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Improving Health Risk Assessment as a Basis for Public Health Decisions in the 21st Century

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One-fifth of the way through the 21st century, a commonality of factors with those of the last 50 years may offer the opportunity to address unfinished business and current challenges. The recommendations include: (1) Resisting the tendency to oversimplify scientific assessments by reliance on single disciplines in lieu of clear weight-of-evidence expressions, and on single quantitative point estimates of health protective values for policy decisions; (2) Improving the separation of science and judgment in risk assessment through the use of clear expressions of the range of judgments that bracket protective quantitative levels for public health protection; (3) Use of comparative risk to achieve the greatest gains in health and the environment; and (4) Where applicable, reversal of the risk assessment and risk management steps to facilitate timely and substantive improvements in public health and the environment. Lessons learned and improvements in the risk assessment process are applied to the unprecedented challenges of the 21st century such as, pandemics and climate change. The beneficial application of the risk assessment and risk management paradigm to ensure timely research with consistency and transparency of assessments is presented. Institutions with mandated stability and leadership roles at the national and international levels are essential to ensure timely interdisciplinary scientific assessment at the interface with public policy as a basis for organized policy decisions, to meet time sensitive goals, and to inform the public.

KEY WORDS: Climate; COVID-19; health risk assessment; policy; risk management

1. INTRODUCTION

One-fifth of the way through the 21st century, the health and environmental challenges of pandemics and climate change could not be more compelling; both are extraordinary in scope. The framework of risk assessment and risk management continues to be a useful framework for refining research to fill gaps in scientific knowledge to inform public health and environmental policies.

Why were the novel approaches developed in the late 20th century for evaluating scientific information and managing risk so successful? What has been achieved and what unfinished business remains? How can health risk assessment be improved to address the open issues of the 20th century and face the new challenges of the 21st century? The role of science in times of crisis is dramatic.

The authors of this article provide firsthand knowledge of the efforts that founded the fields of risk assessment and risk management. We helped organize the institutional efforts that ensured the success of risk assessment and risk management

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policies and the outreach programs that informed social and economic acceptance.[1] In this article, we reflect on experiences of the past to inform current scientific and institutional challenges necessary to achieve greater gains in public health and environmental sustainability.

In this article we address the following six questions necessary to complete unfinished business and to provide a basis for public health decisions in the 21st century.

1. How can the fundamentals of risk assessment and management developed during the last 50 years inform current critical risk-related challenges?
2. How can the level of cooperation built among federal agencies, the National Academies of Sciences, and public/private partnerships be replicated and extended to more effectively respond to 21st century challenges?
3. How can we balance the needs and independence of science in risk assessment with the powers and responsibilities of decisionmakers in order to make more scientifically grounded and acceptable risk-related decisions?
4. How may we more effectively use comparative risk analysis to advance environmental health outcomes thinking and analysis?
5. When should we reorder risk assessment and risk management to more effectively address current environmental health challenges?
6. How can the risk analysis paradigm be used to inform the challenges of pandemics and climate change?

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2. HOW CAN THE FUNDAMENTALS OF RISK ASSESSMENT AND MANAGEMENT DEVELOPED DURING THE LAST 50 YEARS INFORM CURRENT CRITICAL RISK-RELATED CHALLENGES?

There appear to be similarities between societal awareness of the need for change in the mid-20th century and now. Almost nothing happens without societal awareness and some expectation of improvement. The public health approaches adopted in 1976 changed forever the scientific foundations for public health and environmental policy decisions. This paradigm applied the principles of risk assessment derived from earlier experience with radiation to a host of substances in the environment forming a basis for defining safe levels of exposure based on explicit weight-of-evidence evaluations. These policies discarded the concept of zero tolerance, an expectation found to be impossible to achieve and endorsed transparency in the scientific assessment process to address the questions of potential hazard and quantitative methods to decide acceptable risk for public health protection. As described below, this bold paradigm shift followed mounting social engagement in matters of health, the environment, and social policies.

Following the publication of Rachel Carson's *Silent Spring* in 1962, a generation was inspired to focus on the environmental and public health consequences of the industrial era and the need for change. Millions of people marched for health and environmental improvements on the first Earth Day in April 1970. Public attention was largely focused on what was regarded as an epidemic of cancers and the belief that exposures to environmental and chemical agents were responsible. Concurrent demonstrations to protest the Vietnam War created an atmosphere of social involvement with expectations that involvement could bring change.

In the 2015 perspective article "Whither risk assessment: New challenges and opportunities a third of a century after the Red Book," (Greenberg et al., 2015) the authors provided historical context to address applications as broad as homeland security, transportation, chemical risks, risk communication, and other pressing challenges for risk assessment scientists. To briefly summarize relevant history, the U.S. Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) were formed in 1970. There was a wave of environmental legislation in the 1970s, with

transformative amendments to the Clean Air Act (CAA) in 1970, the Clean Water Act (CWA) in 1972, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in 1972, and the enactment of the Safe Drinking Water Act (SDWA) in 1974. Although these specific legislative mandates had significant differences, a major theme was protecting public health with an adequate margin of safety. Modifying factors included balancing risk and benefits for beneficial use pesticides under FIFRA, as was long true for pharmaceuticals, and considering feasibility of control under the SDWA. One provision stands out as health based alone, the CAA sections on setting National Ambient Air Quality Criteria Standards (NAAQS). Various statutes distinguished between beneficial chemicals, for example, pesticides. Twenty years later, in the CAA Amendments of 1990, a new strategy was introduced for Hazardous Air Pollutants (HAPs), using maximum achievable control technology (MACT), to be followed by a later risk assessment to ensure adequate protection of health. This new strategy followed almost two decades of ineffective solutions to the well-recognized risks associated with the burden of nationwide toxic substances in air; recognized but not easily well characterized by complete risk assessments.

Expectations for eradication of risk were embodied in the Food, Drug, and Cosmetics Act's 1958 Food Additives Amendment, the Delaney Clause, which called for zero tolerance of additives intentionally introduced into foods that were shown to cause or be associated with the occurrence of tumors in animals or humans (Anderson, 1983). More than a decade later zero-tolerance expectations for suspect carcinogens were transferred to EPA with far reaching social and economic implications for all substances subject to regulation under wide ranging statutory authorities, for example, pesticides, gasoline (containing benzene and many other chemicals), and a multitude of pollutants emitted to air, water, remaining in drinking water, or found at waste sites. In the early 1970s, the only scientific evidence that determined the fate of a perceived pollutant, with focus on suspect carcinogens, was the classification of tumors in animals or humans. If tumors were found in test rodents given high doses of the chemical, the zero-tolerance goal for nonthreshold suspect carcinogens was applied in the earliest decisions at EPA, 1971–1975. However, this zero-tolerance/zero-exposure goal was found to be unachievable. It was recognized that risks are accepted in everyday life and achievement of zero tolerance for many economically important substances and source facilities would be seen as too disruptive for long-term achievement of environmental goals and unnecessary to achieve public health protective goals (Anderson, 1983). It became clear that more common ground was needed.

When the first risk assessment guidelines were issued at EPA in 1976 and signed into policy, they were completely novel (Albert, Train, & Anderson, 1977). The idea of risk acceptance was new. Establishing dose/response curves, comparing cancer incidence in animals or humans associated with exposure levels for quantitative expressions of risk, was unheard of in the world of regulation, except for ionizing radiation. Bioassay testing data to define dose response were limited. Remarkably, these approaches were adopted across all federal agencies, facilitated by the Interagency Regulatory Liaison Group (IRLG) in 1980, and by states, academic institutions, and international organizations. To be sure, these approaches were not perfect, but they stimulated further scientific study, facilitated evidence-based debate, and formed the basis for regulatory decisions. Previously, expert panels had been assembled to review the results of epidemiology and animal bioassay studies and make a qualitative judgement about the agent's potential to cause disease. These outcomes lacked clarity and consistency; often these panel decisions could be anticipated by knowing who served on the committee.

In summary, in the mid-20th century, science, policy, and a sense of mission converged to create a profound risk-based paradigm shift that proved reliable for changing course from an out of control, pollution filled environment. Today, the urgency created by concerns over present and future pandemics and the health, environmental, and socioeconomic consequences of climate change converge to drive expectations that science can again help societies meet the demands for solutions and corrective actions worldwide.

3. HOW CAN THE LEVEL OF COOPERATION, ACHIEVED IN THE MID-20th CENTURY, THAT WAS BUILT AMONG FEDERAL AGENCIES, THE NATIONAL ACADEMIES OF SCIENCES, AND PUBLIC/PRIVATE PARTNERSHIPS BE REPLICATED AND EXTENDED TO MORE EFFECTIVELY RESPOND TO 21st CENTURY CHALLENGES?

During the latter half of the 20th century, institutions to ensure continuity of scientific leadership, with permanence at the national and international levels, have been effective in providing consistent and reliable scientific assessments to achieve significant gains in public health and the environment. Success was achieved through timely interdisciplinary assessments, implementation continuity, and checks and balances through scholarship and peer review. In 1971, many newly formed institutions helped ensure the success of the environmental movement. Over the next decade, EPA, OSHA, the U.S. Food and Drug Administration (FDA), the U.S. Consumer Product Safety Commission (CPSC), and the Food Safety Office at the U.S. Department of Agriculture (USDA), assisted by representatives from the National Cancer Institute (NCI) and the National Institute for Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH), joined forces to form the IRLG and forge agreed upon guidelines for risk assessment. The Office of Science and Technology Policy (OSTP) subsequently chaired an update of the IRLG interagency guidelines published in 1986. Their guidelines ensured consistency across regulatory agencies in the United States and eventually across all states. Similarly, other countries and international organizations adopted similar approaches for assessing health risks from exposures to chemicals, often called "toxic chemicals." In the United States other institutions were formed to support the environmental sciences, including the National Toxicology Program (NTP) to support testing programs and provide an annual report to Congress on environmental carcinogens and the Agency for Toxic Substances and Disease Registry (ATSDR), attached to the Centers for Disease Control and Prevention (CDC), to investigate and declare emergencies at superfund waste sites and work with local communities. International organizations similarly became involved in this rapidly spreading effort to gain consistency and advance the sciences of risk assessment. The World Health Organization (WHO), formed in 1948, organized the International Agency for Research on Cancer (IARC) in 1965 and the International Program on Chemical Safety in 1980.

The OSTP earlier contributed the important concept of "risk characterization," bringing together the scientific conclusions, the quantitative risk assessment, and the narrative about the nature, consequences, and treatability or reversibility of health effects (Calkins et al., 1980). In Section 4 we address the interface of science and judgment, which evolved from this emphasis on risk characterization. In Section 7.1 and in Fig. A1 in the Appendix, we show the prominent place of risk characterization for the challenges of pandemics.

The National Academy of Sciences (NAS) was regularly called on to address scientific issues in risk assessment. The most prominent of the time, and still a landmark document, is its report *Risk Assessment in the Federal Government: Managing the Process* (1983), called "The Red Book" (NRC, 1983) The Red Book extended the EPA paradigm and the OSTP emphasis on risk characterization to explore the intricate relations between science and policy that inform us to this day. The controversies that triggered the request to the NAS remain salient: formaldehyde from insulation, nonnutritive sweeteners, nitrite preservatives, asbestos, invisible air pollutants, lead in old buildings, and reproductive hazards. At the time the NAS/National Research Council (NRC) Committee on the Institutional Means for Assessment of Risks to Public Health (also known as, the Red Book Committee) met, EPA had completed 150 carcinogen risk assessments of important agents in the environment and had largely addressed most through risk management, arriving at regulatory decisions consistent with its statutory mission to protect health and the environment (Anderson, 1983). The novel EPA approach of risk assessment and risk management was on trial; the Red Book endorsed these approaches and further defined the paradigm still in use today. EPA Administrator William Ruckelshaus highlighted the recommendations of the Red Book during his return to EPA (Ruckelshaus, 1985).

Further scholarship to advance the scientific methods used in risk assessment was assured by the formation of scientific groups and journals, notably the International Society of Risk Analysis and its flagship journal, *Risk Analysis*: An International Journal, and the commencement of programs to teach risk assessment and risk management in most major universities worldwide. These approaches worked because they organized all known relevant

science to lay out the weight-of-evidence that an agent might be capable of causing disease and, if so, the quantitative consequences, relying on models and extrapolations. A persistent goal has been the development of biomarkers of early effects, exposures, and individual variation in susceptibility.

The CAA Amendments of 1990 mandated a report from the NRC on "*Science and Judgment in Risk Assessment*" (NRC, 1994). The report made a useful distinction between variability and uncertainty, both of which are important in evaluating scientific studies of health effects and emission pathways and translating the scientific assessments into risk communication and risk management. The 1990 CAA also mandated the Presidential/Congressional Commission on Risk Assessment and Risk Management, which held hearings around the country and was influential internationally (EPA, 1997). The Commission addressed concepts like "bright lines" for exposures, individual variation in susceptibility (long mandated by the CAA), challenges in extrapolating effects from rodent models to human populations, and examples of strong evidence from mechanisms of action that certain chemicals produced serious health effects in rodents but not in humans. Furthermore, the Commission called attention to chemical mixtures and proposed a creative means for proactively engaging stakeholders, especially from exposed publics.

In summary, accomplishments of the 20th century included the adoption and refinement of accepted scientific approaches to describe and validate evidence of health and environmental risks. The future course was set by establishing institutions clearly charged with various roles in applying and advancing these methods to define public policies for risk management and regulatory decisions, informing the public and inviting public participation, and advancing scholarship and guidelines to inform interpretation of scientific evidence. Subsequent acceptance of these approaches extended to all health end points and public health policy decisions. Health risk assessment guidelines have been refined and extended since 1976. Both governmental and academic institutions remain in place to support and lead risk assessment and risk management efforts. Collectively these institutional involvements have assured the continuing acceptance and reliance on these approaches and have extended public confidence and involvement. During this period of accomplishment, it is notable that the focus was on scientific leadership with far less emphasis placed on national and world-wide political objectives.

Today a fresh look at institutional support in the 21st century is needed with a view toward defining the institutional roles necessary to meet current challenges. It is our view that interdisciplinary scientific committees are not as quickly assembled to address challenges and report out timely recommendations today as in the past. Examples of past interdisciplinary committees include the NAS/NRC Red Book Committee, the committees on Biomarkers from the NRC Board on Environmental Studies and Toxicology, and the NAS/NRC Committee on Remediation of PCB-Contaminated Sediments. Another productive model, especially for the mobile sources of air pollutants, has been the private/public partnership Health Effects Institute (HEI), founded in 1980 with Archibald Cox as chairman and funded one-half by EPA and one-half by 28 manufacturers and marketers of vehicles. HEI has produced >260 research reports with independent critical reviews, often examining the broader context of mobility and global comparisons.

Another of today's challenges and going forward is the constitution of expert and advisory committees. From the 1970s until recently, expertise dictated advisory committee appointments; however, currently the source of funding often determines who should serve and who should not. The basic principle that the greatest gains in scientific understanding will come from those most expert in an area, regardless of funding source, is useful in this regard. Critical review of all of the evidence is essential. Scientists are taught that peer review and efforts to come together to seek the truth should prevail. Of course, direct conflicts of interest must be disclosed and managed appropriately, as done at the NAS, for example. This principle is helpful to guide the selection of interdisciplinary expertise to advise public health decisions.

In summary, institutional leadership, with permanence and national and international roles, ensured the success of the scientific approaches and methods necessary to define risk assessment and risk management that were so important to the health and environmental gains of the last 50 years. Examples include the fact that heavily polluted rivers are now swimmable, and air pollution has greatly improved so that Los Angeles, Denver, Pittsburgh, and London are no longer plagued by heavy smog and limited visibility. To be successful going forward, similar institutional leadership will be necessary to address

the looming and most significant issues of the 21st century, at present defined by pandemics and climate change.

4. HOW CAN WE MOST EFFECTIVELY BALANCE THE NEEDS AND INDEPENDENCE OF SCIENCE IN RISK ASSESSMENT WITH THE POWERS AND RESPONSIBILITIES OF DECISIONMAKERS IN ORDER TO MAKE MORE SCIENTIFICALLY GROUNDED AND ACCEPTABLE RISK-RELATED DECISIONS?

Three statements address this question:

1. Science should not be simplified to ease the burden of risk management.
2. Clarifying the blurred lines between science and judgment can facilitate decisions.
3. The evolving choices of science-based judgments are becoming too complex and chemical specific for reliance on a simple set of agreed-upon judgmental choices (e.g., animal to human extrapolations) or to define single quantitative values for regulations and policy decisions.

Dating back to the Red Book in 1983, there has been a call for a clear distinction between science and judgment (NRC, 1983; Omenn, 2011). Dr. Roy Albert, the first Chairman of the EPA's Carcinogen Assessment Group (CAG), would often comment on this; to paraphrase: "attorneys would like a single answer because it would make their job easier. In fact, it is the responsibility of scientists to express clearly what is known and not known and present the results as clearly as possible. Most often the outcome will not be a simple categorical expression for weight of evidence, nor can a single quantitative number definitively establish safety." Often the lines are blurred, and judgment to address uncertainty is confused with scientific observation. The degree of scientific uncertainty must be expressed and considered in arriving at public policy decisions. Any expectation that science alone can deliver simple answers all too often overburdens science, leading to prolonged debate and stalled processes.

4.1. What Lessons Were Learned from Practices to Simplfy the Health Assessment Process in lieu of Evaluation of the Entire Body of Evidence?

The earliest decisions at EPA turned first to expectations that science alone could define safety and that the complexity of the array of sciences involved could be simplified to rely on only one or two disciplines. At that time, for suspect carcinogens, decisions relied solely on whether an agent could cause tumors in animals or humans, usually based on information from experimental studies in rodents. A nonthreshold dose–response relationship was accepted policy, resulting in zero tolerance for exposure.

The earliest regulations of suspect carcinogens at EPA targeted several highly visible substances. These decisions preceded the adoption of risk assessment; they rested primarily on pathology and tumor classification, clearly an oversimplification. One example from the administrative hearings was the decision to cancel the registration for the important pesticides aldrin/dieldrin and chlordane/heptachlor, which involved the testimony of several pathologists (Anderson, 1983). Some saw only cancer, others saw no cancer, and some reported inconclusive results. Efforts were made to refine experimental pathology criteria including use of blind coded slides and multihead microscopes through which multiple pathologists might reach consensus, but they all failed to do so. The fact is that there is no repository of infinite wisdom for such scientific conclusions. Understanding the complexities of the potential public health burden from exposures to these substances required consideration of much more than pathology alone. This example illustrates that, where definitive scientific agreement on one element of a complex array of scientific considerations is the basis for important societal decisions, debate can stall the decision process. In this instance, the expectation that a simplified set of pathology results alone, resulting in zero tolerance, could form the basis for effective gains in public health failed (Anderson, 1983). Outrage resulted from the simplified "cancer principles" codified in the legal documents for these decisions that basically defined a pathology finding in laboratory animal studies as a definitive definition of a human carcinogen for regulatory action. These oversimplifications formed the basis for the creation of risk assessment and risk management approaches. The intent of the original risk assessment guidelines was to lay out clearly the basis for determining the weight-of-evidence that an agent might be a carcinogen and then to

incorporate information about that agent's potency and the exposures to populations or single highly-exposed individuals as a basis for allowing the decision process to go forward. The expectation was that science and judgment would be clearly expressed. The resulting decision process, though not perfect, attests to the success of this shift from reliance on a single disciplinary consideration to a complex set of considerations dictated by use of the risk assessment paradigm. In search of simplifications in risk assessment, we can still observe the practice of heavily weighting single disciplines or qualitative factors while deemphasizing others, placing an emphasis on quantitative values while often ignoring the weight of the evidence.

4.2. How Can the Integrated Risk Information System or Any Single Repository of Health Risk Assessment Information, Including Cancer Potency Factors, and Reference Doses and Concentrations, Pivotal for Public Policy Decisions, Be Improved to Facilitate Risk Management?

Any expectation that a database can provide simple "look up tables" as the basis for complex and costly regulatory decisions is likely to fail. This observation is based on several decades of experience that repeatedly record failures to move forward toward the greatest gains for public health and the environment when shortcuts to simplify complex science are taken. Examples are reliance on a single qualitative consideration such as pathology, or simple letters to represent complex weight-of-evidence considerations. The 1976 and subsequent EPA guidelines avoided simple categorical designation; the exception was categorical letter designations for weight of evidence defined in the 1986 guidelines. Blurring lines between science and judgment to express a simplified quantitative value pivotal to costly public policy decisions remains a current problem.

For at least the last decade or longer, the Integrated Risk Information System (IRIS) database at EPA has been under review for failure to provide a single repository of timely, updated risk assessment information for a vast number of substances as a basis for public policy decisions within EPA and abroad. The NRC/NAS presented a review of IRIS in 2014 (IRIS, 2014). Certain high-profile IRIS documents took years to become final, for example, dioxin.[2]

One solution can be found in a review of the original mission of IRIS that differs from the current expectations that IRIS can provide a clear scientific departure for public policy decisions. A second reason for the stalled process is reliance on IRIS as source for simple quantitative "look up" values for cancer potency factors, and reference doses (RfDs) and reference concentrations (RfCs) for noncarcinogens. This use of IRIS is an oversimplification that places regulatory focus only on the quantitative values as presented while ignoring the role of science and judgement from which these values are derived and the qualitative weight of evidence for hazard evaluation. There are several reasons for the current conundrum. Initially at the EPA and in the NAS/NRC Red Book, judgmental factors were deemed necessary and methods for conventions to provide layers of public health protection were well-defined and often partly science and judgement-based conventions. However, over time, more complex methods for addressing uncertainties have evolved (e.g., modes of action, pharmacokinetics, and pharmacodynamics), have resulted in a complex array of judgmental choices that lack agreement based on convention and uniformity. Often, these judgmental choices may be chemical specific, which contribute further to inconsistent assessment outcomes. The simple, past agreements to ensure consistency and upper bound public health protection (e.g., a 10-fold safety factor for animal-to-human sensitivity) did not include many choices that vary among assessments and chemicals. Blurred lines between science-based evidence and judgmental decisions that address scientific uncertainty, intended to err on the side of public safety, are often hotly debated. Today the lines between science and judgment are neither commonly nor clearly expressed, leading to prolonged debates that stall decisions. The IRIS database is the most obvious target of these debates.

First, the original mission of IRIS was to serve the EPA internal needs for consistency in risk

[2]To date only the dioxin noncancer IRIS assessment is final, with the cancer reassessment still pending. The IRIS file, last updated in 2012, states "On August 29, 2011 EPA announced a plan to separate the Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments into two volumes: Volume 1 (noncancer assessment) and Volume 2 (cancer assessment and uncertainty analysis). The noncancer assessment and TCDD RfD are provided in this document. EPA will finalize Volume 2 as expeditiously as possible."

assessment results across program offices and, where inconsistencies did arise, to reach consensus or justify differences.[3] The IRIS database was not intended to serve as a repository of cancer and noncancer information for public policy decisions across all EPA programs and extend well beyond to support national and international organizations. Simply, IRIS was not intended as a repository of wisdom that could go unchallenged and remain up to date, especially where simple expressions are the basis for a wide array of public policy decisions.

In light of its original assignment, today's mission and expectation of the IRIS need to be reconsidered. These considerations must focus on the fact that no single database can be expected to provide an always up-to-date reference for quick and accurate classification of health endpoints and quantitative cancer potency factors, RfDs, or RfCs to support public policy decisions. The expectation that scientific assessment can be timely and simply available defines a mission impossible, one that can stall the decision process.

An effective separation of science and judgment within the IRIS files could go a long way toward clarifying the weight-of-evidence and quantitative expressions of potency for the decision process to go forward. Important lessons from carcinogen risk assessment can inform risk assessments for noncarcinogens. The same two important questions must be answered: (1) How likely is the agent to have the ability to impact human health for any end point? (2) And, on the assumption it can, what is the magnitude of the impact?

As for suspect carcinogens' weight-of-evidence (hazard) consideration, the best evidence is human evidence, backed up by animal bioassay outcomes, and supported by *in vitro* studies; next, the same signal repeated in multiple animal studies across species, strains, and sex, showing a clear dose–response relationship; then from studies that provide some, but lower, levels of confirming evidence. Weight-of-evidence statements that accompany RfDs or RfCs in IRIS focus on assigning the level of confidence for the selected study, not on the evidence that the agent associated with the critical end point in the first place. Rarely do comprehensive weight-of-evidence statements accompany RfDs or RfCs.

For suspect carcinogens, there is already recognition of an acceptable risk range between 1 in 1,000,000 and 1 in 10,000 (10^{-6} and 10^{-4}), with no bright line at 10^{-4}. However, there is no range clearly described for RfDs and RfCs, but a range based on science and judgment is possible.

In compliance with the intent of the Red Book and past risk assessment experience, IRIS assessments should include weight-of-evidence assessment for all noncancer endpoints (hazard) and make clear distinctions between science and judgment for describing quantitative outcomes that express RfDs and RfCs as a range rather than a single number. The shortcomings of focusing attention to a single number as the primary outcome from the noncancer endpoint assessment have been noted by others (Beck et al., 2016). From prior history, transparent expressions of these factors could greatly diffuse the controversies that stall the completion of single IRIS assessments and timely updates of previous assessments. Where further research can provide evidence-based science, judgments can be appropriately modified. Furthermore, transparent expressions of judgments may help clarify research priorities. Scientific uncertainty clearly expressed within a range can facilitate the wide array of public policy decisions that rely on these assessments, likely defusing some of the debate that stalls this assessment process.

4.3. Can Evidence-Based Science Be Separated from Judgment to Clearly Express Risk Assessment Outcomes?

We believe that the answer is yes, the pursuit of this separation will improve the risk assessment process and more accurately deliver foundational evidence for risk management. First, we observe that the assumption of the past that regulation of nonthreshold suspect carcinogens would amply protect against impacts of noncancer end points has been challenged for some substances where regulatory levels are defined below those of suspect carcinogens. Currently, the attention focused on defining the appropriate RfDs for a subset of per- and polyfluoroalkyl compounds (PFAS) based on a

[3] As chair of the first EPA intraagency risk assessment committee, ELA proposed, and the committee agreed to establish this database. In the beginning, all risk assessments were performed by the health assessment office within the research arm of EPA but as regulatory program offices commenced their own assessments, it became clear that different judgments across these offices were leading to different values of public health protective levels for the same substance and that a database to ensure consistency or, at a minimum explanations for the different outcomes was required.

combination of science and application of judgment factors illustrates this point.

The example of perfluorooctanoic acid (PFOA) is instructive, because, currently, different recommended RfDs have been suggested by several advisory committees and regulatory agencies. These differences derive from the interface of scientific evidence with the use of precautionary judgments to replace scientific uncertainty. The correct or most supportable value is a hotly debated matter. What is the correct answer? Is it the lowest RfD/RfC, or are some committees' judgments better than others? Careful consideration of the reasons for the differences leads to differences in selection of judgmental factors rather than in evidentiary science. The combined adjustment factors result in low levels approaching zero, reminiscent of zero-tolerance policies for suspect carcinogens.

PFOA has been extensively studied. In June 2018, ATSDR issued a major review of PFAS in its Draft Toxicological Profile (public review draft) (ATSDR, 2018). ATSDR evaluated 17 health endpoints form 271 studies of PFOA. Counting by study and endpoint, ATSDR indicates there were 231 human study-endpoints and 244 animal study-endpoints.[4] Human evidence for disease causation is inconclusive[5]; animal data have been used to derive RfDs and corresponding drinking water guidance levels (DWGLs).

Table A1 focuses attention on the role of precautionary judgments used to derive the noncancer reference doses (RfDs) and corresponding DWGLs for PFOA by EPA, ATSDR, and certain state public health agencies. They largely had the same scientific information available; their selection of different critical endpoints from different laboratory mouse studies account for 39-fold differences in the points of departure (PODs) used.[6] Additional precautionary judgments that lower the PODs to levels deemed protective range from 100 to 1,000 for the total of the uncertainty factors. Notable is the consistency amongst the previously defined, conventional judgement factors to address the possibility that humans might be more sensitive than animals or that human subpopulation groups might be more sensitive. In addition, a dose adjustment factor is used to account for differences in chemical persistence and volume of distribution between mice and humans ranging from 0.99×10^{-4} to 1.65×10^{-4} L/kg-day (a factor of 1.7), which further lowers the associated levels compared to traditional dose adjustment from mouse to human (based on body surface area). The RfDs derived by the different approaches range from 0.45 to 20 ng/kg-day, a 44-fold range. The relative source contribution factor (RSC), the fraction of the total exposure assigned to the source in question, drives the protective levels chosen lower when applied in the final derivation of the DWGL; the RSCs range between 20% and 50%.[7] The resulting range of DWGLs derived by these committees is from 2 to 70 ng/L (a 35-fold difference).

For risk characterization purposes, several comparisons are possible: margins of exposure (MOEs), comparison to other drinking water maximum contaminant levels (MCLs), and comparisons to levels for other nonthreshold, well-characterized carcinogens. Using the EPA definition, the MOE for drinking water at the EPA guidance level of 70 parts per trillion (ppt) is about 264,000 when comparing the animal dose at the lowest observed adverse effect level (LOAEL) to the human dose drinking water at

[4]These totals are the studies enumerated on ATSDR (2018) Figure 2-1. A study with more than one health endpoint examined would be counted more than once.

[5]ATSDR (2018) summarized the human evidence thus: "Although a large number of epidemiology studies have examined the potential of perfluoroalkyl compounds to induce adverse health effects, most of the studies were cross-sectional in design and do not establish causality. Epidemiology studies have found statistically significant associations between serum perfluoroalkyl levels and several health effects, although the results were not consistent across studies. Many of the studies reported dose-related trends, but these trends were not as apparent when comparing across studies; some effects were observed in populations with background PFOA levels but not in populations with high serum PFOA levels. Given the inconsistencies, a weight-of-evidence approach was used to evaluate whether the available data supported a link between perfluoroalkyl exposure and a particular health effect, taking into consideration the consistency of the findings across studies, the quality of the studies, dose–response, and plausibility. It should be noted that although the data may provide strong evidence for an association, it does not imply that the observed effect is biologically relevant because the magnitude of the change is within the normal limits or not indicative of an adverse health outcome" (p. A-3).

[6]The range of lowest observable adverse effects levels from different rodent studies and endpoints selected for the scientific points of departure, expressed as serum concentrations, is from 970 to 38,000 ng/mL, a 39-fold range. EPA (2016) would not have had the Li (2017) study, used by California (to derive the lowest DWGL and lowest RfD), but the others could have.

[7]The RSC is intended to reflect the fraction of an individual's exposure from the source, that is, drinking water. The DWGL is directly proportional to the RSC.

70 ppt (EPA, 2012),[8] and 1,400 when comparing the drinking water dose to the human equivalent dose at the point of departure from the animal study (EPA, 2014).[9] The lower end of the DWGL range, 2 ng/L, is about 35-fold lower primarily because of the choice of a different study for the extrapolation. Values in parts per trillion are rare and low for DWGLs. For example, all values within this range would be considered protective (estimated cancer risk range of 10^{-9}–10^{-6}) drinking water levels for well-characterized carcinogens, for example, benzene, arsenic, and vinyl chloride, and for PCBs (Aroclor 1254; estimated cancer risk range of 10^{-7}–10^{-6}), which have a half-life somewhat longer than PFOA (ATSDR, 2018; Ritter et al., 2011).[10]

Finally, the PFOA (and other PFAS) drinking water standard and risk reduction plans are a salient issue for risk communication in many states. A clearer expression of science at the interface with judgment would facilitate both decisions and public understanding, a purpose that disagreements about judgmental factors among committees cannot achieve. Bringing added importance, RfDs have many applications beyond drinking water. It is important to note that any published RfD, or range of RfDs, for any agent will be used for a variety of risk management decisions, not only for setting a drinking water MCL, which is also a risk management decision. Other uses of this RfD will include setting cleanup levels for superfund sites, water quality criteria for rivers, streams, sediments, soils, and safe levels in foods.

In summary, decisions would be facilitated if the entire array of judgments could be displayed, and risk management decisions judged to be adequately protective could be made accordingly. This approach has been the case with carcinogens where a clear weight-of-evidence statement for hazard is made. For application of quantitative judgments, a range of cancer risk probability in the range of 1 in 1 million to 1 in 10,000 (10^{-6}–10^{-4}) was defined by EPA as acceptable (EPA, 1991). Defining ranges of acceptable risk around the judgmental assumptions for noncarcinogens would be more transparent, would defuse debates about which judgements are the best, and could greatly facilitate a multitude of risk management decisions. In addition, for risk characterization, an MOE is useful for transparency and for placing various risk management considerations in context.

5. HOW MAY WE USE COMPARATIVE RISK ANALYSIS TO ADVANCE ENVIRONMENTAL HEALTH OUTCOMES THINKING AND ANALYSIS?

The sciences underlying risk assessment can be refined and beneficially leveraged to achieve the most significant net gains from public policy decisions in two ways as follows: (1) by setting priorities across an array of challenges and (2) by considering the net benefit of alternative risk management decisions. In this paradigm, the focus shifts from consideration of single incremental risk to net risk improvements, all with the goal of maximizing gains for public health and the environment.

Although not a new concept, comparative risk assessment appears to have lost its original use, that is in setting priorities for national and international agendas to maximize overall gains in public health and environmental improvements. Continued focus on small-incremental health and environmental improvements that may take years to achieve may be redirected to areas where the issues are urgent and where substantial gains may be expected. The purpose of comparative risk assessment is to establish priorities for resource direction, institutional focus, and scientific research. With more emphasis on national priorities, greater gains in public health and environmental improvements can be expected.

As a basis for public policy decisions on specific issues, net risk benefit to society can be considered through comparative risk assessment, for instance,

[8]MOE is defined by EPA as "the ratio of the toxicity effect level to the estimated exposure dose. The MOE is a ratio of the toxicity effect level to the estimated exposure dose. Uncertainty factors are used to determine the acceptable margin of exposure. An acceptable MOE for a NOAEL/NOEC-based assessment is 100 and for a LOAEL/LOEC-based assessment add an additional factor of 10 to give an acceptable MOE of 1,000 for a LOAEL/LOEC-based assessment." EPA Sustainable Futures/P2 Framework Manual (section 13 Quantitative Risk Assessment Calculations). https://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual

[9]The MOE is the ratio of the POD (in this case a LOAEL) to the actual exposure from drinking (in this case drinking water with 70 ppt PFOA). The POD LOAEL dose in the Lau et al.'s study used by EPA was 1 mg/kg/day; the human dose from drinking water at 70ppt is 0.00000378 mg/kg/day (70 ng/L ÷1,000,000 ng/mg × 0.054 L/kg-day) the MOE is about 264,000 (1/0.00000378). Using the human equivalent dose at the POD (Table 1) the MOE is 1,402 (5,300 ng/kg-day ÷ [70 ng/L × 0.054 L/kg-day]).

[10]Cancer risk at 2 ppt and 70 ppt based on scaling EPA regional screening levels for tap water are, respectively, 3.8×10^{-8} and 1.3×10^{-6} for arsenic, 4.3×10^{-9} and 1.5×10^{-7} for benzene, 1.1×10^{-7} and 3.7×10^{-6} for vinyl chloride, and 2.6×10^{-7} and 9.0×10^{-6} for PCB Aroclor 1254.

by comparing the risk reduction gained by the management alternative to the risk increase prompted by a range of different possible decisions. For example, the NAS report, *A Risk-Management Strategy for PCB-Contaminated Sediments* (NRC, 2001), endorsed a comparative risk assessment step. Before making a cleanup decision, the risk associated with the decision should be compared with the risk associated with the alternatives. The net risk reduction was endorsed as the most supportable public health basis for defining a cleanup decision going forward. This guidance became part of the EPA regional directives for these cleanup processes. Sediments are a particularly well-suited topic, because there is lots of disruption of the environmental site in any proposed cleanup, with potential adverse effects. Additionally, FIFRA anticipates that a comparative risk assessment be performed for the replacement of alternatives to cancellation and registration decisions for pesticide products.

For a long time, comparative risk assessment was controversial, in part because a common comparison proposed for accepted risks was cigarette smoking, whose aggregate harm to the population dwarfs harms from most other exposures. Our construct is focused on risk reduction alternatives within narrow categories of exposures and risk management actions.

6. WHEN SHOULD RISK ASSESSMENT AND RISK MANAGEMENT BE REORDERED TO MORE EFFECTIVELY ADDRESS CURRENT ENVIRONMENTAL HEALTH CHALLENGES?

For some compelling issues, where a serious risk is evident, the complexities involved in first defining that risk with certainty can lead to prolonged delays. For large and compelling challenges, moving the risk management component forward, with detailed risk assessment of remaining risks to follow, may expedite decisions and allow tangible and timely improvements in public health and the environment. Such was the case with the burden of toxic substances present in air nationwide; the risk conceptually was clear but data and methods to define the national risk for each air toxicant posed an enormous hurdle.

The experience with HAPs is instructive. In the original CAA, these section 112 pollutants that are suspect cancers and reproductive, neurological, or other severe. generally irreversible health effects were differentiated from the criteria air pollutants regulated by NAAQS under section 109. The initial risk assessment efforts focused on defining nationwide risks for individual substances. For suspect carcinogens, from 1976 forward, the scientific judgment applied linear dose–response to zero exposure, and then the statute required applying an "ample margin of safety," even more than the "adequate margin of safety" required for criteria pollutants. Debate over implementation persisted throughout the 1980s, with only asbestos, vinyl chloride monomer, and benzene put forward for regulation among the 187 HAPs originally listed. Moreover, vinyl chloride and benzene regulations were debated all the way to the Supreme Court. EPA's decision to shift priorities to other not-yet regulated HAPs rather than further regulation of vinyl chloride was upheld by the Court. For benzene, the Court instructed EPA to define what risk level would be deemed "adequately protective." EPA deemed a risk range from 10^{-4} to 10^{-6} lifetime upper-bound risk appropriate, with 10^{-4} defined as a presumptive "safe" level, that is, no bright line. After two decades, the CAA Amendments of 1990 introduced a pragmatic solution for source categories of 100 HAPs: first, identify and require the MACT by industry category, often dramatically reducing emissions and exposures; then within eight years conduct a determination of "residual risk" to adjust standards to protect health with an ample margin of safety and protect against adverse environmental effects. The latest chemical to be proposed for listing is 1-bromo-propane, for which EPA published a Federal Register notice on 18 June 2020. This two-step approach builds on the venerable practice of applying safety principles and available engineering technologies to reduce risks of exposure "as low as reasonably achievable," which originated in radiation protection.

After 30 years, MACT standards (step 1) have resulted in controls being installed on thousands of HAP sources. The follow-up residual risk reviews (step 2) have been completed for many HAP source categories.[11] These efforts underscore the heavy resource implications of trying to write federal risk-based standards for diverse sources scattered around the country, with the inevitable differences in exposure from site to site. Reliance on a risk management step before definitive risk assessment brought major success to what was termed "paralysis by analysis" by

[11] See https://www.epa.gov/stationary-sources-air-pollution/risk-and-technology-review-national-emissions-standards-hazardous

former EPA Assistant Administrator David Hawkins in 1981 in response to the book "*Clearing the Air: Reforming the Clean Act*" by Lave & Omenn (1981). In February 2018, EPA withdrew the 1995 "Once in, Always in" MACT policy, leaving only the area source standards that had been set for lower emitters.

In summary, 21st century policymaking can benefit from assessments that include evaluating the possibility that risk management may expedite improvements in public health and the environment followed by more detailed consideration of remaining risks to ensure adequacy and appropriateness of the chosen remedies.

7. HOW CAN THE RISK ANALYSIS PARADIGM BE USED TO INFORM THE CHALLENGES OF PANDEMICS AND CLIMATE CHANGE?

The last 50 years of experience that has led to substantial improvements in public health and the environment teach us that the following three components are necessary to meet these 21st century challenges:

1. Societal endorsement and understanding that change is needed and feasible to improve public health and the environment.
2. Adherence to scientific guidelines to ensure systematic approaches for research to support health and environmental risk assessments and provide an informed basis for public policy decisions and clear public communications.
3. Stable institutional leadership to ensure appropriate, timely, and comprehensive scientific inquiry, consistency, and clarity of communication, including clear evaluation of strengths and weaknesses of the scientific evidence and overall confidence in results.

Societal involvement in current 21st century challenges, seeking health, environmental, and social justice, is reminiscent of the societal stage set in the mid-20th century and discussed earlier in this article. From our 50-year history, we observe that momentum depends on informed social acceptance to improve health and the environment.

In this regard, the risk assessment/risk management paradigm can provide a basis for organizing complex, interdisciplinary inquiry and assessment to express what is known and unknown as a basis for informing the public and managing risk to achieve the greatest gains in public health and the environment. Transparency is essential for societal acceptance and for allowing essential scientific inquiry and effective public health decisions to move forward on both the pandemic and climate change challenges.

Institutional scientific leadership, both national and international, both governmental and academic, remains a challenge; lessons of the past 50 years establish the need for clear mandates to institutions, with a degree of permanence, to engage the best interdisciplinary scientists to ensure successful, timely gains in public health and the environment and the rightful place of science as a basis for effective decisions. We find that the two great challenges of the 21st century are likely interrelated; wide-ranging stresses of climate change may play a role in pandemic occurrence now and in the decades to come (Kunreuther & Slovic, 2020).[12]

7.1. Pandemics

The long history of pandemics includes the 1918 virulent influenza that killed 50–100 million people; the 2002 SARS outbreak that was largely contained; the 2012 Middle East Respiratory Syndrome virus (MERS-CoV) that infected 1,800, of whom one-third died; the 2014–2015 Ebola outbreak in Africa that killed 11,000; and a variety of pandemic influenzas in 2005, 2006, and 2009 that infected millions worldwide (NSTC, 2016; Osterholm, 2005). Viruses often exist without harm of pandemic proportions; for examples, the Zika virus was discovered about 70 years ago in Africa but had caused only mild disease and occasional outbreaks before dying out before outbreaks in 2015–2016, and Ebola had been known for decades but had previously infected no more than 500 people. Moreover, the human immunodeficiency virus (HIV) was dormant in Africa for decades before spreading globally and causing millions of AIDS deaths.

The number of outbreaks appears to have been increasing since 1980 (Smith et al., 2014). These outbreaks include new and re-emerging diseases with potential to cause impacts on public health with adverse economic consequences. One analysis predicted in 2005 that, despite modern advances, a severe influenza pandemic could kill at least as many people as the 1918 pandemic and bring about a global recession (Osterholm, 2005).[13] The awareness of pandemics together with the historical identification and

[12] See Kunreuther and Slovic (2020)
[13] World Bank (2008)

control of massive spread of such infectious agents as tuberculosis, measles, smallpox, polio, and chickenpox strongly support the need for effective strategies to manage pandemic threats. No doubt, these strategies must rely on interdisciplinary scientific expertise for emergency response, global surveillance for zoonotic animal to human transmission, and longer-term pandemic management. A clear framework for assessing complex scientific information and directing short- and long-term research efforts is necessary as a basis for effective public health policies and communication. For short-lived pandemics, emergency response and control measures may be effective; however, for longer duration events, managing the continuing spread of infection while awaiting effective treatment and vaccines becomes more challenging. Well-organized scientific national and international institutional leadership is critical, especially for managing persistent viral spread, as is the case with SARS-CoV-2 and the resulting COVID-19 illness.

7.1.1. The Need for Permanent Institutional Leadership

The National Academies represent a resource that does not have large swings in priorities or risk management direction often associated with political transitions. The website contains 51 study and workshop reports from the past 20 years, and especially during 2020, directly applicable to specific aspects of hazard identification, exposure assessment, and risk management for the current pandemic. There are detailed reports relevant to our example that follows about aerosol transmission (Anderson et al., 2020). Continuity in the government is desirable, as well, and often is overseen by the OMB or the interagency National Science and Technology Council (NSTC) led by the OSTP. We reviewed existing models for organizing institutional and national leadership to address pandemics.

In 2016, the executive office of the President created the Science and Technology Working Group of the NSTC (NSTC, 2016). The 2016 Pandemic Playbook laid out clear responsibilities for executive branch departments and White House staff, including the OSTP and the National Security Council (NSC). The Working Group disappeared with the change of administration.

The current COVID-19 advisory group to the President, chaired by the Vice President, is another model and is supported by existing departments within the federal government, prominently including the NIH Institute of Allergy and Infectious Diseases, FDA, CDC, Surgeon General, Biomedical Advanced Research and Development Authority, Veterans Administration, Federal Emergency Management Administration (FEMA), Department of State, NSC, and Department of Homeland Security (DHS). Since the first committee met to advise the federal government on bioterrorism in 2004 (EPA, 2004), the DHS has been assigned a special role to ensure the adequacy of preparedness for emergency response and surveillance. Currently for the SARS-CoV-2 pandemic, DHS compiles master questions and reports on evolving publications of research efforts in certain categories to inform across governmental agencies. In this current model, the focus is on disease epidemiology and reactive public health measures to control public health impacts. Far less focus is placed on a comprehensive plan to define and carry out research to answer the compelling questions of risk assessment to inform interdisciplinary investigations of all factors necessary to guide further research, public policy decisions, and public communications, for example, all factors involved in virus characterization, survival, and transmission.

The earlier model of 2016 has the advantage that it provided leadership with cross-agency expertise to address the pandemic threat. Its weakness was that it anticipated more a need for immediate pandemic response and management with less emphasis on longer-term interdisciplinary strategies for addressing persistent pandemics. The weakness of the current Presidential Task Group is that it is largely reactive rather than focused on a coherent program for advanced preparation and strategies that would be expected of a permanent agency or institute. Both lack mandated permanence and well-defined missions.

Lessons learned so far from the SARS-CoV-2/COVID-19 pandemic suggest that a permanent interdisciplinary institution with cross-agency membership, supported by outside advisory groups, for example, the NAS, and active across international communities is justified for both proactive planning in advance of a pandemic and to manage a continuing pandemic. A permanent institutional approach can organize and inspire needed research and supervise an orderly assessment of all of the evolving scientific evidence to inform public policy decisions, direct/coordinate short- and long-term research needs, and inform more strategically focused and permanent solutions for present and future

risk assessment and risk management public policy decisions for evolving pandemic challenges.

7.1.2. Interdisciplinary Risk Assessment and Risk Management Paradigm: Science and Public Health Strategies

Use of the risk assessment and risk management paradigm can bring essential scientific focus to research needs in order to inform scientific assessment and public health directives. The first line of defense against pandemics is global surveillance for emerging infections, particularly evidence in known animal hosts and evidence of animal-to-human transmission. Mounting early risk-based approaches to focus on science can provide an organized and sound basis for containment of the pandemic and development of more specific public health guidance to protect and prevent the spread of disease. Early and continued focus on infectious disease epidemiology is required to identify populations at risk, define the characteristics of spread, and determine immediate control measures; however other important considerations, for example, transmission, must not be ignored. Immediate response control measures may employ blunt instruments of shelter in place, physical/social distancing, disinfection, contact tracing, and quarantine of infected individuals. If the outbreak is adequately controlled by virus die-out, existing immunity, specific treatment, or effective vaccines, no further characterization may be necessary. For SARS-CoV-2/COVID-19, use of the risk paradigm can guide better characterization of the virus, infecticious dose, survival conditions and transmission. Clear focus on scientifc assessment can eliminate conflicting and confusing public health guidance that leads to varying degrees of compliance. Strategically focused public health solutions based on scientific understanding are essential for defining options to limit social and economic impacts.

For SARS-CoV-2, effective reactive policies employed to date have deployed public health control measures primarily based on monitoring of newly identified cases, hospital admissions, and mortality statistics. The absolute meaning of the numbers remains elusive, except perhaps for comparison of mortality statistics, because the denominators are difficult to define. The public grows restless as social and economic stress continue. The risk assessment and risk management paradigm accommodates the search for effective solutions by structuring clearly what is known and unknown at any point in time, identifying the most significant gaps in knowledge that can be effectively filled with better scientific information, and informing the public of the reasons for various public health directives.

The risk assessment and risk management paradigm as applied to the continuing SARS-CoV-2/COVID-19 pandemic is outlined in Figure A1. Research falls into three primary categories: the need to further characterize SARS-CoV-2, treatment strategies, and vaccine development. Each of these research areas has primary lines of inquiry that can be organized to direct and inform risk assessment which in turn informs public health policy and risk communication. Clear tracking of progress and inquiry is important for policy and communication purposes.

For hazard identification, there is no doubt that this virus poses a hazard of illnesses and death, but many lines of inquiry remain open. Why is the virus so virulent in some, while other infected individuals develop only mild symptoms or no symptoms? While age and health status explain some of the observations, much remains unknown. What specific lines of inquiry might best contribute answers? Centralized risk assessment approaches can encourage a highly structured, scientific approach to inform and advise.

For dose–response, there is only limited definition of infectious dose, but principles from environmental health inquiry contribute the long-accepted principles that dose is duration, concentration, and frequency dependent. For example, a brief elevator ride provides a far different opportunity for exposure/transmission than a long dinner, a choir practice, or an eight-hour workday. Yet today the public seems uninformed of these basic principles.

Multiple disciplines are needed to identify and refine exposure/transmission factors for policy and communication purposes, for example, the role of duration, ventilation and other enclosure factors, exertion (the role of aerosol size and delivered to respiratory tract), temperature, humidity, aerosol/air transport, and surface exposures (under differing conditions). Some of this information can be obtained easily, for example, temperature and humidity influence on organism viability and implications for transmission. From prior experience, we know that public acceptance and compliance is greatly improved when the public feels included in the decisions and when the messages are consistently supported by the latest scientific information.

7.1.3. Use of Risk Assessment Paradigm to Investigate the Evidence for Aerosol Transmission

We were the first to apply the risk assessment/risk management paradigm to the limited question of the potential for small particle airborne aerosol transmission, as described in our publication of May 1, 2020, consideration of aerosol transmission of COVID-19 and implications for public health (Anderson et al., 2020), now being reported in an increasing number of publications. The July 8, 2020 WHO response to a letter signed by 239 scientists calling for acknowledgement of the importance of airborne transmission via aerosols is not necessarily a debate that should be occurring in July 2020; note in October 2020 the CDC guidance finally recognized that air borne transmission by aerosols as a compelling factor in the spread of COVID-19. Earlier investigation and assessment could have produced the needed information to inform a clear decision for public health protection and explanation for public consumption, including a consistent and well-articulated policy for masks and considerations of enclosure safety (e.g., buildings, homes, aircraft, and ships); shelter in place, if the wrong place could lead to greater spread.

In our publication, we propose that the potential importance of aerosol-related transmission may be investigated within the risk paradigm. This is but one use of the risk assessment paradigm for addressing pandemics, nevertheless an instructive one. While this is primarily an exposure issue, it carries implications for hazard identification and dose–response.

Hazard identification. Can infectious aerosol transmission of particles less than 1 μm in diameter deliver infection to the deep lung alveoli and, if so, be a factor in rapid disease progression in some individuals and communities? If so, information about exposure history might inform rapid treatment decisions and remedial actions, for example, mask use and infectious disease potential investigations within buildings and under conditions where epicenters have been noted.

Dose response. What role does aerosol size play in defining dose–response, and how would this inform public health policies? How does dose response vary with aerosol and droplet size? Might the same infectious larger bio-droplet-delivered dose to only the upper respiratory track be less infectious than the same dose to the deep lung, for example, by aerosols smaller than 1 μm in size?

Exposure/transmissions assessment. Answers to the following questions are important to guide science-based public health policy, especially to containing the surge in cases and defining conditions to reopen the economy. Short-term research, defined within the risk paradigm, can be directed to answer some of the following questions with the indicated importance for risk management and public policy decisions.

- Why is this virus so easily spread? This observation implies an important role for aerosol–air pathway transmission, as has been observed for other such infectious agents as measles and chickenpox. If so, risk management and public policies can better address a wide range of issues for distancing, management of air and transmission control measures within buildings, and mask use.
- What mechanism can account for the spread of the virus by asymptomatic individuals? A substantial role of transmission by asymptomatic individuals is now strongly implied (Li et al., 2020; Prather, Wang, & Schooley, 2020). The role of aerosol transmission is clearly supported. Risk management will require other means, especially viral testing, to identify and quarantine these asymptomatic cases with implications for defining age group interactions. To prevent aerosol transmissions, mask wearing is clearly necessary to protect one's self as well as others. For this simple measure, perfect evidence is not necessary. In our publication of May 1, 2020 we presented the evidence for airborne-aerosol transmission implying strongly a role for mask mandates; however it has not been until months later that some states have mandated masks as important public heatlh measures for protection and re-opening the economy (Anderson et al, 2020).
- What do the epicenters of outbreaks—for example cruise ships, certain types of nursing homes but not others, prisons, and disadvantaged neighborhoods—have in common that might guide future public health policies? For example, are certain types of buildings (enclosures) more infectious than others by design? Does shelter in place put some individuals at

greater risk in certain circumstances defined by housing? Risk management and public policy decisions can benefit from short-term research to further elucidate these factors as a basis for risk management of indoor environments and to provide guidance for reopening the economy and schools.

- Overall, what is the role of air transport of infection by aerosol? Beyond the disease model that addresses bio-droplets of >5 μm to prescribe 6-foot guidance, does the potential of longer air transport support additional guidance? For example, limited weight-of-evidence can justify precautionary measures such as clearly recommended mask use where the benefits are enormous, and the monetary or societal burden of implementation is small. If recognized early, can more strategically designed measures provide protection while providing a safe reopening for certain parts of the economy?
- What is the effectiveness of certain types of masks? Are simple cloth masks likely to be as effective as N95 or other medical grade protective means for the public? As the pandemic continues, clear information and communication can reduce confusion and aid in public acceptance and compliance.

Assembling information about approach and result under each topic in the risk paradigm can inform scientific advancement, the risk assessment process, public policy guidance, and information for public understanding. Currently the DHS online effort to assemble all available publications under a series of broad questions of inquiry is helpful but lacks interdisciplinary scientific assessment to interpret the meaning and significance of the evolving evidence. From our health and environmental risk assessment background, we note that public health decisions to regulate or not to regulate must be made in the face of scientific uncertainty; better decisions rely on a careful and full assessment of all of the evidence; future adjustments can be made as gaps in knowledge are filled. The same proposition may be advanced for this pandemic.

A framework for organizing what is known and unknown about SARS-CoV-2 in all respects is needed to address the surging spread of COVID-19, to better inform an understandably distrustful public, and to guide the reopening of societal functions worldwide.The aerosol transmission issue is but one of the many practical examples of risk factors to be addressed as a basis for further sharpening the effectiveness of public health guidance and for gaining societal acceptance.

7.2. Climate Change

Approaches to date have made some important advances world-wide toward recognition and control of climate change, but effects continue at a pace that may be outdistancing improvements. Lessons learned from the dramatic reversal of environmental declines in the first half of the 20th century advise that more aggressive science-lead initiatives are necessary to address climate change.

In this section, we provide a brief history of current progress to recognize and address challenges of climate change. From lessons learned in the past 45 years of health and environmental progress, we address the following essential elements of risk-based strategies to organize and advance progress. A risk assessment framework can structure and guide effective strategies to achieve definable goals for reversing climate change where the magnitude and urgency of the risk is clear. Emphasis is needed to define risk management strategies that are socially and economically achievable. To define and achieve these alternatives will likely require a paradigm shift to place emphasis on risk management solutions, in addition to regulation of emissions. This effort will likely involve legislatively empowering national scientific, interdisciplinary leadership to identify and guide research, and solutions to achieve risk-based goals while facilitating effective international solutions. Finally, it is imperative to set timely goals for achievement, marked by landmarks along the way (defined by risk assessment), to clearly advise the public of progress and ensure societal support.

For several decades we have known that climate change and global warming present a serious threat to the United States and the world. Science described the greenhouse gas (GHG) effect in the 20th century, and our ability to monitor global temperatures has improved dramatically over decades. Since the late 1980s, many scientists had been convinced that global warming is real and a significant threat. In 1989 the Intergovernmental Panel on Climate Change (IPCC) was established. In 1991 the National Academies published a report recommending preemptive action for a triple benefit: reducing air pollution health effects, relieving dependence on Middle Eastern oil, and reducing carbon loading that would increase global temperatures with serious

consequences (IOM, 1991). In 1997, the United States and many other countries signed the Kyoto Protocol, committing to global reduction in GHG emissions. In the United States the Interagency Climate Change Adaptation Task Force, composed of over 20 federal agencies and executive branch offices, was formed in 2009 (EOP, 2010).[14]

EPA has achieved many milestones in the advancement of climate change science and regulation.[15] In 2007, 30 EPA scientists shared the Nobel Peace Prize for their international work on climate change. In 2009 EPA issued its GHG endangerment finding requiring GHG to be regulated under the CAA. Other actions included the GHG fuel efficiency standards for trucks and buses (EOP, 2010), a proposed carbon pollution standard for new power plants (EPA, 2012), updates to air pollution standards for oil and natural gas (EPA, 2012), and guidelines proposed to cut carbon pollution from existing power plants (2014).

In 2013, the Office of the President issued the Climate Action Plan, a multifaceted approach to reduction of GHG, involving many parts of the federal government (EOP, 2013). Three of the key aspects were to (1) cut carbon pollution, (2) prepare for impacts of climate change, and (3) lead international efforts. The plan included increased funding for clean energy and investment in energy technologies as alternatives to carbon emissions. Recent discussions have highlighted five sectors of particular interest (Perciasepe, 2020):

1. Electricity/power: Implementation of renewable energy, need to address emissions from coal and natural gas and develop clean energy standards.
2. Transportation: Much progress on technology has been made by the auto industry (e.g., electric). Need for electricity and perhaps hydrogen infrastructure.
3. Industry: A complex category, electricity, heat, chemical processes.
4. Buildings: Operational and "embodied" carbon (e.g., steel manufacture).
5. Agriculture: Carbon sequestration, biofuels, and food production.

In late 2015, 195 countries adopted the Paris Climate Agreement, which allows for setting targets for GHG reductions and reporting of their results. It is universally recognized that international, global-scale action is needed to combat and mitigate climate change, and that any actions in the United States alone would not be enough to curb the problem. Thus, international cooperation is paramount.

Much has been done in the field of climate science results from a broadly characterized, risk-based understanding of this serious challenge. Institutional knowledge is deep. What is happening to the atmosphere and the oceans is well-established and modeled for the coming decades, and what must be done is known. So, the question becomes how to go about achieving effective goals to curb climate change on an urgent basis?

The commonality of urgency and mission of the mid-20th century can inform the 21st century grand challenge of climate change. Like past challenges, climate change has both health and environmental consequences. The risk assessment and risk management framework can be used to inform effective programs. Addressing climate change requires a highly coordinated effort across virtually all governments, nationally and internationally. Also, close cooperation with industry and other affected sectors is necessary. Efforts in developing technologies and economically beneficial solutions must be made in parallel with development of new regulatory approaches that inspire and facilitate major risk management solutions to address climate change, placing risk management solutions at the fore front. The search for effective risk management solutions and reformulation of regulatory approaches that differ from chipping away at the issues through only regulation of emissions, implies that classic command and control regulation is not the only tool in the toolbox. Risk communication with the public is also an important part of the effort. The better informed the public is, the more likely it is to understand and accept proposed changes and resist self-interested short-term-oriented opposition.

Leadership is needed from strong and permanent national and international institutions. The paradigm of risk assessment and risk management

[14]These include the following departments, agencies and councils: agriculture, commerce, defense, education, energy, health and human services, homeland security, housing and urban development, interior, state, transportation, treasury, Agency for International Development, U.S. EPA, National Aeronautics and Space Administration, National Intelligence Council, Millennium Challenge Corporation, and the Council on Environmental Quality. See https://www.epa.gov/sites/production/files/2015-12/documents/interagency-climate-change-adaptation-progress-report.pdf

[15]See https://www.epa.gov/history/milestones-epa-and-environmental-history

provides an effective framework for more clearly organizing what is known and unknown to curb the alarming rate of climate change. Like worldwide environmental health risk assessment challenges, preparedness and response to climate change require interdisciplinary scientific approaches.

If predicted global climate impacts are to be reduced, time sensitive goals need to be set with a commensurate series of risk assessment and risk management steps to make achievement possible, with emphasis on replacing fossil fuels in many industries with alternative, effective substitutes while mitigating major societal disruption. Public-private partnerships may provide definable risk management solutions for dramatic reductions in fossil fuel reliance. Assessing improvements to moderate climate change by management of major causes suggests a role for reversing the risk assessment/risk management step, similar to the example of the CAA regulation of HAP sources where technology standards were applied and then followed by evaluation for residual risk. Fortunately, wind- and solar-based alternative energy sources are becoming more efficient and much more cost-competitive. Of course, that comparison would be even more attractive if the full costs of the environmental burden of fossil fuels were captured in the cost comparison. Additional alternatives might include advanced carbon capture, sustainable forests, battery technology, fuel cells, and possibly small advanced nuclear reactors (Perciasepe, 2020).

Policy decisions to increase reliance on energy production from one form of fossil fuel to another, for example natural gas production from hydrofracking, run counter to the need for a paradigm shift to other reliable, sustainable energy alternatives (Howarth, 2019). Although lower in quantitative abundance, methane can contribute a disproportionate warming impact compared to carbon dioxide (a pound of methane has up to 80 times the greenhouse effect of a pound of carbon dioxide). Consequently, policy decisions need to address near-term climate warming impacts from differing fossil fuel sources as well as shifting to alternatives. Impacts on climate change from near-term releases also must be considered and controlled while implementing a paradigm shift to fossil fuel alternatives, for example, methane releases from abandoned hydrofracking sites (Tabuchi, 2020).

Climate change has far reaching implications that include impacts on human health and spread of infectious diseases. Similarities between the management of climate change and pandemics have been described (Bernstein & Salas, 2020; Liu et al, 2020;Perciasepe, 2020; University of Pennsylvania, Wharton, 2020). With regard to COVID-19, the WHO states,

> "[C]limate change may indirectly affect the COVID-19 response, as it undermines environmental determinants of health, and places additional stress on health systems, especially in coastal regions. More generally, most emerging infectious diseases, and almost all recent pandemics, originate in wildlife, and there is evidence that increasing human pressure on the natural environment may drive disease emergence. Strengthened health systems, improved surveillance of infectious disease in wildlife, livestock and humans, and greater protection of biodiversity and the natural environment would reduce the risks of future outbreaks of other new diseases." (WHO, 2020)

The IPCC intends to report on its evaluation of links between pandemics (e.g., zoonotic diseases) and human pressures on the natural world to guide policymakers in its 2021 climate report (Doyle, 2020). The challenges for risk management approaches share the common threads of urgency, the need to be proactive, and the need for institutional, national, and international leadership to arrive at meaningful solutions to these problems.

8. DISCUSSION AND CONCLUSIONS

Worldwide 21st century challenges such as pandemics and climate change require timely and interdisciplinary scientific assessments to focus research agendas and guide public policy actions. Unfinished business remains from the last 50 years of progress to protect public health and restore the environment. In order to maintain critical scientific focus to meet these challenges, we recommend the following steps:

- Recognize and take advantage of current societal attention and expectations for solutions, reminiscent of that of the last half of the 20th century, to address the devastating impacts of the current SARS-CoV-2 and future pandemic threats and climate change.
- Rely on the proven risk assessment framework to guide near- and long-term research agendas into the various unknown facets of COVID-19 which would ensure focused investigation on a national scale to organize and effectively focus and supplement the work being initiated by individual researchers. For example, short-term research to answer practical questions of transmission potential and virus viability and safety

measures within enclosed spaces could be immensely helpful to strategies to limit spread and reopen schools and businesses.

- Place major emphasis on developing new risk management approaches through new forms of regulatory considerations and public–private partnerships to define and provide incentives for a dramatic and timely shift from reliance on fossil fuels. Continuing climate change is not being sufficiently mitigated even though some progress has been achieved by traditional regulations and agreements to limit emissions, primarily from the use of fossil fuels.
- Legislatively mandate stable institutions to ensure strong interdisciplinary scientific leadership for pandemics and climate change, similar to actions taken in the 20th century to ensure public health improvements and environmental restoration. For pandemics, stable leadership is needed to focus not only on emergency preparedness but also on long-term national and international research and assessments to support the multifaceted scientific challenges presented by pandemics and climate change. Similarly, to dramatically mitigate climate change impacts, coherent leadership is required to define integrated programs with timelines; focused scientific risk-based approaches are needed to redefine the new directions and new approaches needed for timely progress.
- Adopt a consistent approach to scientific assessment and policy analysis for management of both pandemics and climate that can define research agendas and assessments as a basis for public policy and timely progress to meet scientific goals for improvement.
- Reframe the currently polarized science advisory board processes to ensure that the most knowledgeable experts are convened to advise on scientific assessments; funding sources of relevant peer-reviewed research should not discredit important scientific contributions; rather, critical review of all scientific information can sort the credible contributions to assemble the best and most supportable conclusions. Clearly, direct conflicts of interest and bias to protect a business interest or to secure repeat funding for academic research are to be avoided. Balance, expertise, and relevant scientific breadth brought together through peer-review should prevail. Historically this approach has served well.
- Inform the impacted public of the scientific foundations for each policy decision or public health guideline with consistency and clarity. Public acceptance and compliance are best achieved by meaningful public engagement, providing clearly articulated scientific bases for public health decisions and guidance.
- Make improvements in scientific assessment at the interface with public policy to address the unfinished business after a half century of achievement to protect public health and the environment. Over forty-five years of use, the risk assessment and risk management framework has matured in many positive directions, but a drift toward simplification of complex scientific assessments has resulted in misunderstandings and obstructions to decision making.
- Recognize that the complexity of scientific uncertainties should not be simplified to ease the process of risk management and public policy formulation. Categorical expressions for weight-of-evidence can mask the underlying scientific uncertainty and blur lines between science and judgment. Weight-of-evidence statements for suspect carcinogens are common and should be extended to qualitative evaluation of noncancer endpoints. Historically, guidance for carcinogen weight of evidence evaluations have provided a systematic assessment of data from human studies alone, human evidence backed up by animal bioassay studies, and for combinations of animal bioassay studies. Similar guidance should apply to the relevance of signals from noncancer endpoint investigations.
- Recognize that quantitative measures of potency from dose response information for suspect carcinogens and noncarcinogens have multiple applications for a wide variety of public policy decisions with varying societal impacts. Single expressions to reflect cancer potency for suspect carcinogens and RfDs or RfCs for noncarcinogens carry considerable significance but do not reflect the range of uncertainties underlying these expressions; they often lead to prolonged debates that stall the risk management decision process.
- Separate science and judgment as originally called for in the Red Book from the NAS. Express a range of values for RfDs and RfCs rather than a single value. Expressing ranges of values can facilitate the assessment process, including IRIS database assessments, and allow

decision processes to go forward. The common practice of applying agreed upon judgmental safety factors to account for uncertainties for humans based on signals determined in laboratory animal studies and for variation in sensitivity among humans has become more substance specific. However, multiple judgmental or uncertainty factors that taken together markedly reduce RfCs and RfDs define a range of very low, single-point values often below those identified for carcinogens.

- Include risk characterization for each risk assessment that characterizes the context and reasonableness of the results after application of a series of judgmental or selective factors. Effective risk characterization can include comparison to suspect carcinogens, values for other similar agents, understanding of the nature and reversibility of harm, and use of margins of exposure.
- Refresh the use of comparative risk assessment to direct our resources to the most important health and ecosystem threats. Achieving the greatest gains in public health and environmental restoration has long been the foundational goal of the environmental movement and the policy focus of the regulatory process commencing with EPA in December 1970. In addition, comparative risk assessment can ensure maximum net benefits among alternative public policy choices for individual decisions. Currently, systematic consideration of comparative risk is most often lacking. Prolonged debates to achieve small incremental gains can divert resources from opportunities to make major improvements in health and the environment.
- Reverse the steps of risk assessment and risk management for specific matters to achieve the most beneficial and acceptable results, as was the case to achieve nationwide improvements from the burdens of air toxics under provisions of the 1990 CAA. Moving earlier to the widely recognized need for risk management can sometimes facilitate timely results with reduced resistance. For example, in the case of air toxics assessment of residual risks following application of best available technologies. Similarly, reversing climate change may rely on risk management focused on reduction of carbon emissions from fossil fuels; cooperative and diligent pursuit of workable alternatives can facilitate results. Public–private partnerships may facilitate workable risk management solutions. A paradigm shift in regulations may be necessary to place emphasis on solution driven strategies rather than those focused primarily on emission regulations.
- Seek to maintain scientific leadership on matters that are scientific. While risk analysis has become more prominent, political intervention at the federal level in many countries across the globe has made it more difficult to ask good questions, find good answers, and implement decisions based on science. It is not just the United States that has this challenge. Leadership is hard to establish in anti-science environments. The foundational principles of the risk paradigm articulated by the NAS emphasize the importance of maintaining an effective separation between risk assessment and risk management ensuring the integrity of the scientific, health risk assessment process.

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Appendix

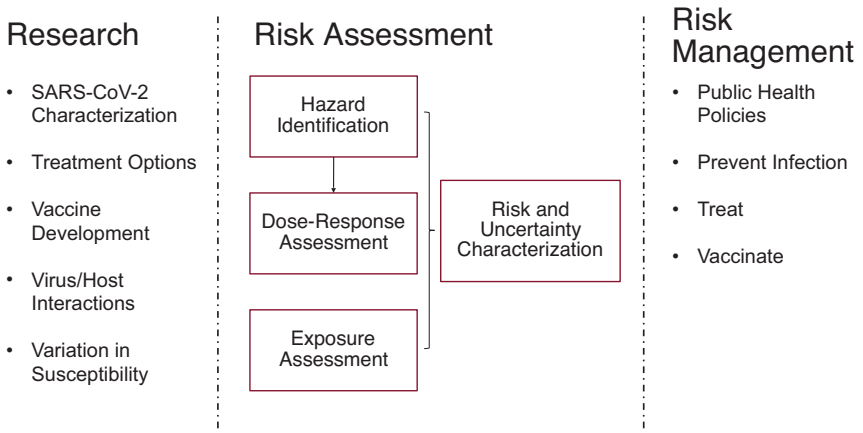

Fig A1. Risk assessment paradigm to address COVID-19

Table A1. Drinking Water Guidance for PFOA

	Parameter	Units	USEPA	MNDOH	MADEP	ATSDR	MDHHS	MSAW	NJDWQI	NHDES	CA OEHHA
Year			2016	2018 (August)	2019	2018	2019	2019	2016 (June)	2019 (June)	2019
PFOA	DW guidance level	ng/L	70	35	20	*10.5:*	9	8	14	12	2
Key Study Information	Key Study Reference	-	Lau et al. (2006)			Onishchenko et al. (2011); Koskela et al. (2016)			Loveless et al. (2006)		Li et al. (2017)
	Species	-	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse
	Study Exposure Duration	days	17	17	17	20	20	20	14	14	28
	Selected Critical Endpoint	-	Developmental (reduced ossification, accelerated puberty)	Delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased maternal liver weight; + several co-critical effects listed	Developmental (reduced ossification, accelerated puberty)	Neurodevelopmental effects (decreased number of inactive periods, altered novelty induced activity) in mice (Onishchenko et al. 2011); Skeletal alterations in mice (Koskela et al. 2016)	Neurobehavioral effects (decreased number of inactive periods, altered novelty induced activity); (Onishchenko et al. 2011) skeletal alteration such as bone morphology and bone cell differentiation in the femurs and tibias.	Neurobehavioral effects (decreased number of inactive periods, altered novelty induced activity); (Onishchenko et al. 2011) skeletal alteration such as bone morphology and bone cell differentiation in the femurs and tibias.	increase in relative liver weight	increase in relative liver weight	Hepatic mitochondrial membrane potential changes, increased biomarkers of apoptosis, increased oxidative DNA damage

(*Continued*)

Table A1 (Continued)

	Parameter	Units	USEPA	MNDOH 2018	MADEP	ATSDR	MDHHS	MSAW	NJDWQI 2016	NHDES 2019	CA OEHHA
Year			2016	(August)	2019	2018	2019	2019	(June)	(June)	2019
PFOA	DW guidance level	ng/L	70	35	20	*10.5:*	9	8	14	12	2
Dose-Response	Dose-Response POD Modeling Method	-	LOAEL	LOAEL	LOAEL	LOAEL	LOAEL	LOAEL	BMDL	BMDL	LOAEL
	POD Serum	ng/mL	38,000	38,000	38,000	8,290	8,290	8,290	4,350	4,351	970
	POD Human Equivalent Dose	ng/kg/day	5,300	5,300	5,300	821	*1,368*	1,163	*610*	*610*	*136*
Uncertainty Extrapolation	Human Variability (UF_H)	unitless	10	10	10	10	10	10	10	10	10
	Animal to Human (UF_A)	unitless	3	3	3	3	3	3	3	3	3
	Subchronic to Chronic (UF_S)	unitless	1	1	1	1	1	1			1
	LOAEL to NOAEL (UF_L)	unitless	10	3	10	10	10	3			3

(*Continued*)

Table A1 (Continued)

	Parameter	Units	USEPA	MNDOH 2018	MADEP	ATSDR	MDHHS	MSAW	NJDWQI 2016	NHDES 2019	CA OEHHA
Year			2016	(August)	2019	2018	2019	2019	(June)	(June)	2019
PFOA	DW guidance level	ng/L	70	35	20	*10.5:*	9	8	14	12	2
	Database or Modifying (UF_D)	unitless	1	3	3	1	1	3	10	3	3
	Total Composite (UF_T)	unitless	300	300	1000	300	300	300	300	100	300
Reference Value - RfD, MRL, or 'toxicity value'	Serum	ng/mL	*127*	130	*38*	*28*	28	28	14.5	43.5	3.2
	Human Equivalent Dose (RfD)	ng/kg/day	20	18	5.3	3	5	3.9	2.0	6.1	0.45
Receptor		-	Lactating women	Breast fed infant, life	Lactating women	Na	Breast fed infant, life	Breast fed infant, life	2 L/day drinking water consumption, 70 kg adult body weight	Breast fed infant, life	lifetime average drinking water intake rate of 0.053 L/kg-day
Exposure Parameters	Ingestion Rate	L/day	-	-	-	Na	-	-	-	-	-

(*Continued*)

Table A1 (Continued)

	Parameter	Units	USEPA	MNDOH	MADEP	ATSDR	MDHHS	MSAW	NJDWQI	NHDES	CA OEHHA
Year			2016	2018 (August)	2019	2018	2019	2019	2016 (June)	2019 (June)	2019
PFOA	DW guidance level	ng/L	70	35	20	*10.5:*	9	8	14	12	2
	Body Weight	kg	-	-	-	Na	-	-	-	-	-
	Normalized Drinking Water Intake	L/kg-day	0.054	-	0.054	Na	-	-	0.029	-	0.053
	Relative Source Contribution	unitless	20%	50%	20%	Na	50%	50%	20%	50%	20%
Kinetics	Method to Derive Human Equivalent Dose	Chemical-Specific Clearance Rate or Dose Adjustment Factor L/kg-day, based on first order kinetic clearance rate, = (Vd x (ln 2 ÷ $t_{\frac{1}{2}}$))									

(*Continued*)

Table A1 (Continued)

	Parameter	Units	USEPA	MNDOH 2018	MADEP	ATSDR	MDHHS	MSAW	NJDWQI 2016	NHDES 2019	CA OEHHA
Year			2016	(August)	2019	2018	2019	2019	(June)	(June)	2019
PFOA	DW guidance level	ng/L	70	35	20	*10.5:*	9	8	14	12	2
	Half-Life, $t_{1/2}$	days	839.5	840	839.5	1400	840	840	840	840	*840*
	Volume of Distribution, Vd	L/kg	0.17	0.17	0.17	0.2	0.2	0.17	0.17	0.17	*0.17*
	Dose Adjustment Factor	L/kg-day	1.40E-04	1.40E-04	1.40E-04	9.90E-05	1.65E-04	*1.40E-04*	1.40E-04	1.40E-04	1.40E-04

Notes:
Italicized values are not presented in the original documents and have been calculated. :ATSDR does not calculate DW levels, the value shown is calculated using the ratio of ATSDR's MRL to EPA's RfD.
USEPA: Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). U.S. Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division Washington, DC 20460 EPA Document Number: 822-R-16-005. May, 2016;MNDOH: Toxicological Summary for: Perfluorooctanoate. Health Based Guidance for Water Health Risk Assessment Unit, Environmental Health Division, Minnesota Department of Health. Adopted as Rule: August 2018;
MADEP: Technical Support Document. Per- and Polyfluoroalkyl Substances (PFAS): An Updated Subgroup Approach to Groundwater and Drinking Water Values. Office of Research and Standards, Massachusetts Department of Environmental Protection, December 26, 2019;
ATSDR: Toxicological profile for Perfluoroalkyls. (Draft for Public Comment). Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, June 2018;
MDHHS: Public health drinking water screening levels for PFAS. Michigan Department of Health and Human Services, Division of Environmental Health Michigan PFAS Action Response Team Human Health Workgroup February 22, 2019;
MSAW: Health-Based Drinking Water Value Recommendations for PFAS in Michigan Drinking Water. Michigan Science Advisory Workgroup. June 27, 2019;
NJDWQI: Public Review Draft Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). New Jersey Drinking Water Quality Institute Health Effects Subcommittee. June 27, 2016;
NHDES: Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS) […]. New Hampshire Department of Environmental Services, June 28, 2019;
CA OEHHA: Notification Level Recommendations. Perfluorooctanoic Acid and Perfluorooctane Sulfonate in Drinking Water. Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, August 2019.

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