRDM. Understanding the remaining considerations (i.e., for the contextual and outcome constructs) allows one to navigate within the limits/boundaries surrounding these considerations, but also when to cross them. For example, developing a potential, NextGen approach requires one to carefully consider existing risk decision-making processes prior to developing a strategy to NGRDM. Consequently, this analysis creates a 'boundary/limit' which is only crossed after a

determination is made to transition into the mechanism construct and considerations required for developing an approach to NGRDM.

As the risk culture (C6) also depends on the interplay between the individual and institutional mindset relevant to risk decision-making, the population health approach is linked with our understanding of ethics and how this relates to risk and decision-making theories. In our previous work exploring ethical principles for risk decision-making (Bhuller et al., 2024d), we demonstrated how institutional ethics (values and moral norms), risk, and decision theories play a significant role in supporting rational decision-making (Borgonovo et al., 2018; Frederickson et al., 2012; Howard, 1966; Jensen, 2012; Roeser et al., 2012; Simon, 1997). Established moral norms, such as beneficence (doing more good than harm), govern intrinsic behaviours and fundamental beliefs embedded in societal values. Further, institutional norms and values can also guide the attitudes, character, and actions of risk assessors, managers, and decision-makers throughout the decision-making process (Vanem, 2012). As noted in *Driving Health Canada's Science and Research Excellence – Impact Report 2024*: "A strong science culture fosters trust in evidence-informed decision-making, empowers employees to thrive, and drives meaningful progress and innovation within the organization" (Health Canada, 2024). Coupled with the risk decision-making process and principles (Bhuller et al., 2024b; Krewski et al., 2022b), the available evidence creates the knowledge and understanding required for a collaborative approach to the evaluation of health and environmental risks (Aven, 2018). It also provides opportunities to weigh facts, values relating to the acceptability of risks (Sexton & Linder, 2014), consider general principles (Sexton, 2013), and other considerations such as public perception of risk relevant to decision-making (Bouder et al., 2007; Sexton & Linder, 2014).

In the next section, we discuss how a principle-based mindset provides a mechanism to build the NGRDM approach using the upstream and downstream attributes (C5) and the risk culture (C6) grounded in core values, ethics, and principles. When navigating within these boundaries, institutions in leadership positions, such as regulatory bodies, are also responsible and accountable for adhering to the public service code of ethics, international standards, and national legislative requirements (Government of Canada, 2023; OECD, 2000). There are also instances where these institutions must navigate paradigm shifts (Hilton et al., 2023a) and cross boundaries or go beyond existing limits (e.g., by requiring amendments or establishing new statutes, processes, and approaches to support the proposed approach). The transition to non-

animal testing strategies (Bhuller et al., 2024e), incorporation of sex, gender and other intersecting identity factors (e.g., age, culture, and education) using Gender-Based Analysis plus (Canadian Institutes of Health Research, 2022), advancing science and technology (e.g., artificial intelligence (Wamala-Andersson et al., 2023)), and learning about reconciliation and the impact of colonialism on decision-making structures and pathways (Greenwood et al., 2018) provide additional examples of these shifts towards NGRDM.

6.9.2 Risk culture (C6): Using a principle-based mindset

The cross-cutting attributes - engaging interested and affected parties, open and transparent communication, and continuous learning and improvement – are important considerations for the risk culture (C6) required to establish and maintain an approach to NGRDM. Engaging interested and affected parties along with open and transparent communication are also universal risk principles relevant to a vast majority of risk contexts (Bhuller et al., 2024b). Leadership and direction, including governance (e.g., clearly identifying roles and responsibilities of the various leaders involved in the decision-making process), and the cross-cutting attributes are also key in promoting multidisciplinary and collaborative behaviours for accessing the required evidence and knowledge pertinent to NGRDM (Bhuller et al., 2024a).

When considering an approach to NGRDM, there are several publications and theories for understanding the role of behaviour and governance in managing change (Auspos & Cabaj, 2014; Chess, 2001; Dearing & Cox, 2018; Rothstein et al., 2006; Simon, 1997; Spikin, 2012). For example, Herbert A. Simon's Administrative Behavior discusses the modes of influence and how these relate to decisions within administrative settings, which includes the public sector (Simon, 1997). This work explains how "influence" requires an understanding of external aspects - when to impose authority, provide advice, and share information - and internal elements – establishing the criterion for efficiency and organizational identification by understanding the habits, attitudes, and behaviours. In developing an approach to NGRDM, these external and internal aspects align with several of the elements of the risk culture consideration (e.g., leadership and direction and continuous learning). Another example is the Diffusion of Innovation Theory, by E.M. Rogers, and how the process of adoption follows a normal distribution curve (National Cancer Institute, 2005). Innovators (lowest percentage of the population; extreme left of the curve) is followed by early adopters and the middle of the curve includes the early "majority" or late "majority" adopters. The tail end of the curve has the final

population, the laggards. In developing a NGRDM approach, the application of this theory can help in determining, for example, when and how to apply cross-cutting attributes to help engage the interested and affected parties. Lastly, considering "repertoires" (e.g., ethics, adequate funding, and social goals) and their interconnections and intersections within the context of paradigm shifts (Ankeny & Leonelli, 2016; Leonelli & Ankeny, 2015) aligns with the interplay between all the considerations of the NGRDM kaleidoscope.

While theories and other publications are important to help define and characterize the risk culture, the core values of an organization also provide insights into risk governance, behaviour, and the overarching risk culture (C6). This information is typically positioned using a vision/mission or mandate statement or a fundamental proposition which serves as the foundation for the institution (i.e., it is an agreed upon principle). Consequently, in the NGRDM kaleidoscope, we are recommending, at minimum, to use a principle-based mindset as a means for considering the various elements required for establishing the behavior and governance (risk culture) for developing a NGRDM approach. This mindset serves to focus on a common set of core values and principles (Bhuller & Trevithick-Sutton, 2024) and helps in understanding patterns, systemic structures, and mental models for risk decision-making principles (Bhuller et al., 2024b). A principle-based mindset also incorporates ethical considerations for some of the deeply rooted and foundational principles for risk decision-making (Bhuller et al., 2024d). Further, in our analysis of risk decision-making approaches, most publications explicitly refer to core values and principles (Bhuller et al., 2024a). Therefore, a principle-based mindset, developed using the deeply rooted core values, principles, and the common set of cross-cutting attributes, serves as a good starting point for building the risk culture (C6) – behaviour, governance structure, and decision-making pathway - required for NGRDM. As the NGRDM approach develops, this mindset can also become a useful tool for addressing divergence in views and resistance to change by focusing on common elements resonating with all the interested and affected parties.

6.9.3 Using a One Health lens (C7): Establishing the structure and decision-making pathway

In the *Fundamentals of Regulatory Design*, Dr. Malcom K. Sparrow discusses how a diverse range of factors (e.g., performance-based) serve as important considerations relevant for regulatory design. These fundamentals include a shift from a strict "program-centric" design to including a more holistic and "problem-centric" approach relying on "regulatory craftsmanship"

- a term used to encompass the use of all relevant regulatory tools (Sparrow, 2020). Several of these fundamental elements are also aligned with the NGRDM considerations. This includes adopting a principle-based mindset to identify the most relevant information (evidence and knowledge) required to establish the NGRDM design (scope and steps). Further, bringing together program and problem-centric approaches reflects the NGRDM recommendation of using a ONE-Health lens (C7) for establishing an integrated, fit-for-regulatory purpose, and adaptable structure/NGRDM pathway.

Several international and national authorities recommend a ONE Health paradigm as an integrated, unifying approach to considering the health of people, animals, and ecosystems (Phelan & Gostin, 2017; Public Health Agency of Canada, 2024). This approach is particularly useful for addressing complex and global health issues such as antimicrobial resistance (AMR) (Balkhy et al., 2018; Chandra et al., 2021; Ferri et al., 2017; Lobie et al., 2021; Lusti-Narasimhan et al., 2013; Public Health Agency of Canada, 2023; Ruckert et al., 2020). More recently, there has also been a recommendation for considering a *ONE Environment-ONE Health* strategy to better link research activities with future regulatory needs (National Academies of Sciences Engineering and Medicine, 2023b).

As with any fully integrated approach, ONE Health presents the same set of challenges we previously highlighted for policies using a systems thinking approach; i.e., how to successfully identify and maintain a common set of priorities, resources (human, financial, and technical), time, and governance structures throughout the process (Boswell et al., 2021; Trochim et al., 2006). For example, addressing AMR requires country-specific national actions plans, which are challenging to develop due to barriers including limited funding or not having AMR on the policy-agenda (Anderson et al., 2019; Berman et al., 2023; Essack et al., 2017; Honda et al., 2023; Orubu et al., 2020; Shabangu et al., 2023; Willemsen et al., 2022; World Health Organization, 2019b). In our published work on principles for risk decision-making, we also demonstrated the complex nature of ONE Health by analyzing the feasibility of implementing several risk principles relevant to AMR and the national action plans (Bhuller et al., 2024b; Gates, 2016; Peters, 2014).

To address and embrace the complexity associated with systems thinking and ONE-Health approaches, we have previously recommended the use of a systems thinking lens (Bhuller et al., 2024b; Bhuller et al., 2024c) and a ONE-health lens (Bhuller et al., 2024d). For NGRDM, this

approach requires the design phase to be viewed from a broader perspective which considers the impact on human, environmental, and animal health. However, it also provides the flexibility for establishing the NGRDM structure so that it can range from a simple and partially integrated approach (e.g., focused on addressing human and environmental health) to a fully integrated, complex, ONE Health pathway for decision-making (Bhuller et al., 2024a). A ONE-Health lens (C7) also provides an opportunity to account for all the considerations, including the boundaries created by the regulatory context and the deeply rooted, foundational elements. This type of understanding is critical before determining the best NGRDM pathway for addressing the issue, which is why it is incorporated in the mechanism construct of the CMOc. **Table S1** (**Supplementary Material**) includes the next set of questions to help navigate through this phase of the *NGRDM kaleidoscope*.

6.10 The outcome of a NGRDM approach: Promoting and protecting health

The last three considerations – broader regulatory "PESTLE" factors (C8), "REACT" risk management considerations (C9), and risk communication (C10) – are part of the outcome construct of the CMOc. Like the mechanism considerations, the outcome considerations are projected from the institutional to the global level. **Figure 1** displays these considerations as well-defined structures which incorporate pragmatic strategies from the existing literature (Bhuller et al., 2024a). Specifically, for the outcome considerations, the NGRDM kaleidoscope incorporates the PESTLE framework (HM Treasury, 2004), the REACT (regulatory, economic, advisory, community-based, and technological) options for managing the risk (Krewski et al., 2007; Westphal et al., 2017), and the risk communication memory aid, BroadCAST-3Cs (Bhuller & Trevithick-Sutton, 2024).

Several risk-decision frameworks emphasize the importance of allocating sufficient time and resources for upfront planning and problem formulation (Bhuller et al., 2024a). For the approach to NGRDM, this includes considering and incorporating PESTLE (broad regulatory factors (C8)) and REACT (risk management options (C9)) at the outset of the NGRDM process. For example, during the context phase, a preliminary cost-benefit analysis could be explored to determine the implications of PESTLE and REACT on the NGRDM approach being envisioned. Similarly, considering BroadCAST-3Cs and how effectively communicating the NGRDM approach includes the broad (potentially global) level, the context and mechanism constructs can start developing the message using 'CAST-3Cs'; i.e., the core message for the target audience,

identification of the ideal spokesperson, and the timelines for delivering a clear and concise message that is aligned with the context. Visually, the *NGRDM kaleidoscope* depicts the incorporation of the outcome considerations by raising the platform for this construct so that it appears as having the potential to slide, rotate, and be considered during the phases occupied by the other two constructs.

The outcome construct for NGRDM builds from a common and desired ending/resolution for all risk-based approaches: promoting and protecting the health of humans, animals, and the environment (Bhuller et al., 2024b). Adopting a ONE Health lens (C7) during the mechanism stage of the CMOc links well with the ultimate outcome of promoting and protecting health. The outcome construct of the CMOc also brings together all the considerations from the previous constructs. At this stage, the boundaries for incorporating the broader regulatory factors, risk management options, and risk communication approach are established, along with the deeply rooted core values and principles (C5). The behaviour and risk culture (C6), at all levels, is also established, thereby creating a seamless transfer as one moves within the process to create an appropriate decision-making pathway for NGRDM. This is important because the outcome step of the process provides an opportunity to reconsider and then finalize certain factors. For example, selecting the REACT risk management options (C9) for the NGRDM approach and determining how best to communicate (C10) the NGRDM-based decision for promoting and protecting health are finalized at this stage of the CMOc. **Table S1** (**Supplementary Material**) provides the final set of questions for this phase and **Table S2** includes ten recommendations for developing an approach to NGRDM.

6.11 Analyzing the CMOc using a SWOT analysis

The CMOc, the corresponding ten considerations, and the NGRDM-related questions (**Table S1**, **Supplementary Material**) are used as indicators for the SWOT analysis of top-down, bottom-up, and risk science approaches to NGRDM. Through this analysis, we aim to demonstrate how the *strengths* of each approach take advantage of opportunities while avoiding *threats*. Similarly, introducing new *opportunities* for reducing *weaknesses* or minimizing threats (Benzaghta et al., 2021) are also explored for all three types of NGRDM approaches.

6.11.1 Top-down, regulatory approaches

Several regulatory authorities are taking a top-down approach for modernizing existing and overarching frameworks and strategies to risk assessment, management, and decision-making (Bhuller et al., 2024a), including Health Canada (Bhuller et al., 2021; Bhuller & Trevithick-Sutton, 2024). As the NGRDM approach is program area-specific, the *strengths* of taking a top-down, institutional-level approach include a good understanding of the historical and contemporary context (C1-4). Further, as the program area is the lead in developing the approach, they also have a good understanding of the institutional mindset, attributes, and risk culture (C5-6), and how this relates to the evolution in internal and external risk decision-making practices (C8-10). This acquired knowledge and insight guides the development of fit-for-regulatory purpose (C3) approaches ranging from roadmaps (United States Food & Drug Administration (FDA), 2017) to reforms in regulations so that institutions can support more precise approaches reflecting contemporary NGRDM (Gabriela et al., 2022; Hilton et al., 2023a). The internal weaknesses of such an approach include the extensive time and resources (human, technical, and costs) required for creating individual, program area-specific documents. Consequently, there could be duplication in effort, especially when there is limited collaboration and engagement, along with significant delays in the desired outcome of implementing a fully functional NGRDM approach in a timely manner.

An external *threat* includes publishing the NGRDM approach only for staff or, when published externally, the document does not link to the overarching risk decision-making framework. In both instances, it makes it difficult for interested and affected parties to fully understand the historical context and evolution in decision-making. For example, the *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks* (Health Canada, 2000), published over two decades ago, serves as the overarching, foundational, and parent document for more recently published approaches. While some of the more recent documents explicitly reference the overarching framework (Bureau of Microbial Hazards, 2017; Pest Management Regulatory Agency, 2021; Public Health Agency of Canada, 2017), this does not appear to be consistently applied to all pertinent documents. Further, as there does not appear to be a consolidated listing of considerations for developing such approaches, another external *threat* is the actual or perceived lack of consistent criteria/trigger (C4) for the publication of these NGRDM approaches.

The potential for exploring all ten considerations (C1-C10) of the NGRDM kaleidoscope provides external *opportunities* for engagement thereby increasing the *strengths* and conversely the *weaknesses* for considering top-down approaches. During foresight and planning (C1) activities, regulatory authorities can rely on the input from affected and interested parties to assess the pros/cons for moving away from an existing risk-based approach to an NGRDM paradigm (C4). These institutions can also consider the role of research and development (C2) and multi-stakeholder collaborative strategies aligned with the ONE-Health lens (C7). For example, Health Canada's decision-making framework for pest control products provides a structured, one-way decision-making process that takes a ONE-Health lens by undertaking and integrating the health, environmental, and animal risk and value assessments (Pest Management Regulatory Agency, 2021). Further, as top-down approaches are typically multi-year strategies, there is also an opportunity for a more detailed understanding of the regulatory (C3), internal risk culture (C6), and outcome considerations (C8-C10) for the NGRDM approach. This provides flexibility for also considering partial to fully integrated strategies.

6.11.2 Bottom-up approaches for addressing paradigm shifts

The paradigm shift towards the adoption of non-animal solutions presents several barriers, including differences in how various regulatory authorities adopt these methodologies using existing risk-based approaches (Stucki et al., 2022). One strategy for addressing these challenges includes modernization of legislative frameworks (Hilton et al., 2023a) and updating regulatory data requirements (Avila et al., 2020; Clippinger et al., 2022; Gilmour et al., 2022; Hilton et al., 2022; Hilton et al., 2023b; Kim & Choi, 2023; Schmeisser et al., 2023). Another option is developing bottom-up and integrated NGRDM approaches.

In October 2020, the non-profit and global institution, Health and Environmental Sciences Institute (HESI), announced its intention to launch the second edition of the Agricultural Chemical Safety Assessment Committee (Health and Environmental Sciences Institute, 2020). While the original committee focused on human health concerns, the next iteration, referred to as *Transforming the Evaluation of Agrochemicals* (TEA), would set in motion a "paradigm shift" by understanding the regulatory needs from a local and global perspective. The outcome envisioned would be a cross-disciplinary framework relevant to all interested and affected parties. This NGRDM and agrochemical-specific framework would harness state-of-the-art

science and maximize the "quality, consistency, and relevance of risk-based decision-making" (Health and Environmental Sciences Institute, 2020).

The *strengths* of the TEA committee include the multidisciplinary and collaborative approach, which builds from the successes and lessons learnt from the previous committee and the experiences of its current members. The pragmatic and lived experiences of committee members played a key role during the foresight and planning (C1) activities, resulting in the creation of the TEA project landscape map, a problem formulation and exposure-driven proposal, and three pillars for creating the NGRDM approach: scientific gradualism, mindset innovation, and transformation innovation (Wolf et al., 2022). Another *strength* is the use of systems thinking in developing the TEA project landscape map and the NGRDM approach. The TEA committee's commitment towards partnering with a diverse range of scientists interested in advancing this project is another strength. The inclusion of well-versed experts, new to this type of thinking, is also well-aligned with the recommendations from the 12th World Congress on Alternatives and Animal Use in the Life Sciences (Bhuller et al., 2024c).

Considering the systems thinking and collaborative approach for the TEA project, one of the challenges (and *weaknesses*) of this initiative is the time required to complete the various activities, with the progression of the work being heavily dependent on the collaborators. The leads for this project are responsible for managing working groups, publishing several papers or reports, developing outreach strategies, and maintaining engagement with scientists representing various sectors. This also presents an external *threat* if the various members and partners can no longer commit the time for the diverse set of activities. Further, the creation of a bottom-up NGRDM approach, which is not linked to any overarching framework, is another threat as it could impact the uptake of the final approach to NGRDM by sectors who are not actively engaged throughout this multi-year endeavour. There is also a *threat* from not having an incentive or mandate given the disconnect with overarching statues or frameworks.

To address these external *threats*, the TEA project is divided into tangible deliverables (e.g., publication of a specified number of articles) which allow for the incorporation of expert input and state-of-the-art science (C2). These deliverables are also communicated using the HESI site and through publications in peer-reviewed journals (Wolf et al., 2022). The multidisciplinary and collaborative approach, involving scientists with diverse expertise, also provides an opportunity to discuss whether the state-of-the-art science is fit-for-regulatory purposes (C3). Further, the

discourse and outreach activities creates a mechanism to increase the overall understanding of the upstream and downstream attributes (C5), such as the core values, moral norms, and risk culture (C6) required to create a bottom-up, NGRDM approach for agrochemicals (C4). The use of participatory action research (Baum et al., 2006), the *TEA Global Challenge* – a competition designed to acquire "creative" and "cutting-edge solutions" for modernizing agrochemical risk assessments (Health and Environmental Sciences Institute, 2024) – along with the ongoing collaboration also provides a better understanding of the various and broad regulatory factors (C8), risk communication (C10) approaches, and risk management options (C9) relevant for this project.

6.11.3 A fully integrated approach to risk science

The final example in this SWOT analysis explores a fully integrated framework for next generation risk science, where risk science encompasses the scientific enterprise of risk assessment and management actions for reducing risks (Krewski et al., 2014). This risk science framework integrates the most essential elements from *the Toxicity Testing in the 21st Century* (National Research Council, 2007), *Population Health Risk Assessment's Integrated Framework for Risk Management and Population Health* (Krewski et al., 2007), and *Science and Decisions: Advancing Risk Assessment* (Westphal et al., 2017). This includes new risk assessment methodologies and a resulting framework which is fully integrated and structured to support decision-making using a population health approach and up-front consideration of a broad array of regulatory and non-regulatory risk-management options (Krewski et al., 2007; Krewski et al., 2014).

This next generation framework for risk science includes several *strengths* that are aligned with the NGRDM's CMOc and considerations (**Figure 1**). For example, the up-front consideration of broad risk management options is consistent with how the NGRDM integrates the regulatory factors (C8) in the context construct and then supports their use, along with the risk management (C9) options and elements fostering effective risk communication (C10), throughout the process. The NGRDM also integrates a population health approach in establishing the upstream and downstream attributes (C5) and the use of a ONE Health lens (C7) for the mechanism construct. Krewski and colleagues identified the population health approach as a cornerstone for their framework as it considers risk from a broader population health perspective: this includes the

strength of simultaneously examining multiple determinants of health and how they interact to determine the health status of a population (Krewski et al., 2007; Krewski et al., 2014).

There are several challenges (*weaknesses*) in the implementation of the next generation risk science framework. This includes the shift in the risk assessment approach from using traditional, apical measures of toxicity (morbidity and mortality) towards *in vitro* systems and measurements of perturbations in toxicity pathways (Krewski et al., 2014). The framework's focus on population health also creates a perception of not being able to use a ONE Health lens (C7). There are also external *threats* such as the need to further characterize several toxicity pathways, evaluate multiple health determinants that may modify or interact with the main risk factor(s) of interest, and consider an expanded range of risk management options due to the adoption of a population health approach (Krewski et al., 2014). As the development may have only accounted for the upstream and downstream attributes (C5) and risk culture (C6) of the institutions involved or aware of this initiative, another important threat is the potential for limited uptake of this framework by these organizations.

To address these *threats*, Krewski and colleagues included a crosswalk between the current and next generation risk science approach along with a series of case study prototypes intended to show how their framework can be deployed in practice (Krewski et al., 2014). This framework has also been referenced and shared at various meetings with interested and affected parties. Further, there are also *opportunities* for additional integration with ongoing work. For example, the authors have developed an evidence-based risk assessment framework (Krewski et al., 2022), which could be linked with their Next Generation Risk Science framework to further enrich its value.

6.12 Discussion

The SWOT analysis of top-down, bottom-up, and risk science frameworks provided an opportunity to test the proposed CMOc and the ten considerations for developing an approach to NGRDM. As summarized in **Table 2**, several of the SWOT inputs included one or more of the CMOc considerations. For example, one of the *opportunities* afforded by a top-down approach is the flexibility in exploring all ten considerations (C1-10). The SWOT inputs were populated based on the information from the respective document for each NGRDM approach, which represented the views of diverse experts. Consequently, this further confirmed how the *a priori*

hypothesis and the proposed CMOc are appropriate for establishing and analyzing the *strengths*, *weaknesses*, *opportunities*, and *threats* of various NGRDM approaches. All three approaches demonstrated how NGRDM requires an understanding of the intersections between the research, regulatory, and risk contexts of the proposed CMOc. Further, an institutional mindset and culture, which integrates a population health approach to maximize upstream and downstream attributes for risk decision-making and relies on a ONE Health lens (mechanism), was a key strength to promoting and protecting the health of humans, animals, and the environment (outcome). Conversely, limiting or narrowing the focus of the NGRDM approach (e.g., to population health) was identified as a *weakness*.

Table 2: Summary of the SWOT analysis for NGRDM approaches

SWOT parameters	NGRDM approach		
	Top-down	**Bottom-up**	**Risk science**
Strengths	• Used by several regulatory authorities to develop fit-for-regulatory (C3) purpose and precision/ program area-specific NGRDM approaches • Program area has good understanding of historical and contemporary context (C1-4) • Led by program area and thus, good understanding of institutional mindset, attributes, leadership and direction, and culture (C5-6), and how all these factors relate to the evolution of risk decision-making practices (C8-10)	• Used to develop novel approaches which are not linked to an overarching framework • These approaches are focused (e.g., program-area or product specific frameworks) • Multidisciplinary and collaborative • Foresight and planning (C1) and subsequent constructs of the CMOc (C2-10) build from the diverse pragmatic and lived experiences of the multidisciplinary team members and other collaborators	• Used to develop a fully integrated, next generation risk science framework which is not linked to a specific overarching risk decision-making framework • A complex framework with upfront and broad consideration of regulatory factors (C8), risk management (C9) options, and elements for effective risk communication (C10) • Integrates a population health approach to allow for simultaneous examination of multiple determinants of health
Weaknesses	• Extensive time and resources (human and cost) commitments • Potential for duplication in effort, especially when there is limited collaboration and engagement • Potential for significant delays in the timely implementation of a fully functional NGRDM approach	• Participatory, collaborative, and multidisciplinary approach requires extensive time to complete the various activities • Project leads are responsible for managing multiple working groups • Progression is heavily dependent on the collaborators	• Challenges in the implementation of the framework due to significant shifts in traditional and well-established practices • Population health focus may result in a perception for not using a ONE Health lens (C7)

Opportunities	• Explore all ten NGRDM considerations (C1-10) and multi-year approach provides opportunities for attaining a more detailed understanding of all considerations including the regulatory (C3), internal risk culture (C6), and outcome considerations of the NGRDM approach (C8-10) • Foresight and planning (C1) activities can incorporate external input (e.g., through consultation) • Flexibility to consider existing risk-based approaches (C4), role of research and development (C2), and multi-stakeholder collaborative opportunities taking a ONE-Health lens approach to risk decision-making (C7)	• Establish a project plan with tangible deliverables incorporating state-of-the art science (C2) • Multidisciplinary and collaborative discourse to determine science that is fit-for-regulatory (C3) purposes • Collaborative approach increases overall understanding of upstream and downstream attributes (C5), risk culture (C6), regulatory factors (C8), risk communication (C8) approaches, and risk management options (C9) required for creating the bottom-up, NGRDM approach (C4)	• Develop crosswalks to demonstrate the transition from traditional to NGRDM approaches • Knowledge transfer by publishing and sharing the NGRDM approach at various meetings • Further integrate the approach with state-of-the-art science and other, relevant frameworks, which includes considering a ONE health lens (C7)
Threats	• Limited availability (e.g., published only for internal use) • Not connecting program area-specific NGRDM approaches with an overarching framework • Potential for black box scenarios when interested and affected parties are not able to fully understand the context and evolution in risk decision-making • Actual or perceived lack of consistent criteria/trigger for the NGRDM approach (C4)	• Departure or lack of input from collaborators • Creation of a bottom-up NGRDM approach resulting in limited uptake by sectors not actively involved in the development of the approach • Lack of incentive or mandate	• Next generation risk science approach's dependence on the external development of indicators and additional strategies for supporting its implementation • Creation of a complex, next generation risk science framework resulting in limited uptake by sectors not actively involved in the development of the approach

6.12.1 Collaboration, context, and culture matter

The SWOT analysis demonstrates the importance of multidisciplinary engagement, collaboration, strong leadership and direction, and a culture that supports a principle-based mindset in developing a NGRDM approach. Top-down and bottom-up approaches include 'time' for collaboration and

engagement as a challenge (*weakness*), which is a common feature of approaches requiring systems thinking (Boswell et al., 2021). It is also understandable how the demands for more time (and resources) increase as one moves from a partially to a fully integrated approach. This might also be an explanation for the finite number of published and fully integrated NGRDM approaches (Bhuller et al., 2024a). Collaboration is also reported as an *opportunity* to better understand the context (C1-4), upstream and downstream attributes (C5), and underlying risk culture (C6) required to develop and implement the NGRDM approach. Further, the lack of active engagement is another challenge (*weakness*) of approaches relying heavily on various contributors. The lack of engagement is also a threat given the potential to limit the eventual uptake by sectors not actively involved in the development of the NGRDM approach. Consequently, while partnerships, engagement, collaborative governance, and establishing a principle-based mindset take time, they are critical for understanding the context and risk culture required for developing optimal approaches for NGRDM.

6.12.2 The relevance of frameworks

The use of frameworks for developing an approach to NGRDM ensures consistency and completeness in identifying, assessing, managing, and communicating risks. In the SWOT analysis, three different approaches to NGRDM were analyzed. Interestingly, a common feature for the risk science, bottom-up (agrochemicals), and several of the top-down Health Canada approaches was the use of a framework for establishing the design and final structure for the decision-making pathway. Frameworks also provide flexibility in considering a broad range of factors and integration with other frameworks. For example, the top-down and integrated approaches analyzed in the SWOT analysis support the integration of overarching strategies with Health Canada, program area-specific NGRDM frameworks and state-of-the-art science and relevant frameworks (e.g., evidence integration), respectively. Frameworks also provide the flexibility for being adopted or adapted to address a diverse range of next generation risk decision-making issues. This is consistent with the contextual risk consideration (C4) where one evaluates existing risk-based approaches prior to developing a strategy for NGRDM.

6.12.3 An iterative approach to NGRDM

The *NGRDM kaleidoscope* visualizes the application of the CMOc in a circular manner where the context and mechanism considerations are shown as being more abstract when compared to the

outcome construct (**Figure 1**). This visualization is designed to demonstrate how the context and mechanism are more iterative. While the outcome considerations do not preclude taking an iterative approach during this phase of the CMOc, the more structured design of these considerations reflect best practices applicable to a vast majority of risk-based strategies. This also means that the NGRDM approach and the outcome construct are dependent on the context and mechanism constructs and considerations. This dependence is seen in the three examples of the NGRDM approaches analyzed in the SWOT analysis. For example, the TEA project's outcome is based on understanding the context and mechanism for developing an overarching NGRDM framework intended to reflect a paradigm shift for evaluating agrochemicals (Wolf et al., 2022). The dependence on all three outcome considerations (C8-10) is also shown in the NGRDM kaleidoscope by having these elements extend from a raised platform. Visually this shows the potential for the outcome construct and considerations to shift and move around the CMOc so that it can be co-located in a space occupied by the other two constructs thereby allowing for upfront exploration of these considerations.

6.13 Conclusion

The decision-making context, underlying principles, values, and processes involved in risk decision-making have evolved over the last five decades (Bhuller et al., 2024a). These changes need to be understood prior to designing the scope, steps, structures, and decision-making pathways for NGRDM. To comprehend the complex nature of risk decision-making, we have previously recommended next generation learners and readers to take an "astronaut's view" - this perspective allows one to see the entire system along with all the interactions between risk science and analysis (Bhuller et al., 2024c). We take a similar stance in this paper by creating the NGRDM kaleidoscope to help orient and display the realist paradigm-derived CMOc and ten considerations relevant for NGRDM (**Figure 1**). Consequently, all the considerations in this system, how they intersect, and transition from the institutional to the global level are visible to the reader interested in building an awareness and understanding of the requirements for developing an approach to NGRDM.

Developing a NGRDM framework is challenging, with the complexity increasing as one transitions from partial to fully integrated approaches such as One Health (Public Health Agency of Canada, 2024). We hope the creation of a realist paradigm-inspired NGRDM kaleidoscope, CMOc and considerations, and the SWOT analysis provides insights on how to recognize and

embrace these challenges. We consider the kaleidoscope model to be flexible and scalable as the design and final NGRDM pathway builds from a deep awareness of the context and understanding of the mechanism (i.e., underlying risk culture and behaviour), and then considers well-established best practices to establish the desired outcome. We encourage everyone interested in learning more about NGRDM to use the kaleidoscope and the additional information provided in the supplementary material (**Tables S1** and **S2**). We also welcome additional analysis to help determine which approach has the greatest impact. From our limited and collective experience, top-down approaches seem to be more prevalent given the linkage to established laws and overarching frameworks. Lastly, as a tool for advancing risk decision-making, we hope this information will help to create a path for embracing the complexity in NGRDM and navigating beyond these challenges by using the NGRDM CMOc and kaleidoscope model.

6.14 References

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Supplementary material: Tables S1 and S2 and summary of key articles

This document is intended to supplement the information provided in the manuscript. **Table S1** is a consolidated listing of questions for building awareness and understanding around the *NextGen Risk Decision-Making* (NGRDM) approach, including the fundamental question of whether such a strategy is necessary for the current context. These questions are not designed to be a checklist *per se*. Rather, they are intended to guide the user towards carefully judging each consideration as they use the *NGRDM kaleidoscope* to move through the Context, Mechanism, and Outcome configuration (CMOc) paradigm. These questions were also used to develop the inputs for the *Strengths, Weaknesses, Opportunities,* and *Threats* (SWOT) analysis of NGRDM strategies.

Table S2 provides a list of ten recommendations for guiding the development of an approach to NGRDM.

The **Summary of key articles** provides a brief description of six publications, which were instrumental in developing the CMOc and the considerations appearing in the *NGRDM kaleidoscope*. The last section includes a listing of **references** noted in this document.

Table S1: Consolidated listing of questions for building awareness, understanding, and the outcome of an approach to NGRDM

Consideration (C1-10)	Questions
Foresight and planning (C1)	What type of NGRDM approach do you need now? Is there an existing risk-based approach (see (C4) risk context) you can adopt/adapt? If not, what are the resources (human, financial, technical, and time) for developing this NGRDM approach? Have you considered design thinking (Bhuller et al., 2021) or another agile approach in planning the NGRDM strategy?
Research and development (C2)	Are the current or future research and development initiatives, for developing the NGRDM approach, fit-for-regulatory purposes?
Regulatory context (C3): Consideration of relevant factors including politics, legislation, policy, public, science, and technology	Have you considered the Political, Economic, Socio-cultural, Technological, Legal, and Environmental (PESTLE) factors and their implications on the plausible NGRDM approach being envisioned (HM Treasury, 2004)? What risk management options - Regulatory, Economic, Advisory, Community-based, and Technological (REACT) - should be considered for this approach (Krewski et al., 2007; Westphal et al., 2017)? What elements of effective risk communication (i.e., BroadCAST-3Cs (Bhuller & Trevithick-Sutton, 2024)) are required for this approach?
Risk context (C4): scoping, prioritization, hazard evaluation, risk assessment, risk-benefit assessment, risk tolerability, risk science, or	In the event where you need to start developing a NGRDM approach, will it be a top-down, bottom-up, or fully integrated and multi-disciplinary strategy?

next generation risk decision-making	
Upstream and downstream attributes (C5)	Do you have support and direction from your leadership team to develop the NDRDM approach? Are you using a principle-based mindset to determine the core and shared values and norms (e.g., promoting and protecting health) while understanding diverse positions and the underlying reasons for such stances (Bhuller & Trevithick-Sutton, 2024)? Do you have access to the relevant resources including the evidence and knowledge required to develop the approach, which includes the governance structure and decision-making pathway?
Risk culture (C6)	Do you have support and direction from your leadership team to develop the NDRDM approach? Do you have access to the relevant resources including the evidence and knowledge required to develop the approach?
ONE Health lens (C7)	Did you take a more holistic approach to establish the NGRDM structure and pathway by viewing the health risk concern using a ONE Health lens?
Broad regulatory "PESTLE" factors (C8)	How will the PESTLE factors (HM Treasury, 2004) impact the use of the NGRDM approach for promoting and protecting health?
REACT risk management considerations (C9)	What REACT options (Krewski et al., 2007; Westphal et al., 2017) are most relevant for the NGRDM approach?
Risk communication (C10)	Is the communication of the NGRDM approach aligned with the components of BroadCAST-3Cs (Bhuller & Trevithick-Sutton, 2024)? **Broad** captures the range for effective communication and "CAST-3Cs" stands for: the **core** message, adjusting the message to meet the needs of the target **audience**, identifying the **spokesperson** responsible for delivering the message, relaying the message in a **timely** manner, and ensuring the message is **context**-specific, **clear**, and **concise**.

Table S2: Ten recommendations for developing an approach to NGRDM

No.	Recommendation
1	The unspoken rule: simple before complex. Consider established risk-based approaches before developing a NGRDM strategy.
2	Address uncertainty (lack of evidence or knowledge) by incorporating the outcome considerations early and then throughout the process, what failure means at the onset of the process, and lessons learnt from those who have already embarked on developing a similar NGRDM approach.
3	Understand the main constructs of the NGRDM kaleidoscope (context, mechanism, and outcome) and how the considerations guide the development of NGRDM.
4	Develop a project plan with tangible deliverables using SMART (specific, measurable, achievable, relevant, and timebound) objectives.
5	Modernize established, program-centric frameworks using top-down, bottom-up, or a novel approach to NGRDM.
6	Take a holistic approach: Aim to develop the NGRDM approach using a multidisciplinary and collaborative process.

7	Challenge constraints by understanding and embracing the barriers. Use this knowledge to navigate the NGRDM approach within these boundaries and when (and how) to go beyond them.
8	Create a risk culture using a principle-based mindset, focused on core and shared values and norms (e.g., promoting and protecting health). This includes understanding diverse positions and the underlying reasons for such stances (Bhuller & Trevithick-Sutton, 2024). Further, risk culture requires strong leadership, governance, stewardship, and access to evidence and knowledge for developing the scope and steps (design) of the NGRDM approach;
9	Develop knowledge transfer tools for engaging and sharing the NGRDM approach at the institutional and global level.
10	Consider using a SWOT analysis (or another approach) to evaluate the NGRDM approach.

Summary of key articles

The knowledge synthesized from previous publications along with input from experts, using an embedded research model, guided the development of the realist paradigm-derived context, mechanism, and outcome configuration (CMOc) for the main paper. Further tailoring and integration of the risk decision-making attributes, from a scoping review of risk decision-making frameworks (see article #3 below), resulted in the creation of the considerations, which appear in the *NGRDM kaleidoscope model*. This model also created awareness and understanding of next generation risk-decision-making by providing the key considerations for characterizing the context, mechanism (underlying risk culture and behaviour), and desired outcome for NGRDM. Here is a summary of each article:

Key article #1: Relevance and feasibility of principles for health and environmental risk decision-making

In 2022, Krewski and colleagues published a seminal report which provided ten guiding principles for risk decision-making (Krewski et al., 2022). The risk principles paper (article #1) expanded on this work by using an embedded research model and engaging regulatory practitioners at Health Canada. These experts were asked to evaluate the feasibility and importance of these principles along with additional ones relevant to the Canadian regulatory context (Bhuller et al., 2024b). Building from a realist review/synthesis of established risk principles, a realist paradigm generated an *a priori* hypothesis which was tested through this original research. The knowledge product/article for this work included the identification and characterization of risk principles into distinct categories (i.e., universal, fundamental, guiding, and foundational principles), which is further visualized using the *Systems Iceberg Model* (Sheffield et al., 2012).

Key article #2: Ethical principles for regulatory risk decision-making

The ethical considerations and principles paper (article #2) engaged experts from diverse sectors and used the knowledge translation approach to create the *projector model* for ethical principles and considerations relevant for risk decision-making (Bhuller et al., 2024d). This model helped visualize the intersections of ethical considerations and principles between ethical, risk, and decision-making contexts and the broader, regulatory worldview. It also demonstrated how the risk and ethical contexts interact with the decision-making process, and how ethical principles and considerations play a key role in promoting and protecting human, environmental, animal, and global health. The *projector model* also displayed the link between the data ecosystem and how data/information feeds into the risk decision-making process.

Key article #3: Key attributes of health and environmental risk decision-making: A scoping review

The scoping review (article #3) of risk assessment, management, and decision-making frameworks spanning over fifty years, analyzed thirty-nine publications to help visualize the evolution and transformation in risk decision-making over this period. Further, the analysis also resulted in the identification and characterization of these ten attributes for risk decision-making: trigger/issue, regulatory context, regulatory factors, core values, risk decision-making principles, cross-cutting attributes, design (scope and steps), structure, decision-making pathway, and evidence-knowledge requirements for risk decision-making. (Bhuller et al., 2024a). This review demonstrated how the risk assessment-management paradigm has transitioned from simple to more complex and integrated frameworks. The ten attributes for risk decision-making were also transformed into key considerations for NGRDM (main paper) based on a realist paradigm-inspired kaleidoscope model

Key article #4: Canadian regulatory perspective on next generation risk assessments for pest control products and industrial chemicals

This publication (article #4) provided insights on the theoretical approach and mindset used to advance new approach methodologies and how to link these methodologies to next generation risk assessments (Bhuller et al., 2021). For pest control products, this included incorporating the design thinking framework, as a theory-based tool, for forecasting, planning, developing, and visualizing non-animal testing approaches. For science and risk-based organizations, elements of design thinking (e.g., building, experimenting, and testing) share similarities with the scientific process.

Consequently, this article also demonstrated the utility of using design thinking (e.g., during the planning stage) for science and risk-based institutions.

Key article #5: Building knowledge of NAMs through risk science

This paper (article #5) recognized the importance of taking a broad perspective, identified as an "astronaut's view", to help understand and build knowledge of the links between risk science and analysis and how this relates to learning and improving new approach methodologies (NAMs) and the risk assessment process (Bhuller et al., 2024c). The importance of such a broad, systems thinking perspectives is also incorporated in the main paper's *NGRDM kaleidoscope model* as the mechanism construct includes the use of a ONE Health lens.

Key article #6: Risk communication: lessons from an ethnographic, pragmatic, and Canadian regulatory perspective

This publication (article #6) continued to demonstrate the importance of taking a broad, systems thinking lens as risk decision-making (and communicating risks) can be to a broad audience (e.g., the entire country) (Bhuller and Trevithick-Sutton, 2024). This paper also provided tools to improve effective risk communication along with a diagram situating the core risk assessment/decision-making process within a broader policy-political-publics space. A memory aid known as: *BroadCAST-3Cs*, was also included in this article, which combined several risk communication attributes relevant for effective communication. "Broad" is a reminder that regulatory risk communication, by necessity, is often for a large and heterogeneous population (Goerlandt et al., 2020). "CAST" stands for **core,** the underlying reason for the risk communication, **audience**, **spokesperson**, and the importance for providing the risk communication message in a **timely** manner. The "3Cs" is a mnemonic for conveying information that reflects the risk **context**, must be **clear** (sometimes written as **clarity**), and **concise.** The article, therefore, reminds risk communicators to adjust messages to meet the 3Cs of each target audience thereby informing them in a useful and meaningful way.

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CHAPTER 7: DISCUSSION

Chapter overview

This chapter summarizes the study findings from all four articles included in this thesis. Additionally, it also discusses the contributions to population health and how this work can be used to further advance next generation risk decision-making (NGRDM) using the conceptual framework and models presented in this thesis.

7.1 Summary of findings

This thesis analyzed the pragmatic application of key principles for risk decision-making by engaging experts from Health Canada using an embedded research model (Chapter 3). Further, experts from the regulatory and non-regulatory sectors (e.g., non-governmental organizations and academia) participated in the development of the *projector model* for ethical principles and considerations for risk decision-making. This model helped visualize the intersections of ethical considerations and principles between ethical, risk, and decision-making contexts and the broader, regulatory worldview (Chapter 4). The scoping review demonstrated how the risk assessment-management paradigm has transitioned from relatively simple to more complex and integrated frameworks. The descriptive analysis and comparison of various approaches also helped identify best practices and ten attributes for risk decision-making (Chapter 5). These attributes were further transformed into key considerations for NGRDM based on a realist paradigm-inspired *kaleidoscope model* (Chapter 6). Collectively, these articles have addressed knowledge gaps by: (i) providing a contemporary scoping review of the evolution in risk decision-making over the last fifty years; (ii) demonstrating how the transformation in risk decision-making includes approaches incorporating foundational elements while integrating additional factors; (iii) developing the *projector model* for ethical considerations and principles and showing its utility in risk decision-making; and (iv) tailoring and integrating key attributes to create the *kaleidoscope model*, which includes ten underlying considerations for building awareness and understanding on how to develop a NGRDM approach.

7.1.1 Summary of Article 1

In 2022, Krewski and colleagues published a seminal report which provided ten guiding principles for risk decision-making (Krewski et al., 2022). Article 1 (Bhuller et al., 2024)

expanded on this work by requesting regulatory practitioners, at Health Canada, to evaluate the feasibility and importance of these principles along with additional ones relevant to the Canadian regulatory context. The results from this research endeavour fully supported the ten guiding principles previously recommended by the experts in risk sciences. Further, measuring the relevance of these principles using two variables – feasibility and importance – provided a mechanism to further characterize these principles into four distinct categories: universal, fundamental, guiding, and foundational principles. The *Systems Iceberg model* (Sheffield et al., 2012) helped in visualizing how these groupings relate to the overarching regulatory and risk decision-making contexts. Specifically, while universal principles were shown to be well above the wave and in the same space as the event/risk decision context (visual spectrum), the remaining principles were below the wave (invisible spectrum). Further, this model also helped demonstrate why some of the deeply rooted principles (i.e., guiding and foundational principles) are often difficult to recognize as they are connected with underlying systemic structures and core mental models. The application of the consolidated listing of risk principles to global health and environmental health issues demonstrated the utility of these principles in understanding the complexities associated with risk decision-making processes. It also supported how risk-based regulators is another important foundational principle given the underlying beliefs and values (mental model) in using a risk based approach to decision-making.

7.1.2 Summary of Article 2

The identification and categorization of key risk decision-making principles (Article 1) demonstrated the need to further investigate ethical principles and considerations relevant to decision-making. Consequently, experts and global thinkers in risk, health, regulatory, and animal sciences were convened to share their lived experiences in relation to the intersection between risk science and analysis, regulatory science, and public health. Through a participatory, iterative, and knowledge translation approach, the engagement and discourse built from existing ethical principles. What was unique to this initiative is the incorporation of these principles based on an overarching framework designed to help develop the integrated *projector model* for ethical considerations and principles for risk decision-making (**Figure 2, Chapter 4**). This model helped visualize how the ethical principles and considerations interact between the ethical, risk, and decision-making contexts and the broader, regulatory worldview. Further, the application of the

model demonstrated the utility of the ethical principles and considerations across diverse contemporary health issues.

7.1.3 Summary of Article 3

To determine the underlying contextual considerations, mindset, and culture for developing a NGRDM approach, it was important to first consider how the risk assessment-management paradigm has evolved over time and also further investigate if existing frameworks rely on risk and ethical principles. A scoping review was determined to be an appropriate tool for addressing these parameters because it provided a mechanism to systematically analyze the literature using a robust and iterative process (Arksey & O'Malley, 2005; Peters et al., 2020). As described in **Figure 2** (Chapter 5) of this thesis, the results of the scoping review portray the evolution as a sigmoidal curve. The initial publications prescribed the foundational elements which was followed by a rapid growth representing the expansion in publications providing precision to specific areas of the risk decision-making process or more robust and integrated frameworks for risk decision-making. The final segment of the curve, referred to as the summative years, represented more recent frameworks and approaches, including even more complex and integrated strategies such as *One Environment-One Health* (National Academies of Sciences Engineering and Medicine, 2023). The scoping review also confirmed how risk and ethical principles are important for risk decision-making along with the following attributes: trigger/issue, regulatory context and factors, core values, cross-cutting attributes, design (scope and steps), structure, decision-making pathway, and the evidence-knowledge required for risk decision-making.

7.1.4 Summary of Article 4

In the concluding remarks of Article 3, there is a statement acknowledging the evolution and transformation in the risk decision-making processes while identifying the need to further tailor and integrate this knowledge to better understand the key considerations for next generation approaches to decision-making for health and environmental risks. Article 4 addresses this gap by proposing the *kaleidoscope model* with ten considerations for developing an approach to NGRDM. This model is developed using a realist *a priori* theoretical construct (i.e., the context, mechanism, and outcome configuration (CMOc)). The CMOc reflects the knowledge generated from the previous, three articles, which included a realist review/synthesis of data generated

from mixed methods research activities (Pawson et al., 2004; Pawson et al., 2005), and other relevant information (e.g., the supplementary papers (Chapter 8)). The *kaleidoscope model* (and the CMOc) is further tested using a strengths, weaknesses, opportunities, and threats (SWOT) analysis. The SWOT analysis demonstrated how top-down, bottom-up, and risk science approaches to NGRDM incorporate the ten considerations of the CMOc, which are visualized in the *kaleidoscope model*. The results from the SWOT analysis also show how these considerations are relevant to all three approaches to NGRDM. Consequently, the model can be used as a tool to build additional awareness and understanding of these considerations, which can be important in further advancing the development of additional approaches to NGRDM.

7.2 Contributions to population health

In 1974, the federal government of Canada released a landmark White Paper titled: *A New Perspective on the Health of Canadians*, which highlighted the importance of population health and how it builds on a long tradition of public health and health promotion (Lalonde, 1974). The Lalonde Report transformed how the world viewed health and continues to be one of the foundational documents for health promotion. The *Ottawa Charter for Health Promotion* (World Health Organization, 1986) and *Achieving Health for All: A Framework for Health Promotion* (Epp, 1986) expanded on the White Paper by focusing on broader determinants of health, which included factors such as income level, education, and the physical environment where one lives. Indigenous leaders, such as the Honorable Dr. Margo Greenwood, provided additional insights on the impact on Indigenous health from multiple determinants (e.g., colonialism, culture, early childhood development, environment, and geography) through publications such as the *Determinants of Indigenous Peoples' Health – Beyond the Social* (Greenwood et al., 2018). In this thesis, Indigenous elders, leaders, and scholars spearheading various initiatives also directed me on how to braid in the voices and references to resources providing detailed insights from Indigenous Science and Knowledge-related efforts relevant to NGRDM (e.g., the OCAP™ principles).

Several institutions, including regulatory authorities, apply a population health approach as it provides a broad, systems view for focusing on interrelated conditions and factors influencing the health of populations. This includes accounting for both upstream (deeply rooted factors) and downstream determinants of health. Within the context of risk decision-making, Krewski and colleagues (2007) have also proposed frameworks which integrate population health with the

management of risks (Krewski et al., 2007). In 2014, these experts also published *A Framework for the Next Generation of Risk Science* where the risk assessment phase incorporated a population health approach. Consequently, this accounted for the multiple determinants of health along with advanced approaches to risk assessment methodologies and new directions in toxicity testing (Krewski et al., 2014).

In this thesis, I incorporated a population health approach by taking a broad, holistic, and systems thinking perspective in the design of the conceptual framework (Chapter 1), development of the *projector model* for ethical principles and considerations (Chapter 4), and reliance on an *a priori* and theoretical based construct used to develop the *kaleidoscope model* for developing a NGRDM approach (Chapter 6). My contribution to population health, therefore, is the adaptation of the population health approach as a means to enhance the collective knowledge on the underlying determinants for risk decision-making. For example, the *projector model* demonstrates how the risk decision-making context (ethical, risk, and decision-making process) is linked to the broader regulatory worldview through a ONE Health lens. Further, the broader worldview includes the importance of population health along with environmental, animal, and global health. Similarly, the *kaleidoscope model* incorporates both upstream and downstream risk decision-making attributes, which are the underlying determinants for understanding the risk culture, structure, and decision-making pathway required for establishing a NGRDM approach.

7.3 Addressing uncertainty and the role of experts in risk decision-making

Traditional, conventional, and next generation approaches to risk decision-making inevitably involve the need to address uncertainty and incorporate expert judgement. All the chapters of this thesis include information related to uncertainty (including data gaps) and the role of experts in risk decision-making. For example, the scoping review (Chapter 5) provides a listing of references where some of the frameworks include insights on algorithms and differential approaches to address uncertainty. *The Tolerability of Risk: A New Framework for Risk Management* (Bouder et al., 2007) includes detailed information on the role of judgement. Further, the *Structured benefit–risk evaluation for medicinal products: review of quantitative benefit–risk assessment findings in the literature* is another example with explicit reference to the value of judgement in using a quantitative benefit-risk assessment (Kurzinger et al., 2020). In this thesis, there was also an emphasis on the application of the precautionary principle in risk

assessment in the presence of uncertainty (Rogers 2003). As the precautionary principle encourages risk management actions to be taken in the presence of threats which can result in serious or irreversible harm, even though there is substantial uncertainty about the risks, this also raises ethical considerations relating to the allocation of risk management resources in the absence of accurate information about potential hazard and risk (Ahteensuu and Sandin, 2012; Carolan, 2016; Lokke, 2006; Saltelli and Funtowicz, 2005). Further, the inherent uncertainty in potentially all risk scenarios implies that each risk assessment has only a probability of being correct, calling for a probabilistic risk assessment (Maertens et al., 2022, 2024) to make this transparent and in part quantifiable. Consequently, when dealing with risk and uncertainty, the ethical principle (EP3) - maintain respect and trust (Chapter 4) - noted how the expert judgement, by all individuals who are part of the decision-making process, shall strive to deliver all risk decision-making activities and actions in a considerate and reliable manner. This includes being inclusive and upholding all the elements of the other ethical principles described in this chapter.

7.4 Advancing next generation risk decision-making

One of the goals for this thesis is to advance the knowledge products/articles, generated using the conceptual framework and various research activities, by making this information available to the broader scientific community. Consequently, all the articles were submitted to diverse and reputable journals supporting open science publications. Each article also included an open invitation by requesting the reader to advance this work (e.g., by incorporating the information in their respective projects). Further, the embedded research model provided a strategy to create networks with several experts including Canadian regulatory practitioners, leaders from non-governmental organizations, and academia. These engagements have resulted in opportunities for additional discourse, which includes sharing the results from this thesis through various communities of practices, meetings, and conferences. Advancing next generation risk decision-making also includes our next generation of leaders who were interested in learning about this topic. In 2024, a mini-course, *Building Knowledge of NAMs through Risk Science,* was developed and successfully delivered to students aged 13-16 years (Bhuller et al., 2024). These types of platforms provide yet another mechanism to transfer the knowledge from this thesis and continue to build awareness and knowledge of NGRDM approaches.

7.5 Conclusion

Risk decision-making continues to be grounded in foundational elements such as the fundamental steps to assessing risks. However, the evolution and transformation in risk decision-making reflects a continually ongoing incorporation of additional factors, thereby resulting in more complex and integrated approaches. While risk decision-making continues to be rooted in strategies and established factors designed to produce results for protecting and promoting health, there is a gap in the knowledge on the underlying contextual and mechanism-related (behavioural and cultural) considerations for developing next generation risk decision-making approaches. In this thesis, I address this gap using a knowledge mobilization and translation approach, which relies on an embedded research model and a realist paradigm. The initial knowledge products/articles – risk principles, ethical considerations and principles for risk decision-making, and a scoping review – serve as building blocks for the development of a theoretical-based *kaleidoscope model*. This model also incorporates a population health approach to better understand upstream and downstream attributes for risk decision-making and the use of a ONE Health lens to develop NGRDM approaches. Our goal is to continue to advance this work through ongoing engagement and opportunities with regulatory practitioners (e.g., at Health Canada) while developing learning material for our next generation leaders. I also encourage all who are interested in risk decision-making to apply the models within their specific areas of interest and report on their findings, as this will help in further enhancing the collective awareness, knowledge, and understanding of NGRDM.

7.6 References

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CHAPTER 8: APPENDIX

Chapter overview

This chapter includes a summary of three supplementary articles, which contributed to the development of the fourth article provided in Chapter 6 of this thesis. The full articles are also provided as supplementary information to this appendix.

8.1 Summary of supplementary articles

The first article, *Canadian Regulatory Perspective on Next Generation Risk Assessments for Pest Control Products and Industrial Chemicals* (Bhuller et al., 2021), provides insights on the theoretical approach and mindset used to advance new approach methodologies (NAMs) and the link to next generation risk assessments. As described in Chapter 6 of the thesis, for pest control products, this includes incorporating the design thinking framework as a tool for forecasting, planning, developing, and visualizing non-animal testing approaches. For science and risk-based organizations, elements of design thinking (e.g., building, experimenting, and testing) share similarities with the scientific process. Consequently, this article also demonstrated the utility of using design thinking (e.g., during the planning stage) for science and risk-based institutions.

The second article, *Building Knowledge of NAMs through Risk Science* (Bhuller et al., 2024), recognizes the importance of taking a broad perspective, identified as an "astronaut's view", to help understand and build knowledge of the links between risk science and analysis and how this relates to learning and improving NAMs and the risk assessment process. The importance of such a broad, systems thinking perspectives is incorporated in the next generation risk decision-making (NGRDM) kaleidoscope (Chapter 6 of the thesis) through the recommendation of using a ONE Health lens.

The final paper, *Risk communication: lessons from an ethnographic, pragmatic, and Canadian regulatory perspective* (Bhuller and Trevithick-Sutton, 2024), continues to demonstrate the importance of taking a broad, systems thinking lens given that the outcome of a risk assessment requires communicating the risks, which can be to a broad audience (e.g., the entire country). This paper also provides tools to improve effective risk communication and a visual with factors linking the core of the risk assessment and decision-making process and with the broader policy-political-publics space.

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Supplementary article 1: Canadian Regulatory Perspective on Next Generation Risk Assessments for Pest Control Products and Industrial Chemicals

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In 2012, the Council of Canadian Academies published the expert panel on integrated testing of pesticide's report titled: Integrating emerging technologies into chemical safety assessment. This report was prepared for the Government of Canada in response to a request from the Minister of Health and on behalf of the Pest Management Regulatory Agency. It examined the scientific status of the use of integrated testing strategies for the regulatory health risk assessment of pesticides while noting the data-rich/poor dichotomy that exists when comparing pesticide formulations to most industrial chemicals. It also noted that the adoption of integrated approaches to testing and assessment (IATA) strategies may refine and streamline testing of chemicals, as well as improve results in the future. Moreover, the experts expected to see an increase in the use of integrated testing strategies over the next decade, resulting in improved

evidence-based decision-making. Subsequent to this report, there has been great advancements in IATA strategies, which includes the incorporation of adverse outcome pathways (AOPs) and new approach methodologies (NAMs). This perspective provides the first Canadian regulatory update on how Health Canada is also advancing the incorporation of alternative, non-animal strategies, using a weight of evidence approach, for the evaluation of pest control products and industrial chemicals. It will include specific initiatives and describe how this work is leading to the creation of next generation risk assessments. It also reflects Health Canada's commitment towards implementing the 3Rs of animal testing: reduce, refine and replace the need for animal studies, whenever possible.

Keywords: next generation risk assessment, integrated approach to testing and assessment, adverse outcome pathways, new approach methodologies, weight of evidence

INTRODUCTION

Evidence-based decision-making, rooted in robust scientific risk assessments, is paramount for the initial market-approval and subsequent evaluations of registered pest control products and industrial chemicals in Canada. The federal regulatory frameworks governing the life-cycle management of these products provides sufficient flexibility for the responsible regulatory authority to evaluate scientific studies from a wide variety of published and unpublished sources. It also provides an agile approach to considering alternative strategies to health risk assessments and incorporating non-animal technologies, when applicable, for hazard identification. The health risk assessment process itself, a function of both hazard and exposure, is well described in several documents and is aligned with international approaches. These include technical documents, describing program-specific decision-making frameworks (Health Canada, 2021a), and non-technical ones, such as Health Canada's primer on scientific risk assessment (Saner, 2010). Further, in the area of industrial chemicals assessment, efforts have been made to advance the development and implementation of novel scientific assessment approaches through the publication of science approach documents (Health Canada, 2021b). Health Canada has also progressively introduced new methods to effectively identify and address substances of varying concern and continues to update their data requirements (Health Canada, 2013a) thereby enabling them to be well positioned to transition to next generation risk assessments (Krewski et al., 2014).

In 2012, the Council of Canadian Academies (CCA) published the expert panel report on integrating emerging technologies into chemical safety assessment (CCA, 2012). This report was prepared for the Government of Canada in response to a 2009 request from the Minister of Health and on behalf of the Pest Management Regulatory Agency (PMRA). It was the first Canadian report that provided the scientific status on integrated strategies and identified the potential paradigm shift for a more inclusive approach where integrated approaches to testing and assessment (IATA) go beyond using them just for data-poor chemicals (e.g., pesticide formulants and industrial chemicals). The report also included a 10-year vision for the evolution of IATA within the regulatory context and a foundational starting point that included these elements: using a common vocabulary, data platforms and standards, digitization of legacy data, international coordination, stakeholder communication, and functional collaboration. The CCA and other international reports, such as the National Research Council's report (NRC 2007), have been pivotal in establishing the Canadian regulatory approach for identifying, exploring, and implementing IATAs. Some IATAs utilize adverse outcome pathways (AOPs) and more recently new approach methodologies (NAMs). Publications, such as the 2020 article on toxicity testing in the 21st century (Krewski et al., 2020), provide insights on the advances in biological sciences and how these have led to this ongoing paradigm shift. Future perspectives on the continued evolution of toxicity testing to strengthen regulatory risk assessment are also noted, which includes ensuring that any alternative approach adheres to the established health and safety standards required for these products.

This article now provides the first Canadian regulatory update on how the regulatory authorities responsible for pest control products and industrial chemicals are advancing the incorporation of alternative and non-animal strategies. It demonstrates how these program areas have successfully positioned themselves for the next generation of risk assessments by elaborating on early conceptual frameworks. References to recent and key publications are provided along with insights on how these areas have been contributing to this paradigm shift through the establishment and successful maintenance of a strong, multi-stakeholder collaborative approach.

REGULATION OF PEST CONTROL PRODUCTS AND INDUSTRIAL CHEMICALS

Chemical substances, which includes pest control products and industrial chemicals, are stringently regulated in Canada to protect human health and the environment (Health Canada, 2017a). While Health Canada is the responsible federal department for the market approval and

subsequent oversight of pest control products and industrial chemicals, there are two program areas that are accountable for this work. Specifically, Health Canada's PMRA is responsible for pesticide regulation in Canada while, in part, the Healthy Environments and Consumer Safety Branch (HECSB) in collaboration with Environment and Climate Change Canada is responsible for industrial chemicals.

Under authority of the Pest Control Products Act, Health Canada registers pesticides after a stringent, science-based risk assessment, re-evaluates pesticides on the market on a cyclical basis, and is actively involved in national and international science-policy initiatives. As noted in the 2019–2020 annual report, PMRA continues to evaluate pesticides in cooperation with other jurisdictions and over the last 2 years, the Agency's focus has been on a major transformation of its pesticides program (Health Canada, 2021c). The latter is exploring a further integration of the pre- and post-market activities, which includes incorporation of next generation approaches to risk assessment.

The Canadian Environmental Protection Act, 1999 (CEPA, 2019; CEPA) provides the legislative framework for industrial chemicals, including new chemical substances (domestic and imports) as well as substances that are currently on the Canadian market (i.e., existing substances). Leading the world in chemicals management, Canada was the first to systematically categorize or prioritize the 23,000 substances on the Domestic Substances List (DSL) for risk assessment, initiating the Chemicals Management Plan (CMP) in 2006 (Health Canada, 2016a). Risk assessments of the approximate 4,300 priority chemicals were conducted over three phases (2006–2021) and required the development of new methodologies and scientific approaches to continue to effectively deliver an evolving risk assessment program. For industrial chemicals, there is a range of toxicity data available, from data-rich to data-poor, and an ongoing need to prioritize, assess and manage diverse and increasingly complex substances and mixtures. The Government of Canada is also building on the successes of the CMP to renew its approach to chemicals management including follow-up considerations on the report from the House of Commons Standing Committee on Environment and Sustainable Development on the statutory review of CEPA (Environment and Climate Change Canada, 2018).

MODERNIZING APPROACHES TO RISK ASSESSMENT

In comparison to industrial chemicals, pesticides and pest control products are considered data-rich chemicals. The regulatory submissions rely on a prescribed list of data requirements that include several animal studies and often comprise in silico (quantitative-structure activity relationship (QSAR)), in vitro assays, and more recently NAMs (e.g., defined approaches for skin sensitization (OECD, 2021a). Similarly, when considered equally or better suited to measure toxicity, alternate approaches, such as in vitro data, read-across using surrogate data, weight-of evidence (WoE) for substance classes, and QSAR data from internationally accepted models, are examples of frequently accepted NAMs for industrial chemicals.

In contrast, there are no prescribed data requirements for existing substances, under CEPA, and assessments make use of best available data. Accordingly, the program has progressively advanced the use of NAMs from computational modelling, read across and category approaches to more complex evidence integration approaches to identify and address emerging priority substances. Typically, a WoE approach is relied upon by evaluating the results from the alternative approaches along with the totality of evidence, which includes published information. Enriching evidence integration for WoE assessment has been supported through the development of IATA methodologies; endocrine activity has been one area of focus in this respect for the existing substances program at Health Canada. Workflows to assimilate data collected from traditional and NAM sources to generate predictions regarding potential endocrine disruption activity for a subset of chemicals of regulatory interest has illustrated that NAMs can be a protective approach for human health risk assessment (Webster et al., 2019).

The year 2022 marks a decade since the release of the CCA report and significant progress has been made on a variety of NAMs, which includes in silico based approaches. The latter has found the most widespread use and acceptance in regulatory data submission and assessment. To address existing substances in Canada, efforts have focused on validation exercises to increase confidence in the application of a suite of models for the DSL chemical space (Kulkarni and Barton-Maclaren 2014; Kulkarni et al., 2016) as well as contributing to imperative steps forward to promote international harmonization. Key developments have included progress on standardized in silico toxicology (IST) protocols (Myatt et al., 2018; Hasselgren et al., 2019), endorsement of OECD guidance for defined approaches to testing and assessment (OECD 2016a), and grouping of chemicals and read across (OECD 2017). Evolving these approaches

further, cheminformatics-based methods for read across of point of departures (PODs) are being explored to build confidence in quantitative read-across to specific endpoints (Yang et al., 2021).

Notably, in vitro and omics-based approaches are also being explored quite broadly across Health Canada. Specifically, transcriptomics data is currently used in a WoE to better understand chemical mode of action, justify read-across groupings, and fill data gaps (Yauk et al., 2019). Health Canada's CMP phthalate assessment demonstrated that gene expression patterns could be used to support category development and the selection of specific compounds for cumulative risk assessment (Health Canada 2015). Transcriptomics also holds promise in the selection of PODs for prioritization and quantitative risk

assessments. Results from recent case studies focused on flame retardants demonstrated that in vitro transcriptomics data, coupled with in vitro to in vivo extrapolation (IVIVE), provide PODs that are protective of human health and allow for potency ranking (Gannon et al., 2019; Rowan-Carroll et al., 2021). Similarly, quantitative high-throughput screening assays, that provide mechanistic and quantitative data across a broad toxicological space, also have established utility in the assessment of potential for human health risk. Specifically, a multi-agency retrospective case study conducted under the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative demonstrated that in vitro data from the ToxCast program, comprising nearly 1400 toxicological endpoints, could be used to derive points of departure for risk assessment activities (Paul Friedman et al., 2020). Building on the approach and learnings from the collaborative case study, Health Canada published a science approach document providing a rationale and guidance for how to apply the approach as an early screen of potential for risk in the context of the CMP (Health Canada, 2021d).

IMPORTANCE OF MULTI-STAKEHOLDER COLLABORATION

As an OECD member, Health Canada is involved in several initiatives related to IATA, NAMs, and ongoing developments of several technical guidelines. An underlying reason for this international collaboration continues to be rooted in the 3R principles: reduce, refine and replace animal studies, when possible. However, another aspect is the mutual acceptance of data whereby harmonizing requirements provides a common basis for all authorities (OECD, 2021b).

To allow for broader acceptance of IATAs, NAMs, and no longer routinely requiring specific animal assays for toxicity testing, Health Canada continues to rely on the North American Free

Trade Agreement (NAFTA) Technical Working Group on Pesticides (TWG) and the Canada-United States Regulatory Cooperation Council (Health Canada, 2016b; 2020; RCC). This cooperation has resulted in successful collaboration with stakeholders and global experts from all areas including Industry, Academia, and Non-Governmental Organizations. Health Canada's participation also provides an opportunity to provide guidance so that outputs are fit-for regulatory purpose and build regulatory, public, societal, and scientific confidence in NAMs. This is consistent with the 2018 Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) strategic roadmap for establishing new approaches to evaluate the safety of chemicals and medical products in the United States (ICCVAM, 2018). Individual project plans are also built upon the strategy noted in the CCA report by first focusing on retro-analysis and less complicated assays such as the acute toxicity studies (Health Canada, 2017b; Linke et al., 2017; Allen et al., 2021). The NAFTA TWG has also been used to develop science-policies, which are then brought for broader acceptance through OECD. For example, built on the NAFTA QSAR document (NAFTA TWG, 2012), which was primarily focused on pesticides, the OECD guidance document expanded to cover industrial chemicals with added focus on mechanistic considerations (OECD, 2015). Similarly, the NAFTA developmental neurotoxicity study guidance (NAFTA TWG, 2016) as well as PMRA's guidance document for waiving or bridging of mammalian acute toxicity tests (Health Canada, 2013b) were also used as the foundational pieces for completed (OECD, 2016b) and/or ongoing OECD technical guidelines.

With parallel goals in mind, industrial chemicals have the additional pressures of lack of data, aggressive priority setting and assessment mandates. In turn, RCC has also played a role in advancing assessment methods for Health Canada's industrial chemicals programs (Health Canada, 2017c), as has the OECD Hazard Assessment Programme related to the improvement and acceptance of approaches intended to minimize the need for animal testing. Foundational work upon which HECSB continues to build include concepts, guidance and lessons learned related to IATA (OECD, 2020; OECD, 2021c) and guidance on physiologically based kinetic models for regulatory purposes (OECD, 2021d). Considerable momentum for regulatory application of NAMs has been gained through research regulatory partnerships, nationally and internationally, including regulatory, academic, and stakeholder communities. The APCRA network, co-led by the US EPA, Health Canada and the European Chemicals Agency (ECHA), is another example of a successful collaboration between international and intergovernmental

bodies (Kavlock et al., 2018). The Friedman et al. and Health Canada work highlighted above are examples of complete progression from collaboration to development of a Canadian-specific approach. It is important to also note that partnerships between risk assessment and research experts to achieve the goal of demonstrating robustness, reliability and readiness of non-animal based approaches in regulatory applications is also a model of interest beyond the chemicals assessment community (Chauhan et al., 2021).

MOBILIZING TEAMS AND ESTABLISHING THE REGULATORY PIVOT

The transition from exclusively relying upon conventional testing approaches to inclusion of NAMs requires a high level of engagement and collaboration given the pivot required to consider incorporating such approaches in regulatory decision-making. Specifically, some complex issues to address include validation, interpretation and application frameworks, guidelines for NAMs or other disruptive technologies, and ethical considerations for using big data (Mittelstadt and Floridi, 2016). There are also legal considerations along with how the public and society will view this transition. While these areas are beyond the scope of this perspective, they continue to be part of ongoing discussions. This section will now focus on the approaches used to mobilize Health Canada scientists.

The model used to engage regulatory scientists and establish the pivot for exploring non-animal testing strategies has relied upon an adaptation of the design-thinking approach (**Figure 1**). Briefly, a top-down approach that relies on the user experience (UX) with conventional assays required for regulatory purposes is the starting point. This insight is then incorporated from concept through to application using a process that understands the data gaps/uncertainties, explores approaches through collaboration, and materializes by learning from successes and failures from the UX perspective. The implementation is then achieved through publication to allow for broader distribution and potentially acceptance of the alternative approach.

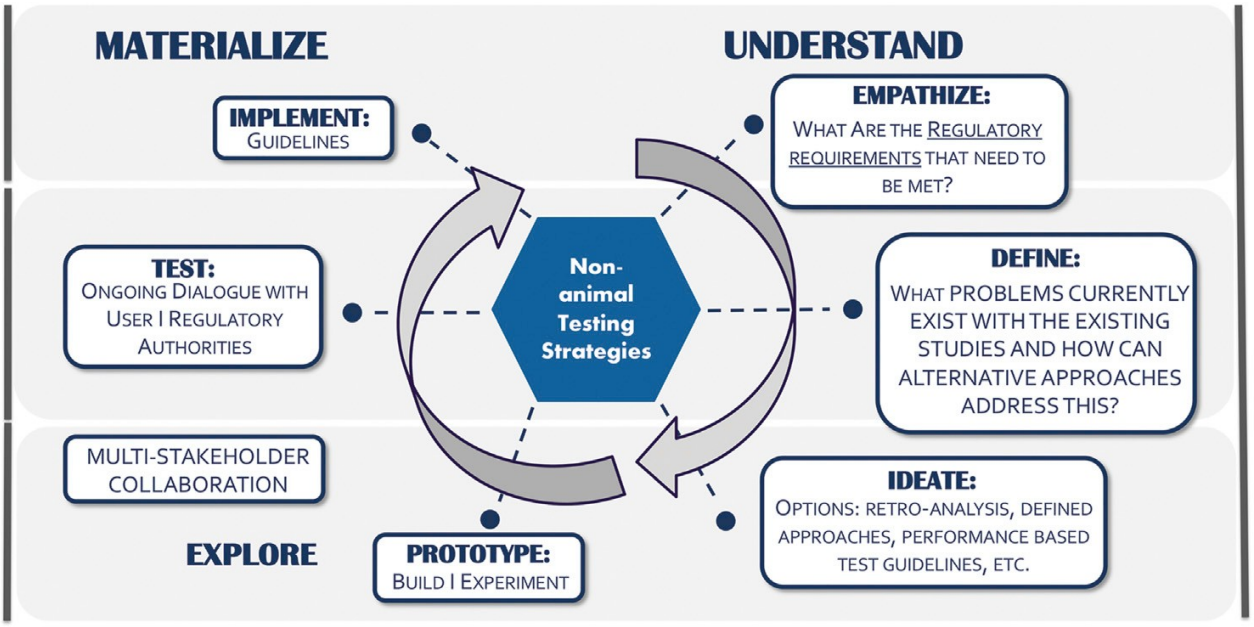

Figure 1 | Non-animal testing approaches: Using design thinking.

Translating case study findings into applications, using a framework that incorporates both innovation and acceleration, has also been extremely useful in the exploration and implementation of NAMs (**Figure 2**). Through the use of practical case studies designed to address specific regulatory needs, methods can be informed by proof of concept research and lessons learned to develop best practices and guidance for the application of fit-for-purpose approaches. Consistent with focused efforts internationally, Health Canada has as an objective to enhance innovation and risk assessment modernization to maintain a world-class chemicals management program. The overarching program and risk assessment principles that have been key for success to date must be reinforced and incorporated to effectively provision the proposed path toward modernization. A multi-pillar approach is envisioned for the transition to modernization of some elements of the program through the accelerated development and acceptance of new methods, taking into consideration a wide range of use and decision contexts. Importantly, the aim is to bring all of these elements together in order to use the most relevant data for the protection of human health and the environment.

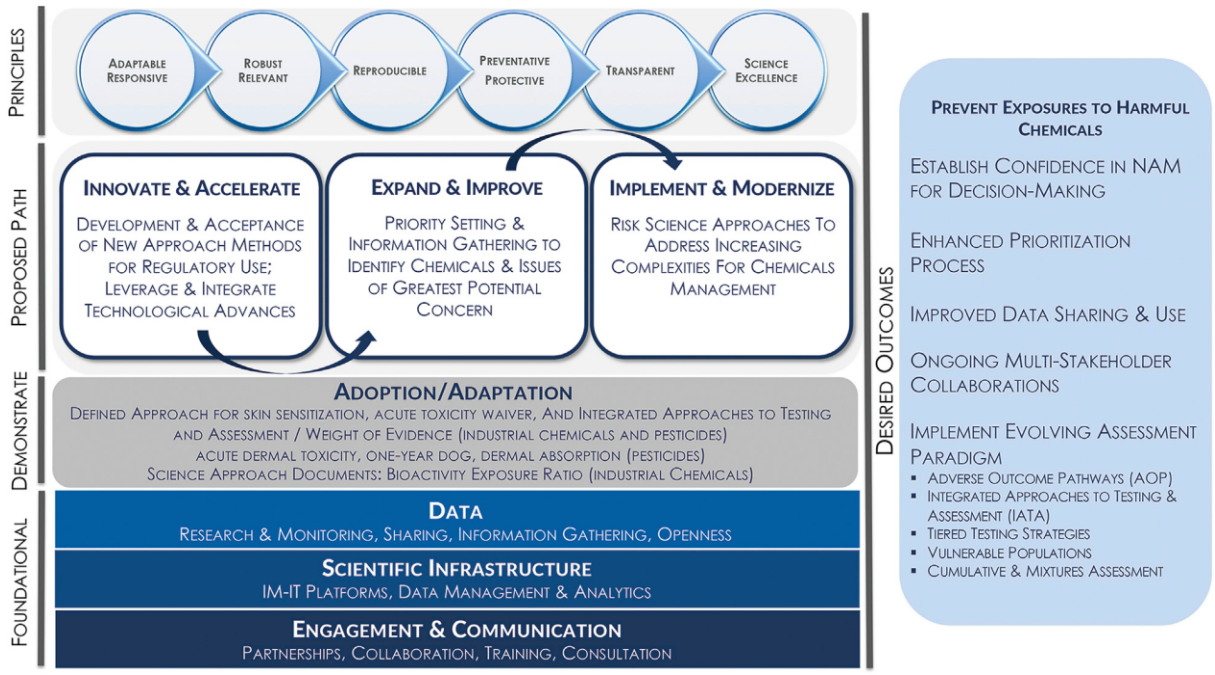

Figure 2 | Innovate and accelerate use of NAMs: Translating case study findings into applications.

DISCUSSION AND NEXT STEPS

This perspective provides the first Canadian regulatory update on how Health Canada is advancing the incorporation of alternative, non-animal strategies for the evaluation of pest control products and industrial chemicals. It includes specific, multi-stakeholder initiatives that are aligned with the Department's commitment towards implementing the 3Rs of animal testing, whenever possible. While beyond the scope this paper, it notes that the incorporation of alternative approaches includes critical discussions around challenges for regulatory implementation. Building upon best practices, such as communication of NAMs through standard regulatory platforms (e.g., guidance documents) along with publications in peer-reviewed journals, presentations at conferences, and more recently through social media, will also continue to be pivotal for advancing this work. Decades of international efforts have gone into developing legal frameworks and data requirements. While NAMs are largely in the early phases, conventional strategies such as the development of OECD guidelines, defined approaches, IATA case studies and reporting formats will continue to play a key role. Many regulators are also currently relying on testing conducted by governmental or academic research groups to develop proof of concept case studies related to the incorporation of NAMs. With

established methods and acceptance criteria, broad scale testing will ultimately require industry uptake (similar to what is currently in place with traditional testing methods).

Multi-stakeholder collaboration will also continue to be important in the broader acceptance of NAMs and in enabling a better understanding of what is required for regulatory purposes. This includes initiatives led at the national level by regulatory authorities along with ensuring that the regulatory bodies continue to be engaged in key activities led by organizations such as, but not limited to the Health and Environmental Sciences Institute (HESI), PETA Science Consortium International (PSCI), and NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). There are also several academic-led initiatives along with research and consulting firms that are immersed in developing models, which includes open source. This includes the Canadian Centre for Alternatives to Animal Methods (CCAAM) and the Canadian Centre for the Validation of Alternative Methods (CaCVAM), which aims to develop, validate, and promote non-animal, human biology-based platforms in biomedical research, education, and chemical safety testing.

There is also a need to bring all of this work together for regulatory risk assessments and decision-making. This is where frameworks, such as the Next Generation Risk Assessment as described by Krewski et al., 2014, and the recently enacted HESI committee that is responsible for the project titled Transforming the Evaluation of Agrochemicals will play a key role, in addition to other ongoing IATA and NAM-related activities at the national and global level.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YB and TSB-M designed the concept of the manuscript, the formulation of figures and wrote the manuscript. All authors contributed important intellectual content and helped in the writing and revisions of the article. All authors read and approved the final manuscript.

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Supplementary article 2: Building knowledge of NAMs through risk science

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ABSTRACT

The 12th World Congress on Alternatives and Animal Use in the Life Sciences provided a platform for mobilizing and exchanging knowledge on the advancements in science and technology. It also provided an opportunity for experts to discuss how to accelerate the adoption of new strategies and tools. One of these recommendations advocated the need to bridge the gap between the next generation of scientists who have yet to learn about 'New Approach Methodologies' (NAMs) and the current generation of thought leaders who have pioneered the development and validation of these non-animal approaches to toxicological risk assessment. Consequently, a mini-course, held at Canada's University of Ottawa, was developed for students, aged 13–16 years, interested in learning about risk science and how NAMs can be used to inform human health risk assessment. This course also served as a platform for creating a virtual training roadmap, provided in this paper, thereby bringing this knowledge to a broader audience of learners who are establishing their careers in the field of risk science.

Keywords: Risk science, NAMs, World congress, Knowledge transfer, Next generation

1. Introduction

Globally, there are ongoing multi-stakeholder initiatives related to non-animal toxicity testing strategies - commonly referred to as new approach methodologies (NAMs). These include the development and availability of several NAMs providing similar if not better results when compared to the traditional animal bioassay (Gilmour et al., 2022; OECD, 2023). The shift towards using these alternative solutions reflects advances in science and technology, along with a commitment to move towards strategies where animals are no longer required and consequently not harmed. Several roadmaps and reports are also available to build scientific and regulatory confidence in these approaches (Clippinger et al., 2022; Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), 2018; National Academies of Sciences Engineering and Medicine, 2023; United States Food & Drug Administration (FDA), 2017; van der Zalm et al., 2022). Regulatory bodies are also committed to incorporating NAMs as a means of replacing, reducing, or refining animal studies (Avila et al., 2020; Bhuller et al., 2021; Stucki et al., 2022; Villela and Machado, 2022). The US Environmental Protection Agency (EPA) has also recently conducted an in-depth study of the value of information provided by a new short-term EPA transcriptomic assessment product showing considerable promise as an alternative to long-term animal toxicity tests (Devito, 2024).

The World Congress on Alternatives and Animal Use in the Life Sciences is an example of a global platform designed to share knowledge and build confidence around the application of NAMs (e.g., for regulatory purposes). During the 12th World Congress (WC-12), held in Niagara Falls, Canada in 2023, experts shared their knowledge on the advances in non-animal strategies and provided proposals for accelerating the adoption of NAMs. One of the recommendations included bringing NAMs to the attention of next generation researchers and leaders (Bhuller et al., 2024b). This transfer in knowledge would serve to bridge the gap between creators/users of these alternative approaches and young leaders who are establishing their career pathways and thus, may not be aware of NAMs.

2. Knowledge transfer for next generation learners

Each year, Canadian students, aged 13–16 years, attend mini-courses hosted by the University of Ottawa and Carlton University on diverse topics. In 2024, twenty students attended a 5-day course entitled *Let's Talk About Risk Sciences,* where they gained experience and knowledge about how modern risk science is making increasing use of NAMs (Tyshenko et al., 2024).

Students were introduced to various concepts and the fact that risk is part of daily life. **Table 1** summarizes the key terms brought to their attention.

Table 1
Key terminology.[a]

Term	Definition
Hazard	The intrinsic property of an agent making it capable of causing adverse effects to occur in humans or the environment under specific conditions of exposure.
New approach methodologies	A term used to encompass non-animal methods, alternatives, and technologies which reduce reliance on traditional animal toxicology studies (Bhuller et al., 2024b).
Risk	A measure of both the harm resulting from being exposed to a hazardous agent, together with the likelihood that the harm will occur.
Risk analysis	A distinct science covering the risk assessment, management, and communication processes and how this relates to other factors such as risk perception, governance, and policy.
Risk science knowledge	Research, methodologies, and knowledge to learn and improve specific risk activities (Type A) or develop generic or fundamental (Type B) concepts such as novel risk principles and approaches.

[a]Unless specified, the definitions are based on the Society of Risk Analysis Glossary (Society of Risk Analsysis, 2024) and Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks (Health Canada, 2000).

When summarizing the key take-home messages, all students indicated they did not know about NAMs prior to taking the course, which included the availability of microphysiological systems or organ-on-chip (Hartung et al., 2024; Smirnova and Hartung, 2024). They also appreciated the link between risk science knowledge and risk analysis through continuous learning and improving (Aven, 2018, 2020). Students demonstrated their understanding of the course material based on how they performed and discussed their views through various activities. For example, creating a poster demonstrated the importance of effective risk communication, visually and in writing, and how the information must be tailored to the audience. Another activity involved preparing a briefing note which provided an opportunity to see how policy (what needs to be put into action), politics (the spokesperson was the mayor), and public (there were three distinct audiences to choose from) intersects with science, and, again, the need to adapt risk communication messages to the target audience. All participants also supported the use of the primer (Saner, 2010) as the starting point for discussing risk and learning the four steps of the risk assessment process.

When discussing systems thinking and the use of the iceberg model (Bhuller et al., 2024a), collaboration was identified as an important element. Further, all students had a better appreciation of how NAMs requires multistakeholder approaches, strong collaboration, and

effective communication. Using the analogy ‘be an astronaut’ also helped in visualizing the importance of all the systems and connections in the risk assessment-risk management paradigm.

3. Going beyond the mini-course on risk science

An underlying objective of this in-person, mini-course was to subsequently translate the curriculum, content, and lived experience into a virtual tool with links to the publicly accessible material (**Table 2**). The two co-authors, Morgan Gale and Fevrelyn Yadao, were also students from the mini-course who agreed to review this paper based on their in class experience and understanding of the course/training material. Consequently, this resulted in the creation of a virtual training roadmap, which starts with the concept of scientific risk assessments (Topic A) and then data principles (Topic B) with a general overview on risk and data, respectively, prior to embarking on animal welfare and testing (Topic C) and the paradigm shift towards NAMs (Topic D). The subsequent areas (Topics E to G) capture the remaining and pertinent areas related to risk

analysis. The overall design allows anyone interested in building their knowledge on NAMs, through risk science, to use the virtual training roadmap in the same, sequential manner used during the mini-course; i.e., one would start their virtual risk sciences training with Topic A: A Primer on Scientific Risk Assessment at Health Canada (Saner, 2010). The table also includes the links for the relevant learning material.

Table 2:
Virtual training roadmap (Topics A - G)

Topic A: Primer on scientific risk assessment
Read the primer and the story of a fictional character, Sophie, whose interactions with various products provides a mechanism for sharing an overview of risk and the four steps of a scientific risk assessment process: (i) Identify the hazard; (ii) Characterize the hazard (dose-response and severity: mild, medium, moderate, or severe); (iii) Assess the exposure (margin and likelihood); and (iv) Characterize the risk (low, medium, or high). *https://www.canada.ca/en/health-canada/services/science-research/reports-publications/about-science-research/primer-scientific-risk-assessment-health-canada-health-canada-2010.html
Topic B: Key data principles
Risk assessments rely on data which creates information, evidence, and eventually knowledge. Use the links to view two videos on these key data principles: (i) FAIR: Findable, Accessible, Interoperable, and Reusable (Martínez-Lavanchy, 2019)* and (ii) the First Nation Principles of OCAPTM: Ownership, Control, Access, and Possession (First Nations Information Governance Centre, 2014).** These principles (along with CARE: Collective benefit, Authority to control,

Responsibility, and Ethics) are important, for example, when relying on existing data to help reduce the need for conducting additional animal studies.

*https://www.youtube.com/watch?v=5OeCrQE3HhE
**https://www.youtube.com/watch?v=y32aUFVfCM0&t=120s

Topic C: Animal welfare and testing

Identifying and characterizing hazards includes reliance on animal studies and NAMs. View these videos to understand the paradigm shift towards NAMs (Hilton et al., 2023) while learning about animal welfare and the reliability of animal testing for human health risks assessments: (i) Save Ralph (Humane Society International, 2021)* and (ii) Is animal testing reliable? (Humane Society of the United States, 2024)**

*https://www.youtube.com/watch?v=G393z8s8nFY
**https://www.youtube.com/watch?v=nVoPpuYsMUU

Topic D: Risk science, risk analysis, and NAMs

With an understanding of the risk assessment process and the role animal testing plays in identifying and characterizing the hazard, please view the video on What are Risk Analysis and Risk Science about? (Society of Risk Analysis, 2021)*

*https://www.youtube.com/watch?v=wDUphVbzEcw&t=60s

Now, refer to **Figure 1** and how an astronaut's perspective provides an opportunity to observe all the various components including NAMs. As shown in this figure, risk science and analysis provide the opportunity to generate knowledge through 'learning' and 'improving'. A good example is the shift from using animal studies to NAMs by: (1) supporting scientific knowledge generation (Type A risk science knowledge) for specific activities such as a new approach method/test guideline for skin sensitization (OECD, 2023); and (2) covering scientific knowledge for developing overall (Type B (generic or fundamental) risk science knowledge) concepts, principles, approaches, methods, and models for understanding, assessing, characterizing, communicating, managing, and governing risk. Consider, for example, reducing reliance on vertebrate animal testing under the Strengthening Environmental Protection for a Healthier Canada Act (Government of Canada, 2023).

Topic E: Risk communication & systems thinking 'lens'

Read the article Risk communication: lessons from an ethnographic, pragmatic, and Canadian regulatory perspective to understand the importance of effective communication, taking a systems thinking lens (astronaut's view) throughout the risk assessment process, and applying the tool BroadCAST-3Cs (Bhuller & Trevithick-Sutton, 2024).*

*https://doi.org/10.3389/fcomm.2024.1235055

Refer to **Figure 2** and the application of BroadCAST-3Cs to help create a visual communication/poster of a novel risk issue. The poster is designed so that the key messages - do not eat and danger - are provided in a clear and concise manner. The context and information are also relayed using the visual and written medium, which provides a mechanism to relay the information to a broad audience. 'Do not eat! Ne manage pas!', as the core message, are also the first set of words that appears in the poster.

Topic F: Conducting a dietary health risk assessment

Understand some of the technical concepts, such as no observed adverse effect level (NOAEL), composite assessment factor (CAF), acceptable daily intake (ADI), and margin of exposure (MOE), required for conducting a basic risk assessment to determine if there is a dietary risk from consuming a food product with substance x. Provided below is the data you need for this risk assessment.

Hazard identification and characterization
Based on the animal studies and NAMs, the NOAEL = 30 mg/kg bw/day. You intend on accounting for the difference between extrapolating from animal data to humans (10X) and variation within species (10X). So, the CAF = 100 (10 x 10) and the ADI = 0.3 mg/kg bw/day (i.e., 30 mg/kg bw/day ÷ 100).

Exposure
The amount of substance x in the product is 0.003 mg/kg bw/day and you have determined a strong likelihood of human exposure to this product. Consequently, you now have to determine if there is a sufficient MOE between this amount and the calculated ADI.

Risk assessment
Is the dietary risk low, medium, or high? (Hint: Your calculation should result in a percent value of 1% of the ADI)

Topic G: Risk decision-making

While the focus of this course is to understand risks and how this relates to NAMs, it is important to understand how the final risk decision depends on additional factors, such as effectively communicating the science (risk assessment) to various audiences.

Using BroadCAST-3Cs and a recent news article on a health risk issue, prepare a one-page briefing note comprised of these three sections: (i) Title/issue - this is your headliner; (ii) Key points - 3 to 5 bullets explaining the issue/context and what is the hazard, exposure, and risk; and (iii) Contact and links for additional information.

The note is for a City Mayor who will communicate the issue to one of these audiences: university students, seniors in a retirement home, or women residing in a hostel. Please adapt your writing style based on the audience. For example, using scientific and technical words would suffice for university students; however, this approach is not appropriate for seniors in a retirement home.

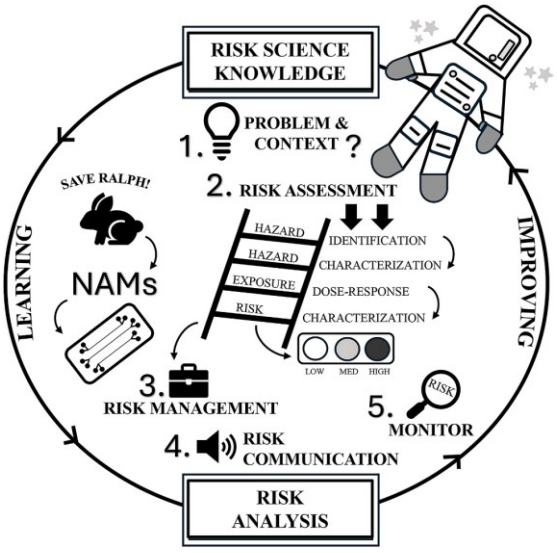
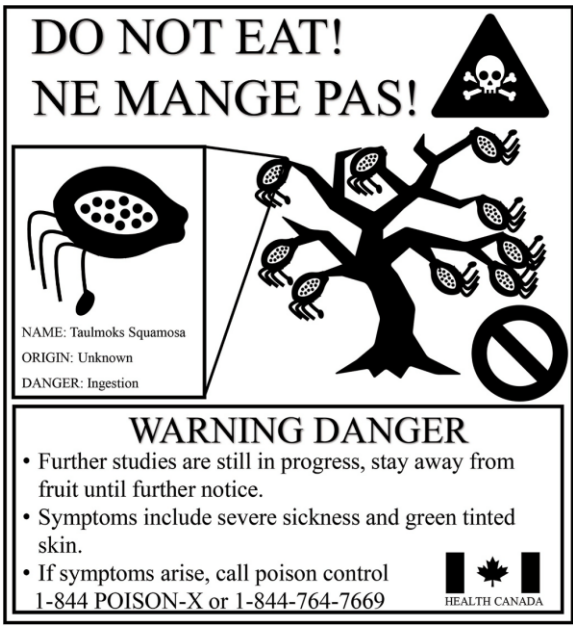


Fig. 1. Taking a systems thinking lens

By being an astronaut, one can view the various components, interactions, and how risk science knowledge and risk analysis work together when it comes to 'learning' and 'improving' NAMs. Image created for the class participants by the lead author (YB)

Fig. 2. Visual risk communication

An example of a poster using BroadCAST-3Cs to visually communicate information on an invasive fruit species; adapted with permission of the mini-course participants. Participants also discussed how further studies can include NAM



4. Conclusion

This paper demonstrates how the knowledge transfer, using a minicourse, successfully addressed one of the recommendations from the WC-12: Involve our next generation of leaders. Our goal, through the publication of this work, is to address some of the other recommendations, such as broadening the 'WC-NAM community' and building next steps for collaboration and engagement by providing the content and experience from the in-person, mini-course. By creating and sharing the virtual training roadmap, with open access to information in the public domain, we hope to reach an even broader audience of learners who are interested in building their knowledge about risk science and NAMs. For those who are embarking in a new career related to risk science, we hope you will find the virtual roadmap clear, concise, and useful. The topics, objectives, activities, and examples are intended to be stimulating as you take on the role of an 'astronaut' in viewing and understanding the world of risk science and analysis, and how this knowledge is essential for the adoption of NAMs.

CRediT authorship contribution statement

Yadvinder Bhuller: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **Morgan Gale:** Writing – review & editing. **Fevrelyn Yadao:** Writing – review & editing. **Daniel Krewski:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that there was no funding for this work and they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Supplementary article 3: Risk communication: lessons from an ethnographic, pragmatic, and Canadian regulatory perspective

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In a regulatory context, it is important to understand how effective risk communication fits into the overall risk assessment, management, and decision-making process. This includes recognizing the intersections between risk analysis and the 3Ps: policy, politics, and publics, and understanding the barriers to effective communication. Risk communication is especially challenging when it requires the audience to follow and act on authoritative information or advice. Risk communicators must factor attributes such as risk perception, tolerance, and behaviors, and tailor the delivery of messages to diverse audiences. This paper captures the discourse from an intradepartmental workshop on risk communication with participants from Health Canada and the Public Health Agency of Canada. The workshop provided an opportunity to discuss and share references to existing frameworks, pertinent documents, and examples of

effective risk communication strategies based on the authors' ethnographic and pragmatic experiences. The workshop aimed to strengthen risk communication by better understanding the value in collaborating with interdisciplinary teams, applying a systems thinking lens, and finding opportunities to experiment and evaluate risk communication strategies for regulatory purposes.

Keywords: Health Canada, regulatory context, risk communication, ethnographic, pragmatic

1 Introduction

1.1 Background & regulatory context

Health Canada is responsible for maintaining and promoting the health of people living in Canada by regulating and communicating risk information on diverse products such as pharmaceuticals, vaccines, medical devices and natural health and pest control products (Government of Canada, 2014a). The organization's governance structure and legal framework supports the various programs and activities at the national/federal level.

The COVID-19 pandemic provides an excellent example of the government's responsibilities for addressing health risks at the federal, provincial/territorial, and local levels (Government of Canada, 2022c). Under the *Food and Drugs Act,* Health Canada, federally, held responsibility for evaluating, approving, and communicating risk-related information on the messenger RNA vaccines. Health Canada also worked alongside portfolio partners in the Public Health Agency of Canada (PHAC), who were responsible for implementing public health measures while working in collaboration with the provinces and territories (Government of Canada, 2022a,b) Health Canada has an overarching, health risk decision-making framework (Health Canada, 2000), a strategic risk communications framework (Health Canada, 2006), and a range of tailored, program area-specific documents on risk decision-making (Health Canada, 2000, 2012; Government of Canada, 2013a,b; Health Canada's Consumer Product Safety Program, 2015; Bureau of Microbial Hazards, 2017; Pest Management Regulatory Agency, 2021). *A Primer on Scientific Risk Assessment at Health Canada* (Saner, 2010) provides additional perspectives on established risk assessment processes while publications on next generation risk assessments (Bhuller et al., 2021; Stucki et al., 2022) show Health Canada's commitment toward more modern approaches to evaluating risks.

1.2 Risk communication

Health Canada's health risk decision-making framework defines risk communication as: "Any exchange of information concerning the existence, nature, form, severity or acceptability of health or environmental risks" (Health Canada, 2000). This overarching decision-making framework is also integrated in Health Canada/PHAC's *Strategic Risk Communications Framework and Handbook*, which provides guiding principles, a seven-step process, and a detailed handbook for communicating risks (Health Canada, 2006).

Health Canada communicates risks through product-specific information, such as labels, inserts, and monographs, as well as messages provided using other platforms (e.g., social media). For each communication, the message is tailored for the audience (Council of Canadian Academies, 2015; Lee and Lee, 2022). This presents one of the greatest challenges in communicating risks as audiences can be extremely broad and heterogeneous. Consequently, the communication modalities need to be diverse and flexible so that they can go from two-way to more complex approaches involving "multi-way" communication. This requires accommodating a varying degree of knowledge, perceptions, attitudes, and behavior of all parties involved (Balog-Way et al., 2020). Further, the ethical (respect) and instrumental (reciprocity) imperatives for effective science communication, and the importance of recognizing the audience's reaction, can also improve clarity and delivery of a message (Moore, 2022).

Some of the Canadian regulations include requirements for communicating risks to help people make informed decisions. For example, *Division 5* of the *Food and Drug Regulations* describes the requirements for human clinical trials. *Section C.05.010* of these regulations provides requirements for communicating risks and anticipated benefits arising from participating in a clinical trial. A published guidance document further expands and clarifies the intent of these regulations (Health Canada, 2022a). The challenge is that policies and guidance documents can make the presentation and language more technical. Further, as enforcement activities are typically focused on the regulated industry, certain risk communication products, such as product labels, are also legally enforceable. Therefore, risk communication, in these instances, is intentionally more rigid, when compared to other types of messages.

2 Role of risk science

Risk science provides a mechanism to generate knowledge based on the information acquired from the multiple dimensions of risk analysis (i.e., from assessing to managing and

communicating risks). This includes identifying gaps in current approaches to communicating risks and how to address them. It can also play an integral role in developing or modernizing risk-based regulations, policies, research, and communication approaches to better reflect the current processes and methodologies for risk analysis (Krewski et al., 2014; Aven, 2018, 2020).

Knowledge mobilization and translation are also an integral component for sharing best practices (Graham et al., 2006; Health Canada, 2017). This includes insights from applying a risk science-based mindset to understanding and improving current approaches to communicating risks. At Health Canada, this extends to staff-driven initiatives aimed at enhancing the capacity, reputation, and overall excellence of organization's workforce. Examples of these endeavors include the *Task Force on Scientific Risk Assessment* (Health Canada, n.d.) and a working group on developing and sharing learning opportunities around science literacy and communication (e.g., the *Workshop on Risk Communication* described in this paper).[1] Another example are ongoing collaborative initiatives aimed at clarifying the role of risk analysis, risk science knowledge, and understanding the underlying elements of contemporary and future risk decision-making at Health Canada. One of these elements is the principle of communicating in an effective way, throughout the risk decision-making process (see **Figure 1**; Health Canada staff, personal communication, February 17, 2022).

Effective risk communication ". . . involves determining the types of information that interested and affected parties need and want, and presenting this information to them in a useful and meaningful way" (Health Canada, 2000). Dr. Vincent T. Covello's *Communicating in Risk, Crisis, and High Stress Situations: Evidence Based Strategies and Practice* provides additional and detailed insights on the principles, theories, tools, and techniques for communicating risks (Covello, 2022). Risk communication is also an integral component of emergency preparedness and response. Therefore, publicly available and reputable manuals and tools [e.g., the *Crisis & Emergency Risk Communication* platform (Centers for Disease Control and Prevention, n.d.)] and models designed for spokespersons [e.g., the *IDEA* model (Sellnow and Sellnow, 2019)] further strengthen effective communication while complementing the guidance provided in the *Strategic Risk Communications Framework and Handbook* (Health Canada, 2006).

[1]This working group is led by Dr. Colleen C Trevithick-Sutton and the workshop was delivered by both authors.

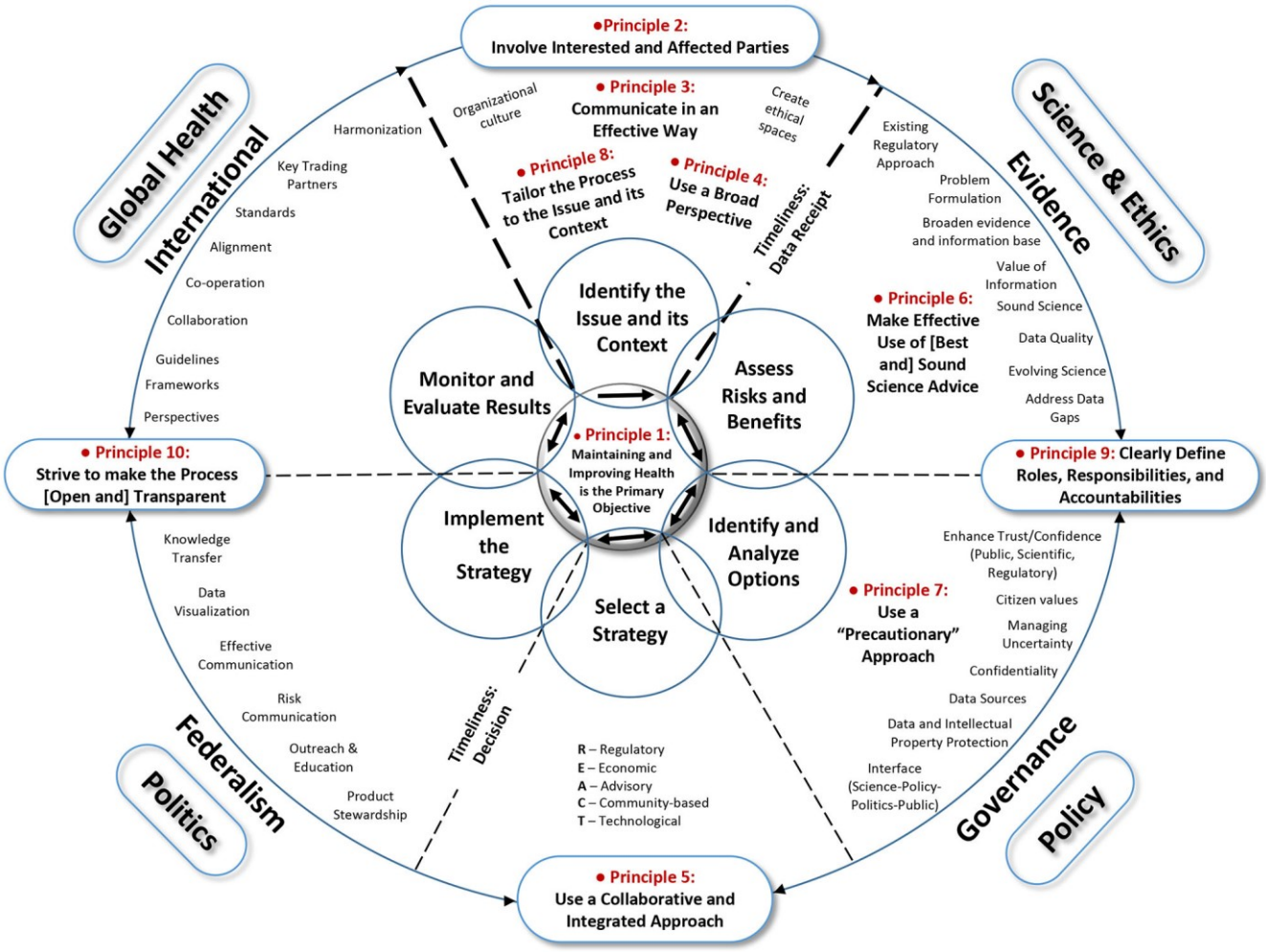

FIGURE 1: Integrated risk decision-making. This visual incorporates *Health Canada's Decision-Making Framework for identifying, assessing, and managing health risks* into a sphere with broader contextual factors. At the center/core of the image is Health Canada's mandate (principle 1) with the layers of attributes relevant to decision-making around it. The importance of communicating in an effective way (principle 3) is relevant from the beginning of the decision-making process (first slice) and then throughout the decision-making process.

When determining the most "useful and meaningful way" for communicating risks effectively, risk communicators should also consider risk science-based knowledge on how to strengthen the messaging through visualizing the science. For example, Lee and Lee (2022) showed how participants in a study recalled more information and had favorable attitudes toward genetically modified food when the science news was presented using infographics. It is also useful to consider less contemporary material, such as the National Research Council's *Improving Risk Communication*, as these documents provide historical contexts and can help inform what attributes for communicating risks have not changed (National Research Council, 1989).

3 Workshop objectives & key messages

The virtual workshop (Microsoft Teams) provided an interactive venue for discussing effective risk communication considerations and best practices. The event engaged the scientific, regulatory, and research community across Health Canada and PHAC, and over 200 participants attended the session.

The workshop's format included an armchair discussion (between the two authors) followed by an open session where the principal author addressed the top ten pertinent questions raised by the participants and collected using Slido.com (**Table 1**). Based on the participants' feedback during the workshop, this format was well received and supported the sharing of strategies for effective risk communication.

Table 1: Top 10 questions

1. How do you communicate when risk is uncertain? How do you accurately communicate when risk is changing?
2. Although risk can often be calculated objectively, it is often perceived subjectively. How can we overcome these differences in short, one-off communications?
3. How can one be proactive in our messaging to address those sharing counter messages/misinformation to the public while being transparent in communicating risks?
4. How does one deal with a situation where your audience has a deep level of mistrust against the source of information (e.g., government, drugs/chemicals, industry, etc.)?
5. Many have emotional reactions when talking about risk. What is an elevator pitch to leaders to successfully communicate without being seen as "fear mongering"?
6. How does behavioral science work in today's age of social media, vs. in the "old days" where people had far fewer avenues of information?
7. How to communicate the difference between hazard and risk and what is best approach to communicate risk when there are many factors that affect risk?
8. What is the most common and experienced misunderstanding about risk? How can we reduce misunderstandings?
9. There is tension between policy and science at times, conflicting information overload, and polarized views of issues—what is prioritized or deemed a risk?
10. What are common issues new science/risk communicators have? Are there any quick recommendations on how to deal with these issues?

The objectives of this workshop were to: (i) engage staff from Health Canada and PHAC interested in learning more on risk communication at Health Canada, and (ii) use the *Strategic Risk Communications Framework and Handbook* as a starting point for a broader discourse on communicating risks. The key points discussed during this workshop are summarized below using four discrete themes and includes information addressing the ten questions raised by the participants during the workshop.

3.1 Consider a holistic, systems thinking approach

Complex health and environmental issues, such as the opioid crisis (Belzak and Halverson, 2018), require collaborative efforts and governance from all sectors of society and levels of government. Systems thinking, defined as ". . . seeing how things are connected to each other within some notion of a whole entity" (Peters, 2014), provides a holistic strategy for decision-makers to consider multiple perspectives necessary for addressing these types of wicked problems.

Using a systems thinking lens, **Figure 1** shows how Health Canada's risk management decision-making process is integrated through various steps (visualized as circles) which are further positioned inside a broader system of elements (visualized as slices and bubbles with text). The significance of systems thinking is the ability to recognize the complexity, intersections, and interactions of the overall system and how an impact in one area can affect another or the entire decision-making process. Further, systems thinking and tools to mobilize additional knowledge, such as causal loop diagrams (Haynes et al., 2020), provide insights which could assist in optimizing the strategy for addressing the risk issue. For example, an international decision to ban a particular product could trigger the first step of the risk management process (i.e., identify the issue and its content) at the national level. Once the process starts, a systems thinking approach could help determine the strategy for communicating the risks. For complex issues this includes considering a Pan-Canadian approach and collaboration at all levels of Government (i.e., Federal, Provincial/Territorial, and Local). A systems thinking lens also provides an opportunity to adapt the message based on an understanding of the science behind human behavior and attributes such as risk perception and tolerance (Krewski et al., 2006; Council of Canadian Academies, 2015; Kelly and Barker, 2016).

Health Canada (2000) has historically relied on this type of broad thinking and collaborative approach and the federal government's decision to re-label certain over-the-counter cough and cold products to no longer permit the use of certain products in children under 6 years of age provides one example. To aid in communicating this decision, Health Canada collaborated with various sectors of society, including the public. Further, each sector also discussed their role in delivering the message once the revised labels were in the marketplace (Health Canada, 2008, 2023; Shefrin and Goldman, 2009). More recent examples include the federal approach toward addressing antimicrobial resistance (Government of Canada, 2014b; Public Health Agency of Canada, 2015, 2017), incorporating new approach methodologies into risk assessment (Bhuller et al., 2021; Bury et al., 2021; Clippinger et al., 2022; Gilmour et al., 2022; Stucki et al., 2022; Van Der Zalm et al., 2022), and the management of the COVID-19 pandemic (Government of Canada, 2022a,b,c).

Some of the challenges of taking a systems thinking approach include the time, resources (both human and financial), and governance structure required to establish and maintain the collaborative space (Trochim et al., 2006; Boswell et al., 2021). Another challenge is effectively communicating risks within an organization when collaborating with diverse programs. Consequently, while developing strategies for communicating risks externally, sufficient time is also required to ensure a mutual, internal understanding.

While systems thinking is not required for all health and environmental risk issues, applying a systems thinking lens can help guide complex issues (Peters, 2014; Gates, 2016). Further, for global public health risks, systems thinking can provide mechanisms for incorporating agile approaches to knowledge mobilization by developing concepts through experimentation (Haynes et al., 2020). For example, improving the communication of risk within an internal and interdisciplinary team using several rounds of the (*broken) telephone game.* For those unfamiliar with this game, each person whispers a message to their immediate neighbor; at the end of the line, the last person says the message aloud to the room. In this example, members of an interdisciplinary team relay the risk communication message with a goal for making the outcoming response less technical. This type of exercise helps guide a team's understanding of choosing practical and easily understandable words and language for use in communicating risks.

3.2 Incorporate BroadCAST-3Cs

Experts in risk communication have published key attributes, principles, and characteristics that can generate and strengthen messages (Health Canada, 2006; Lundgren and McMakin, 2013; Council of Canadian Academies, 2015; Aven, 2020; Covello, 2022; Friedman and Rogers, 2023; Peters, 2023). Another tool is a memory aid known as: *BroadCAST-3Cs* which brings together several of these risk communication attributes.[2] "Broad" is a reminder that regulatory risk communication, by necessity, is often for a large and heterogeneous population (Goerlandt et al., 2020). "CAST" stands for **core,** the underlying reason for the risk communication, **audience**, **spokesperson**, and the importance for providing the risk communication message in a **timely** manner. The "3Cs" is a mnemonic for conveying information that reflects the risk **context**, must be **clear** (sometimes written as **clarity**), and **concise.** Risk communicators, therefore, should adjust messages to meet the 3Cs of each target audience thereby informing them in a useful and meaningful way.

When identifying the **core** of a health or environmental risk issue, it is important to develop this concept from a principle-based mindset and not a position-based one (e.g., risk sciences vs.policy). Further, if the core principle is promoting health and safety, each member of an interdisciplinary team may approach a risk issue from a unique perspective, but what unites them is the core principle. It is also important to recognize that the technical leads for an issue may not be the **spokesperson** responsible for relaying the information to the public. Similarly, the **audience** can also change from internal staff to external stakeholders, partners, and publics. As a result, the **spokesperson** must adjust the messaging according to the **audience** while delivering the message in a **timely** manner, and models, such as "IDEA," can also provide useful insights for this process (Sellnow and Sellnow, 2019).

Given the technical nature surrounding risk sciences, assessment, and management, there sometimes is a misconception that the plain language principles **clear** and **concise** are not applicable to risk communication. There are also expectations that any communication with the public must be at a certain grade level, which is not the case. Plain language principles can be applied to all types of communication. Updates to the international standards (ISO Standards, 2023) and national guidance documents (Government of Canada, 2020) aim to provide additional guidance in this regard (plain language expert, personal communication, June 17, 2021).

[2]BroadCAST-3Cs is a memory aid created by the principal author

3.3 Address uncertainty (data gaps), misinformation, and advances in scientific knowledge

During the COVID-19 pandemic, governments at all levels had to manage uncertainty, misinformation, and advances in science. Health Canada continued to update and communicate regulatory advice using various platforms. Further, providing independent, regulatory, and timely input aligned with recommendations on how to maintain public trust and confidence during a global crisis (Mihelj et al., 2022). Health Canada officials also successfully used this approach to address the changing environment by providing clear communication for the safe use of diverse products, such as ultraviolet radiation-emitting devices (Health Canada, 2022b).

With advancements in technology, access to information and opinions is easier than ever before. Users acquire risk information from traditional sources, such as radio, articles, and television, and more recent forms of social media and artificial intelligence technologies. This imposes an additional burden to release effective regulatory risk communication in a timely manner, especially when dealing with uncertainty and misinformation (Howell and Brossard, 2021).

Regulatory risk communication must also address the concerns of the audience by understanding their position, behavior, and level of receptivity. This is no small feat to deliver on the multitude of platforms currently in use. Consequently, checking the "pulse" on how the audience received the information is also important in confirming that the message was delivered in the right context and by the appropriate spokesperson. Further, risk communicators must also ensure that audiences can access and use credible and trustworthy sources, a responsibility that extends to all public servants as they can inform individuals in their respective sphere of influence.

3.4 Plan time to learn from setbacks and successes

In 2015, the Council of Canadian Academies published *Health Product Risk Communication: Is the Message Getting Through?* These experts described the regulatory context for health product-related risk communication, documented existing best practices and tools, and recommended methods to evaluate the extent of reach to the target audience and impact of the conveyed message (Council of Canadian Academies, 2015). Additional recommendations included the importance of performance measurements using theory- and paradigm-based evaluations, such as realism (Pawson and Tilley, 2004; Pawson et al., 2005; Blamey and Mackenzie, 2016; Breuer et al., 2016; Pawson, 2017; Treasury Board of Canada Secretariat, 2021, n.d.).

There are several barriers in undertaking evaluations and here we identify three key barriers to robustly evaluating risk communication: resource constraints (time, human, and funding), complex performance measurement indicators, and limited expertise. Federal resources are typically devoted to core activities and projects. Developing an underlying theory for evaluation and measurement can be time consuming and complex. Consequently, it may be difficult to find teams with appropriate expertise. However, these barriers should not prevent authorities from dedicating time to, at least, discuss and reflect on lessons learned. This is especially important for initiatives without a formal evaluation component.

4 Discussion

Risk communication is complex because it requires one to consider all the layers and attributes in the decision-making process (see Figure 1) as well as how the audience will receive the message. However, this complexity must not prevent one from taking measures to effectively communicate risk. This means recognizing how to adapt messages to meet the requirements of each target audience. One way to help clarify and further strengthen the message, for real world risk communication, is to incorporate approaches, such as the (*broken) telephone game* and lessons learned activities.

Effective communication occurs throughout the decision-making process and is an essential element for bringing together the risk assessment (science) phase with the management (science-policy) and broader (policy-political-publics) space. As the risk communication message develops within an organization, the individual/team responsible for optimizing the message relies on the input from various staff. Further, regulatory risk communication often depends on established policies, guidance documents, templates, and in-house expertise to help develop and strengthen the message. We also include pertinent references to help encourage everyone to review this information along with other models and frameworks designed to strengthen risk communication.

In the workshop, we started from the existing federal risk communication framework and presented the memory aid, *BroadCAST-3Cs*, which integrate key attributes for effective risk communication. We see the pragmatic application of this mnemonic in assisting risk assessors, managers, communicators, and staff who are part of a risk team or are providing input to such a team by addressing some of the challenges associated with communicating risks (see **Table 1**).

For example, taking a "broad" approach and seeking feedback from an interdisciplinary team can help the spokesperson understand how to address uncertainties, be more proactive, account for the subjective perceptions of risks, and tailor the messages from the "science" to the "policy, political, and broader publics" spaces. This insight includes an understanding of how any adaptations to the communication are not based on wordsmithing alone or providing information in plain language. Rather, it is a deeper reflection of the diversity in the underlying values, ideological orientations, and sociocultural beliefs related to the risks of concern. Further, a systems thinking lens provides a mechanism to recognize how a principle-based mindset is important (e.g., at the interface between science-policy); however, this does not preclude the need to understand diverse positions and the underlying reasons for such stances, especially at the policy-political-publics space, as this is critical in tailoring the message according to the audience. A systems thinking lens also ensures that the spokesperson is aware of how risk communication in one space can have an impact on other areas within the system and that the risk assessment, management, and communication steps are positioned within a broader set of elements, which are also important for the overall risk decision-making process (see **Figure 1**).

In closing, our key messages align well with recent publications on risk communication practices and available models and frameworks for effective risk communication. The participants from the workshop left the session motivated to: (i) Embrace the complexities of effective risk communication; (ii) Incorporate the concepts developed from our lived experience; (iii) Explore other relevant and credible sources of information; and (iv) Apply a systems thinking lens to help develop effective risk communication. We hope this paper encourages you to do the same.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YB and CT-S designed the concept of the workshop, contributed important intellectual content, and helped in the writing and revisions of this paper. All authors read and approved the final manuscript.

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Conflict of interest

While Health Canada's Pest Management Regulatory Agency covered the costs to publish this work, the workshop and subsequent report were conducted in the absence of any commercial or financial relationships which could be construed as a potential conflict of interest. Further, the information provided in this paper reflects the authors' views and is not representative of the opinions or policies of Health Canada or the Government of Canada.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CHAPTER 9: GLOSSARY OF TERMS

Hazard	The intrinsic property of an agent making it capable of causing adverse effects to occur in humans or the environment under specific conditions of exposure.
New approach methodologies	A term used to encompass non-animal methods, alternatives, and technologies which reduce reliance on traditional animal toxicology studies.
NextGen risk decision-making (NGRDM)	An iterative process linking the intersections between the research, regulatory, and risk contexts and an institutional mindset and culture, which, as an underlying mechanism, integrates a population health approach by maximizing upstream and downstream attributes for risk decision-making and uses a ONE Health lens to attain the outcome of promoting and protecting the health of humans, animals, and the environment.
NGRDM attributes	Inherent characteristics of pertinent factors (e.g., risk principles, governance, and decision-making pathways) related to the risk decision-making context and process.
NGRDM considerations	Includes NGRDM attributes, well-established best practices for health and environmental risk decision-making, and any other scientific or extra-scientific factors relevant to risk decision-making in a particular risk context.
Risk	A measure of both the harm resulting from being exposed to a hazardous agent, together with the likelihood that the harm will occur.
Risk analysis	A distinct science covering the risk assessment, management, and communication processes and how this relates to other factors such as risk perception, governance, and policy.
Risk assessment	Divided into four major steps - hazard identification, dose-response assessment, exposure assessment, and risk characterization - a risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate.
Risk decision-making principles	Extrinsic, objective, fundamental, and impersonal rules. These can also include ethical principles grounded in institutional values and moral norms.
Risk governance	Relates to the respective actors, rules, conventions, actions, processes and mechanisms concerned with how relevant risk information is collected, analysed, communicated, and how decisions are managed.

Risk management	Typically describes the collective events and considerations involved in addressing and communicating risks through various inter-related activities, factors, and considerations. It is also referred to as risk control, estimation, evaluation, and response.
Risk science	Encompasses both the scientific enterprise of risk assessment and the risk management actions taken to reduce risk. Consequently, it is like risk analysis, but by extending the definition to include the scientific enterprise, risk science also includes elements of risk governance.
Risk science knowledge	Research, methodologies, and knowledge to learn and improve specific risk activities (Type A) or develop generic or fundamental (Type B) concepts such as novel risk principles and approaches.