# Future directions in risk science

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**Abstract:** The NexGen framework published in Environmental Health Perspectives integrates three different views on the future of chemical risk assessment. The NexGen framework emulates a fundamental change towards in chemical testing for toxicity, as outlined 2007 NRC report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*. This framework integrates population health approaches with chemical risk assessment methods, by integrating determinants of health into the risk assessment process. Additional perspective comes from the recommendations of the 2009 NRC report, *Science and Decisions: Advancing Risk Assessment*. The report also calls for changes within the risk assessment process, including the enhanced role of problem formulation, the unification of non-cancer and cancer methods for deriving dose-response relationships, and cumulative risk assessment. The integration of these three driving concepts is discussed in this review expanding the strengths of these three frameworks and what they brought to the NexGen framework for risk science.

**Keywords:** NexGen; risk science; risk assessment; risk management; risk characterisation toxicity pathway; systems biology; environmental agents; population health.

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## 1 Introduction

The manner in which human health risk assessment is conducted continues to evolve. With the enormous increase in the use of chemicals and industrialisation that has taken place in the late 19th and in the 20th century, there was a need to develop new methods

of demonstrating chemical and industrial safety. More recently, new technological advances such as nanotechnologies (Tyshenko and Krewski, 2008), endocrine disrupting chemicals (WHO and UNEP, 2012), and genetically modified organisms (Chao and Krewski, 2008a, 2008b, 2008c) have presented new challenges in risk science.

With the publication of pioneering texts such as *Of Acceptable Risk* by Lowrance (1976) and *An Anatomy of Risk* by Rowe (1977), risk science began to emerge as a distinct interdisciplinary field, providing scientific tools and methodologies for the assessment of health risks, and principles and strategies for managing such risks. Since its beginnings over 30 years ago, an important component of risk assessment has been the understanding of how toxic environmental agents can cause adverse health effects in humans.

Over this same period, the field of population health, which seeks to understand the determinants of health and how the health of populations may be enhanced, also developed into a well-established interdisciplinary area of investigation. The genesis of population health can be traced back to early contributions in the 1970s, including the seminal report, 'A conceptual framework for health' (Lalonde, 1974). Subsequent work in this area has served to reinforce the notion that the health of populations depends on factors beyond medical care and health services, including genetic and biological, environmental and occupational, and social and behavioural factors (Krewski et al., 2007). These factors have collectively come to be known as 'determinants of health' (WHO, 2014).

The evolution of the fields of risk science and population health, which have followed largely independent trajectories, has provided powerful new tools for understanding the factors that affect human health in both positive (health determinants) and negative (risk factors) ways. This work has also led to the development of strategies for improving population health status and mitigating risks to health. With a common goal of enhancing population health, the fields of risk science and population health provide a strong foundation for guiding evidence-based health policy development. A major part of any risk-related field is risk communication, perception, and management (Krewski et al., 2007).

Tracing the historical development of risk science, Krewski et al. (2007) noted that a number of conceptual frameworks for assessing and managing human health risks have been proposed over the years. Perhaps the most influential was the 1983 NRC report on *Risk Assessment in the Federal Government: Managing the Process* commonly referred to as the 'Red Book' because of the colour of its cover (National Research Council, 1983). This report offered the first structured description of the process of health risk assessment and management. The framework consists of three components: research, risk assessment, and risk management. The risk assessment component in turn is divided into four stages: hazard identification, dose-response assessment, exposure assessment, and risk characterisation. This framework's four-step risk assessment process has been widely adopted by regulatory agencies around the world, and continues to provide the foundation for much of the current work in the risk assessment and risk management of chemicals.

Another major contribution to risk science was, *The Framework for Environmental Health Risk Management* developed by the US Presidential/Congressional Commission on Risk Assessment and Risk Management in 1997. This framework was intended primarily for risk decisions related to setting standards, controlling pollution, protecting health, and cleaning up the environment. It includes seven components: establishing the

risk context; identifying risks and benefits; enumerating risk management options; making a risk management decision as to which option, or set of options, is most appropriate; implementation of that decision; monitoring and evaluation of the effectiveness of risk management actions; and stakeholder engagement throughout the process. This framework was designed to assist risk managers, including government officials, private sector businesses, and individual members of the public, in making good risk management decisions about environmental health risks. The framework was intended to be iterative and interactive, with effective risk communication among interested and affected parties involved at all stages (The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). A framework used by Health Canada (2000) for issues related to health risks is based on the commission's framework.

Building on the context provided by the preceding historical perspective, the objective of this paper is to describe the development of the NexGen framework recently published in detail (Krewski et al., 2014), which merges key contributions of three previously published frameworks. These frameworks are:

1 the NRC vision framework for toxicity testing (TT21C) (National Research Council, 2007), which promotes an evidence-based approach to risk assessment based on high throughput *in vitro* methods combined with *in silico* computation

2 the framework for population health risk assessment (Krewski et al., 2007; Chiu et al., 2013), which represents a first attempt to integrate the fields of risk science and population health

3 the Science and Decisions framework for the advancement of risk assessment (National Research Council, 2009), which outlines new directions in the design and conduct of risk assessment of environmental agents.

All of the above frameworks have independently evolved to improve risk assessment and, collectively, these three contributions constitute the building blocks on which the NexGen framework for risk science was developed. The manner in which each framework evolved and contributed to the NexGen framework will be discussed in the following sections. The US Environmental Protection Agency (EPA) developed the NexGen program in an effort to address the current challenges facing chemical risk assessment, to advance the next generation of risk science methods, and to incorporate TT21C into a workable platform. The NexGen project, initiated in 2011, aims to incorporate TT21Cs new and improved scientific tools and technologies into risk science in an effort to make risk assessment faster, more scientifically robust, and less costly (Cote et al., 2012). The full report discussing the framework, the case studies and a tiered risk assessment approach is now available (US EPA, 2014).

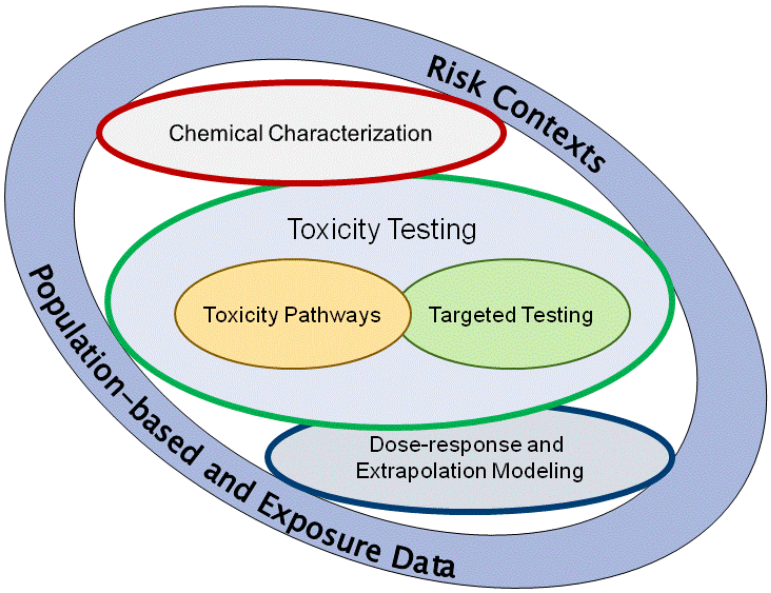
### *1.1 Understanding toxicity pathways*

Toxicological methodologies and regulatory requirements developed over the latter decades of the 20th century mandated the use of *in vivo* animal models to provide the evidence base for determinations of acceptable chemical exposure levels for human safety. As the number of chemicals in commerce increased, traditional testing methods have proven very costly, required a large and growing number of test animals, and took years to complete. As a result, a backlog of newly produced chemicals went untested and

risk assessors were faced with data-poor situations that undermine risk assessment and evidence-based decision-making regarding the tens of thousands of chemicals in the environment. In 2004, the US EPA and the US National Institute of Environmental Health Sciences (NIEHS) requested that the US National Research Council (NRC) review the current scientific methods used for toxicity testing and propose feasible alternatives. The NRC completed two reports; the first, *Toxicity Testing for Assessment of Environmental Agents*, was released in 2006 (National Research Council, 2006); the second, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (now commonly known as TT21C), was released in 2007 (National Research Council, 2007). Although the first report gave a comprehensive review of the status of standardised toxicity testing, it was the second report released in 2007 that caught the attention of the scientific community and governmental agencies and sparked movement towards improving the scientific methods used in toxicity testing (Collins et al., 2008).

The 2007 NRC report recommended modernising the toxicity testing process in a cost effective manner by promoting high throughput (HTS) *in vitro* screening assays, computational methods, and other predictive modelling systems to replace costly and cumbersome *in vivo* methods. The high-throughput screening assays were intended to focus on the identification of pathway perturbations that are associated with initiating possible adverse health outcomes. The TT21C framework first published in 2007 is shown in Figure 1. The report suggested that the improvement and validation of new laboratory tools and techniques would increase our understanding of pathways targeted by chemicals and could be the basis of better methods to assess the potential for human risks from environmental exposures (National Research Council, 2007).

**Figure 1** NRC vision for the future of toxicity testing




*Source:* Adapted from NRC (2007) Report

In 2009, the US EPA *Strategic Plan* articulated a long-term vision for toxicity testing based, in part, on the 2007 NRC report (US EPA, 2009). With this plan in place, alongside a partnership of four top governmental agencies[1] signing a memorandum of understanding (MOU) in 2010, the science and technologies contributing to risk assessment have advanced at a substantial rate. What is currently known as the Tox21 consortium has made substantial progress in moving the 2007 NRC vision forward (US EPA, 2012). Krewski et al. (2011) have shown that these new tools and technologies are compatible with the well-established risk assessment paradigm laid out in the 1983 Red Book and case studies have demonstrated the feasibility of using these new methods for risk assessment (Krewski et al., 2014). Although these *in vitro* methods are not yet able to identify hazardous chemicals directly, this remains a possibility in the future. These goals will be substantially supported upon the completion of the human toxome project, where all toxicity pathways will have been catalogued and mapped (Hartung and McBride, 2011).

The US EPA has conducted a large body of research investigating potential toxicity pathways through ToxCast Phase I and II programs and subsequently, Tox21 Phase I and II programs. The predictive capacity of high throughput *in vitro* assays was analysed with over a thousand data-rich reference chemicals tested in over 600 assays, and 1100 endpoints compared with *in vivo* data (Dix et al., 2007; Tice et al., 2013). Judson et al. (2010) found that statistical comparisons between the two types of data (i.e., *in vivo* versus *in vitro*) showed that if a chemical is toxic, it tends to perturb many different types of *in vitro* pathways. However, at this point in time, hazard identification relying exclusively upon *in vitro* assays is an approach that is still in its infancy. Although some correlation and predictive capacity between *in vitro* pathways and *in vivo* health outcomes has been demonstrated in case studies, further research is needed (Krewski et al., 2014). Others argue that the contribution of these new test methods will be through predicting regions of safety, not in predicting high dose apical responses that serve as a point-of-departure for a traditional risk assessment. Also many scientist feel that *in vivo* methods are flawed and do not predict toxicity as much as they classify compounds on a preliminary basis for risk of toxicity extrapolated to human exposure (Andersen and Krewski, 2010).

The scientific tools and techniques as outlined in Krewski et al. (2014) are already being used in case studies commissioned by the NexGen project and dossier portfolio submission for the REACH program in the EU and will continue to be streamlined for risk assessment purposes. Table 1 outlines some of the promising risk assessment tools and methodologies currently under development (Krewski et al., 2011). Thomas et al. (2013) have developed a tiered approach following recommendations from the NexGen project outlining three tiers and the manner in which various new data streams might be used in toxicity testing, prioritisation and standard setting. *In vitro* assays could be considered a first tier of analysis for chemicals, and models developed using reserve toxicokinetics, the concept of a biological pathway altering dose (BPAD), and associated margins of exposure have allowed for prioritisation of chemicals (Rotroff et al., 2010; Wetmore et al., 2012, 2013).

**Table 1** Promising risk assessment tools and methodologies

| *Tool* | *Application* |
|---|---|
| High throughput screens | Efficiently identify critical toxicity pathway perturbations across a range of doses and molecular and cellular targets |
| Stem cell biology | Develop in vitro toxicity pathway assays using human cells produced from directed stem cell differentiation |
| Functional genomics | Identify the structure of cellular circuits involved in toxicity pathway responses to assist computational dose-response modelling |
| Bioinformatics | Interpret complex multivariable data from HTS and genomic assays in relation to target identification and effects of sustained perturbations on organs and tissues |
| Systems biology | Organise information from multiple cellular response pathways to understand integrated cellular and tissue responses |
| Computational systems biology | Describe dose-response relationships based on perturbations on cell circuitry underlying toxicity pathway responses giving rise to thresholds, dose-dependent transitions, and other dose-related biological behaviour |
| Physiologically-based pharmacokinetic models | Identify human exposure situations likely to provide tissue concentrations equivalent to in vitro activation of toxicity pathways |
| Structure-activity relationships | Predict toxicological responses and metabolic pathways based on the chemical properties of environmental agents and comparison to other active structures |
| Biomarkers | Establish biomarkers of biological change representing critical toxicity pathway perturbations |
| Molecular and genetic epidemiology | Incorporates molecular markers of exposure and biological change into population-based studies; integrates the knowledge of the human genome into epidemiological studies to understand genetic susceptibility and gen-environment interaction in disease causation |

*Source:* Krewski et al. (2011)

## *1.2 A population heath perspective*

Understanding toxicity pathways in disease causation is essential in population health risk assessment, since it contributes to understanding the multifactorial basis of disease and the susceptibility of vulnerable populations. Our knowledge of pathway perturbations will increase over the next few decades, which will ultimately improve the health of the population as a whole.

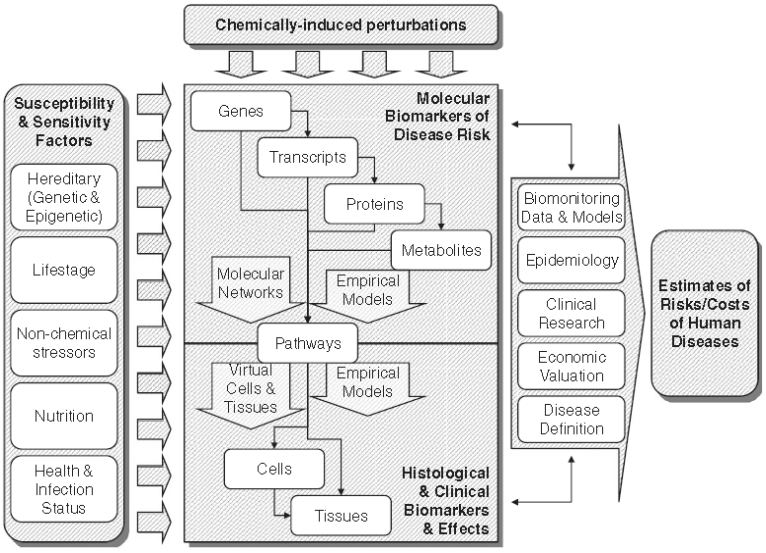
One example of how understanding a disease pathway has improved population health is the elucidation of the toxic pathogenesis of prion diseases, and how this pathway could play a role in several other neurodegenerative diseases. Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and related dementias may all involve to some extent a common toxicological pathway resulting from the misfolding of prion proteins (Aguzzi and O'Connor, 2010). The toxicity of misfolded prions depends on downstream prion-dependent processes, culminating in neuronal dysfunction and death (Aguzzi and Calella, 2009).

In 2000–2001, neurodegenerative diseases accounted for 6.7% of the total cost of illness in Canada (CIHI, 2007). A large part of their impact stems from lack of early

diagnosis and identification of susceptible populations. High-throughput and high content bioassays described by the NRC (2007) can be used to examine prion-dependent toxicity pathways early in the disease process, so that neurodegenerative diseases might be easily diagnosed and individuals who are susceptible to these diseases might be easily identified. High throughput techniques are expected to evolve in the next 10 to 15 years and to lead to the generation of high-profile data that can be used for the mechanistic interpretation of complex disease pathways and the prediction of apical responses in susceptible populations without the need for *in vitro* or *in vivo* testing.

Krewski et al. (2007) proposed a framework for addressing complex health risk issues from a population health perspective. The framework is intended to ensure that the most important determinants of health were identified and assessed and that the most efficient risk management strategies were implemented. This framework incorporates multiple health determinants and multiple interventions to manage population health risk (Krewski et al., 2007). A more recent publication by Chiu et al. (2013) discusses many of the same principles among a more modern dynamic of scientific tools and techniques (see Figure 2).

**Figure 2** A framework for new models of human disease risk using toxicogenomics, related technologies, and systems biology




Notes: The determinants of human disease are above (chemical exposures) and to the left (other factors), interacting at various levels of biological organisation (genes, tissues). These biological systems at various scales are interrelated (solid arrows), with various computational methods for modelling them (block arrows inside). There is also feedback between this biological information and knowledge and methods to estimate the risks and/or costs of human disease (large block arrow pointing to the right). Examples of non-chemical stressors include factors such as amount of exercise, access to healthcare, and socio-economic status.

*Source:* Reproduced from Chiu et al. (2013)

Determinants of health, those factors that make people healthy or not, include those mentioned above, and many others such as income and social status; education;

employment; physical environment; personal health practices; early childhood development; biology; gender; and culture. Table 2 presents a list and description of health determinants developed by the World Health Organization (WHO) and the Commission on the Social Determinants of Health (World Health Organization, 2008, 2011, 2014).

**Table 2** Comprehensive list and description of determinants of health

| *Determinants* | *Description* |
|---|---|
| | *Biology and genetics* |
| Biology and genetics | Inheritance plays a part in determining lifespan, health, and the likelihood of developing certain illnesses. |
| Personal health practices | Eating habits, activity levels, smoking, drinking, and how individuals deal with life's stresses and challenges all affect health. |
| Sex | Men and women suffer from different types of diseases at different ages. |
| Healthy child development | Early child development (ECD) – including the physical, social/emotional, and language/cognitive domains – has a determining influence on subsequent life chances and health through skills development, education, and occupational opportunities. Through these mechanisms, and directly, early childhood influences subsequent risk of obesity, malnutrition, mental health problems, heart disease, and criminality. |
| | *Environment and occupational* |
| Physical environment | Safe water and clean air, healthy workplaces, safe houses, communities and roads all contribute to good health. |
| Employment/working conditions | People who have more control over their working conditions are healthier. |
| | *Social and behavioural* |
| Gender | Society determines roles, personality traits, attitudes, behaviours, values, and relative power of males and females. |
| Personal health practices and coping skills | The health of an individual is influenced by their personal health practices (e.g., whether or not they exercise regularly) as well as how well they handle stress. Coping skills allow people to be self-reliant, solve problems, and make informed choices that enhance health. |
| Employment/working conditions | People who are employed are healthier than people who are unemployed. |
| Education and literacy | Low education levels are linked with poor health, more stress, and lower self-confidence. |
| Social environment | Reflects the values and norms of a society. Good social stability and cohesive communities contribute to good health. |
| Healthy child development | Early child development (i.e., the physical, social/emotional, and language/cognitive domains) influences health and lifetime opportunities through skills development, education, and occupational opportunities. |
| Culture | Customs and traditions, and the beliefs of the family and community all affect health. |

*Source:* WHO (2008, 2011, 2014)

Determinants of health can be separated into three categories: 'Biology and genetics'; 'Environment and occupational' and 'Social and behavioural' (see Table 2). Biological determinants may include immune function, age, sex and genetic determinants such as genetic variability or polymorphisms that can result in the genetic susceptibility of individuals to the adverse effects of certain chemicals. Environmental determinants include exposure to pathways of contaminants from their source to the environment such as air, soil and water, whereas occupational factors that impact toxicological exposure are specific to the individual's profession or trade and working conditions. Exposure assessment is now a science that can change a chemical's priority significantly (Hubal et al., 2010a, 2010b). The last group of determinants shown in Table 2, social and behavioural determinants, refer to factors such as education or income or a particular behaviour (e.g., culture, personal health practices) that influence the exposure of a subpopulation to contaminants (Krewski et al., 2007). Other frameworks that should be considered for evaluating complicated health risk situations with social dimensions are Multiple Exposures Multiple Effects (MEME) (Briggs, 2003; WHO, 2015) and Driving Force-Pressure-State-Exposure-Effect-Action (DPSEEA) developed (Corvalán et al., 1996).

The health determinants within these categories can interact to further impact health status. For example, specific environmental factors responsible for exposure of a population to a toxicant would be identified in the exposure assessment; however, the behaviour of the population within that environment (e.g., smoking cigarettes) would also be taken into account at this stage of the risk assessment. Other interactions that could be considered are genotoxicology and gene-environment interactions (epigenetics) where genes changes as a result of pre-exposure and this change could influence outcome at a later date (Martinez et al., 2011; Ren et al., 2011). In a scenario where the risk of radon exposure on human health was assessed, taking all of the determinants or risk factors into account would greatly impact the outcome of the risk assessment because smokers are more likely to develop radon-induced lung cancer than non-smokers (WHO, 2009). Sensitive biomonitoring techniques that quantify *in vivo* concentration of substances or biomarkers within body fluids or tissues could calibrate real-world human exposures and determine whether existing regulatory guidelines are sufficient (Hubal et al., 2010a, 2010b).

Determinants of health are intrinsically linked to exposure assessment and dose-response assessment and therefore must be taken into account in risk assessments, not only to give context to the risk issue but also to ensure that susceptible subpopulations are identified, that risk is estimated for these groups during the assessment and that appropriate risk management strategies are employed to protect those who are sensitive to exposure. A study by Johnsen et al. (2008) provides one example of a quantitative and qualitative exposure assessment that takes determinants into account. Personal dust measurements of over 2,500 employees in 15 Norwegian smelters were taken, and employees also participated in a respiratory survey and health examinations. Gender was one of the determinants of exposure found to be significantly related to dust exposure levels, with female employees found to be less exposed to dust than males. Other risk factors included age, current smoking, job category and previous exposure. The combination of population health and risk science approaches in the same framework

encourages the consideration of all of the determinants of a health outcome, rather than examining a single factor as is usually done in traditional risk assessment (Krewski et al., 2007).

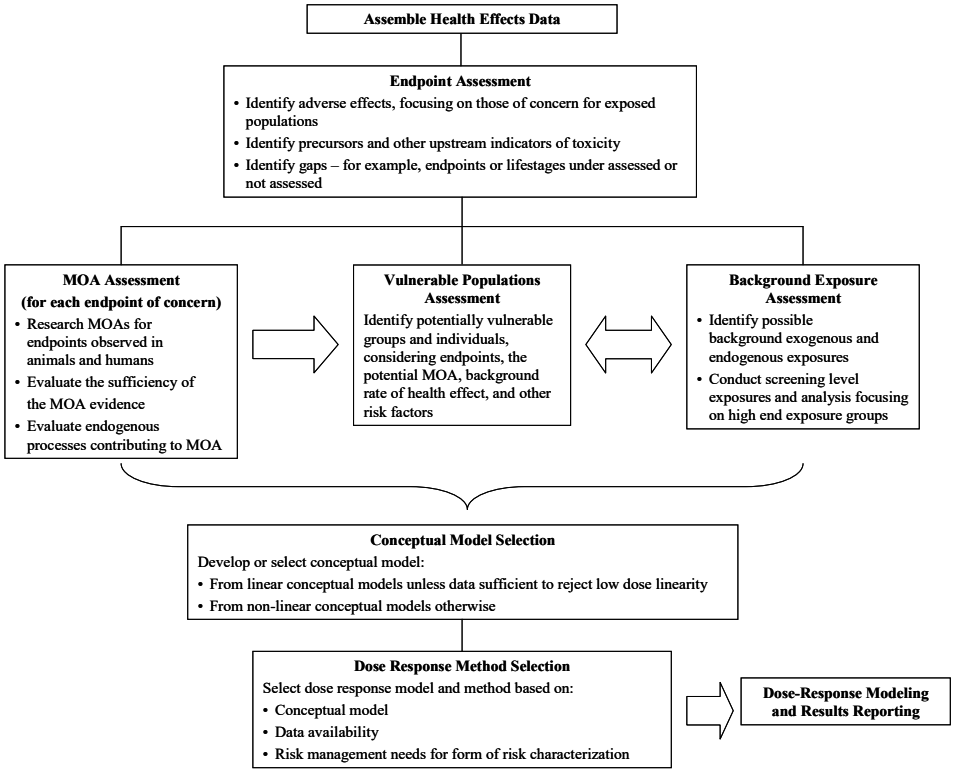
Determinants of health should also be examined and considered in risk assessment because they help inform decision-making in the risk management process. Dev et al. (2004) demonstrated how the examination of determinants influenced risk assessment for acquisition of hepatitis C and helped determine what risk reduction strategy was required. Ethnicity influenced the perception and knowledge that individuals had of risk factors associated with disease contraction. The authors of the paper recommended that education should better address the concerns of all populations with the disease to ensure risk reduction.

The use of multiple interventions may present more efficient and cost-effective options to help reduce or prevent the occurrence of population health risks as opposed to employing a single risk mitigation strategy. Evidence-based health risk policy analysis supports the development and implementation of multiple risk mitigation strategies, ensuring that the right interventions are chosen. Although both regulatory and non-regulatory risk intervention strategies have been previously employed in risk management, greater attention is now being paid to non-regulatory risk management options more typically used in the field of population health. The five health risk intervention categories that can be employed simultaneously within this integrated framework and that can interact to mitigate risk form the REACT approach, which includes *r*egulatory, *e*conomic, *a*dvisory, *c*ommunity *a*ction and *t*echnological interventions. After multiple interventions are selected and implemented, their impact on population health risk is evaluated, preferably through indicators of population health improvement (Krewski et al., 2007; Chui et al., 2013).

### *1.3 New risk assessment methodologies*

NRC (2009) issued a report entitled, *Science and Decisions: Advancing Risk Assessment*, also known colloquially as 'the Silver Book'. *Science and Decisions* was originally commissioned by US EPA to take stock of methodological advances in risk science and examine how such advances may be used to strengthen risk assessment practices. The report recommended a number of changes to the design and conduct of risk assessments. One of the more significant recommendations dealt with the need to unify approaches to dose-response assessment (see Figure 3). The committee noted that the approaches to risk assessment for cancer and non-cancer health outcomes had evolved down two very distinct and discordant pathways. These pathways led to very different treatment of these types of health outcomes throughout the process, including their role in risk management. The committee determined that this separation in approach was not scientifically justified and posed a key threat to the integrity and utility of risk assessment for risk management purposes. The report describes the key components of a unified approach to dose-response assessment (Chapter 5 of NRC, 2009). Important aspects of the unified approach have significant concordance with several of the themes in the TT21C toxicity testing framework, and with the determinants of health approach espoused in the McLaughlin Centre's population health framework.

**Figure 3** Unified approach to dose-response assessment




*Source:* Science and Decisions: Advancing Risk Assessment (NRC, 2009)

The unified approach to dose-response assessment does not approach the assessment task differently for cancer and non-cancer health outcomes. This is compatible with both the TT21C vision (in which *in vitro* testing would identify pathway perturbations that can lead to cancer or any other adverse health outcome in a common approach) and the population health approach (addressing cancer and non-cancer health endpoints and their causative determinants in a common framework). The unified approach calls for the consideration of a number of key aspects which will determine the dose-response relationship separately for the individual and the population level response. These aspects include the mode-of-action or pathways through which the chemical may cause adverse health outcomes, the extent of background exposures, endogenous exposures and background disease processes that may contribute or affect these same pathways of harm, and the consideration of specific vulnerable populations.

It is clear that the explicit consideration of mode-of-action has similar purpose to the identification and elaboration of toxicity pathways within the TT21C approach. In addition, the other considerations in the unified approach are closely related to the consideration of the many highly variable determinants of health in the population. Background exposures can be driven by environmental, socio-economic and occupational determinants, endogenous exposures can be affected by determinants such as sex, lifestyle and genetic differences and, in general, identifiable vulnerable populations can be associated with all of the determinants of health identified in the population health approach to risk management.

As a result, the NexGen approach to chemical risk assessment represents a substantial departure from traditional risk assessment while providing a key opportunity to re-unify the approach to chemical risk assessment such that the traditional divide between cancer and non-cancer risk assessment would no longer dominate approaches to risk assessment and risk management. The focus on pathway perturbations from the TT21C framework integrates the need to consider the causal mechanism (mode-of-action) by which the chemical can cause adverse health outcomes called for in the *Science and Decisions* unified approach. The NexGen framework's inclusion of individual and population determinants of health contributes directly to the need called for in the unified approach for consideration of background exposures, parallel disease processes, and vulnerable populations, and for characterising the nature of the dose-response relationship separately for individuals (probability of response of an individual at a given dose) and populations (the proportion of the population responding at a given dose).

This 2009 report also included two key areas of recommendations that operate at the 'framework' level for risk assessment. One recommendation encouraged detailed problem formulation activities, ideally resulting in an initial array of decision-making options. The second recommendation was to design the risk assessment (including the data and knowledge acquisition components), as often as possible, with the purpose of providing discriminatory information to facilitate selection among these decision-making options.

A key by-product of the availability of candidate decision-making options was the potential to employ the concept of the value-of-information. Value-of-information is defined as a decision-centric concept that places value on information that reduces uncertainty, and therefore could improve the outcome of decision-making. In this frame, information (e.g., a proposed *in vitro* test) is not considered to have generic value. This is in sharp contrast to the scientific perspective on the same test result, which may find it to be valuable for very different reasons. It is only valued in its capacity to improve decision-making by adding information about the risk itself or any excess costs associated with mitigating that risk (NRC, 2009). The value attributed to the information is accrued by reducing the probability and impact of sub-optimal decisions that might be taken in the absence of the new information.

It is important to distinguish information from the concept of an information system. A specific piece of information is typically relevant to one or more decisions. Information systems provide support to a portfolio of decisions. The suite of NexGen tools will yield data and analyses that constitute a new form of information system that informs a broad portfolio of decisions, including many which will be made outside of EPA. From that perspective, the NexGen risk assessment framework may be best seen as catalysing the interaction between the evolving NexGen information system and the portfolio of decisions facing EPA (and others whose decisions will be informed by NexGen data) (Krewski et al., 2014).

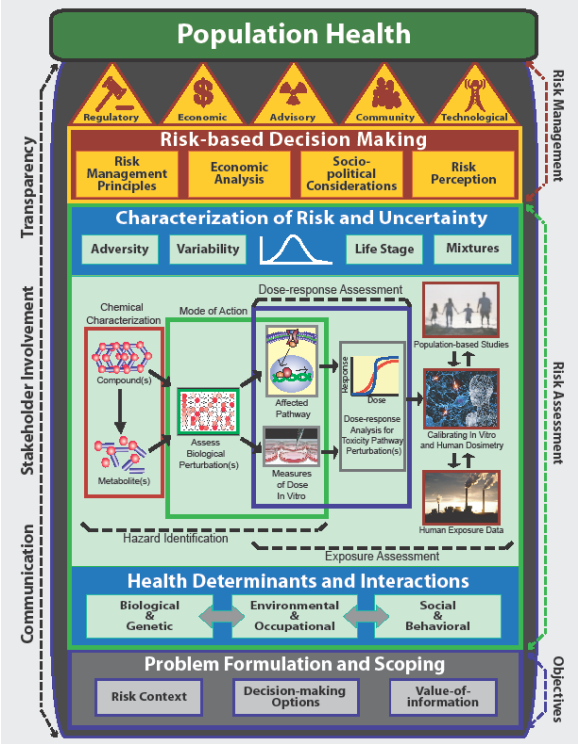
This perspective of risk-based decision-making starts with analysing current, near-future and longer-term decision-making to determine, with sufficient technical detail, exactly how it might be done differently in the presence of NexGen data, tools and methods (see Table 3). Rather than focussing on what will be knowable in the future through NexGen technologies, the risk-based decision-making perspective would focus attention on the means by which decision-making will be improved (NRC, 2009).

**Table 3** Risk assessment methodologies (current and NexGen approaches)

| *Methodology* | *Current approach* | *NexGen approach* |
|---|---|---|
| | *Hazard identification, dose-response assessment and exposure assessment* | |
| Hazard identification | Based largely on animal toxicity testing, mainly in rodent species. | Based primarily in vitro testing in human cells, and computational methods in biology and toxicology. |
| Dose-response assessment | Empirical or biologically-based models describe apical endpoints, and determine an appropriate point of departure (such as the benchmark dose) for establishing a reference dose. | Computational systems biology pathway models describe dose-response relationships for pathway perturbations, reflecting dose-dependent transitions throughout the dose range of interest. |
| Dose and species extrapolation | Dose and species extrapolation translate animal test results to humans. | Cellular assays provide direct measures of toxicity pathway perturbations in humans. IVIVE techniques and pathway modelling calibrate in vitro and in vivo exposures. Sensitive in vitro tests are used to evaluate risk directly at environmental exposure levels. |
| Exposure assessment | Estimates of human exposure based largely on measurements in environmental media (air, food, water, soil). | Expanded use of high throughput biomonitoring data reflecting critical toxicity pathway perturbations. |
| | *Characterisation of risk and uncertainty* | |
| Adversity | Apical outcomes in mammalian systems, or precursors to these outcomes, generally serve as the basis for risk assessment. | In vitro assays identify critical toxicity pathway perturbations, which serve as the basis for risk assessment, even in the absence of a direct link with an apical outcome. |
| Variability | Adjustment factors used in establishing reference doses account for inter-individual variability in pharmacokinetics and pharmaco dynamics. Variability in exposure is also taken into account. | Variability in biological response is characterised through the use of a diverse range of human cell lines. Dosimetry models link variation in human exposure with corresponding in vitro doses. |
| | *Characterisation of risk and uncertainty* | |
| Life stage and susceptible populations | Life stage, genetics, and socioeconomic and lifestyle factors determine susceptible population groups. | Molecular and genetic epidemiology defines susceptible populations in terms of critical pathway perturbations. |
| Mixtures and multiple stressors | Common experimental protocols include testing of mixtures and factorial experiments with joint exposures. However, there are only a limited number of such studies because of cost and complexity of experimental design. | Cost-effective high throughput technologies permit expanded testing of mixtures and multiple stressors. |
| Uncertainty analysis | Uncertainty considerations include species differences in susceptibility, low-dose and route-to-route extrapolation, and exposure ascertainment. | Probabilistic risk assessments characterise overall uncertainty, and identify the most important sources of uncertainty that guide value-of-information decisions. |

*Source:* Krewski et al. (2014)

**Figure 4** The next generation framework for risk science




Notes: This framework is divided into three phases, each of which involves several components. *Phase I: Objectives:* **Problem Formulation and Scoping** takes into consideration the risk context, decision-making options, and value-of-information. *Phase II: Risk Assessment:* **Health Determinants and Interactions** incorporates a population health approach that takes into account multiple health determinants that interact with the risk factor(s) of interest, such as biological and genetic, environmental and occupational, as well as behavioural and social determinants of health. Hazard identification, dose-response assessment, and exposure assessment make use of new scientific tools and technologies, based on high-throughput screening assays and computational methods in biology and toxicology for hazard identification and dose-response assessment; in vitro to in vivo extrapolation methods for calibration of in vitro and human dosimetry; molecular and genetic epidemiology to identify toxicity pathway perturbations in population-based studies; and high-performance mass spectrometry to generate human exposure data, to assess risk. **Risk Characterisation and Uncertainty** applies new risk assessment methodologies, including methods for evaluating adversity, variability, life stages, and mixtures to develop human exposure guidelines. *Phase III: Risk Management:* **Risk-Based Decision Making** considers fundamental risk management principles, economic analysis, socio-political consideration and risk perception to select one or more risk management interventions of a regulatory, economic, advisory, community-based, or technological nature for risk management. (The central panel on Hazard identification, dose-response assessment, and exposure assessment is adapted from Figure 2 in Krewski et al. (2011), *Annual Review of Public Health*, p.C-1).

*Source:* Reproduced from Krewski et al. (2014)

## 2 Summary and discussion

A NexGen framework for risk science (Krewski et al., 2014) was developed by integrating the most essential elements of each framework as described in this paper (see Figure 4):

1 Toxicity Testing in the 21st Century

2 the Population Health Risk Assessment's Integrated Framework for Risk Management and Population Health

3 Science and Decisions: Advancing Risk Assessment.

The new framework will support the transformation of human health risk assessment from a process that examines apical endpoints in animal models *in vivo* to one based on tiered risk assessment practices that would integrate the data generated from emerging tools and techniques with the assessment of broad determinants of health and multiple interventions to link to overall population health. The 2009 NRC report explored a number of directions in risk assessment methodology that will also be important for the future of risk science.

The first of the three cornerstones is based on understanding the toxicity pathways by which environmental agents may cause health detriment through critical pathway perturbations; the risk assessment goal is to employ high throughput assays and computation methods in toxicology to efficiently identify such agents, and establish human exposure guidelines that will allow the avoidance of these pathway perturbations. The second cornerstone views risk from a broader population health perspective, simultaneously examining multiple determinants of health that interact in complex ways to determine population health status. The third cornerstone provides guidance on new directions in risk assessment methodology to improve the relevance to decision-making, as well as calling for a unified approach to dose-response that considers mode-of-action, background exposures and disease processes, and vulnerable populations which are closely tied to determinants of health. Although it is clear that each of these building blocks will be useful in charting future risk assessment principles, procedures, and practices, their integration into an overarching NexGen risk assessment framework will continue to evolve as the technologies and the decision analytic approaches mature. Taken together, these three building blocks contributed to a NexGen framework that will shape the future of health risk science (Krewski et al., 2014).

The elements of the three key paradigms provided the foundation and supported the development of the NexGen Framework. TT21C vision, described in detail in the previous section of the paper, ensures the availability of new in-vitro pathway toxicity data for the NexGen framework, and allows for the inclusion of emerging advanced technologies as they are developed and validated. Furthermore, TT21C will allow the simultaneous assessment and the analysis of a large quantity of chemical substances, complex chemical mixtures, and metabolites at different life stages in a cost-effective efficient manner. The second approach based on a population health risk assessment approach provides the holistic population health perspective by taking into account the multiple determinants of adverse health outcomes. This framework (Figure 2) emphasises the importance of integrating population health, risk assessment, and risk management before appropriate risk can be assessed for human populations. By incorporation the essential element of this framework, NexGen becomes the first attempt to include

population health and its determinants as a driving force for consideration in assessing environmental health risks. This population health perspective on risk assessment adds the many factors, such as socioeconomic, genetics, and environments, that impact population health status and variability. Lastly, NRCs (2009) *Science and Decisions: Advancing Risk Assessment* contributes sound decision-making principles to the framework by incorporating extensive problem formulation and planning that involves all stakeholders, at the onset of the project. The approach for risk assessment that NexGen framework advocates is to formulate clear questions and set lucid objectives associated with the initial problem before the risk assessment is initiated. The approach also aims to determine the type of data needed to address the problem and presents a shift in focus on the emerging risk assessment methodologies for supporting robust science and evidence-based risk assessment and risk management decision-making. The NexGen framework emphasises the value of formulating a concrete problem in the context of the risk presented in order to ensure that rational and appropriate options are available for the risk assessment and decision-making process. The NexGen framework, depicted as Figure 4, has been described in detail in Krewski et al. (2014).

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## Notes

1 The consortium members include:

- a the US EPA Office of Research and Development (ORD), National Center for Computational Toxicology (NCCT)
- b the US National Toxicology Program (NTP) headquartered at NIEHS
- c the National Chemical Genomics Center (NCGC) and National Institutes of Health (NIH) headquartered at the National Human Genome Research Institute (NHGRI)
- e the US Food and Drug Administration (FDA).

## Abbreviations

EPA US Environmental Protection Agency.

HTS HIGH-throughput screening.

NRC US National Research Council.

Tox21 The Tox21 consortium comprised of EPA, NIH, and FDA.

TT21C Toxicity testing in the 21st century.