EXPLORATION OF CONTEXTUAL INFLUENCES ON THE INCORPORATION OF CHEMICAL- AND SCENARIO-SPECIFIC DATA IN THE DERIVATION OF ENVIRONMENTAL HEALTH AND OCCUPATIONAL EXPOSURE LIMITS FOR CHEMICALS

MICHELLE LEIGH DEVEAU, MSc(A), ROH

Thesis submitted to the University of Ottawa
in partial Fulfillment of the requirements for the
Doctorate in Philosophy degree in Population Health

Population Health, Interdisciplinary School of Health Sciences
Faculty of Health Sciences
University of Ottawa

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 7

CHAPTER 8

CHAPTER 9

LIST OF FIGURES

CHAPTER 6

CHAPTER 7

CHAPTER 8

CHAPTER 9

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Allowable daily intake
AEGL	Acute Exposure Guideline Level
AIHA	American Industrial Hygiene Association
ALARA	As low as reasonably achievable
ALARP	As low as reasonably practicable
AOP	Adverse outcome pathway
ATSDR	(US) Agency for Toxic Substances and Disease Registry
BBDR	Biologically based dose–response
BE	Biomonitoring equivalent
BEI	Biomonitoring exposure index
BLV	Biological Limit Value
BMC	Benchmark concentration
BMD	Benchmark dose
BMDL	Benchmark dose concentration lower bound
BOELV	Binding occupational exposure limit value
CFD	Computational fluid dynamic
CIB	Current Intelligence Bulletin
CICAD	Concise International Chemical Assessment Document
CMP	Chemicals Management Plan (Canada)
CONTAM panel	Panel on Contaminants in the Food Chain (EFSA)
CPSC	(US) Consumer Product Safety Commission
CSAF	Chemical-specific adjustment factor
D5	Decamethylcyclopentasiloxane
DAF	Dosimetric adjustment factor
DDEF	Data-derived extrapolation factor
DDUF	Data-derived uncertainty factor
DECOS	Dutch Expert Committee on Occupational Standards
DMEL	Derived minimal effect level
DNAN	2,4-dinitroanisole
DNEL	Derived No-Effect Level
EC	European Commission
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMH	Extramedullary hematopoiesis
ERPG	Emergency Response Planning Guideline
FQPA	Food Quality Protection Act
GCDWQ	Guidelines for Canadian Drinking Water Quality
GHS	Globally Harmonized System (of Classification and Labeling of Chemicals)
HEC	Human equivalent concentration
HED	Human equivalent dose

HRAC	Health Risk Assessment Committee
IDLH	Immediately Dangerous to Life and Health
IEUBK	Integrated Exposure Uptake Biokinetic
ILO	International Labour Organisation
IOELV	Indicative occupational exposure limit value
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JECFA	Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives
JMPR	Joint Food and Agricultural Organization/World Health Organization Meeting on Pesticide Residues
LOAEC	Lowest observed adverse effect concentration
LOAEL	Lowest observed adverse effect level
MAC	Maximum allowable concentration
MAK	Maximale Arbeitsplatz-Konzentration
MOA	Mode of action
MOE	Margin of exposure
MRL	Minimal Risk Level
NAS	National Academy of Science
NEG	Nordic Expert Group
NESHAP	(US) National Emission Standards for Hazardous Air Pollutants
NIOSH	(US) National Institute for Occupational Health and Safety
NOAEL	No observed adverse effect level
OARS	Occupational Alliance for Risk Science
OECD	Organization for Economic Cooperation and Development
OEL	Occupational exposure limit
OPP	Office of Pesticide Programs
OSHA	(US) Occupational Safety and Health Administration
PBPD/TD	Physiologically based pharmacodynamic/toxicodynamic
PBPK-PD	Physiologically based pharmacokinetic-pharmacodynamic
PBPK/TK	Physiologically based pharmacokinetic/toxicokinetic
PEL	Permissible Exposure Limit
PFOA	Perfluorooctanoic acid
PFOS	Perfluoroocatnesulfonic acid
PMRA	Pest Management Regulatory Agency (Canada)
POD	Point of departure
PPR panel	Scientific Panel on Plant Protection Products and their Residues (EFSA)
PPRTV	Provisional Peer Reviewed Toxicity Value
PSL	Priority Substances List (Canada)
QSAR	Quantitative structure-activity relationship
RAC	Risk Assessment Committee (ECHA)
RAR	Risk Assessment Report
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REL	Recommended Exposure Limit
RfC	Reference Concentration
RfD	Reference Dose

RIAQG	Residential Indoor Air Quality Guideline
RO	Research objective
RPF	Relative potency factor
RQ	Research question
SCOEL	Scientific Committee on Occupational Exposure Limits
SN	Skin notation
STEL	Short-term exposure limit
TEF	Toxic equivalency factor
TEQ	Toxic equivalency quotient
TLV	Threshold Limit Value
TRV	Toxicological reference value
TTC	Threshold of toxicological concern
TWA	Time-weighted average
UF	Uncertainty factor
US EPA	United States Environmental Protection Agency
WEEL	Workplace Environmental Exposure Level
WHO	World Health Organization

ABSTRACT

Outputs of dose–response assessments can be used as benchmarks that help to identify the need for risk management measures to reduce population health risks associated with exposure to chemicals. Various approaches can be used to facilitate the incorporation of chemical- or scenario-specific data into dose–response analyses, as a means of replacing or influencing default assumptions and extrapolations. The goal of the first part of this thesis was to examine the evolution of approaches to the incorporation of chemical- and scenario-specific data in dose–response assessments in regulatory settings, and identify contextual factors that serve as barriers and facilitators to the use of approaches. A main focus of the investigation was on physiological modelling, which is the most commonly-used category of approaches enabling extrapolations that depart from default assumptions. Evaluations of the dose–response applications of physiological modelling in the peer-reviewed scientific literature and in regulatory reports were conducted. Similarities between the scientific literature databases and regulatory reports were observed with respect to the evolution of physiological modelling in dose–response assessments, notably related to the timing, quantity, and annual frequency of publications. These similarities indicate that a factor in the low dose–response application of physiological modelling, relative to the overall production of physiological models, is an absence of data. However, variability in adoption of physiological modelling in regulatory dose–response assessments was observed among—and even within—organizations faced with the same data, indicating that other factors influence regulatory uptake of physiological modelling. Analysis of a survey indicated that factors acting as barriers or facilitators to regulatory risk assessors' incorporation of increasingly data-informed approaches originated in both external and internal contexts. The external context was composed of the regulatory environment, domestic and international alignment, availability of external expertise, background of peer reviewers and stakeholders, availability and accessibility of software and tools, and chemical-dependent factors. The internal context was influenced by problem formulation, time and financial resources, organizational and management support, and training. A conceptual framework demonstrating how these factors impact a risk assessor's ability to incorporate chemical- and scenario-specific data in dose–response analysis was developed, and subsequently used to

provide recommendations on actions that could be taken to increase regulatory adoption of increasingly data-informed approaches.

The second part of the thesis focused on the development of a knowledge translation tool designed to assist risk managers in the evaluation of dose–response analyses. The tool was focused on occupational exposure limits (OELs), and provides a guide to occupational hygienists in evaluating the relevance and reliability of individual OELs. When occupational hygienists are faced with multiple varying OELs for a chemical of interest, these evaluations can support the selection of the most appropriate OEL for a given situation. The usefulness of the tool was demonstrated for the selection of OELs for an OEL-rich compound (n-hexane), an OEL-poor compound (methamphetamine), and one additional compound (manganese). Such a tool can improve occupational hygienists' understanding of the basis of OELs and the levels of protection afforded by each, which can contribute to more informed risk management decisions.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the support and guidance of many different individuals and communities. I am ever thankful for all that you have done to help me in so many ways. A written list cannot convey the magnitude of my gratitude to all of you, so I hope to be able to return the favours over time.

To those who came before me. My colleagues in the 2010 Population Health cohort—we have now all completed our theses! I greatly enjoyed our discussions and the different perspectives we brought to issues, and the time we spent together in the early years. Special thanks for ongoing support, guidance, and friendship from Deepa Rao and Catherine Chesnay. Additional thanks to others from later cohorts, especially Tanya Hewitt and James Crispo, who provided advice throughout the process.

Thanks to colleagues and friends in attendance at SRA and AIHce over the past decade, and members of the WEEL committee. Your insight, whether in discussions directly on my research or on broader risk assessment topics, helped to shape my outlook and encouraged me to consider diverse perspectives.

To those who were with me. Thanks to the many people who provided guidance on the research. In particular, thanks to Dan Krewski, for being supportive and positive, never putting any pressure on me, helping me to form connections with others, and providing excellent ideas while also providing me the flexibility to choose my own path. Bette Meek, I'm always grateful for your excellent insight and the perspectives you offer from both the regulatory world and work that is being done internationally; on a personal note, a comment you once made in passing during a non-work related discussion stuck with me, and influenced a major change in my life. Thanks to Andy Maier for your continuously helpful input on the work, for providing me with the opportunity to be immersed in the world of occupational exposure limits, and for being an excellent model of somebody with his feet in both industrial hygiene and toxicological risk assessment.

Thank you to other co-authors on the chapters in my thesis—Chen-Peng Chen, Gunnar Johanson, John Lipscomb, Rick Niemeier, Karen Niven, Susan Ripple, Paul Schulte, Jennifer Silk, Ken Still, Jan Urbanus, and David Zalk. Your comments on the draft materials were always astute and respectful, and provided great improvements to the manuscripts.

I am grateful to those at Health Canada who provided support on the furthering of my education while still working full-time. Special thanks to Richard Carrier and Katherine Guindon-Kezis, my two main supervisors during the time I was a student—you allowed me to take time off when I needed it, and adjusted my workplans and schedules to help me balance work, school, and life. Thanks to all of the co-workers who were able to cover for me and pick up the slack when I wasn't around. Continuing to work while performing my research helped to maintain a focus on regulatory perspectives, and without all of you, I wouldn't have been able to do both.

Much appreciation to Scott Dotson, for your mentorship and sharing your experiences at NIOSH. You also were an excellent model of somebody who made their lovely family their highest priority in life.

I am indebted to all who provided administrative help through the duration of my studies at the University of Ottawa. In particular, I would like to thank Roseline Savage, Stéphanie Breau-Godwin, Nicole Bégnoche, and François Dubé for always being available to answer my many questions and for providing assistance when needed.

I am thankful for financial support from the University of Ottawa, McLaughlin Centre for Population Health Risk Assessment, and Health Canada.

Thanks to Carole Yauk, James Gomes, and George Gray, for taking the time to read my (very long) thesis, and for providing insightful discussions during my surprisingly fun oral defense.

And most importantly, words alone cannot express my appreciation to **those who will be with me afterwards.** Thanks to the many friends who provided mental support, helped me to take my mind off my thesis, kept accepting that I would be finished "next year," and put up with me always having my laptop with me on trips or at dinners. Tamara Gomes, Emily Macpherson, Marie-Sophie Desaulniers, Jade Puddington, Jennifer Shortall, Nathalie Acar, Mélissa Nadeau, Jeff Meyer, Krista Baker, Dalia Smith, Melinda Lontoc-Roy, Sally Gore, Saima Husain, Diane Medeiros, Ivy Moffat, Jane MacAulay, Julie Bourdon-Lacombe, Sarah Labib, Stéphanie McFadyen, Teresa Brooks, Gordon Yasvinski, Fran Childs, Nick Charman, Sarah Jane Payne, Joelle Barake-Leblanc, Stephanie Wille, Jocelyn Moore, Philana Dollin, Morgan MacNeill, Christine Brown, Noor Sunba, Tianna Huang, Katrina Morrison, Reilly Grywacheski, Ann Parker, Patricia Nance, and Janet Gould—thanks for being patient when I was bad at staying in

touch, and I'm looking forward to being able to spend more quality time with each of you afterwards (when we're all vaccinated!).

To Bonny and Paul Deveau, thanks for fostering my curiosity and love of learning, and shaping me into the person I've become. You have been immensely helpful taking Louis for walks while I complete my thesis, and cooking meals so that I can devote more of my time to my work. And to Louis, thanks for being a good sleeper—giving me time for my thesis—and for providing the motivation for me to finish.

Finally, to Darren MacPherson, thanks for supporting me throughout my PhD and earlier education efforts. You are always a great sounding board, and your insight has helped to shape my philosophy on occupational health and life in general. You have calmed me when I'm stressed and anxious, and helped me make it through many challenges. You have been an excellent father and role model for Louis, and your level of involvement with him has allowed me to continue to achieve my educational goals. Like so many other things, I couldn't have done this without you.

This thesis is dedicated to five beloved family members who embarked on my thesis journey with me, and were in my thoughts through its completion.

Molly Baker (1932–2011)
Louis Alphonse Deveau (1923–2011)
Robert Barry (Bob) Swinwood (1944–2018)
Lena Chantal Bishop Swinwood (1946–2019)
Marie Apolline (Pauline) Deveau (1921–2020)

"It has been said that 'If we knew what to do when we started we'd call it search, not research.'" – Clewell et al. 2008

COAUTHORSHIP

Many individuals contributed their valuable expertise to this thesis. The involvement of co-authors and contributors of each of the major chapters is outlined below.

Chapter 2 – Michelle Deveau conceived the project, performed the research, and developed the manuscript. Daniel Krewski, Bette Meek, and Andrew Maier contributed to discussions identifying the approaches for inclusion in the initial search strategy, and provided nominations for validation articles. Lindsey Sikora provided input and advice on the need for a systematic review, the development of the search strategy, and other systematic review elements. Daniel Krewski, Bette Meek, and John Lipscomb provided feedback on draft versions of the chapter.

Chapter 3 – Michelle Deveau conceived the project, performed the research, and developed the manuscript. Daniel Krewski and Bette Meek contributed to identification of regulatory organizations for inclusion. Daniel Krewski provided feedback on draft versions of the chapter.

Chapter 4 – Michelle Deveau conceived the project, performed the research, and developed the manuscript. Daniel Krewski and Bette Meek contributed to identification of regulatory organizations to be surveyed. Daniel Krewski and anonymous pilot survey participants provided feedback on the survey. Daniel Krewski provided feedback on draft versions of the chapter.

Chapter 6 – Michelle Deveau performed the literature search and developed the manuscript. Kenneth Still invited Michelle Deveau to write the chapter, and wrote the version of the chapter published in the first edition of the textbook, on which minimal portions of the current version of the chapter were based. Daniel Krewski, Andrew Maier, Kenneth Still, and peer reviewers provided feedback on draft versions of the chapter. Leslie Beyer provided editing guidance on the chapter.

Chapter 7 – Michelle Deveau and Andrew Maier co-conceived the overall concept of the manuscript. Michelle Deveau developed the manuscript. Andrew Maier invited Michelle Deveau to write the manuscript for a special issue of the journal. Richard Niemeier performed the initial

literature search, which was updated by Michelle Deveau. Other co-authors (Chen-Peng Chen, Gunnar Johanson, Karen Niven, Susan Ripple, Paul Schulte, Jennifer Silk, Jan Urbanus, and David Zalk), NIOSH reviewers, and peer reviewers provided feedback on draft versions of the chapter. Gino Fazio provided graphic design based on draft versions of figures.

Chapter 8 – Michelle Deveau conceived the work, performed the research, and developed the manuscript. Jan Urbanus and Karen Niven wrote a section on sulphur dioxide that was included in earlier versions of the draft manuscript, but excluded from the thesis. Daniel Krewski, Andrew Maier, Jan Urbanus and Karen Niven provided feedback on draft versions of the chapter.

Chapter 9 – Michelle Deveau conceived the work, performed the research, and developed the manuscript. Daniel Krewski invited Michelle Deveau to present the framework at a manganese symposium, and the manuscript was published in symposium proceedings. Daniel Krewski, Andrew Maier, and peer reviewers provided feedback on draft versions of the chapter.

APPROVALS OBTAINED TO CONDUCT RESEARCH

Approval to conduct the surveys described in Chapter 4 was received from the University of Ottawa Research Ethics Board (#H06-14-02) and the Health Canada Research Ethics Board (REB 2014-0021).

CHAPTER 1 – Introduction

1.0 Introduction and Background

Risk assessment is a technique used in many different disciplines to evaluate a variety of hazards. In the field of environmental health, risk assessment is generally used for the characterization of potential adverse human health outcomes associated with exposure to environmental hazards (1), such as chemicals found in air, water, soil, and food. These risk assessments are performed in many different sectors, including government, industry and academia. A landmark publication in regulatory risk assessment was the 1983 National Academy of Sciences' (NAS) *Risk Assessment in the Federal Government* (1), commonly referred to as the "Red Book". This publication lays out a framework to guide the risk assessment process, which has been broadly adopted in regulatory environments (2-4), and continues to be incorporated in updated risk assessment frameworks (5, 6).

Dose–response assessment is one of the major stages of risk assessment in the NAS framework, in which the likelihood of health effects occurring under particular exposure circumstances is identified (1, 5). Outputs of dose–response analyses can include exposure guidelines or risk-specific doses, or can be used directly in margin of exposure assessments.

Exposure guidelines or toxicity reference values are benchmarks against which concentrations of chemicals in various environmental media—including water, air, soil, and food—can be compared. In their simplest form, exposure guidelines are derived by dividing a point of departure (POD)—a concentration at which an adverse effect, or absence thereof, is observed—by assessment factors representing potential uncertainty or variability, as a means of providing a safety cushion (7). Lower risk levels are associated with exposures below these guidelines, and an increased potential for adverse health effects occurs with higher exposures above the guidelines.

Derivation of risk-specific doses can be performed using different approaches. One common tactic is the use of linear dose–response analysis, which begins with the calculation of a slope factor, which is the slope of the linear curve between the selected POD for an adverse effect and the origin (factoring in background incidence). The slope factor can then be used to

estimate a unit risk (i.e., the risk level associated with a unit of exposure, such as 1 μg/kg-day intake, 1 μg/L in water, or 1 $\mu g/m^3$ in air) or the concentration associated with a negligible risk level (8, 9). The determination of negligible or *de minimis* risk is a policy decision that varies among organizations—for carcinogens, acceptable risk levels often range from 10^{-6} to 10^{-5} (1 in 1,000,000 to 1 in 100,000) over the course of a lifetime for exposures to the general population (10, 11), and 10^{-5} to 10^{-3} (1 in 10,000 to 1 in 1,000) for occupational exposures over a working lifetime (12-15). The linear risk-specific doses described above are typically used for carcinogens that are suspected of mutagenicity or for which the mode of action is unclear; however, they have also been recommended (5) and used (16) for non-cancer risk assessments.

In some cases, rather than using a dose–response analysis for the derivation of an exposure guideline or risk level, it can be used directly in a risk characterization to identify the margin of exposure. Margin of exposure assessments directly compare PODs for adverse effects with exposure levels (17). The magnitude of the margin between the POD and estimated or measured exposure concentrations is used to evaluate the need for risk management interventions. Judgement of the sufficiency of the size of margins of exposure is based on the uncertainty factors (UFs) and negligible risk levels used in exposure guidelines and risk-specific doses (18-20).

All of the outputs of dose–response assessment can be used to gauge the level of risk associated with potential exposures to chemicals present in the human environment. The outputs facilitate the identification of recommended maximum levels of exposure that are based on potential risk to a chemical, rather than attempting to eliminate exposures completely or reduce them to the minimal levels possible using the best available technology (21). Available dose–response outputs can be used by risk managers to identify whether interventions to reduce a population's exposures to chemicals are required (7). If comparison of measured or estimated exposure concentrations with the dose–response outputs indicates a potential concern, risk managers can take a variety of actions to reduce exposure levels of the population until they are below these health-based benchmarks (6, 7, 22, 23).

Optimal inputs to dose–response analyses would involve exposure data for a variety of human subpopulations—including those that are particularly vulnerable—for chemicals at real-world concentrations, and measure a range of health outcomes. Epidemiological studies are preferable for human risk assessment as they represent relevant exposure levels in the target

species and can also measure variability within a population (24); however, due to limitations in the epidemiology databases for all but a few chemicals, dose–response assessments are mainly performed using animal studies (4). This results in a need for "inference options" to extrapolate to relevant human exposure scenarios (1). Such extrapolations need to address factors such as uncertainty or variability between species, within the human population, and among durations and patterns of exposure (7, 23, 25-27).

Traditional methods or default assumptions are commonly used to perform these extrapolations. One example of these default approaches includes the use of 10-fold UFs. The origin of the 10-fold defaults is attributable to Lehman and Fitzhugh in their 1954 communication on food additives (28); these values are sometimes considered to have been derived relatively arbitrarily (7). In their proposal of the 100-fold UF, which is commonly interpreted as 10-fold UFs each for inter- and intraspecies variability, Lehman and Fitzhugh (28) state that the value is "a good target, but not an absolute yardstick as a measure of safety," and that:

> "…this factor of 100 appears to be high enough to reduce the hazard of food additives to a minimum and at the same time low enough to allow the use of some chemicals which are necessary in food production or processing. The application of simple statistical rules indicates that the probability of human injury decreases with each increase of the margin of safety." (p. 35)

Although Lehmann and Fitzhugh did not provide concrete quantitative justification for their order-of-magnitude assessment factors, various efforts since have performed evaluations that support the sufficiency of 10-fold values for most—but not all—compounds, based on larger databases of chemicals (29-32). Therefore, although these UFs were not data-informed in the sense that they were based on data for any particular compound, they are data-supported as they have been demonstrated to be protective for a broad range of chemicals.

The use of the traditional default approach is therefore often "presumed protective," and compared with approaches that are refined by incorporating chemical- or scenario-specific data into dose–response assessments, or "biologically-based predictive" (33, 34). These two approaches form the opposite ends of a continuum, along which increased data incorporation results in increased refinement and decreased inherent uncertainty (27, 33). Decreasing uncertainty and relying on more refined extrapolations of variability, rather than on assessment

factors that are protective for a wide variety of compounds, commonly results in less conservative risk estimates (34). However, default assumptions might not address all chemicals or scenarios (35); in these cases, refinements might result in more protective risk values. Specific examples for which 10-fold UFs for interspecies variability are not sufficient are for perfluorinated compounds, which have much longer biological half-lives in humans than animals due to decreased clearance rates (32, 36, 37), and diacetyl, which has 40-fold higher deposition in bronchioles in humans than rats (38, 39).

Over the past four decades, approaches have been developed to facilitate quantitative incorporation of chemical-specific knowledge into dose–response assessments. The approaches of relevance for this thesis—and therefore incorporated in the thesis search strategy—are presented in Table 1. Although these approaches are presented separately, their applications can be linked together (40). Table 1 also lists more advanced dose–response assessment concepts that are not directly approaches to incorporate chemical- and scenario-specific data, but that were included in the search strategy as they could be used in combination with increasingly data-informed approaches. These advanced dose–response concepts were included in case they helped to identify other increasingly data-informed approaches that were not considered in the initial list.

Although dose–response analyses are founded in science, many decisions made throughout the process are policy decisions. Opting to depart from a default approach to incorporate chemical- or scenario-specific data into dose–response assessments is one such policy decision (41). Consequently, risk assessments performed by different sectors or organizations could presumably reach different conclusions on the need to depart from defaults. The use of increasingly data-informed approaches to depart from defaults has been perceived as being higher in research than in regulatory contexts, plausibly due to regulatory mandates of protection of the health of human health of broad populations (42-46). Although some recent efforts have examined the regulatory incorporation of chemical-specific approaches to depart from defaults (32, 47), comparative analyses of the adoption of approaches among organizations and between government and other sectors have not been performed. Moreover, recent publications discussing barriers to the adoption of increasingly data-informed approaches focused primarily on technical rather than contextual factors (47-49).

Table 1 – Increasingly data-informed approaches considered in the literature search

Approach	Description of included methods
Quantitative change of POD or UFs	
Physiological modelling	The use of chemical-specific physiological models (PBPK, dosimetry, and BBDR) for extrapolations based on pharmacokinetics or pharmacodynamics (e.g., for route, dose levels, and inter- and intraspecies) that influence POD and UF selection or derivation.
CSAF or DDEF	The use of chemical-specific pharmacokinetic or pharmacodynamic data to derive inter- and intraspecies UFs.
Population variability	The incorporation of chemical- and population-specific data for sensitive subpopulations and lifestages. Relevant approaches will include the use of physiological modelling, CSAFs, or statistical methods to incorporate distributional data for parameters related to dose–response.
Quantitative alteration of final exposure guidelines / interpretation of final guidelines	
Duration adjustment	Quantitative adjustments performed to extrapolate for different exposure patterns that reflect the pharmacokinetic nature of the target chemical. Can be performed to adjust PODs in key studies to the target exposure pattern, or used in risk characterization to interpret previously-performed dose–response analysis results for a different exposure duration.
Cumulative risk assessment (including for non-chemical stressors)	Consideration of combined adverse health effects resulting from multiple hazards, using approaches that quantitatively reflect hazard-specific differences in kinetics or dynamics. Combined exposures can be for multiple chemicals, or chemicals combined with non-chemical stressors (including social determinants of health). Can be used to impact POD or UF selection, or used in risk characterization to interpret outcomes of combinations of exposures.
Uncertainty analysis	Quantitative presentation of the range of uncertainty in various aspects of the dose–response that result in a range of potential values for the POD, UFs, and/or final exposure guideline.
Mechanistic weight of evidence analysis	
MOA analysis and AOPs	Quantitative and systematic evaluations of key pharmacodynamic events that result in an adverse effect. Designed to help make decisions on appropriate PODs, and can be a driver for incorporating approaches that quantitatively change the POD or UFs, including the need to apply physiological modelling, derive CSAFs, and other relevant approaches.
Comparison approach – not chemical- or scenario-specific approach	
BMD analysis	Statistical approach that does not incorporate chemical- or scenario-specific data. Because BMD modelling eventually became a well-adopted departure from the default use of NOAELs and LOAELs as PODs, a parallel exploration of the approach was considered to allow for comparison with the adoption of increasingly data-informed approaches.
Other concepts included in literature search	
Additional search terms	Keywords related to various additional dose–response concepts (including computational systems biology; categorical regression; route, dose, and species extrapolation; weight of evidence and decision frameworks) were included when developing the literature search strategy. Although the concepts alone are not increasingly data-informed approaches, they are more advanced risk assessment concepts that can be used in combination with the approaches above to incorporate chemical-specific decisions. Keywords related to these concepts were therefore included in the search strategy in the event that they identified results additional chemical- or scenario-specific approaches not outlined above.

POD: point of departure; UF: uncertainty factor; PBPK: physiologically based pharmacokinetic; BBDR: biologically based dose–response; CSAF: chemical-specific adjustment factor; DDEF: data-derived extrapolation factor; MOA: mode of action; AOP: adverse outcome pathway; BMD: benchmark dose; NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level.

2.0 Research questions and objectives

The goal of this thesis was to examine the incorporation of chemical- and scenario-specific data in regulatory dose–response assessments, including the identification of whether there were any delays in governmental agencies' use of the approaches, compared with the broader scientific community, and contextual factors associated with any delays. The results of this evaluation would then be used to make recommendations or develop tools that could be used to improve the regulatory uptake of increasingly-data informed approaches, as necessary. The research questions (RQs) for the thesis were as follows.

RQ1: How have increasingly data-informed approaches been used over time in the general scientific literature?

RQ2: How have increasingly data-informed approaches for dose–response assessments been adopted by regulatory organizations that perform dose–response assessments for human exposure to environmental substances?

RQ3: Is there a delay in the uptake of increasingly data-informed approaches in regulatory agencies, compared with the general scientific literature?

RQ4: How has the regulatory context influenced the likelihood that increasingly data-informed approaches are applied in regulatory dose–response assessments for human exposure to environmental substances?

RQ5: How can regulatory agencies improve the uptake of increasingly data-informed approaches in dose–response assessments of environmental chemicals?

The research objectives (ROs) associated with the research questions outlined above were as follows:

RO1: Use systematic approaches to examine the evolution of the incorporation of increasingly data-informed approaches in peer-reviewed publications in scientific literature databases from 1983 to 2018.

RO2: Examine the evolution of the adoption of increasingly data-informed approaches in reports from a variety of regulatory organizations, from 1983 to 2018.

RO3: Compare and contrast the evolution of adoption of increasingly data-informed approaches in dose–response assessments in the general scientific community with that of the regulatory community.

RO4: Survey regulatory risk assessors to identify contextual influences that may hinder and promote the application of increasingly data–informed approaches in regulatory dose–response assessments.

RO5: Propose and develop solutions to overcome barriers and maximize facilitators to the application of increasingly data-informed approaches in regulatory dose–response assessments.

The initial idea for RO5 was to develop knowledge translation outputs—guidelines or other useful tools—that could be used by risk assessors who are performing dose–response assessments. However, as will be outlined in Chapters 4 and 5, the need for such tools became less apparent throughout the research. Consequently, RO5 was instead achieved by updating a conceptual framework describing contextual factors that could act as barriers and facilitators to the incorporation of increasingly data-informed approaches in regulatory dose–response assessments. The framework was then used to provide recommendations on reducing identified barriers. As the interest in a knowledge translation output remained, a different focus for such a tool was identified. As will be discussed in Chapter 5, the need to encourage risk managers to critically evaluate the basis of exposure guidelines was identified; this was particularly relevant for occupational hygienists using occupational exposure limits. As such, a new research objective was added as follows.

RO6: Propose and develop a knowledge translation tool to guide risk managers on the evaluation and selection of appropriate exposure guidelines.

3.0 Conceptual framework

The overarching conceptual framework used to guide the research is the US Environment Protection Agency NexGen framework for risk science (6), presented in Figure 1, as it allows for the integration of the population health perspective within the risk assessment process. This framework builds upon the 2007 integrated framework for risk management and population health developed by Krewski and colleagues (22), the first to integrate the theories and principles of the population health and risk assessment fields, which had previously been developed independently. Although the risk assessment focus of this updated framework is on the use of *in vitro* data incorporated into toxicity pathway-based dose–response analyses, which is not the direct focus of this thesis, the NexGen framework provides more developed descriptions of risk

assessment than the 2007 framework. The guiding principles of the framework will therefore be applied to risk assessments based on traditional toxicological and epidemiological data, in addition to those based on the principles of *in vitro* evaluations of toxicity pathway perturbations.

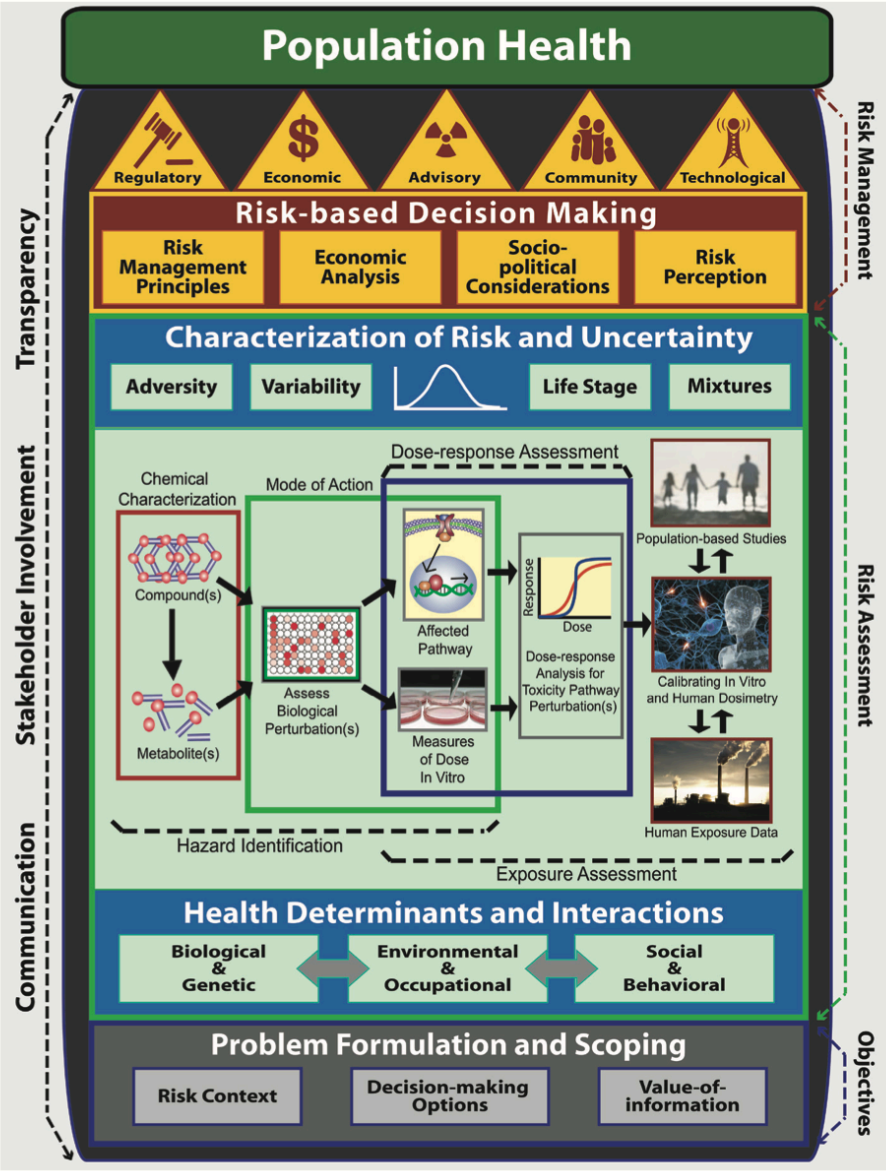


Figure 1. US EPA NexGen framework for risk science
Reproduced from Environmental Health Perspectives (6) with permission from the authors.

The three phases of the framework—objectives, risk assessment, and risk management—combine to develop policy outcomes that influence population health. Underpinning the objectives phase is problem formulation, which designs the appropriate questions to be answered and outlines plans for the risk assessment process, ensuring that risk assessment outputs will meet the needs of stakeholders in a cost-effective manner, considering the available decision-making options. The risk assessment phase of the framework is based on the four-stage process outlined in the NAS Red Book overlaid on population health concepts of determinants of health. The interaction of the three main health determinants categories (biological and genetic; environmental and occupational; and social and behavioural) forms the foundation on which risk assessment is based. In the NexGen framework, these population health determinants manifest in advanced risk assessment approaches that consider human variability in pharmacokinetics and pharmacodynamics, susceptible populations and lifestages, combined exposures to multiple stressors, and uncertainty analysis. The results of risk assessments then inform the development of evidence-based health risk management decisions. The risk management phase is founded on the principles of good and equitable management practices, incorporating economic and sociopolitical considerations, and acknowledges differences in risk perceptions between the public and experts. A main tenet of the framework is that multiple risk management measures—categorized as regulatory, economic, advisory, community, or technological—should be used to address population health risks, and that evaluation of population health improvement should follow implementation of interventions. Common and integral to all phases of the framework are the principles of transparency, stakeholder involvement, and effective communication.

The NexGen framework for risk science is used at a macro level to place the thesis in the context of population health risk assessment. The main focus of the thesis is in the dose–response assessment component of the framework, as influenced by health determinants and interactions, using more advanced risk assessment approaches (i.e., approaches for incorporation of chemical- and scenario-specific data, instead of reliance on defaults) to characterize risk and uncertainty. The framework will be used to guide "big picture" discussions of the implications of dose–response assessment approaches on population health. However, an additional conceptual framework was required to contextualize decision-making processes incorporated into dose–response analyses, to guide the interpretation of results of a survey of regulatory adoption of increasingly data-informed approaches. The second framework was required as the NexGen

framework was designed to be broadly applicable to a variety of scenarios, and did not incorporate discussions on factors influencing decision making in the risk assessment process. The framework, which was designed to contextualize evidence-based policy decision-making processes in the medical field, is presented in conjunction with the survey of regulatory risk assessors on barriers and facilitators to the use of increasingly data-informed approaches in dose-response assessment (Chapter 4).

4.0 Research scope

The present research addresses the time period from 1983 to 2018. The starting point of 1983 was selected because it coincided with the publication of NAS's landmark "Red Book" framework, which defined modern risk assessment approaches for governmental programs. Major milestone manuscripts related to BMD modelling (50) and PBPK modelling for environmental chemicals (51) were also published in 1984. The research only gathered publications until 2018, rather than a more recent date, as the screening processes for the systematic approaches used to gather records from the scientific literature (as outlined in Chapter 2) were time intensive. Regulatory reports were only obtained until 2018, for consistency with the scientific literature database.

The focus of this research is on dose–response analyses of environmental exposures to chemicals. The word "environment" was used broadly to encompass exposures through the general environment, through air, water, soil, and food. Occupational settings were also considered in this broad definition of environment, as workers are exposed to the chemicals through air, and chemicals used in occupational settings can become sources of environmental contamination. As the major sources of exposure to pesticides would be from the general environmental media outlined above, as well as in occupational environments, pesticides were also included in the broader definition of environment. As noted above, food was considered as a source of exposure to environmental substances, and was therefore included in the assessment; however, as food programs also evaluate chemicals that are not of environmental origin (e.g., food additives, packaging materials, veterinary drugs, and chemicals formed during food processing), some judgement was required to select only food assessments pertaining to environmental contamination. Assessments related to non-environmental sources of chemicals, such as exposures through pharmaceuticals or illicit drugs, or consumer products, were excluded

unless they were directly considered as contaminants of environmental media or occurred in the form of occupational exposures.

The exposures considered in this research are also limited to chemical exposures. Some programs evaluating environmental compounds also evaluate biological agents (including toxins produced as metabolic end-products of microbiological organisms) and physical agents (e.g., noise, non-ionizing radiation, radiological compounds). These non-chemical agents were not considered within the scope of the thesis, even if assessments were developed by organizations that were otherwise within scope.

A major focus of the thesis is what are often referred to as "regulatory agencies." The term "regulatory" is often used in this thesis to reflect governmental risk assessments, even if they result in the development of non-regulatory objectives. The term "regulatory" is also used more loosely to include some committees that include non-governmental representatives. For example, various expert committees under the European Chemicals Agency (ECHA), European Food Safety Agency (EFSA), and World Health Organization (WHO) were included in the analyses, even though they are mainly composed of external experts, as the documents are published as ECHA, EFSA, and WHO decisions. American Conference of Governmental Industrial Hygienists (ACGIH) assessments were also included as they are widely used to assess occupational exposures and are frequently adopted in legislation, with heavy reliance on these values in Canadian occupational legislation (52). As the Workplace Environmental Exposure Levels (WEELs)—formerly developed under the American Industrial Hygiene Association, but under the Occupational Alliance for Risk Science as of 2012—are derived by a volunteer committee similar to the ACGIH Threshold Limit Value® (TLV®) committee, and can be used to supplement the TLVs, the WEELs were also included despite not being derived by a governmental organization.

4.1 Narrowing scope

When implementing the research, it became evident the initial objective to evaluate all approaches of interest discussed in Table 1 was too broad. To facilitate completion of the thesis, the scope of the research had to be narrowed. This was done by focusing the research on physiological modelling, which included physiologically based pharmacokinetic (PBPK) models, dosimetry models, and physiologically based pharmacodynamic (PBPD) or biologically based

dose–response (BBDR) models. The reasons for selecting physiological models were two-fold. First, pilot evaluations performed as part of this research identified that the use of PBPK models was the most commonly employed approach to incorporate chemical- or scenario-specific data into dose–response assessments in the assessments targeted in the pilot (see Chapter 5). And second, physiological modelling underpins most of the other approaches that were initially considered in this research. Some examples of this are given below.

- Incorporation of physiological models in higher tiers of assessments of combined exposures to multiple chemicals, to refine chemical- and scenario-specific data (53).
- Use of physiological models to perform duration adjustments that reflect the potential for non-linear pharmacokinetics, when adjusting durations of key studies to identify relevant PODs, or when extrapolating exposure guidelines to multiple or non-traditional durations (54-56).
- Physiological models are a method of quantitatively operationalizing MOAs and AOPs into dose–response analyses (57, 58).
- Quantitatively exploring human variability, by developing models for potentially susceptible subpopulations (e.g., children, pregnant women and their fetuses, nursing mothers and their infants)(59, 60) or incorporation of variability using probabilistic data for various physiological and biochemical parameters (61-63). Physiological models can also be a source of pharmacokinetic and pharmacodynamic data used to calculate data-derived extrapolation factors, such as chemical-specific adjustment factors (32).
- The use of physiological models can facilitate quantitative analysis of pharmacokinetic and pharmacodynamic uncertainty and variability in a dose–response analysis, and can be used in the calculation of uncertainty distributions (64)

As discussed below, the scope of the thesis was only narrowed later in the research process; therefore, many of the earlier steps in the methods reflected all approaches described above and in Table 1. As outlined in Appendix A of Chapter 2, the systematic searches used to obtain potentially relevant publications from databases of peer-reviewed literature were designed for all of the initially-included approaches. The scope of the peer-reviewed literature analysis

was narrowed to physiological models by restricting full-text reviews of publications to those categorized as potentially containing PBPK, dosimetry, or PBPD/BBDR models; this decreased full-text review requirements from 4262 to 1901 publications. An initial pilot of the review of regulatory organizations' risk assessment documentation explored additional dose–response approaches from a small group of organizations; however, a more detailed review of a larger number of regulatory organizations was restricted to the analysis of the use of physiological models. As the survey of regulatory organizations did not require extra effort to investigate the contextual factors impacting incorporation of the broader refined approaches, the survey results apply more broadly than physiological modelling.

5.0 Organization of thesis report

The thesis is divided into three main sections. The first section focuses on the exploration of the incorporation of chemical- and scenario-specific data into dose–response assessments of chemicals of environmental and occupational origin. The second section describes the development of a knowledge translation tool to address an issue identified while developing the first section of the thesis. The final section provides a synthesis of, and reflections on, the research as a whole. The chapters describe the work undertaken to address the research objectives, as outlined below.

PART I – EXPLORATION OF INCORPORATION OF CHEMICAL- AND SCENARIO-SPECIFIC DATA IN DOSE–RESPONSE ANALYSES

- Chapter 2, entitled "Evolution of the Application of Physiological Kinetic and Dynamic Models in Chemical Dose–Response Assessments in Scientific Literature" focuses on the use of physiological models for dose–response applications in peer reviewed literature. The chapter opens with a literature review of the history of development and application of physiological models, as well as a review of published bibliometric reviews of physiological modelling. The chapter then addresses RO1 by summarizing a detailed exploration of the timeline of dose–response applications of physiological models in peer reviewed literature.
- Chapter 3, entitled "The Application of Physiologically Based Kinetic and Dynamic Models in Regulatory Dose–Response Assessments" focuses on the use of physiological models in dose–response assessments published by regulatory

organizations. The chapter addresses RO2 and RO3 through a detailed exploration of the timeline of dose–response applications of physiological models in regulatory risk assessments, and comparing the results with those from the general scientific literature.

- Chapter 4, entitled "Contextual Factors Influencing Incorporation of Chemical- and Scenario-Specific Data in Regulatory Dose–Response Assessments" presents the analysis of a survey of regulatory (and para-regulatory) organizations' experiences in applying approaches to incorporate chemical- and scenario-specific data in dose–response assessments. The chapter addresses RO4 by synthesizing the factors that act as barriers and facilitators to incorporation of the approaches, and RO5 by providing recommendations for increased uptake of the approaches.
- Chapter 5, entitled "Other Approaches and the Need for an Evaluation and Selection Framework for Occupational Exposure Limits" provides a conclusion to Part I, as well as a link between Parts I and II of the report. The chapter discusses adoption of additional increasingly data-informed approaches in dose–response assessments. Other observations on weaknesses of occupational exposure limits (OELs) are provided, with a conclusion on the need to develop evaluation tools for end-users of OELs. To this end, additional preliminary data for RO2 are presented, and the need for RO6 is proposed.

PART II – DEVELOPMENT OF A TOOL TO EVALUATE THE BASIS OF OELs

- Chapter 6, entitled "Derivation of Occupational Exposure Limits" provides a review of the literature describing the process of deriving OELs, particularly focused on dose–response concepts. A section of the chapter outlines some of the approaches to incorporate chemical- and scenario-specific data into OELs, with case studies demonstrating their application.
- Chapter 7, entitled "The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection" reviews the scientific and policy aspects of OEL derivation and their influence on OEL variability. The chapter addresses RO6 by proposing an OEL selection framework that guides occupational hygienists to critically evaluate the basis of OELs.

- Chapter 8, entitled “Application of a Framework to Guide the Selection of Relevant and Reliable Occupational Exposure Limits” addresses RO6 by providing examples of the application of the OEL selection framework, to an OEL-poor compound (methamphetamine) and an OEL-rich compound (n-hexane).
- Chapter 9, entitled “Application of a framework for the selection of an appropriate occupational exposure limit for manganese” addresses RO6 by providing an example of the application of the OEL selection framework to manganese.
- Chapter 10, entitled “Synthesis and Reflections” provides a conclusion to synthesize parts 1 and 2 and provide general reflections on the results within the broader context of population health risk assessment.

REFERENCES

1. NRC. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: The National Academies Press; 1983.

2. Omenn GS. On the significance of “The Red Book” in the evolution of risk assessment and risk management. Human and Ecological Risk Assessment: An International Journal. 2003;9(5):1155-67.

3. Burke TA. The Red Book and the practice of environmental public health: Promise, pitfalls, and progress. Human and Ecological Risk Assessment: An International Journal. 2003;9(5):1203-11.

4. Grandjean P. The Red Book, a red herring, and the red tape: A European perspective. Human and Ecological Risk Assessment: An International Journal. 2003;9(5):1291-5.

5. NRC. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press; 2009.

6. Krewski D, Westphal M, Andersen ME, Paoli GM, Chiu WA, Al-Zoughool M, et al. A framework for the next generation of risk science. Environmental Health Perspectives. 2014;122(8):796-805.

7. Barnes DG, Dourson M, Dourson M, Preuss P, Barnes DG, Bellin J, et al. Reference dose (RfD): Description and use in health risk assessments. Regulatory Toxicology and Pharmacology. 1988;8(4):471-86.

8. Chiu WA, Euling SY, Scott CS, Subramaniam RP. Approaches to advancing quantitative human health risk assessment of environmental chemicals in the post-genomic era. Toxicol Appl Pharmacol. 2013;271(3):309-23.

9. US EPA. Guidelines for Carcinogen Risk Assessment. Wasington, DC; 2005. Report No.: EPA/630/P-03/001F.

10. Sadowitz M, Graham JD. A survey of residual cancer risks permitted by health, safety and environmental policy. RISK. 1995;6:17-35.

11. US EPA. An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether. 2005. Report No.: EPA 600/R-04/123.

12. Ding Q, Schenk L, Hansson SO. Setting risk-based occupational exposure limits for no-threshold carcinogens. Human and Ecological Risk Assessment: An International Journal. 2014;20(5):1329-44.

13. Travis CC, Hattemer-Frey HA. Determining an acceptable level of risk. Environmental science & technology. 1988;22(8):873-6.

14. United States Government Accountability Office. Chemical risk assessment: Selected federal agencies' procedures, assumptions, and policies. Washington, DC; 2001. Report No.: GAO-01-810.

15. NIOSH. NIOSH Chemical Carcinogen Policy. Cincinnati, OH: NIOSH; 2016. Report No.: 2017-100.

16. Health Canada. Lead in Drinking Water: Document for Public Consultation. Ottawa, ON; 2017.

17. US EPA. Integrated Risk Information System (IRIS) Glossary 2011 [Available from: https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary.

18. Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc J-C, et al. Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food and Chemical Toxicology. 2010;48:S2-S24.

19. Benford DJ. The use of dose-response data in a margin of exposure approach to carcinogenic risk assessment for genotoxic chemicals in food. Mutagenesis. 2016;31(3):329-31.

20. US EPA. Sustainable Futures / P2 Framework Manual - Section 13: Quantitative Risk Assessment Calculations. 2012.

21. Finkel AM. Too much of the “Red Book” is still (!) ahead of its time. Human and Ecological Risk Assessment: An International Journal. 2003;9(5):1253-71.

22. Krewski D, Hogan V, Turner MC, Zeman PL, McDowell I, Edwards N, et al. An integrated framework for risk management and population health. Human and Ecological Risk Assessment: An International Journal. 2007;13(6):1288-312.

23. Galer DM, Leung HW, Sussman RG, Trzos RJ. Scientific and practical considerations for the development of occupational exposure limits (OELs) for chemical substances. Regulatory Toxicology and Pharmacology. 1992;15(3):291-306.

24. Goldman LR. Epidemiology in the regulatory arena. American Journal of Epidemiology. 2001;154(12):S18-S26.

25. Ritter L, Totman C, Krishnan K, Carrier R, Vézina A, Morisset V. Deriving uncertainty factors for threshold chemical contaminants in drinking water. Journal of Toxicology and Environmental Health, Part B. 2007;10(7):527-57.

26. Pohl HR, Chou CHSJ, Ruiz P, Holler JS. Chemical risk assessment and uncertainty associated with extrapolation across exposure duration. Regulatory Toxicology and Pharmacology. 2010;57(1):18-23.

27. Renwick AG, Dorne J-LCM, Walton K. Pathway-related factors: The potential for human data to improve the scientific basis of risk assessment. Human and Ecological Risk Assessment: An International Journal. 2001;7(1):165-80.

28. Lehman AF, OG. 100-fold margin of safety. Quarterly Bulletin Association of Food & Drug Officials of the United States. 1954;18:33-5.

29. Dourson ML, Stara JF. Regulatory history and experimental support of uncertainty (safety) factors. Regulatory Toxicology and Pharmacology. 1983;3(3):224-38.

30. Renwick AG, Lazarus NR. Human variability and noncancer risk assessment—An analysis of the default uncertainty factor. Regulatory Toxicology and Pharmacology. 1998;27(1):3-20.

31. Hattis D, Erdreich L, Ballew M. Human variability in susceptibility to toxic chemicals—A preliminary analysis of pharmacokinetic data from normal volunteers. Risk Anal. 1987;7(4):415-26.

32. Bhat VS, Meek ME, Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47(9):729-49.

33. Meek MEB. Application of uncertainty factors in the priority substances program and international harmonization. Human and Ecological Risk Assessment. 1999;5(5):1013-22.

34. Lipscomb JC. Purpose-driven risk assessment. Toxicol Pathol. 2019;47(8):1027-34.

35. Martin OV, Martin S, Kortenkamp A. Dispelling urban myths about default uncertainty factors in chemical risk assessment – sufficient protection against mixture effects? Environmental Health. 2013;12(1):53.

36. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctanoic Acid (PFOA). Ottawa, ON; 2018.

37. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctane Sulfonate (PFOS). Ottawa, ON; 2018.

38. NIOSH. Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione. Cincinnati, OH; 2016. Report No.: 2016-111.

39. Gloede E, Cichocki JA, Baldino JB, Morris JB. A validated hybrid computational fluid dynamics-physiologically based pharmacokinetic model for respiratory tract vapor absorption in the human and rat and its application to inhalation dosimetry of diacetyl. Toxicological Sciences. 2011;123(1):231-46.

40. Meek ME, Berry SC, Boobis AR, Cohen SM, Hartley M, Munn S, et al. Re: Guyton, Kathryn Z., Barone, Stanley, Jr., Brown, Rebecca C., Euling, Susan Y., Jinot, Jennifer, Makris, Susan (2008). Mode of action frameworks: A critical analysis. Journal of Toxicology and Environmental Health, Part B, 11(1): 16–31. Journal of Toxicology and Environmental Health, Part B. 2008;11(8):681-5.

41. NRC. Science and Judgment in Risk Assessment. Washington, DC: National Academies Press; 1994.

42. Clewell HJ, Andersen ME, Blaauboer BJ. On the incorporation of chemical-specific information in risk assessment. Toxicology Letters. 2008;180(2):100-9.

43. McClellan RO. A commentary on the NRC report "Science and judgment in risk assessment". Regul Toxicol Pharmacol. 1994;20(3 Pt 2):S142-68.

44. Clewell HJ. Incorporating biological information in quantitative risk assessment: an example with methylene chloride. Toxicology. 1995;102(1-2):83-94.

45. Andersen ME, Conolly RB, Faustman EM, Kavlock RJ, Portier CJ, Sheehan DM, et al. Quantitative mechanistically based dose-response modeling with endocrine-active compounds. Environmental Health Perspectives. 1999;107 Suppl 4:631-8.

46. Frederick CB. Summary of panel discussion on the 'advantages/limitations/uncertainties in the use of physiologically based pharmacokinetic and pharmacodynamic models in hazard identification and risk assessment of toxic substances'. Toxicology Letters. 1995;79(1-3):201-6.

47. Tan YM, Worley RR, Leonard JA, Fisher JW. Challenges associated with applying physiologically based pharmacokinetic modeling for public health decision-making. Toxicological Sciences. 2018;162(2):341-8.

48. Paini A, Leonard JA, Kliment T, Tan YM, Worth A. Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications. Regulatory Toxicology and Pharmacology. 2017;90:104-15.

49. Paini A, Joossens E, Bessems J, Desalegn A, Dorne JL, Gosling JP, et al. EURL ECVAM Workshop on New Generation of Physiologically-Based Kinetic Models in Risk Assessment. Joint Research Centre; 2017. Report No.: EUR 28794 EN.

50. Crump KS. A new method for determining allowable daily intakes. Fundamental and Applied Toxicology. 1984;4(5):854-71.

51. Ramsey JC, Andersen ME. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicology and Applied Pharmacology. 1984;73(1):159-75.

52. Barn P, Keefe AR, Slot N, Jardine KJ, Ziembicki S, Telfer J, et al. Canada should move toward adopting harmonized evidence-based OELs to consistently and adequately protect workers. Annals of Work Exposures and Health. 2020.

53. Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Van Raaij M, Vickers C. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regulatory Toxicology and Pharmacology. 2011;60(2):S1-S14.

54. NRC Committee on AEGLs. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC; 2001.

55. Lapare S, Brodeur J, Tardif R. Contribution of toxicokinetic modeling to the adjustment of exposure limits to unusual work schedules. AIHA J (Fairfax, Va). 2003;64(1):17-23.

56. Andersen ME, MacNaughton MG, Clewell HJ, rd P. Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model. American Industrial Hygiene Association journal. 1987;48(4):335-43.

57. IPCS. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva; 2010. Report No.: IPCS Harmonization Project No. 9.

58. Meek ME, Barton HA, Bessems JG, Lipscomb JC, Krishnan K. Case study illustrating the WHO IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment. Regul Toxicol Pharmacol. 2013;66(1):116-29.

59. Corley RA, Mast TJ, Carney EW, Rogers JM, Daston GP. Evaluation of physiologically based models of pregnancy and lactation for their application in children's health risk assessments. Critical Reviews in Toxicology. 2003;33(2):137-211.

60. Daston G, Faustman E, Ginsberg G, Fenner-Crisp P, Olin S, Sonawane B, et al. A framework for assessing risks to children from exposure to environmental agents. Environmental Health Perspectives. 2004;112(2):238-56.

61. Barton HA, Chiu WA, Woodrow Setzer R, Andersen ME, Bailer AJ, Bois FY, et al. Characterizing uncertainty and variability in physiologically based pharmacokinetic models: State of the science and needs for research and implementation. Toxicological Sciences. 2007;99(2):395-402.

62. Marino DJ, Starr TB. Probabilistic dose-response modeling: case study using dichloromethane PBPK model results. Regul Toxicol Pharmacol. 2007;49(3):285-300.

63. Bois FY, Jamei M, Clewell HJ. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology. 2010;278(3):256-67.

64. IPCS. Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. Geneva; 2017. Report No.: Harmonization Project Document No. 11.

PART I

EXPLORATION OF INCORPORATION OF CHEMICAL- AND SCENARIO-SPECIFIC DATA IN DOSE–RESPONSE ANALYSES

Chapter 2 – Evolution of the Application of Physiological Kinetic and Dynamic Models in Chemical Dose–Response Assessments in Scientific Literature

ABSTRACT

Physiological kinetic and dynamic models were first developed in the 1920s, with their development for environmental chemicals beginning in the 1970s. Publications on physiological models present a continuum of model development and use, with dose–response analysis being an important application. The adoption of physiological models for use in dose–response analyses began in the 1980s. The objective of this study is to systematically explore the evolution of the application of physiological models in dose–response assessments in the peer-reviewed literature, specifically for chemicals found in the general and occupational environments. Although the number of publications on physiological models has increased steadily over time, the increase in their use in dose–response assessments has been modest, and has even decreased over the last decade. Beginning in 1986, a total of 141 publications in journals or textbooks present original dose–response applications of chemical-specific physiological models. Dose–response analyses, predominantly performed with PBPK models, never exceeded 8 publications per year, and were limited to 84 distinct chemicals of environmental or occupational origin. The use of physiological models in dose–response analyses was most common for environmental exposure scenarios, and was initially performed predominantly by authors from the United States, with contributions from other countries increasing in recent decades. This synthesis of this body of scientific literature proposes factors contributing to the modest uptake of PBPK models for dose–response analysis, along with recommendations for their broader application, including improving the collaborative interface between modellers and the risk assessment community.

1.0 Introduction

Physiological kinetic and dynamic models—such as physiologically based pharmacokinetic or toxicokinetic (PBPK/TK) models, physiologically based pharmacokinetic or toxicodynamic (PBPD/TD) models, dosimetry models, and biologically-based dose–response (BBDR) models—have been used in the dose–response assessment of environmental chemicals for over three decades (1-12). Their development and use for this purpose enables simulating non-linear kinetics and dynamics under a wide variety of exposure circumstances, allowing for more biologically motivated extrapolations among species, routes of exposure, dose levels and durations, and among individuals and subgroups in the human population (2, 5-8, 11-17). These approaches can be used in predictive assessments that reduce the need for default dose–response extrapolations, such as the application of generic 10-fold uncertainty factors (UFs) to represent inter- and intra-species differences (2, 5, 6, 9, 18).

The types of physiological models that are the focus of this publication are those that quantitatively describe the behaviour or biological activity of specific chemicals at a macro level, namely models of tissues and organs, organ systems, or the whole body. They can be considered as increasingly data-informed approaches, which fall along a continuum of methods for dose–response assessments that move toward biologically-based predictivity, as presented in Figure 1. The models use a series of mathematical equations that include parameters representing anatomical, physiological, biochemical, physicochemical and flow dynamics processes to describe toxicokinetics (absorption, distribution, metabolism, and/or excretion) or toxicodynamics (biological processes leading to adverse outcomes) of a chemical within an organ or organism. The definitions used in this analysis for each type of model are given in Table 1, along with the potential role of these models in dose–response analysis. It should be noted that although the different models are often discussed separately in this publication, they are sometimes combined to provide more complete descriptions of the toxicokinetics and toxicodynamics of a chemical within an organism.

Table 1 – Overview of physiological models included in this analysis

Model type	Definition used in this analysis	Incorporation of model into dose–response analysis
PBPK	A series of mass balance equations to describe the flow, partitioning, and metabolism of chemicals in various tissues within the body, often including subsequent excretion.	Identify target organ dose and target organ metabolism associated with externally characterized PODs, which can be subsequently incorporated into dose–response assessments to identify internal points of departure.
Dosimetry	Complex mathematical descriptions of deposition, absorption, metabolism, and/or toxicodynamics specifically in regions of the portal of entry. Although for environmental and occupational exposures these models could also include oral and dermal dosimetry—and dosimetry models for these routes were included in the analysis whenever they were identified—the focus of the background discussions is on inhalation dosimetry models such as CFD models, as these models are more commonly discussed in literature.	Typically provide portal of entry doses associated with externally characterized PODs, that can be subsequently incorporated into dose–response assessments; if models also include descriptions of toxicodynamic processes within the portal of entry, dose–response analyses can be performed directly within the model.
PBPD and BBDR	This paper uses the terms PBPD and BBDR models to describe models that use mathematical equations that include physiological parameters to describe mechanistic processes involved in target organ responses. PBPD models are those that focus solely on the toxicodynamic processes, while BBDR models are those that combine both toxicokinetic and toxicodynamic processes. Pharmacodynamic and BBDR models at the cellular level were considered outside the scope of this research unless incorporated into whole organism or whole organ system (for example, if models were combined with PBPK models so that cellular toxicity calculations incorporated target tissue dose metrics).	Dose–response analyses can be performed directly within the model; doses associated with external PODs are described internally if a toxicokinetic component is included, or as external/applied dose if model is restricted to toxicodynamic components.

PBPK: physiologically based pharmacokinetic; POD: point of departure; CFD: computational fluid dynamic; PBPD: physiologically based pharmacodynamic; BBDR: biologically based dose–response

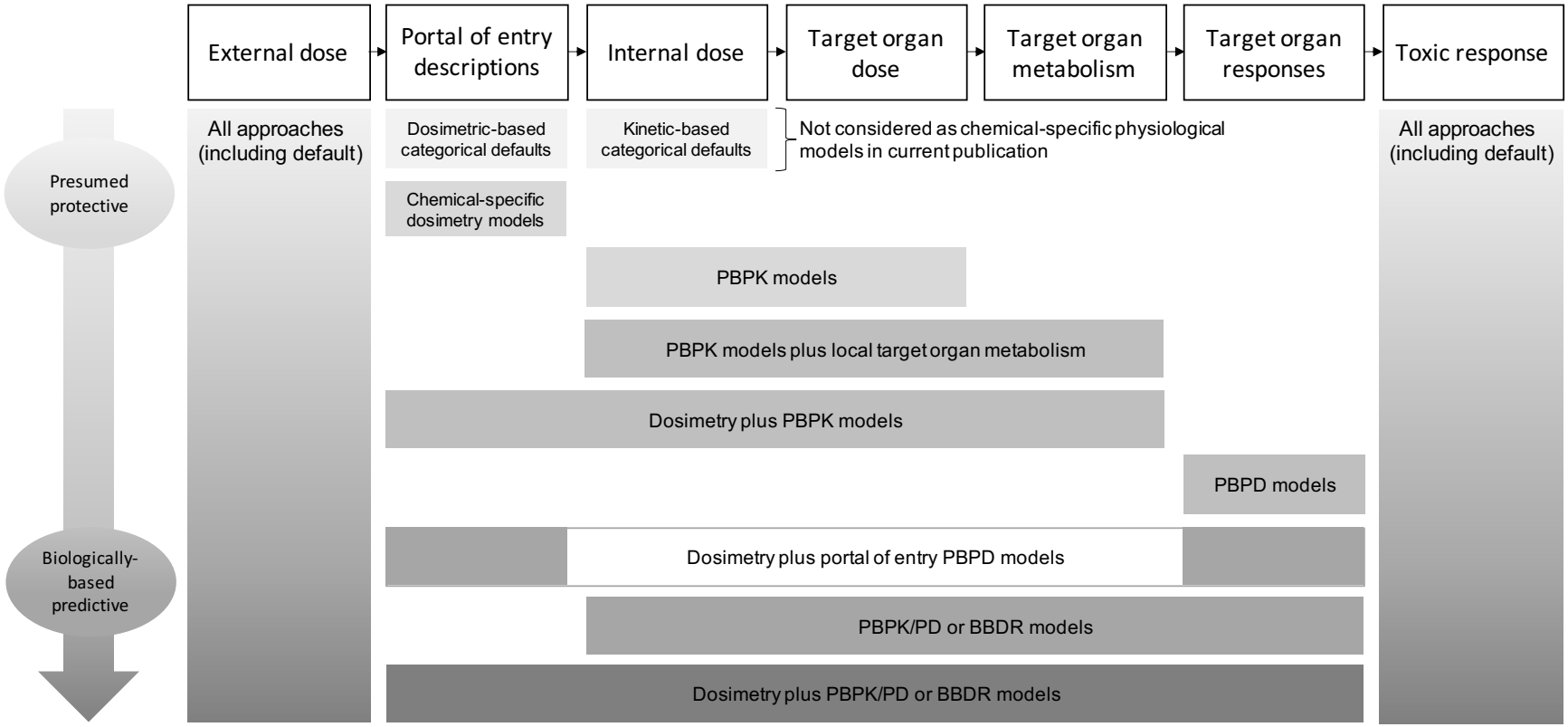


Figure 1. A continuum of data-informed approaches that can be used in dose–response assessments. Builds upon a continuum initially developed by Renwick et al., 2001.

This article also focuses on toxicants in the general and occupational environments. The general environment refers primarily to sources of chemicals in air, water, soil, and food. Pesticides have been included as they can contaminate these environmental sources, and also can contribute to occupational exposure. Non-environmental/ occupational exposures (which can include pharmaceuticals, consumer products, and non-environmental contamination of food, such as food additives, packaging materials, and cooking-generated byproducts) are outside of the scope of the present analysis.

Previous bibliometric searches (6, 13, 19-25) and expert elicitation (9) have explored the use of physiological models over time, including keyword searches for physiological models in common scientific literature databases. These reviews identified a steadily increasing frequency of publications that included terms related to physiological models. Several of the publications included a more detailed exploration of the search results to identify unique PBPK models (23) or the specific scientific fields of development (6, 22, 25). However, the bibliometric reviews were not designed to explore if or how the physiological models were applied, particularly for dose–response purposes. In one publication, both a search of peer-reviewed literature and expert elicitation identified applications of PBPK modelling limited to the derivation of chemical-specific adjustment factors for inter- and intraspecies variability in the timeframe of 2000 to 2016 (Bhat et al., 2017). When considered collectively, most of the reviews focused solely on PBPK modelling, with little attention to dosimetry, PBPD, or BBDR modelling.

The objective of this manuscript is to perform a comprehensive review and synthesis of the history and evolution of the use of physiological models for dose–response modelling that builds upon existing bibliometric reviews. The paper presents a brief narrative overview of the history of the development and dose–response applications of PBPK, inhalation dosimetry, and PBPD or BBDR models, followed by a summary of bibliometric reviews that have quantified the citations of various physiological models in common scientific literature databases. Subsequently, original perspectives are presented, building upon the bibliometric reviews by using elements of systematic review to quantify the publications in scientific literature databases that specifically apply physiological models for the dose–response analysis of chemicals in

the general and occupational environments. The types of dose–response applications that were the focus of the present research include derivation of toxicological reference values (TRVs), quantitative cancer dose–response assessments, and margin of exposure (MOE) assessments, including derivation of points of departure (PODs) and UFs. The present research focuses on the frequency of publication of relevant dose–response applications within these scientific databases, and how this has evolved over time, including exploring who has applied the approaches identified.

2.0 History and evolution of physiological kinetic and dynamic modelling

Several available reviews provide narrative discussions of the history of model development and application, while others quantify development of the models. These reviews are summarized in the following sections.

2.1 Summary of narrative reviews of physiological models

This section presents a summary of the historical development of each of the types of physiological models addressed in this manuscript. The summary is based primarily on review articles identified in the search (see Section 3 for search details) that presented historical information; regulatory dose–response application of the models is discussed if it was presented as an important milestone in the identified reviews.

2.1.1 PBPK models

The history of PBPK model development is described in a range of reviews (5, 18, 25-31). Early development of physiologically-based models has been described as occurring in two parallel streams—for volatile anaesthetics and for pharmaceuticals (18, 27)—with the first model in each stream published in the 1920s and 1930s. In 1924, Haggard (32, 33) developed a simple model of uptake, distribution, and elimination of diethyl ether and similar volatile anaesthetics that was described by blood flow, pulmonary ventilation, and blood:air solubility coefficients. Thirteen years later, the first physiologically-based kinetic model to be introduced for therapeutic compounds was a generic model of drug disposition published by a Swedish physiologist and biophysicist (34, 35). The five-compartment model (absorption site, circulatory system, tissue

distribution sites, renal elimination of drug, and metabolites in tissues) was based on mass balance principles, and incorporated physiological parameters such as organ volumes and perfusion rates. However, limitations in computing capacity delayed the implementation of these early models (5, 18, 25-28).

Development of models in both streams expanded gradually in the 1950s through 1970s. Increasingly complex models of volatile anaesthetics (36-38) extended the Haggard model by combining tissues based on blood flow and tissue partition coefficients (18, 26-28). Pharmaceutical models were expanded to explore distribution in organ sub-components, including vascular, interstitial, and cellular regions (39, 40). An additional refinement to pharmaceutical models included non-linear metabolism and excretion (41-43), allowing for a description of increased toxicity after metabolic saturation (5). Development of models for chemotherapeutic drugs began in the 1970s (25, 29, 30), starting with models for methotrexate that described biliary secretion and reabsorption (44) and impacts of membrane resistance on distribution to certain tissues (30, 45).

The development of physiologically-based models to describe the pharmacokinetics of pharmaceuticals and anaesthetics eventually led to the advent of physiological models for chemicals relevant to environmental and occupational exposures in the 1970s and 1980s. One of the earliest models developed was for dieldrin (46). Gerlowski and Jain (29) listed models for five trace metals or ions and six environmental compounds published between 1970 and 1982. The Fiserova-Bergerova model (47, 48) extended the anaesthetics models by incorporating systemic metabolism, thereby allowing for the use of such models to evaluate occupational exposures to inhaled volatile compounds (5, 18, 26). Although the Fiserova-Bergerova model was a stepping stone for future PBPK models of inhaled solvents, Andersen (49) described the model as an analog of a physiological model that "does not lend itself to an explicit description of the properties of the metabolizing organ." Building upon the Fiserova-Bergerova model, Andersen (49) developed a model of inhalant metabolism that used a physiological approach to describe perfusion, extraction, and clearance. Compartments of the Andersen (49) model included liver, kidney, and well-, moderately-, and poorly-perfused organs, all

of which were described by blood flow rates, volume, and chemical-specific partition coefficients; metabolism was included for the liver compartment.

Although the development of physiological models for environmental chemicals expanded in the 1970s and early 1980s, their use was only popularized after the landmark publication of the Ramsey and Andersen (50) styrene inhalation model (51), which was based on the Andersen (49) inhalant model (27). Compartments of the model included fat tissue, muscle tissue, richly perfused tissue, and a saturable metabolising compartment that was based on the liver but also represented other metabolic tissues; pulmonary compartments were included to describe exposure and systemic absorption (50). The model, which was initially developed for rats and scaled to humans, was used to accurately predict styrene kinetics in oral and intravenous studies in rats and inhalation studies in human volunteers. Because the model allowed for the quantitative description of styrene behavior beyond the initial design of kinetics studies, Ramsey and Andersen (50) highlighted the potential use of the model in high-to-low dose, route-to-route, and animal-to-human extrapolations (5).

The structure of the Ramsey and Andersen (50) styrene model formed the basis of many subsequent PBPK models. One such model was developed for dichloromethane, resulting from a collaboration between the US Air Force and Dow Chemical Company (31). The model contained richly perfused, slowly perfused, fat, and metabolizing liver compartments, with the lung compartment also described as a metabolizing target tissue in addition to a route of exposure (52). Parallel metabolic pathways of cytochrome P450 oxidation and glutathione conjugation were also described, with the former predominant at lower doses but saturating at higher doses, leading to a rapid increase in the latter pathway. Tumour formation in experimental studies in rodents appeared to be more closely associated with production of the glutathione conjugate. Using the human model, it was estimated that glutathione conjugate formation in human tissues at low concentrations was lower than in mice exposed to the same 1 ppm concentrations (52).

The dichloromethane model is particularly notable as it was the first physiologically based kinetic or dynamic model to be proposed for use in a regulatory dose–response assessment. Although Andersen and colleagues (52) used the model to compare internal dose metrics in mice and humans exposed to various concentrations,

they did not extend their analysis to identify human-equivalent PODs or perform estimates of cancer risk in humans, as the model was "initially developed to explore causality between various dose metrics and carcinogenicity" (5). However, the model was provided to US EPA to support their ongoing cancer assessment of dichloromethane (31). The model prompted a National Academy of Sciences (NAS)-sponsored workshop that concluded that PBPK modelling offered a promising approach to improve risk assessment, as uncertainty in extrapolations could be decreased (53). The Health Risk Assessment Committee (HRAC), an interagency working group (composed of members from US EPA, Consumer Product Safety Commission [CPSC], Food and Drug Administration, and Occupational Safety and Health Administration [OSHA]), was formed to evaluate the model and its application in risk assessment (54). The committee published results of the model evaluation (55), with each agency developing its own risk analysis that stemmed from the HRAC evaluation (54). Following the NAS workshop, HRAC evaluation, and EPA Scientific Advisory Board review, EPA published a draft addendum to their earlier inhalation cancer risk assessment (54, 56).

After the incorporation of PBPK modelling into the dichloromethane cancer risk assessment, PBPK modelling activity was reported to have increased (31). Leung (57) published a list of 24 environmental toxicants with PBPK models. In 1995, the list grew to 52 compounds (51). A more recent publication that systematically identified PBPK models in the literature found PBPK models for 307 unique chemicals (23), including compounds other than environmental toxicants.

Although the development of PBPK models grew after the initial adoption of a PBPK model in a regulatory risk assessment, application of the models by regulatory agencies does not appear to have increased as rapidly. A 1995 review noted that no further risk assessments at US agencies had applied PBPK modelling, either for dichloromethane or other chemicals for which models had been developed (31). However, as reviewed by Loizou et al. (7), the model was further used in assessments performed in the US by OSHA (58) and CPSC (59), and in an assessment under the Canadian Environmental Protection Act (60).

2.1.2 Inhalation dosimetry models

In addition to the whole-body physiologically-based kinetic models, physiological dosimetry models have been developed. As explained in Table 1, the term "dosimetry models" could refer to portal of entry dosimetry for various routes of exposure; however, as inhalation dosimetry models such as computational fluid dynamics (CFD) models are more commonly discussed in literature, they are the focus of this section.

Many of the inhalation PBPK models for volatile organic compounds, particularly lipophilic compounds with low water solubility, did not reflect the behaviour of highly water-soluble vapours in the respiratory tract, as the traditional PBPK models used a simplistic assumption of instantaneous uptake of inhaled compounds into venous blood (61). Therefore, models of inhalation dosimetry were developed to explore the deposition and absorption of chemicals in the respiratory tract.

Many anatomical and physiological factors affect the behavior of inhaled water-soluble vapours and gases in the respiratory tract. Mathematical representations of these factors are included in the models, including airflow patterns in the respiratory tract, metabolism and uptake of the compounds in different regions of the respiratory tract, the cyclic nature of respiration (i.e., reflecting both inhalation and exhalation), breathing rates, pulmonary ventilation, blood perfusion rates, gas transport in lumen and air spaces, and partition coefficients (61-63). The anatomical features are often described geometrically as a three-dimensional grid reconstructed from serial cross sections of nasal and airway tissues, influencing the equations that are derived for the different regions of the respiratory tract (61).

The history and evolution of respiratory tract dosimetry models has been reviewed by Overton and Miller (63), Medinsky and colleagues (61), and Cohen Hubal and colleagues (62). These publications generally describe increasing model complexity over time, which is summarized here.

Earlier dosimetry models focused primarily on the lower respiratory tract, possibly because pulmonary disease is typically more severe than nasal lesions and mathematically describing the structure of the lower respiratory tract is simpler than the upper respiratory tract (62). The earliest identified lower-respiratory tract model in humans described a dichotomous branching structure with >8 million paths from the

trachea to the alveoli, but simplified the required equations by assuming that all model paths were equivalent, allowing for the need to develop equations for only one path (63). This model was followed by others that allowed for the incorporation of variability in the different paths (64, 65). The models also evolved from whole lung models to lobar models, allowing for the description of intra-lung differences in dosimetry (64, 65). Early models were also one-dimensional, did not consider chemical reactions with tissues and (liquid) linings, and maintained constant model lung size during breathing. The models eventually became more sophisticated, allowing for chemical reactions with liquid lining and changes in lung dimensions throughout the breathing cycle (66), the latter of which had an essentially negligible impact on results (63).

Early models of the upper respiratory tract were also simple. The models (67-69) tended to describe only length, volume, and surface area of one or more segments (63). Early models described chemical concentrations as varying depending solely on time, with later models incorporating spatial position (62). As discussed by Cohen Hubal et al. (62), models also evolved from one- or two-dimensional (70-73) to more realistic three-dimensional models (74, 75), and some models also incorporated exhalation in addition to inhalation (73, 74). The models also eventually reflected important regional differences in the upper respiratory tract (75, 76), which allowed for further exploration of site-specific tissue damage of some vapours and gases (62).

Although most of the dosimetry models discussed above were designed to simulate the behavior of vapours and gases in the respiratory tract, models have also been developed for particulates. The latter models tended to be generic, with particle deposition and clearance dependent on particle characteristics. One of the early examples of dosimetry models for particulates was US EPA's regional deposited dose model (77). These models identify inhaled concentrations of particulate matter in animals and in humans that result in equivalent deposition to the identified sensitive regions of the respiratory tract. This allows for the calculation of human equivalent concentrations that reflect quantitative differences between animals and humans in particulate deposition in the regions of the respiratory tract relevant for adverse effects for particular compounds (10). The use of the US EPA model gradually declined with the introduction of the multiple path particle dosimetry model (78), which modelled total, regional, and airway-

specific (individual lobes) deposition in rats and humans (10, 79). However, the regional deposited dose model is still used for species extrapolation (10).

Dosimetry models have several different applications in dose–response assessment. One such purpose is to investigate regional deposition, metabolism, absorption, tissue damage, and associated species differences (61). When combined with PBPK components, dosimetric models can also simulate the subsequent behaviour of compounds in the systemic circulation (10). One early example of this was the model by Frederick, Morris (80), which extended the Morris, Hassett (76) model by combining it with a full-body multicompartment model to allow for simulation of dosimetry in extra-nasal tissues after systemic uptake in the respiratory tract. The use of this combined PBPK–CFD approach is especially helpful in describing kinetics of compounds for which respiratory absorption is non-linear, with changes in the rate of absorption at higher concentrations due to saturation of metabolism. Due to an increased absorption of the parent compound at higher doses, the PBPK model will demonstrate increased systemic distribution and hepatic metabolism for these compounds (10).

Dosimetry models have been applied for regulatory purposes. Beginning in the late 1980s, US EPA used such models to derive dosimetric adjustment factors (DAFs) to perform animal-to-human extrapolations in Reference Concentrations (81). The DAFs are categorical defaults that are used to replace the kinetic interspecies UF, and are dependent on the species from which extrapolations are being performed, and the target region of the respiratory tract (82). The target region depends on chemical characteristics, including particle composition and category of gas or vapour (Category I, II, or III, with progressively decreased solubility and reactivity/metabolism in upper regions with increasing category, resulting in progressively deeper penetration and increasing systemic absorption) (10). As categorical defaults are outside the scope of this review (see Figure 1), they are not further discussed in this manuscript; however, detailed descriptions of the derivation of DAFs are available elsewhere (10, 79, 81-84). In addition to the use of dosimetry modelling to develop categorical defaults, chemical-specific dosimetry models have also been used for derivation of risk values in regulatory risk assessments. For example, the Government of Canada's Priority Substances List assessment of formaldehyde included a CFD model and single-path lung dosimetry model (combined

with a two-stage clonal growth model) to derive cancer risk estimates for upper respiratory tract tumours (85).

2.1.3 History of development and application of PBPK-PD or BBDR models

Modelling gradually evolved from solely considering dosimetry and pharmacokinetics to consideration of pharmacodynamics. These models were referred to either as PBPK-PD or BBDR models. In these extended models, physiologically realistic representations of both tissue dosimetry and tissue response were incorporated. These models allowed for a more complete definition of mechanistic processes occurring in tissues following exposure, to more directly link tissue dose to the ultimate biological response without requiring empirical correlations external to the models (5). Model parameters are therefore based on biology rather than fitting of incidence curves of the adverse response (14). Early examples of PBPK-PD or BBDR models referenced in reviews (5, 13, 86) included those developed to model the effects of environmental chemicals on various types of endocrine/hormone activity; fetal development and organogenesis; cancer, including development of pre-neoplastic lesions; and respiratory tract effects. Some were developed as generic pharmacodynamic models (e.g., clonal expansion models of carcinogenesis), and would only be used to investigate chemical-specific effects if incorporated into PBPK models, while others were BBDR models designed to explore adverse effects resulting from exposure to specific chemicals. However, the pharmacokinetic descriptions in these models are typically more complete than the biological response components (5), likely due to better understanding and their lesser complexity (13). As a result, PBPK models are much more prevalent in the literature than BBDR models (13).

BBDR models are considered by many as the best-informed models for low-dose extrapolations in risk assessments, and US EPA cancer assessment guidelines have proposed them as the preferred approach for low-dose–response cancer extrapolations as far back as 1996 (14, 86). However, despite the regulatory support for the development and use of BBDR models, the NAS Committee on Toxicity Testing in the 21st Century concluded in 2007 that BBDR modelling was “still in its infancy” (86, 87). Regulatory

application of BBDR models has been limited, likely due in part to their limited availability.

2.2 Summary of bibliometric reviews of physiological models

In addition to narrative reviews of the history of physiologically-based kinetic and dynamic models, several reviews have also attempted to quantify the frequency of reporting of these models in published literature. These bibliometric reviews present results as overall numbers of publications identified using a particular search strategy. Results include both original research and review papers, and those from domains other than human health risk assessment for environmental chemicals (e.g. for ecotoxicology, veterinary toxicology, or pharmaceuticals).

Although these bibliometric reviews cannot be directly compared, as they all used different search strategies (summarized in Table 2), their collective consideration provides a general overview of trends. In general, the bibliometric reviews suggest an increase in the number of publications over time, with only 245 identified citations between 1990 and 2001 (13), compared with over 2,000 publications in more recent reviews, with search results from 1977 to 2013 (23) and through to 2017 (25). One series of bibliometric reviews that performed the same search at three different time periods indicated an increase over time, with 495 publications through March 2002 (20), 736 publications as of September 2006 (19), and 1151 publications by December 2010 (21).

Several of the bibliometric reviews also presented results by year (6, 22-25), which tended to indicate a gradual increase over time, with a more rapid increase in publications in the most recent decade(s). Results varied somewhat among reviews, likely due to the different search methods used (see Table 2). Overall, the earliest identified manuscript in any of the search results was from 1957, but the specific publication was not cited, precluding its identification. A few additional papers were identified in subsequent decades, and at least one article was published every year beginning in 1981. Publications began to increase more rapidly in the 1990s, with an even greater increase in each subsequent decade. The most recent bibliometric reviews (6, 25) indicate a particularly rapid increase in publications in the 2010s, although much of the increase appears to be due to publications related to pharmaceuticals (6).

Table 2 – Summary of bibliometric reviews of physiological models

Reference	Keywords or search string[a]	Dates included	Database	Number of publications
DeWoskin et al. (13)	PBPK or PBTK	1990 to 2001	MEDLINE	245
Nestorov (20)	Physiologically based pharmacokinetic model	Until March 2002	MEDLINE	495
Nestorov (19)	Physiologically based pharmacokinetic model	Until September 2006	PubMed	736
Edginton and Joshi (21)	Physiologically based pharmacokinetic model	Until December 2010	PubMed	1,151
Tan et al. (22)	[TS = (computational OR "in silico" OR predictive OR model* OR virtual) AND TS = (toxicology) AND TS = (environment*)]	1970 to 2009	Web of Science	397
	Physiologically based pharmacokinetic modeling	Until February 2011	PubMed	769
Lu et al. (23)	PBPK OR ("physiologically based" AND (pharmacokinetic OR toxicokinetic))"	1977 to 2013	PubMed	2,039
Paini et al. (24)	Keywords: PBPK model(s)	1988 to April 2017	PubMed	Not explicitly stated; results presented graphically as number of publications per year
	PBPK models OR PBBK models OR PBTK models OR PBK models			
Tan et al. (6)	PBPK OR physiologically based AND pharmacokinetic OR toxicokinetic	until July 2017	PubMed	1,313
Paini et al. (25)	PBK, PBPK, PBBK, or PBTK	until 2017	PubMed	>2,000

[a]Presented in this table exactly as mentioned in original reference; it was often not clear whether the keywords were the sole keywords used in the search or whether synonymous terms were also included in the search

The more recent bibliometric reviews report additional analyses. Lu et al. (23) identified that the most common results were of PBPK-related papers not associated with any particular chemical, followed by refinement of previously published chemical specific models. Only 307 articles addressed unique chemical-specific PBPK models (corresponding to first time a model was published for a chemical) were identified, making them the least common publications among the 2,039 manuscripts identified by Lu et al. (23). The remainder of the papers focused on application domains. Paini et al. (25) explored scientific fields using keywords (toxicology, pharmacology, chemical safety or risk assessment, forensic sciences, veterinary), and identified a notable increase in the number of publications in most of the domains over the past decade, with the exclusion of toxicology and veterinary medicine. In 2012, Tan et al. added "not pharmaceutic*" to the search string, which only reduced the number of hits only slightly (371 vs. 397 publications). The more recent Tan et al. (6) publication identified that 65% of papers addressed environmental chemicals, and 31% addressed pharmaceuticals; the remaining 4% addressed "endogenous compounds".

Although the identified bibliometric reviews focused primarily on PBPK models, two of the publications included discussions of other types of models. DeWoskin et al. (13) contrasted the development of PBPK with BBDR models. Fewer than 20 BBDR models were developed for risk assessment purposes between 1990 and 2001, while a search of the terms "PBPK" or "PBTK" in MEDLINE during the same time period identified 245 publications. Tan et al. (22) performed a search of general computational models with the intent of identifying CFD (a subset of inhalation dosimetry), signaling pathway, BBDR, clonal growth, fate and transport, and exposure models, in addition to PBPK models. The results of the general computational model search resulted in many fewer results (approximately half of that for PBPK models), which the authors ascribed to the restriction of the search terms to environmental toxicology terms. However, the two searches were not strictly comparable, being performed in different databases. They were also designed quite differently, with the general computational model search not including additional nomenclature for the specific types of models being targeted. The general search did demonstrate a rapid increase in PBPK models beginning in the early

1990s and in CFD models in the early 2000s (albeit at a much lower magnitude than PBPK models), but papers on BBDR models were much less prevalent.

3.0 Application of physiological models for deriving risk values

Although the bibliometric reviews present a helpful snapshot of the increase in publications on physiological models over time, it is not clear whether the ongoing development of such models has translated into a similar increase in dose–response applications. This section presents the search strategy and results for an evaluation of the extent to which physiological modelling has been applied in dose–response analysis, using similar databases of scientific literature as the original bibliometric reviews to facilitate comparisons. The more detailed search and validation strategy differs from that in previous bibliometric reviews so as to identify as many relevant dose–response applications of the models in literature databases as possible.

3.1 Methods

3.1.1 Search strategy

The search strategy was initially designed to gather documents on a wide variety of approaches incorporating chemical-specific or scenario-specific data to inform the dose–response assessment process for chemical risk assessments. The goal was to identify all relevant methods, including methods for weight of evidence analysis that allow for decisions on the relevance/applicability of chemical- or scenario-specific data approaches (i.e., weight of evidence tools specifically designed for the assessment of mechanistic approaches), or methods that affect the application of an exposure guideline, from a dose–response perspective. Although benchmark dose (BMD) modelling did not meet the criteria for inclusion in the study, it was used as a comparison approach for the assessment. BMD modelling is an ideal comparator because many regulatory organizations now consider it in all dose–response assessments, but the adoption of this practice occurred only gradually over time. In later stages of the present research, due to time constraints, a decision was made to narrow the scope of the search to approaches that incorporate physiologically-based kinetic or dynamic modelling; physiological

modelling was the focus of the narrowed scope as it had the greatest number of included publications and because the approaches underpin all of the other increasingly data-informed approaches initially considered in the research. Publications that were considered to be included in the sub-categories (from the initial search strategy) of PBPK, BBDR, or dosimetry modelling were included in the analysis. Details on the topics addressed in the initial search strategy are given in Figure 2.

In consultation with a research librarian, a complete systematic review was determined to be unnecessary to address the research questions for the search, as the goal was to have a broad discussion of a variety of application types, rather than analyzing a best approach. Nonetheless, elements of systematic review were adopted throughout the design and application of the search strategy, with a goal of increasing rigor and transparency in the review.

The databases used in the search (Pubmed [NLM], MEDLINE [Ovid], Embase [Ovid], Toxline [NLM], and Web of Science [Web of Knowledge]) were selected to reflect subject and geographic diversity. The search strategy was initially designed using PubMed and subsequently tailored to the other databases. A combination of subject indexes (when available in databases) and free-text keywords was used. The general design of the search strategies is presented in Figure 2, and the detailed text used in each of the searches is presented in Appendix A. Briefly, the searches were designed to identify articles that contained keywords or subject indexes reflecting each of the three predetermined concepts: 1) risk assessment or risk values; 2) toxicity or environmental sources; and 3) dose–response approaches incorporating chemical-specific data. The various search terms within each of these concepts were combined with ‘or,’ and the three concepts were combined with ‘and.’ An iterative process was used to identify search terms for each of the concepts, ensuring that the search terms included were sufficiently broad to identify relevant articles, without identifying too many irrelevant publications.

Prior to finalizing the search strategy, a validation process was used to ensure the search was identifying relevant documents. For each of the identified approaches listed in Figure 2, at least one article providing guidance on the approach and another applying the approach were used. Whenever possible, a landmark article (e.g., the article that first

proposed the approach), an article related to the use of the approach in occupational risk assessments, and an article not indexed in PubMed or MEDLINE were used as validation articles for each approach. A set of 65 validation articles (58 in the main database and 7 for the BMD database) was selected.

The initial searches were run in each database within a two-day period, with searches limited by date (January 1, 1983 to December 31, 2015) and language (English and French only). The search was later updated to extend the inclusion date to December 31, 2018. Duplicates were removed using duplicate-identification tools in both EndNote (88) and DistillerSR (89).

CONCEPT 1: Risk (Dose–Response) Assessment		CONCEPT 2: Toxicity from Environmental Chemicals		CONCEPT 3: Dose–Response Approaches for Incorporation of Chemical- or Scenario-Specific Data	
Generic risk assessment/ dose–response assessment terms OR Generic risk value terms OR Names of specific risk values OR Organizations performing risk assessments	AND	Generic toxicity terms OR Generic chemical substance terms OR Toxic effects OR Environmental sources	AND	Mode of action or adverse outcome pathway analysis OR Physiologically-based kinetic, dynamic, or BBDR modelling OR Systems toxicology/network analysis OR Chemical-specific adjustment factors OR Population variability/ sensitive subpopulations	OR Combined/ cumulative risks OR Non-chemical stressors OR Uncertainty analysis OR Dosimetry modelling OR Duration adjustment OR General extrapolation terms OR General terms & frameworks
				Comparison approach: Benchmark dose modelling	

Figure 2. Design of initial literature search

3.1.2 Application of inclusion/exclusion criteria

DistillerSR (89) was used to facilitate the process of screening articles for relevance to the study. The general theme for inclusion was that the publication used a chemical-specific or scenario-specific approach to refine quantitative dose–response estimates for humans exposed to environmental chemicals. As many exclusion criteria were identified at the outset of the review as possible; however, due to the breadth of the identified publications, some additional detailed criteria could only be identified during the application stage. An overview of the exclusion criteria is provided in Table 3.

Exclusion criteria were applied by a single reviewer; however, additional measures were applied to verify consistency of inclusion criteria application. After application of the criteria was completed at each level, a random subset of 5% of the articles was blindly re-reviewed to ensure consistency; no verification was performed at Level 3 (abstract-level classification), as the goal of this level was to categorize articles by approach rather than exclude records. In total, 2,571 publications were reviewed twice to ensure consistency of application of inclusion/exclusion criteria. Moreover, as the initial design of the search strategy included a BMD search that was separate from the chemical-specific approaches search (see Figure 1), many studies overlapped in the two parallel databases. The set of 336 publications common to the BMD and chemical-specific databases were also reviewed after all exclusion criteria were applied, allowing the tracking of these publications throughout all four levels of the inclusion process.

Table 3 – Overview of exclusion criteria

Screening level	Screening level objective	Reasons for excluding records
Level 1 – title screen	Eliminate publications for which the title confirms the manuscript did not discuss environmental chemical hazard in humans or human models	- Not a chemical (e.g., biological, physical or radiological agents, unless considered as a non-chemical stressor for a cumulative risk assessment) - Exposure was not resulting from a general environmental source, including air, water, soil, or food from an environmental context, or a workplace environment (e.g., food additives or food contact materials, therapeutic or illicit drugs, smoking or vaping, unless discussed in the context of an environmental or occupational exposure) - Non-human models (e.g., agricultural or domestic animals, wildlife, plants, animal models of ecotoxicity)
Level 2 – abstract screen	Eliminate publications for which the abstract confirms the manuscript did not discuss chemical-specific or scenario-specific dose–response approaches	- Met Level 1 exclusion criteria - Performed hazard identification or exposure assessment, without an accompanying dose–response assessment - Discussed risk management, or otherwise did not discuss risk assessment - Performed dose–response assessment, but without mention of any chemical-specific or scenario-specific dose-response approaches
Level 3 – abstract-level classification	Identify which chemical-specific or scenario-specific dose–response approaches were potentially applied, based on abstract	- No records were completely excluded at this stage, but only those that were tagged as PBPK-PD, BBDR, or dosimetry modelling (or as unable to tell from abstract) were included in Level 4 screening

Screening level	Screening level objective	Reasons for excluding records
Level 4 – full-text screen	Eliminate publications that do not apply physiological kinetic/dynamic models for original, chemical-specific dose–response approaches	- Met Level 1 or 2 exclusion criteria, or were confirmed as not applying PBPK-PD, BBDR, or dosimetry models - Applied a generic model, or did not use a chemical-specific dose–response assessment approach (e.g. derivation of categorical defaults) - Did not apply the model for dose–response assessment in one of the following approaches: o Derivation of a human-equivalent concentration or other similar point of departure (POD; including for individual key events in a mode of action or adverse outcome pathway analysis) o Establishment of data-derived uncertainty factors o Derivation of a toxicological reference value (TRV) o Hazard component of a margin of exposure assessment o Estimation of cancer risk levels, unit risk levels, or concentrations associated with negligible cancer risks - Applied model post facto to the results of any of the above dose–response approaches (e.g., estimating a biomarker equivalent of a previously-derived POD or TRV, or performing duration adjustment on a previously-derived TRV) - Was a review article that did not include an original case study application of the approaches
All levels – administrative criteria	Apply other exclusion criteria of an administrative nature	- Not individual manuscripts (i.e., an entire journal, textbook, or collection of manuscripts) - Not published in peer-reviewed journals or textbooks (e.g., technical reports were excluded) - Full text was not available in English or French - Did not present an example of an original application (e.g., if it was included in a review article that did not include an original example of the approach; if a single application of a model was divided into multiple articles).

3.2 Results

3.2.1 Validation of search strategy

All articles (100%) in the final validation set were identified in at least one database. The identification rate for the BMD subset of articles ranged from 67–100% across the five literature databases searched; for the remaining subset (i.e., all non-BMD articles), 75–98% were found in each of these databases. As expected, the highest identification rates were for MEDLINE and Embase (98% and 96% in main validation set, respectively), as more detailed search functionality could be used in the Ovid platform than in the other platforms used.

3.2.2 Validation of inclusion/exclusion criteria

The primary goal of the verification exercises was to ensure no exclusion of records that should have been included. In performing a second review on a random 5% of articles at each level of the inclusion criteria application, false exclusions (exclusion of records that should have been included) were identified for 0% to 0.5% of the records. All of the falsely excluded records would have been excluded at some later stage of the screening.

When comparing the BMD database with the full database, 90% of records were excluded at the same level. Some records were excluded in both databases, but at different levels—7% were excluded one level apart, while 1.5% were excluded two levels apart. An additional 1.5% had conflicts on whether they should have been excluded or included in the database. Although very few records were excluded when they should have been included, the exercise identified the need to review decisions on records that fell into a few categories (e.g., reviews with case studies, models that were applied for comparison without derivation of a risk value, and models with risk values but that had been excluded based on some other criteria) to ensure no other records were erroneously excluded.

3.2.3 Continuum of application of physiological models

Applications identified in full-text screening of 1901 identified articles are characterized in the continuum in Figure 3. The only component of the continuum considered further in this publication is application in dose–response analysis (the darker-shaded portion of Figure 3), but other components are briefly described here to provide a better understanding of the breadth of publications addressing physiological pharmacokinetic and pharmacodynamic models.

At the bottom of the figure, problem formulation is an essential foundation for all different types of applications of physiological modelling. Although no publications focused solely on problem formulation for physiological model development, this stage was implicit in many publications with an indication to develop or apply models that are fit-for-purpose.

The first phase of the continuum is pre-development. Models were not included in articles in this category; rather, the authors recognized that a physiological model could be useful and should be considered in future research, or generated data that could be used in the development of a physiological model.

Publications in the second phase of the continuum were those in which a physiological model was developed, without an accompanying application. These models were developed for animals or humans (or both), and were often only run for exposure scenarios in experimental or observational studies that were being used for evaluation of model development.

The third phase of the continuum addresses various potential means of applying the physiological models. The focus of the analysis in this manuscript is the application of physiological models for dose–response assessments. This includes the development of risk metrics such as toxicological risk values (or components thereof, such as human-equivalent concentrations or other human-relevant PODs, or data-derived UFs) and cancer risk values, or the application of any of these for margin of exposure or margin of safety analyses. Other model applications identified in the literature—but that did not meet the criteria for inclusion in the database—included the application of models for exposure assessment and for informed mechanistic hypothesis testing. The exposure assessment publications presented useful applications of the models, such as measuring

internal doses at specified applied doses or concentrations (forward dosimetry), estimating external exposures associated with measured internal doses (reverse dosimetry), or performing interspecies or intraspecies comparisons of internally generated doses in different species or human subpopulations. The hypothesis generating and testing applications typically explored the associations between different pharmacokinetic or pharmacodynamic pathways and observed adverse effects in different tissues, species, or following various exposure regimens. Results often provided further insight into the mode of action of chemicals. However, none of the publications in either of these subcategories included the additional step of dose–response analysis in the derivation of risk values.

The fourth phase is application of the models to previously performed dose–response assessments. For publications considered under this category, the physiological models estimate internal doses at the existing risk values. One frequent application in this category was the exploration of exposure duration on derived toxicological reference values. A second type of application was the estimation of internal doses (in tissues or fluids relevant to biomonitoring) associated with toxicological reference values, to be used as biomonitoring guidance values (such as Biomonitoring Equivalents or Biological Exposure Indices). Publications in this category were excluded from the database if the approaches relied on physiological models for exposure-based adjustments of previously-derived (rather than original) dose–response assessments.

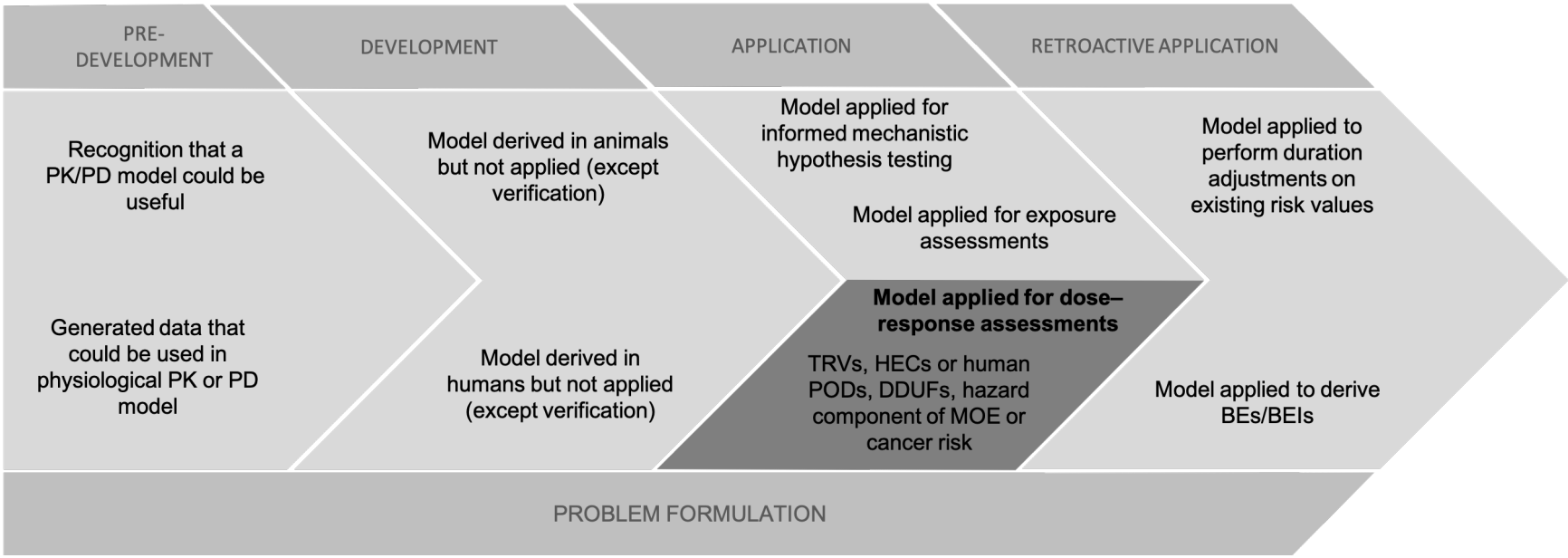


Figure 3. Continuum of development and application approaches of physiological models in risk assessment

PK: pharmacokinetic; PD: pharmacodynamic; TRV: toxicological reference value; HEC: human equivalent concentration; POD: point of departure; DDUF: data-derived uncertainty factor; MOE: margin of exposure; BE: biomonitoring equivalent; BEI: biological exposure index

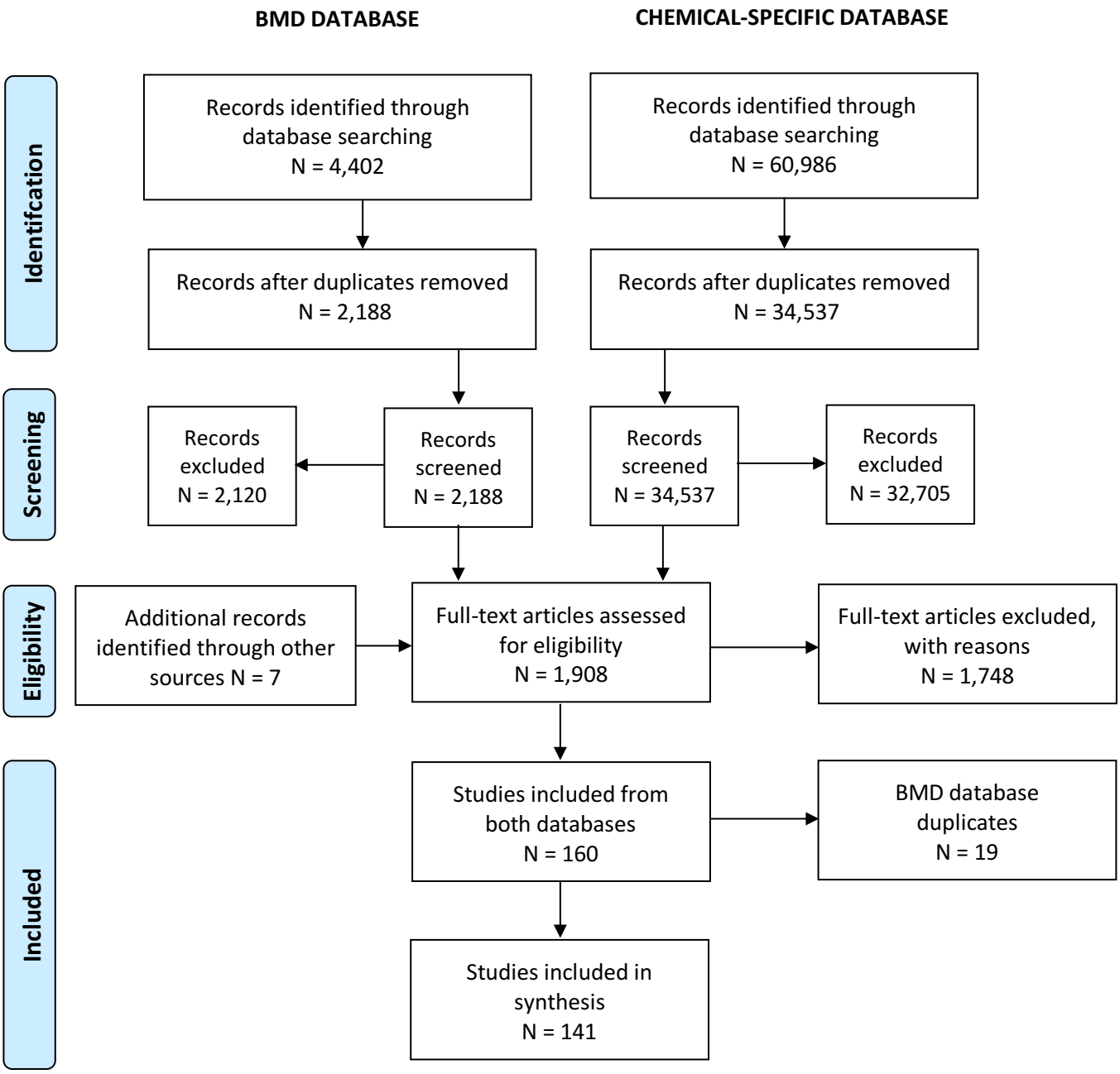


Figure 4. Inclusion and exclusion of records in final database of dose–response applications of physiological models

3.4 Dose-response applications of physiological modelling

A total of 141 records were included in the database of dose–response applications of physiological models, as they met the criteria set out in Table 3. A diagram summarizing the inclusion and exclusion of articles is presented in Figure 4. The evolution of the application of physiological models for dose–response assessments is discussed throughout the remainder of this section.

As demonstrated in Figure 5 and introduced above, dose–response applications of physiological models were first published in 1986 and increased rapidly in the late 1980s, with only a slight increase observed in subsequent decades. The decade with the greatest number of dose–response applications was the 2000s, with an average annual publication rate of 5.9 (vs. 3 in the 1980s and 2.8 in the 1990s); the rate dropped slightly in the 2010s (average of 4.8 per year). The maximum number of publications addressing models applied for dose–response analysis in any single year was 8 (observed in 2000 and 2014).

As seen in Figure 5, when considering the specific types of models applied in the identified dose–response analyses, the vast majority were PBPK models (136, or 96%). The five publications without a PBPK model were inhalation dosimetry models. An additional five models applied inhalation dosimetry in combination with a PBPK model, for a total of 10 inhalation dosimetry models (7%). A pharmacodynamic component (i.e., PBPK-PD or BBDR model) was also included in 16 (11%) publications; all models also included a pharmacokinetic component, which was a PBPK model in 14 publications, and dosimetry model in 2 publications). The first dose–response applications for PBPD/BBDR and dosimetry models were published in 1990 and 1999, respectively, subsequently peaking in the 2000s, and declining in the 2010s.

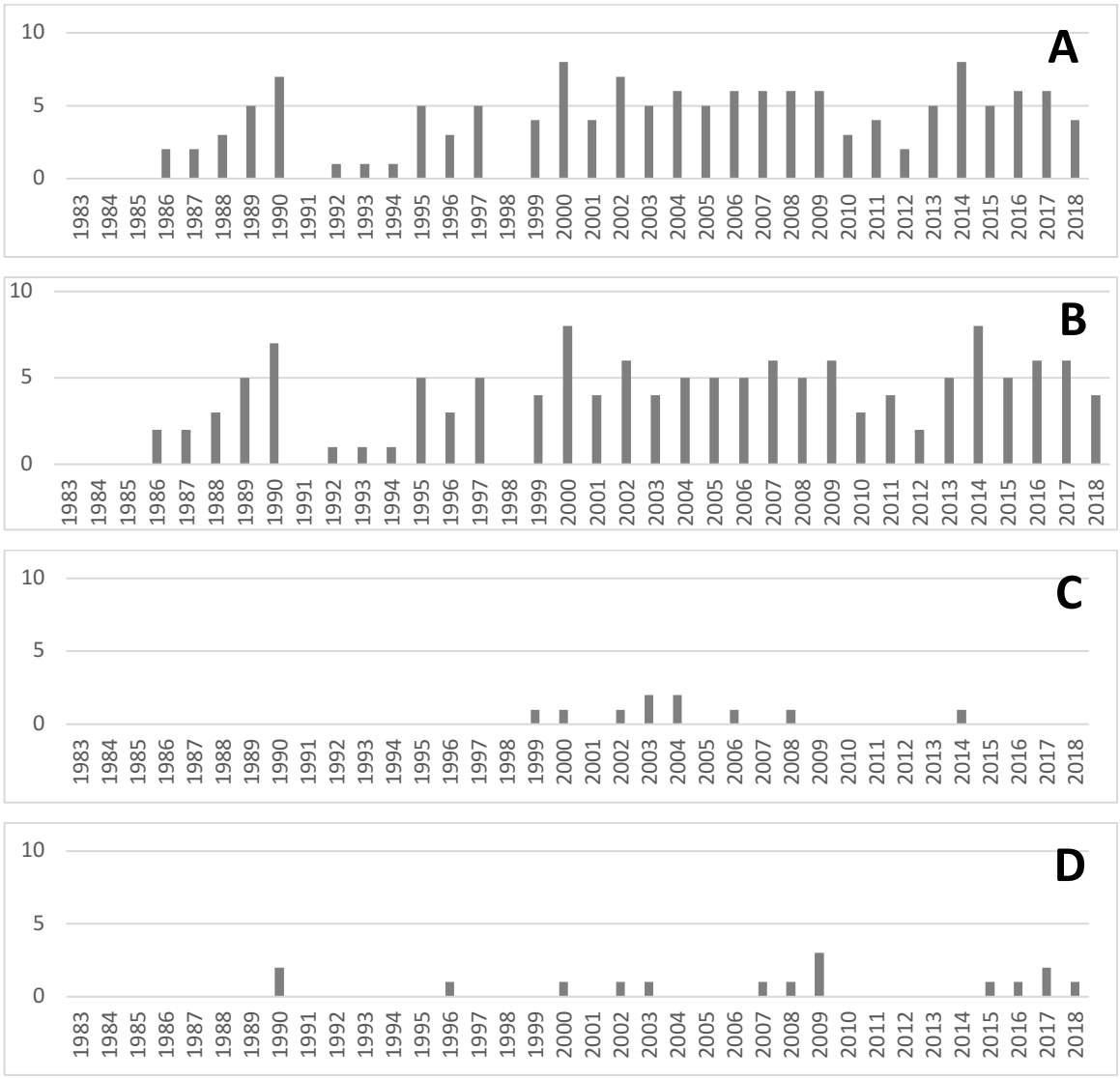


Figure 5. Publications applying physiological models in dose–response analyses by year A) All included model types; B) PBPK models; C) Inhalation dosimetry models; D) PBPD/BBDR models

The database of dose–response applications included models for 84 chemicals. As seen in Table 4, three compounds were each addressed in more than 10 publications: trichloroethylene (n = 17), dichloromethane (n = 16), and chloroform (n = 11). Other compounds with highest numbers of relevant publications were organic solvents (methyl chloroform, n = 9; tetrachloroethylene, n = 8; benzene, n = 7), including those for which the models were first applied in dose–response assessments. These included earliest applications for benzene and trichloroethylene in 1986, tetrachloroethylene in 1987, dichloromethane and methyl chloroform in 1988, and chloroform in 1990. Compounds

other than organic solvents most commonly addressed were arsenic (n = 5), dioxins (n = 5), chlorpyrifos (n = 3), and metals (n = 3 for each of chromium, manganese, and methylmercury). Single dose–response applications were identified for the majority of chemicals (n = 58; 69%).

The domains of application (namely environmental, occupational, food, and pesticides) are presented by decade in Figure 6. The use of models in dose–response assessment was predominantly for environmental exposure scenarios (n = 115; 82%), with the frequency of use over time similar to that in the overall database. Model development for application in occupational scenarios (n = 37; 26%) increased after the 1980s but remained steady from the 1990s through the 2010s. The number of publications reporting dose–response modeling for environmental food contaminants and pesticides was somewhat lower (n = 6 and 9, respectively; equivalent to 4% and 6%), but increased over time, including in the 2010s.

The development for application of the models in dose–response analyses was greatest in the US, with US authors contributing to 77% of the publications, followed by Canada and the Netherlands, both with authorship of 6% of included publications. The earliest publications with model-driven dose–response assessments by non-US authors were those for tetrachloroethylene and trichloroethylene by Japanese authors (90) and a methyl chloroform PBPK model by Belgian and Swiss authors (91). Only two additional relevant papers with non-US authors were identified in the 1990s (92, 93). However, increases in applications of the models in dose–response assessments by non-US authors increased in the following two decades: as seen in Figure 7—34% of included manuscripts had non-US authors in the 2000s, increasing to 44% in the 2010s.

Table 4 – Frequency of physiological model application per chemical

Number of Applications	>10	9	8	7	6	5	4	3	2	1	Total Chemicals
Number of Chemicals	3	1	1	1	0	2	3	7	8	58	84

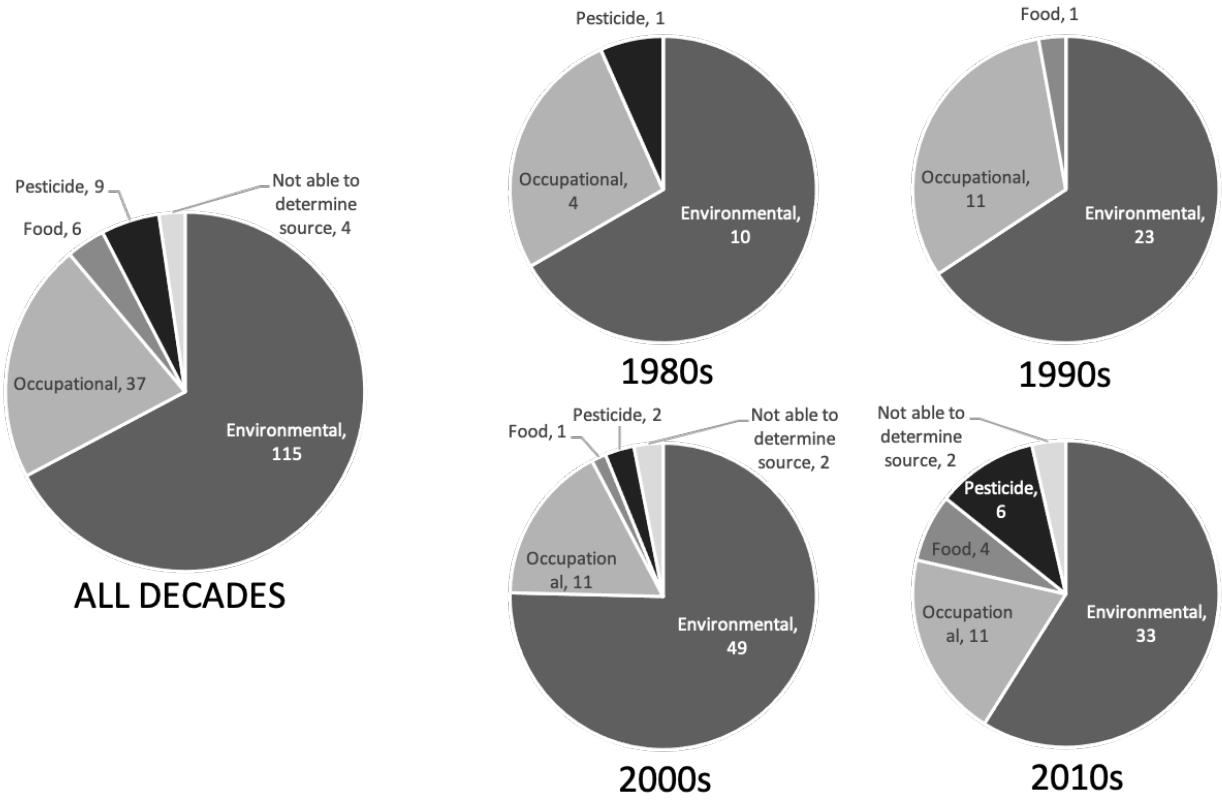


Figure 6. Source of exposure to chemicals in dose–response applications of physiological models for risk value derivation Numbers indicate article counts.

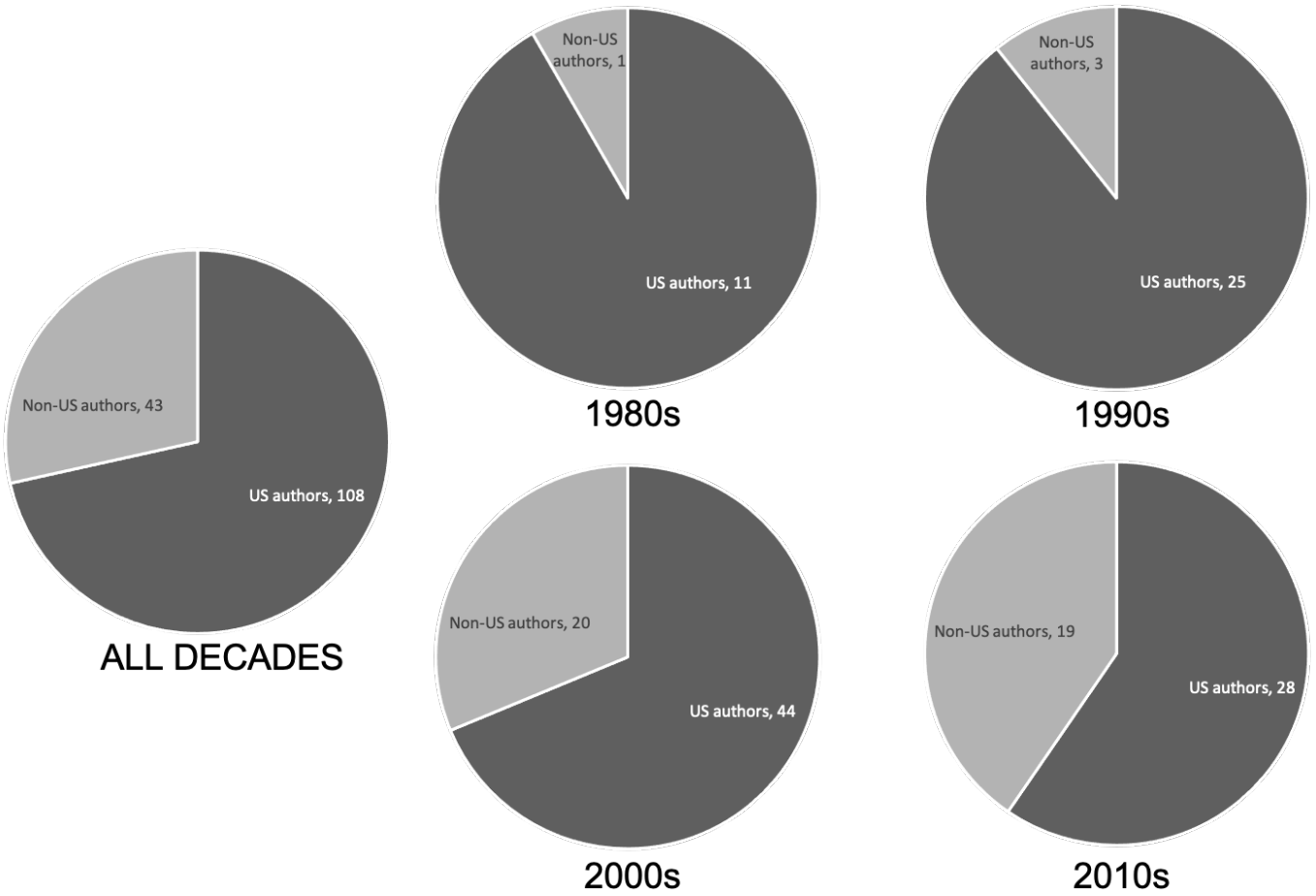


Figure 7. Dose–response applications of physiological models performed by authors from the US vs. other countries
Numbers indicate article counts.

4.0 Discussion and conclusion

As demonstrated in previous publications summarized in this manuscript, the development of physiologically-based kinetic or dynamic models has gradually increased over time, particularly for chemicals of environmental or occupational origin. Although the previous bibliometric reviews focused primarily on model development, it is only one aspect of the continuum of applications of physiological models in risk assessment, as demonstrated in Figure 3. Publications in all of the different phases and subphases of the continuum each serve their own useful purposes, and add to the richness of the physiological modelling literature. However, the focus here was the use of the models in dose–response assessments involved in extrapolations, including those for inter- and intra-species, route-to-route, and high-to-low dose variations, to inform the derivation of PODs and UFs. This manuscript provides a more detailed analysis of trends for the subset of models incorporating chemical-specific data in dose–response analysis, which provides a basis for comparison with the general body of physiological model publications presented in previous bibliometric reviews.

Application of the inclusion criteria to search results in scientific literature databases resulted in the identification of 141 relevant records. This collection of publications relevant to dose-response analysis is only a small fraction of those identified either in the most recent bibliometric reviews (23, 25) or in the publications tagged as addressing physiological models in earlier stages of the development of the present database (see Figure 3). The numbers of publications in these broader reviews approached or exceeded 2,000. Similarly, the number of chemicals for which physiological models exist (307 in Lu et al. (23)) was higher than those applied in dose–response assessments (84 in the current analysis). Based on the inclusion criteria for this database (Table 3), two major factors contribute to this observation. Firstly, publications of physiological models primarily present other uses in the continuum of model applications. Secondly, the current database addresses substances relevant to environmental and occupational exposures to chemicals, and therefore excludes models for other types of substances.

Although the development of physiological models continues to increase over time as demonstrated in bibliometric reviews, the present analysis—though limited by numbers—indicates only a modest increase over time in the development of PBPK models for dose–response assessment, with a recent declining trend. Fewer than eight dose–response applications in any given year were published in the peer-reviewed scientific literature, and the average

number of publications actually decreased in the last decade, possibly due to a shift in the focus of research in toxicology and dose–response assessment. Evaluation of larger numbers of data-poor compounds using high-throughput methods and more generic approaches has been necessitated by legislative requirements worldwide and a need to reduce or eliminate reliance on animal studies (24, 25, 94-98). As the current analysis focused on chemical-specific data, generic approaches such as quantitative in vitro to in vivo extrapolations using high-throughput toxicokinetic modelling (96, 99-102) were not within scope. However, these approaches continue to evolve, for consideration in initial application in risk assessment screening and prioritization efforts, as they provide a framework in which chemical specific data for some data-poor chemicals can be integrated with fundamental physiological processes to estimate blood levels at steady state. Ultimately, this process may reduce the number of animals necessary to develop reliable estimates of human risk.

A further factor potentially contributing to the modest uptake of physiological models in dose–response analyses, compared to the overall number of publications on the models, is that models are not being developed with dose–response in mind. As presented in Figure 3, physiological models are developed for many different purposes, of which dose–response analysis is only one potential application. Problem formulation is a key initial phase in any risk assessment activity, and its incorporation in the early stages of model development can help to ensure that models are fit for purposes such as dose–response analyses. Involving the risk assessment community in early conceptual stages of model design can increase the likelihood that models will meet the needs of those performing dose–response assessments. Notably, the examples presented in the historical review of early dose–response application of physiological models involved regulatory risk assessors. Therefore, improving the collaborative interface between modellers and the risk assessment community would likely increase the adoption of models for dose–response purposes.

The adoption of physiological models for dose–response purposes was initially led by the US, but has evolved over time to include other countries. Publications by non-US authors approached 50% in the last decade of this study, likely reflecting the increasing familiarity with and training on physiological models worldwide. International initiatives, such as the International Programme on Chemical Safety Harmonization Project (103), and more recent

Organization for Economic Cooperation and Development work (104) are potentially contributing at least in part to this phenomenon.

Consideration of the frequency of application of physiological models by domains and types of chemicals (e.g., pesticides, food use, occupational vs. general environmental exposure) revealed some notable findings. One expected observation is that the models were applied more frequently for environmental than for occupational exposure scenarios. This may be a function of the more recent evolution of environmental legislation and associated requirements for transparency concerning the nature and extent of assessment. Alternatively, it may relate to the need to extrapolate to lower levels of exposure. However, one surprising result was that environmental-related exposures for food contaminants and pesticides was quite low (4% and 6% overall, respectively). An explanation for few articles applying the models for food contaminants might be the nature of the inclusion criteria here, which excluded all exposures through food other than environmental contaminants (e.g., food additives, food packaging, or contaminants generated during the cooking process). Alternatively, or in addition, it may derive from food-related legislation and associated requirements for transparency in assessment having been developed much earlier than for the environment. Hypotheses for less frequent application for pesticides may relate to the more onerous legislatively requirements for data for these compounds, compared to other types of environmental contaminants, necessitating less extrapolation.

Historical discussions of physiologically-based kinetic or dynamic models tend to present dichloromethane as the earliest example of the use of a PBPK model in dose–response assessments; however, such applications were identified earlier in the current database. The first identified dose-response analyses incorporating physiological models were from 1986. In one publication, a PBPK model simulated pre-pregnancy hexachlorobenzene concentrations in humans equivalent to a critical effective dose in a rodent reproductive study, for application in a margin of exposure assessment (105). The second publication from the same year identified PODs for trichloroethylene and benzene based on PBPK derived route-to-route and animal-to-human extrapolations (28). Although the dichloromethane model (52) was first published in 1987, and was applied in a regulatory assessment that year (56), application documentation in the scientific literature appeared later, in 1988 (106). In the publication, cancer risk estimates for

both environmental and occupational exposures were derived, and included animal-to-human, high-to-low dose, and route-to-route extrapolations (106).

The most influential limitation of this research is likely that the search was restricted to databases of scientific peer-reviewed literature. Although this approach allowed for a comparison with other bibliometric reviews, it did not allow for exploration of regulatory use of the physiological models for dose–response analyses. This relates to the likelihood that many examples of dose-response application might appear solely in reports published by regulatory agencies, which are often not indexed in the databases searched. Moreover, additional publication of regulatory adoption in summary format in an academic journal might not optimally target resources. In several cases (including those identified here) the regulatory community recognized the need for and was fully involved in developing appropriate applications of physiological models; therefore, this might have translated into subsequent use of the model in a regulatory assessment. The analysis presented in this manuscript constitutes an initial step in identifying potentially influential factors (e.g., lack of consultation in development) in the nature and impact for adoption of proposed application of models in regulatory settings. The analysis here is critical to further work involving identification of regulatory uptake based on sources not addressed in the peer reviewed published literature, including searching of government sources and surveying regulatory risk assessors.

Attempts were made to identify most of the original dose–response applications of physiological pharmacokinetic and pharmacodynamic models in articles and book chapters in the peer-reviewed literature; although 141 relevant publications were identified, it is likely that a small number of potentially relevant publications were missed by the specific search strategy applied. The validation strategy was used to minimize the likelihood of missing publications indexed in literature databases; however, not all relevant sources are included in the databases. Of note, although the search strategy identified some relevant textbook chapters, others were not included. Additional original sources of information on model development for dose-response application (N = 7) were identified through reviewing potentially relevant references cited in relevant publications; all but one of these sources was from a book chapter. This appears to be particularly relevant for older applications, as most of the missed publications were from the 1980s, with one additional source from the 1990s. Furthermore, articles that did not mention physiological modelling (or other dose–response approaches included in the early stages of the

research) in the abstract could have been excluded during the Level 2 (abstract) screening stage. However, given the importance of the envisaged application of a physiological model, the likelihood of its lack of inclusion in the abstract is expected to be low.

Though a full systematic review was considered unnecessary to address the research question, certain elements of such reviews were incorporated to lend additional transparency and rigour to identification of the relevant database. The main elements included applying systematic search strategies and pre-determined inclusion/exclusion criteria applied using systematic review software. However, though a general approach for the analysis was identified in advance, no formal protocol was developed, as discoveries and challenges at each stage warranted refinement. Secondly, the inclusion/exclusion criteria were applied by only a single reviewer, with the same reviewer blindly re-evaluating 5% of records at each level, to ensure consistency of application of the inclusion/exclusion criteria. Finally, no assessment of quality or bias was performed for the studies in the database—all records that met the inclusion criteria were included regardless of quality of reporting and application.

The analyses presented in this publication only quantify the evolution of dose–response applications of physiological models. Discussions around possible reasons for these trends are purely speculative. Follow-up research on this topic will address government applications of physiological models in dose–response assessments, in an attempt to identify whether regulatory use of the models follow the same general trends as identified in scientific literature databases. Furthermore, using the database developed in this study along with additional regulatory dose–response applications, factors distinguishing scientific approaches and science–policy decisions will be considered. These factors, along with results from a further survey on barriers to uptake in government organizations, will be used place the findings in context.

In conclusion, the development of physiological models reported in scientific publications can be considered along a continuum for which dose–response analysis presents only one potential use, albeit an important one that can result in risk estimates that are more predictive of actual risk than default approaches. The development of physiological pharmacokinetic and pharmacodynamic models and publications on the topic have continuously increased over time—particularly since the 1980s for chemicals of environmental and occupational concern. However, the increase in the numbers of publications applying chemical-specific models in dose–response assessments has been relatively modest and more gradual, with

a maximum of 8 publications per year, and has decreased in the last decade. As the publication of high-quality dose–response applications of the models in scientific literature might contribute to their increased uptake for similar purposes in regulatory risk assessments, modellers with dose–response expertise (or access to such expertise) are encouraged to derive PODs and UFs in publications presenting their models, in consultation with regulatory agencies.

REFERENCES

1. Clewell HJ, Andersen ME, Blaauboer BJ. On the incorporation of chemical-specific information in risk assessment. Toxicology Letters. 2008;180(2):100-9.

2. McLanahan ED, El-Masri HA, Sweeney LM, Kopylev LY, Clewell HJ, Wambaugh JF, et al. Physiologically Based Pharmacokinetic Model Use in Risk Assessment-Why Being Published Is Not Enough. Toxicological Sciences. 2012;126(1):5-15.

3. Maruyama W, Aoki Y. Estimated cancer risk of dioxins to humans using a bioassay and physiologically based pharmacokinetic model. Toxicol Appl Pharmacol. 2006;214(2):188-98.

4. Oller AR, Oberdorster G. Incorporation of dosimetry in the derivation of reference concentrations for ambient or workplace air: A conceptual approach. Journal of Aerosol Science. 2016;99:40-5.

5. Andersen ME. Toxicokinetic modeling and its applications in chemical risk assessment. Toxicology Letters. 2003;138(1-2):9-27.

6. Tan YM, Worley RR, Leonard JA, Fisher JW. Challenges associated with applying physiologically based pharmacokinetic modeling for public health decision-making. Toxicological Sciences. 2018;162(2):341-8.

7. Loizou G, Spendiff M, Barton HA, Bessems J, Bois FY, Yvoire MB, et al. Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: the first steps. Regul Toxicol Pharmacol. 2008;50(3):400-11.

8. Meek ME, Barton HA, Bessems JG, Lipscomb JC, Krishnan K. Case study illustrating the WHO IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment. Regul Toxicol Pharmacol. 2013;66(1):116-29.

9. Bhat VS, Meek ME, Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47(9):729-49.

10. Kuempel ED, Sweeney LM, Morris JB, Jarabek AM. Advances in inhalation dosimetry models and methods for occupational risk assessment and exposure limit derivation. J Occup Environ Hyg. 2015;12 Suppl 1:S18-40.

11. DeWoskin RS. PBPK models in risk assessment--A focus on chloroprene. Chemico-Biological Interactions. 2007;166(1-3):352-9.

12. Paini A, Joossens E, Bessems J, Desalegn A, Dorne JL, Gosling JP, et al. EURL ECVAM Workshop on New Generation of Physiologically-Based Kinetic Models in Risk Assessment. Joint Research Centre; 2017. Report No.: EUR 28794 EN.

13. DeWoskin RS, Barone S, Clewell HJ, Setzer RW. Improving the development and use of biologically based dose response models (BBDR) in risk assessment. Human and Ecological Risk Assessment. 2001;7(5):1091-120.

14. Barton HA, Andersen ME, Clewell HJ. Harmonization: Developing consistent guidelines for applying mode of action and dosimetry information to cancer and noncancer risk assessment. Human and Ecological Risk Assessment. 1998;4(1):75-115.

15. Clark LH, Setzer RW, Barton HA. Framework for evaluation of physiologically-based pharmacokinetic models for use in safety or risk assessment. Risk Anal. 2004;24(6):1697-717.

16. Caldwell JC, Evans MV, Krishnan K. Cutting edge PBPK Models and analyses: Providing the basis for future modeling efforts and bridges to emerging toxicology paradigms. Journal of toxicology. 2012;2012:852384.

17. Sweeney LM. Comparing occupational and environmental risk assessment methodologies using pharmacokinetic modeling. Human and Ecological Risk Assessment. 2000;6(6):1101-24.

18. Andersen ME. Development of physiologically based pharmacokinetic and physiologically based pharmacodynamic models for applications in toxicology and risk assessment. Toxicology Letters. 1995;79(1-3):35-44.

19. Nestorov I. Whole-body physiologically based pharmacokinetic models. Expert Opinion on Drug Metabolism & Toxicology. 2007;3(2):235-49.

20. Nestorov I. Whole body pharmacokinetic models. Clin Pharmacokinet. 2003;42(10):883-908.

21. Edginton AN, Joshi G. Have physiologically-based pharmacokinetic models delivered? Expert Opinion on Drug Metabolism & Toxicology. 2011;7(8):929-34.

22. Tan YM, Conolly R, Chang DT, Tornero-Velez R, Goldsmith MR, Peterson SD, et al. Computational toxicology: application in environmental chemicals. Methods in molecular biology (Clifton, NJ). 2012;929:9-19.

23. Lu J, Goldsmith MR, Grulke CM, Chang DT, Brooks RD, Leonard JA, et al. Developing a physiologically-based pharmacokinetic model knowledgebase in support of provisional model construction. PLoS Computational Biology. 2016;12(2):e1004495.

24. Paini A, Leonard JA, Kliment T, Tan YM, Worth A. Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications. Regulatory Toxicology and Pharmacology. 2017;90:104-15.

25. Paini A, Leonard JA, Joossens E, Bessems JGM, Desalegn A, Dorne JL, et al. Next generation physiologically based kinetic (NG-PBK) models in support of regulatory decision making. Computational Toxicology. 2019;9:61-72.

26. Andersen ME. Physiologically based pharmacokinetic (PB-PK) models in the study of the disposition and biological effects of xenobiotics and drugs. Toxicology Letters. 1995;82-83:341-8.

27. Clewell IHJ, Andersen ME. Risk assessment extrapolations and physiological modeling. Toxicology and Industrial Health. 1985;1(4):111-34.

28. NAS. Drinking Water and Health,: Volume 6. Washington, DC: The National Academies Press; 1986.

29. Gerlowski LE, Jain RK. Physiologically based pharmacokinetic modeling: Principles and applications. J Pharm Sci. 1983;72(10):1103-27.

30. D'Souza RW, Boxenbaum H. Physiological pharmacokinetic models: Some aspects of theory, practice and potential. Toxicology and Industrial Health. 1988;4(2):151-71.

31. Clewell H. The use of physiologically based pharmacokinetic modeling in risk assessment: a case study with methylene chloride. In: Olin S, Farland, W., Park, C., Rhomberg, L., Scheuplein, R., Starr, T., Wilson, J., editor. Low-Dose Extrapolation of Cancer RIsks: Issues and Perspectives. Washington, D.C.: ILSI Press; 1995. p. 199-220.

32. Haggard HW. The absorption, distribution, and elimination of ethyl ether: II. Analysis of the mechanismm of absorption and elimination of such a gas or vapor as ethyl ether Journal of Biological Chemistry. 1924;59(3):753-70.

33. Haggard HW. The absorption, distribution, and elimination of ethyl ether: III. The relation of the concentration of ether, or any similar volatile substance, in the central nervous system to the concentration in the arterial blood, and the buffer action of the body. Journal of Biological Chemistry. 1924;59(3):771-81.

34. Teorell T. Kinetics of distribution of substances administered to the body, I : The extravascular modes of administration. Archives internationales de pharmacodynamie et de therapie. 1937;57:205-25.

35. Teorell T. Kinetics of distribution of substances administered to the body, II: The intravascular modes of administration. Archives internationales de pharmacodynamie et de therapie. 1937;57:226-40.

36. Kety SS. The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacol Rev. 1951;3(1):1.

37. Mapleson WW. An electric analogue for uptake and exchange of inert gases and other agents. J Appl Physiol. 1963;18(1):197-204.

38. Riggs DS. The mathematical approach to physiological problems. Cambridge, MA: MIT Press; 1963.

39. Bellman R, Jacquez JA, Kalaba R. Some mathematical aspects of chemotherapy: I. One-organ models. The bulletin of mathematical biophysics. 1960;22(2):181-98.

40. Bischoff KB, Brown RG. Drug distribution in mammals. Chem Eng Progr Symp Ser. 1966;62:32-45.

41. Lundquist F, Wolthers, H. The kinetics of alcohol elimination in man. Acta Pharmacol Toxicol (Copenh). 1958;14(0001-6683 (Print)):265-89.

42. Levy G. Dose dependent effects in pharmacokinetics. In: Tedeschi DHT, R.E., editor. Importance of Fundamental Principles in Drug Evaluation. New York: Raven Press; 1968. p. 141-72.

43. Levy G. Pharmacokinetics of salicylate elimination in man. J Pharm Sci. 1965;54(7):959-67.

44. Bischoff KB, Dedrick RL, Zaharko DS, Longstreth JA. Methotrexate pharmacokinetics. J Pharm Sci. 1971;60(8):1128-33.

45. Dedrick RL. Animal scale-up. Journal of Pharmacokinetics and Biopharmaceutics. 1973;1(5):435-61.

46. Lindstrom FT, Gillett JW, Rodecap SE. Distribution of HEOD (dieldrin) in mammals: I. Preliminary model. Archives of Environmental Contamination and Toxicology. 1974;2(1):9-42.

47. Fiserova-Bergerova V, Vlach J, Cassady JC. Predictable “individual differences” in uptake and excretion of gases and lipid soluble vapours simulation study. Br J Ind Med. 1980;37(1):42.

48. Fiserova-Bergerova V, Vlach J, Singhal K. Simulation and prediction of uptake, distribution, and exhalation of organic solvents. Br J Ind Med. 1974;31(1):45.

49. Andersen ME. A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors: Analysis at steady state. Toxicology and Applied Pharmacology. 1981;60(3):509-26.

50. Ramsey JC, Andersen ME. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicology and Applied Pharmacology. 1984;73(1):159-75.

51. Leung HW, Paustenbach DJ. Physiologically based pharmacokinetic and pharmacodynamic modeling in health risk assessment and characterization of hazardous substances. Toxicology Letters. 1995;79(1-3):55-65.

52. Andersen ME, Clewell HJ, Gargas ML, Smith FA, Reitz RH. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol. 1987;87(2):185-205.

53. NAS. Drinking Water and Health, Volume 8: Pharmacokinetics in Risk Assessment. Washington, DC: The National Academies Press; 1987.

54. Rhomberg L. Use of quantitative modelling in methylene chloride risk assessment. Toxicology. 1995;102(1-2):95-114.

55. EPA U. Technical analysis of new methods and data regarding dichloromethane hazard assessments. Washington, D.C.: US EPA; 1987. Report No.: EPA/600/8-87/029A.

56. US EPA. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action, and Epidemiology. Washington, D.C.; 1987. Report No.: EPA/600/8-87/030A.

57. Leung HW. Development and utilization of physiologically based pharmacokinetic models for toxicological applications. Journal of Toxicology and Environmental Health. 1991;32(3):247-67.

58. Occupational Exposure to Methylene Chloride, Stat. 29 CFR Parts 1910, 1915 and 1926 (1997).

59. Babich MA. Risk assessment of low-level chemical exposures from consumer products under the U.S. Consumer Product Safety Commission chronic hazard guidelines. Environmental Health Perspectives. 1998;106(suppl 1):387-90.

60. Environment Canada and Health Canada. Canadian Environmental Protection Act, Priority Substances List Assessment Report - Dichloromethane. Ottawa, ON; 1993.

61. Medinsky MA, Kimbell JS, Morris JB, Gerde P, Overton JH. Advances in biologically based models for respiratory tract uptake of inhaled volatiles. Fundam Appl Toxicol. 1993;20(3):265-72.

62. Cohen Hubal EA, Fedkiw PS, Kimbell JS. Mass-transport models to predict toxicity of inhaled gases in the upper respiratory tract. J Appl Physiol. 1996;80(4):1415-27.

63. Overton JH, Miller FJ. Dosimetry modeling of inhaled toxic reactive gases. In: Ann Y. Watson SD, Richard R. Bates MD, Donald Kennedy PD, editors. Air Pollution, the Automobile, and Public Health. Washington, DC: The National Academies Press; 1988.

64. Yeh HC, Schum GM, Duggan MT. Anatomic models of the tracheobronchial and pulmonary regions of the rat. The Anatomical Record. 1979;195(3):483-92.

65. Yeh H-C, Schum GM. Models of human lung airways and their application to inhaled particle deposition. Bulletin of Mathematical Biology. 1980;42(3):461-80.

66. Overton JH, Graham RC. The influence of upper respiratory tract models on simulated lower respiratory tract uptake of O3. Program and Abstracts of the 1985 Annual Meeting of the American Associates for Aerosol Research, Nov 18–22; 1985.

67. Swenberg JA, Gross EA, Martin J, Popp JA. Mechanisms of formaldehyde toxicity. In: Gibson JE, editor. Formaldehyde Toxicity. Washington, D.C.: Hemisphere Publishing Corp.; 1983. p. 26-37.

68. Kliment V. Similarity and dimensional analysis, evaluation of aerosol deposition in the lungs of laboratory animals and man. Folia Morphol (Praha). 1973;21(1):59-64.

69. Schreider JP, Hutchens JO. Morphology of the guinea pig respiratory tract. The Anatomical Record. 1980;196(3):313-21.

70. Davies CN, Douglas CG. Filtration of droplets in the nose of the rabbit. Proceedings of the Royal Society of London Series B - Biological Sciences. 1946;133(872):282-99.

71. La Belle CW, Long JE, Christofano EE. Synergistic Effects of Aerosols. Particulates as Carriers of Toxic Vapors. Arch Indust Health. 1955;11(4):297-304.

72. Aharonson EF, Menkes H, Gurtner G, Swift DL, Proctor DF. Effect of respiratory airflow rate on removal of soluble vapors by the nose. J Appl Physiol. 1974;37(5):654-7.

73. Morris JB, Blanchard KT. Upper respiratory tract deposition of inspired acetaldehyde. Toxicology and Applied Pharmacology. 1992;114(1):140-6.

74. Gerde P, Dahl AR. A model for the uptake of inhaled vapors in the nose of the dog during cyclic breathing. Toxicology and Applied Pharmacology. 1991;109(2):276-88.

75. Kimbell JS, Gross EA, Joyner DR, Godo MN, Morgan KT. Application of Computational Fluid Dynamics to Regional Dosimetry of Inhaled Chemicals in the Upper Respiratory Tract of the Rat. Toxicology and Applied Pharmacology. 1993;121(2):253-63.

76. Morris JB, Hassett DN, Blanchard KT. A Physiologically Based Pharmacokinetic Model for Nasal Uptake and Metabolism of Nonreactive Vapors. Toxicology and Applied Pharmacology. 1993;123(1):120-9.

77. US EPA. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Washington, DC; 1994. Report No.: EPA/600/8-90/066F.

78. Anjilvel S, Asgharian B. A Multiple-Path Model of Particle Deposition in the Rat Lung. Fundamental and Applied Toxicology. 1995;28(1):41-50.

79. Jarabek AM, Asgharian B, Miller FJ. Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). Inhalation Toxicology. 2005;17(7-8):317-34.

80. Frederick CB, Morris JB, Kimbell JS, Morgan KT, Scherer PW. Comparison of 4 biologically-based dosimetry models for the deposition of rapidly metabolized vapors in the rodent nasal cavity. Inhalation Toxicology. 1994;6:135-57.

81. Jarabek AM, Menache MG, Overton JH, Jr D, M. L M. Inhalation reference dose (RfDi): an application of interspecies dosimetry modeling for risk assessment of insoluble particles. Health Physics. 1989;57 Suppl 1:177-83.

82. Jarabek AM. The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. Toxicology Letters. 1995;79(1-3):171-84.

83. Jarabek AM. Inhalation RfC methodology - Dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory-tract. Inhalation Toxicology. 1994;6:301-25.

84. Bogdanffy MS, Jarabek AM. Understanding mechanisms of inhaled toxicants: implications for replacing default factors with chemical-specific data. Toxicology Letters. 1995;82-83:919-32.

85. Environment Canada and Health Canada. Priority Substances List Assessment Report: Formaldehyde. Ottawa, ON; 2001.

86. Crump KS, Chen C, Louis TA. The future use of in vitro data in risk assessment to set human exposure standards: challenging problems and familiar solutions. Environmental Health Perspectives. 2010;118(10):1350-4.

87. NRC. Toxicity Testing in the 21st Century: A Vision and a Strategy. . Washington, DC: The National Academies Press; 2007.

88. The EndNote Team. Endnote. Philadelphia, PA: Clarivate; 2013.

89. Evidence Partners. DistillerSR. Ottawa, ON; 2021.

90. Koizumi A. Potential of physiologically based pharmacokinetics to amalgamate kinetic data of trichloroethylene and tetrachloroethylene obtained in rats and man. Br J Ind Med. 1989;46(4):239-49.

91. Verschuuren HG, e Rooij CG. Health risk assessment of environmental exposure to 1,1,1-trichloroethane. Regul Toxicol Pharmacol. 1990;11(1):90-9.

92. Reitz RH, Gargas ML, Andersen ME, Provan WM, Green TL. Predicting cancer risk from vinyl chloride exposure with a physiologically based pharmacokinetic model. Toxicol Appl Pharmacol. 1996;137(2):253-67.

93. Lawrence GS, Gobas FA. A pharmacokinetic analysis of interspecies extrapolation in dioxin risk assessment. Chemosphere. 1997;35(3):427-52.

94. Punt A, Schiffelers MJ, Jean Horbach G, van de Sandt JJ, Groothuis GM, Rietjens IM, et al. Evaluation of research activities and research needs to increase the impact and applicability of alternative testing strategies in risk assessment practice. Regul Toxicol Pharmacol. 2011;61(1):105-14.

95. Wambaugh JF, Hughes MF, Ring CL, MacMillan DK, Ford J, Fennell TR, et al. Evaluating in vitro-in vivo extrapolation of toxicokinetics. Toxicological Sciences. 2018;163(1):152-69.

96. Wambaugh JF, Wetmore BA, Pearce R, Strope C, Goldsmith R, Sluka JP, et al. Toxicokinetic triage for environmental chemicals. Toxicological Sciences. 2015;147(1):55-67.

97. Bell SM, Chang X, Wambaugh JF, Allen DG, Bartels M, Brouwer KLR, et al. In vitro to in vivo extrapolation for high throughput prioritization and decision making. Toxicology in Vitro. 2018;47:213-27.

98. Moxon TE, Li H, Lee M-Y, Piechota P, Nicol B, Pickles J, et al. Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products. Toxicology in Vitro. 2020;63:104746.

99. Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell HJ, Judson RS, et al. Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays. Toxicological Sciences. 2013;132(2):327-46.

100. Wetmore BA. Quantitative in vitro-to-in vivo extrapolation in a high-throughput environment. Toxicology. 2015;332:94-101.

101. Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, et al. Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing. Toxicological Sciences. 2015;148(1):121-36.

102. Paul Friedman K, Gagne M, Loo L-H, Karamertzanis P, Netzeva T, Sobanski T, et al. Utility of in vitro bioactivity as a lower bound estimate of in vivo adverse effect levels and in risk-based prioritization. Toxicological Sciences. 2020;173(1):202-25.

103. IPCS. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva; 2010. Report No.: IPCS Harmonization Project No. 9.

104. OECD. Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes. Paris, France; 2021. Report No.: OECD Series on Testing and Assessment, No. 331.

105. Siegel-Scott C, Johnson AE. A risk analysis of hexachlorobenzene-related reproductive outcomes. IARC Sci Publ. 1986(77):629-34.

106. Reitz RH, Mendrala AL, Park CN, Andersen ME, Guengerich FP. Incorporation of in vitro enzyme data into the physiologically-based pharmacokinetic (PB-PK) model for methylene chloride: implications for risk assessment. Toxicology Letters. 1988;43(1-3):97-116.

Appendix A – Search queries for literature databases

This appendix contains the search text that was used in each of the literature databases to identify references for the review. NOTE: All queries had filters applied (Date: 1983–2015; Language: English; French)

Table A.1 – Search queries for PubMed (NLM)

Search #	Query	Category
1	"Risk Assessment"[Mesh] OR "risk assessment" OR "risk assessments" OR "risk analyses" OR "risk analysis" OR "risk estimate" OR "risk estimates" OR "risk estimation" OR "risk estimations") OR ("Dose-response relationship, drug"[Mesh] OR "dose response relationship" OR "exposure response relationship" OR "dose response assessment" OR "exposure response assessment" OR "dose response analysis" OR "dose response analyses" OR "exposure response analyses" OR "exposure response analysis" OR "dose response modelling" OR "dose response modeling" OR "dose response model" OR "dose response models" OR "exposure response modelling" OR "exposure response modeling" OR "exposure response model" OR "exposure response models" OR "hazard assessment" OR "dose response relationships" OR "exposure response relationships" OR "concentration response relationship" OR "concentration response relationships" OR "dose response assessments" OR "concentration response assessment" OR "concentration response analysis" OR "concentration response analyses" OR "concentration response modeling" OR "concentration response model" OR "concentration response models" OR "dose response curve" OR "dose response curves" OR "exposure response curve" OR "exposure response curves" OR "concentration response curve" OR "concentration response curves") OR ("exposure limit" OR "exposure limits" OR "exposure guideline" OR "exposure guidelines" OR "margin of exposure" OR "margins of exposure" OR "limit value" OR "limit values" OR "margin of safety" OR "margins of safety") OR ("reference dose" OR "reference doses" OR RfD OR RfDs OR "reference concentration" OR "reference concentrations" OR "allowable daily intake" OR "allowable daily intakes" OR "acceptable daily intake" OR "acceptable daily intakes" OR "tolerable daily intake" OR "tolerable daily intakes" OR "toxicological reference value" OR "toxicological reference values" OR "Maximum Allowable Concentration"[Mesh] OR "maximum allowable concentration" OR "maximum allowable concentrations" OR "maximum acceptable concentration" OR "maximum acceptable concentrations" OR "soil quality guidelines" OR sqg OR sqgs OR "maximum contaminant level" OR "maximum contaminant levels" OR MCLG OR "health advisory" OR "health advisories" OR "health based value" OR "health based values" OR "acute exposure guideline" OR "acute exposure guidelines" OR AEGL OR AEGLs OR "Threshold limit values"[Mesh] OR "Threshold limit value" OR "threshold limit values" OR TLV OR TLVs OR "Workplace environmental exposure level" OR WEELs OR "permissible exposure level" OR "permissible exposure levels" OR "permissible exposure limit" OR "permissible exposure limits" OR "recommended exposure limit" OR "recommended exposure limits" OR RELs OR IOELV OR IOELVs OR "derived no effect level" OR "derived no effect levels" OR DNEL OR DNELS OR DMEL OR "cancer slope factor" OR "cancer slope factors" OR "biomonitoring equivalent" OR "biomonitoring equivalents" OR "biological exposure index" OR "biological exposure indices" OR "biological equivalent exposure limit" OR "biological exposure limit" OR "biological exposure limits" OR "biological limit value" OR "biological limit values" OR BLVs OR "risk-specific dose" OR "risk-specific doses" OR "air quality guideline" OR "air quality guidelines" OR "air quality standard" OR "air quality standards" OR "air quality limit" OR "air quality limits" OR "water quality guideline" OR "water quality guidelines" OR "water quality standard" OR "water quality standards" OR "water quality limits" OR "food quality standard" OR "food quality standards" OR "soil quality standard" OR "soil quality standards" OR "exposure guideline" OR "exposure guidelines" OR "exposure standard" OR "exposure standards" OR "exposure limit" OR "exposure limits" OR "exposure recommendations" OR "reference level" OR "reference levels") OR ("health canada" OR "health and welfare canada" OR "pest management regulatory agency" OR "environmental protection agency" OR "food and drug administration" OR "food and drug agency" OR "World Health Organization"[Mesh] OR "world health organization" OR "world health organisation" OR "international programme on chemical safety" OR "international program on chemical safety" OR IPCS OR JMPR OR "Joint FAO/WHO Expert Committee on Food Additives" OR JECFA OR "European Commission" OR "European Chemicals Agency" OR ECHA OR "Registration, Evaluation, Authorisation and Restriction of Chemicals" OR "Registration, Evaluation, Authorization and Restriction of Chemicals" OR "European Food Safety Authority" OR EFSA OR SCOEL OR "american conference of governmental industrial hygienists" OR ACGIH OR "american industrial hygiene association" OR AIHA OR "occupational safety and health administration" OR "OSHA" OR "United States Occupational Safety and Health Administration"[Mesh] OR "national institute for occupational safety and health" OR "NIOSH" OR "National Institute for Occupational Safety and Health (U.S.)"[Mesh] OR "Agency for toxic substances and disease registry" OR ATSDR OR "food and agriculture organization" OR "food and agricultural organization" OR "food and agriculture organisation" OR FAO OR "Committee on toxicology" OR "board on environmental studies and toxicology" OR "science advisory board" OR "clean air scientific advisory committee" OR "national academy of science" OR "national academy of sciences" OR "national academies of science" OR "national academies of sciences" OR "institute of medicine" OR "institutes of medicine")	Risk assessments
2	(toxicants OR "toxins" OR toxicant OR "toxin" OR chemicals OR "chemical" OR "chemical substance" OR "chemical substances" OR "chemical compounds" OR "chemical compound" OR "toxic substances" OR "toxic substance" OR "toxic compounds" OR "toxic compound" OR "toxic chemicals" OR "toxic chemical" OR "hazardous substances" OR "hazardous substance" OR "hazardous compounds" OR "hazardous compound" OR "chemical safety"[Mesh] OR "hazardous substances"[Mesh] OR "specialty uses of chemicals"[Mesh]) OR (cytotoxicity OR cytotoxi* OR cytotoxicant OR cytotoxicants OR cytotoxic OR cytotoxin OR cytotoxins OR "cell toxic" OR "cell toxicity" OR "cellular toxicity" OR "cell toxicant" OR "cell toxicants" OR "cell toxin" OR "cell toxins" OR "cellular toxin" OR "cellular toxins" OR hepatotoxic OR hepatotoxicity OR hepatotoxi* OR hepatotoxin OR hepatotoxins OR hepatotoxicant OR hepatotoxicants OR "liver toxic" OR "liver toxicity" OR "liver toxicants" OR "liver toxin" OR "liver toxins" OR nephrotoxicity OR nephrotoxi* OR nephrotoxicant OR nephrotoxicants OR nephrotoxin OR nephrotoxins OR nephrotoxic OR renotoxic OR renotoxicity OR renotoxi* OR "kidney toxic" OR "kidney toxicity" OR "kidney toxicants" OR "kidney toxin" OR cardiotoxic OR cardiotoxicity OR cardiotoxicant OR cardiotoxicants OR cardiotoxin OR cardiotoxins OR cardiotoxi* OR "heart toxicity" OR "pulmonary toxic" OR "pulmonary toxicants" OR "pulmonary toxin" OR "pulmonary toxins" OR "pulmonary toxicity" OR "lung toxic" OR "lung toxicity" OR "lung toxicants" OR "lung toxin" OR "lung toxins" OR "cardiopulmonary toxicity" OR "bone toxicity" OR "bone toxic" OR "neurotoxicity" OR neurotoxi* OR neurotoxic OR neurotoxicant OR neurotoxicants OR neurotoxin OR neurotoxins OR "neurological toxicity" OR genotoxicity OR genotoxi* OR genotoxic OR genotoxicant OR genotoxicants OR genotoxin OR genotoxins OR "genetic toxicity" OR "genetic toxin" OR "genetic toxins" OR "mutagenicity" OR mutagen* OR teratogenicity OR teratogen* OR fetotoxicity OR fetotoxi* OR fetotoxic OR fetotoxicants OR "fetal toxicity" OR "fetal toxic" OR clastogenicity OR clastogen* OR carcinogenicity OR carcinogen* OR leukemogenicity OR leukaemogenicity OR leukemogen* OR leukaemogen* OR "blood toxicity" OR "blood toxin" OR "reprotoxicants" OR reprotoxi* OR "reproductive toxicity" OR "reproductive toxic" OR "reproductive toxicant" OR "reproductive toxicants" OR "reproductive toxin" OR "reproductive toxins" OR reprotoxic OR reprotoxicity OR reprotoxin OR reprotoxins OR "developmental toxicity" OR "developmental toxicant" OR "developmental toxicants" OR "developmental toxin" OR "developmental toxins" OR teratogenicity OR teratogen* OR immunotoxicity OR immunotoxi* OR immunotoxic OR immunotoxicant OR immunotoxicants OR immunotoxin OR immunotoxins OR "immune toxic" OR "immune toxicity" OR hematotoxicity OR haematotoxicity OR hematotoxi* OR haematotoxi* OR haematotoxic OR hematotoxic OR haematotoxin OR hematotoxin OR hematotoxins OR haematotoxins OR hematotoxicant OR hematotoxicants OR dermatotoxicity OR dermatotoxi* OR "dermal toxicity" OR dermatotoxic OR dermatotoxicants OR dermatotoxin OR "skin toxicity" OR "skin toxin" OR "skin toxins" OR sensitized OR sensitised OR sensitization OR sensitisation OR sensitizer OR sensitizers OR sensitiser OR sensitisers OR "endocrine toxicity" OR "endocrine toxic" OR "endocrine toxicants" OR "endocrine disruptor" OR "endocrine disruptors" OR "endocrine disrupter" OR "endocrine disrupters" OR "endocrine disruption" OR "drug-induced liver injury"[Mesh] OR "respiratory toxicants" OR "respiratory toxin" OR "respiratory toxins" OR "respiratory toxicity" OR "mutagens"[Mesh] OR "carcinogens"[Mesh] OR "abnormalities"[subheading] OR "inhalation toxicity" OR "inhalation toxic" OR "oral toxicity" OR "oral toxin" OR "oral toxins" OR "dietary toxicity" OR "dietary toxicants" OR "dietary toxin" OR "dietary toxins" OR "toxic actions"[Mesh] OR "cell effect" OR "cell effects" OR "cellular effect" OR "cellular effects" OR "hepatic effect" OR "hepatic effects" OR "hepatic tumor" OR "hepatic tumors" OR "hepatic tumour" OR "hepatic tumours" OR "hepatic cancer" OR "hepatic cancers" OR "hepatocellular effect" OR "hepatocellular effects" OR "hepatocellular tumor" OR "hepatocellular tumors" OR "hepatocellular tumour" OR "hepatocellular tumours" OR "hepatocellular cancer" OR "hepatocellular cancers" OR "hepatocellular adenoma" OR "hepatocellular adenomas" OR "hepatocellular carcinoma" OR "hepatocellular carcinomas" OR "effects on liver" OR "liver effect" OR "liver effects" OR "liver tumor" OR "liver tumour" OR "liver tumors" OR "liver tumours" OR "liver cancer" OR "liver cancers" OR "nephron effect" OR "renal effect" OR "renal effects" OR "renal cancer" OR "renal cancers" OR "renal tumor" OR "renal tumors" OR "renal tumour" OR "renal tumours" OR "kidney effect" OR "kidney effects" OR "kidney tumor" OR "kidney tumors" OR "kidney tumour" OR "kidney tumours" OR "kidney cancer" OR "kidney cancers" OR "cardiac effect" OR "cardiac effects" OR "heart effect" OR "heart effects" OR "pulmonary effect" OR "pulmonary effects" OR "pulmonary cancer" OR "pulmonary cancers" OR "pulmonary tumor" OR "pulmonary tumors" OR "pulmonary tumour" OR "pulmonary tumours" OR "lung effect" OR "lung effects" OR "lung cancer" OR "lung cancers" OR "lung tumor" OR "lung tumors" OR "lung tumour" OR "lung tumours" OR "respiratory effect" OR "respiratory effects" OR "respiratory cancer" OR "respiratory cancers" OR "respiratory tumors" OR "respiratory tumours" OR "cardiopulmonary effect" OR "cardiopulmonary effects" OR "skeletal effect" OR "skeletal effects" OR "skeletal cancer" OR "skeletal cancers" OR "skeletal tumor" OR "skeletal tumors" OR "skeletal tumour" OR "skeletal tumours" OR "bone effect" OR "bone effects" OR "bone cancer" OR "bone cancers" OR "bone tumor" OR "bone tumors" OR "bone tumour" OR "bone tumours" OR osteosarcoma OR osteosarcomas OR osteoma OR osteomas OR sarcoma OR sarcomas OR "neurological effect" OR "neurological effects" OR "brain effect" OR "brain effects" OR "effects on brain" OR "neurological cancer" OR "neurological cancers" OR "neurological tumor" OR "neurological tumors" OR "neurological tumours" OR "brain cancer" OR "brain cancers" OR "brain tumor" OR "brain tumors" OR "brain tumour" OR "brain tumours" OR "genetic effect" OR "genetic effects" OR "fetal effect" OR "fetal effects" OR "effects on fetus" OR embryotoxicity OR embryotoxic OR embryotoxicant OR embryotoxicants OR embryotoxin OR "embryo toxicity" OR "embryo toxic" OR "embryo effects" OR mutagenic OR clastogenic OR "chromosomal effect" OR "chromosomal effects" OR "chromosome effect" OR "chromosome effects" OR tumorigen* OR tumorigenicity OR tumorigenic OR tumourigenicity OR tumourigenic OR carcinogenic OR leukemogenic OR leukaemogenic OR "blood	Toxicity from environmental chemicals

	effect" OR "blood effects" OR "effect on blood" OR "effects on blood" OR "blood cancer" OR "blood cancers" OR "blood tumor" OR "blood tumors" OR "blood tumour" OR leukemia OR leukemias OR "effect on the reproductive system" OR "reproductive effect" OR "reproductive effects" OR "developmental effect" OR "developmental effects" OR "immune effect" OR "immune effects" OR splenotoxicity OR splenotoxic* OR splenotoxic OR splenotoxin OR "spleen toxicity" OR "spleen effects" OR "splenic effect" OR "splenic effects" OR thymotoxicity OR thymotoxic* OR thymotoxic OR "thymus toxicity" OR thyrotoxicity OR thyrotoxic* OR thyrotoxic OR thyrotoxicant OR thyrotoxicants OR thyrotoxin OR thyrotoxins OR "thyroid toxic" OR "thyroid toxicity" OR "thyroid toxicants" OR "thyroid effect" OR "thyroid effects" OR "effect on thyroid" OR "effects on thyroid" OR "dermal effect" OR "dermal effects" OR "dermal cancer" OR "tumor of the dermis" OR "dermal tumor" OR "dermal tumors" OR "dermal tumour" OR "dermal tumours" OR "epidermal effect" OR "epidermal effects" OR "skin effect" OR "skin effects" OR "endocrine effect" OR "endocrine effects" OR "inhaled material" OR "inhaled materials" OR toxicity OR toxicities OR "adverse health effect" OR "adverse health effects" OR "tissue response" OR "tissue responses" OR "cellular response" OR "cellular responses" OR "toxicological effect" OR "toxicological effects" OR "toxicological outcome" OR "toxicological outcomes" OR "induced effect" OR "induced effects" OR "Neoplasms by Site"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Cardiotoxins"[Mesh] OR "Neurotoxicity Syndromes"[Mesh] OR "Mutagenesis"[Mesh] OR "Teratogens"[Mesh] OR "teratogenesis"[Mesh] OR "Hypersensitivity"[Mesh] OR "Endocrine Disruptors"[Mesh] OR non-cancer OR noncancer OR non-carcinogen OR noncarcinogen OR non-carcinogens OR noncarcinogens OR non-carcinogenic OR noncarcinogenic OR non-mutagen OR nonmutagen OR non-mutagens OR nonmutagens OR non-mutagenic OR nonmutagenic) OR ("water" OR "water quality" OR "drinking water" OR "water pollution" OR "water pollutant" OR "water pollutants" OR "water contamination" OR "water contaminant" OR "water contaminants" OR "water exposure" OR "water exposures" OR "Drinking Water"[Mesh] OR "Water Quality"[Mesh] OR "air" OR "air quality" OR "air pollution" OR "air pollutant" OR "air pollutants" OR "air contamination" OR "air contaminant" OR "air contaminants" OR "air exposure" OR "air exposures" OR "Air Pollution"[Mesh] OR "soil" OR "soil quality" OR "soil pollution" OR "soil pollutant" OR "soil pollutants" OR "soil contamination" OR "soil contaminant" OR "soil contaminants" OR "soil exposure" OR "soil exposures" OR "food" OR "food quality" OR "food pollution" OR "food pollutant" OR "food pollutants" OR "food contamination" OR "food contaminant" OR "food contaminants" OR "food exposure" OR "food exposures" OR "Food Quality"[Mesh] OR "Legislation, Food"[Mesh] OR "environmental exposure" OR "environmental exposures" OR "occupational exposure" OR "occupational exposures" OR "Environmental Exposure"[Mesh] OR "workplace exposure" OR "workplace exposures" OR "work exposure" OR "work exposures" OR "take home exposure" OR "take home exposures" OR "para-occupational exposure" OR "para-occupational exposures" OR "paraoccupational exposure" OR "paraoccupational exposures" OR exposome OR exposomes OR "environmental pollutants"[Mesh] OR "environmental pollution"[Mesh]) OR ("chemical exposure" OR "chemical exposures" OR "chemical intake" OR "chemical intakes" OR "oral exposure" OR "oral exposures" OR "oral intake" OR "oral intakes" OR "dietary exposure" OR "dietary exposures" OR "dietary intake" OR "dietary intakes" OR "inhalation intake" OR "inhalation intakes" OR "inhalation exposure" OR "inhalation exposures" OR "ambient exposure" OR "ambient exposures")	
3	MOA OR MOAs OR "mode of action analysis" OR "mode of action analyses" OR "mode of action evaluation" OR "MOA analysis" OR "adverse outcome pathway" OR "adverse outcome pathways" OR AOP OR AOPs OR "human relevance" OR "mode of action framework" OR "MOA framework" OR "species concordance" OR "molecular initiating event" OR "pathway perturbation" OR "pathway perturbations"	MOA
4	"non-chemical stressors" OR "risk-modifying factors" OR "psychosocial stress" OR "psychosocial stressors" OR "physical stressor" OR "social stressors" OR "allostatic load" OR "social indicators" OR "environmental justice"	Non-chemical stressors
5	"physiologically based pharmacokinetic" OR "physiologically based pharmacokinetics" OR PBPK OR "physiologically based toxicokinetic" OR "physiologically based toxicokinetics" OR PBTK OR "physiologically based kinetic" OR PBK OR PBPK/PD OR PBTK/TD OR "biologically based dose response" OR BBDR OR "physiological pharmacokinetic" OR "physiological pharmacokinetics" OR "flow-limited model" OR "pharmacodynamic modeling" OR "pharmacodynamic modelling" OR "pharmacodynamic model" OR "pharmacodynamic models" OR "physiologically based model" OR "physiologically based models" OR "physiologically based modelling" OR "physiologically based modeling" OR "mathematical model" OR "biologically based risk assessment" OR "biologically based risk assessments" OR BBRA OR "biomathematical modeling" OR "biological model" OR "biological modeling" OR "biologic model" OR "mathematical translation" OR "mechanistic model" OR "mechanistic models" OR "mechanistic modeling" OR "mechanistic modelling" OR "biologically motivated mathematical models" OR "biologically motivated model" OR "biologically motivated models" OR "dose metric" OR "dose metrics" OR "dosimetric model" OR "dosimetric models" OR "dosimetric modeling" OR "dosimetric modelling" OR PB-PK OR PB-TK OR PB-PD	PBPK and BBDR modelling
6	"pathways of toxicity" OR "network biology" OR "computational toxicology" OR "computational systems biology" OR "systems toxicology" OR "computational method" OR "computational methods" OR "computational approach" OR "computational approaches" OR "NexGen" OR "QIVIVE" OR "IVIVE" OR "reverse dosimetry" OR "exposure reconstruction" OR "exposure reconstructions" OR "toxicity pathway" OR "toxicity pathways" OR "network model" OR "network models" OR "network modeling" OR "network modelling" OR "network analysis" OR "network analyses" OR "network structure" OR "network structures" OR "scale-free network" OR "scale-free networks" OR "network motifs" OR "network centrality" OR "network centralities" OR "pathway approach" OR "pathway approaches" OR "pathway model" OR "pathway models" OR "pathway modeling" OR "bayesian network" OR "bayesian networks" OR "BN model" OR "BN models" OR "network based approach" OR "network approach" OR "dose-dependent transition" OR "dose-dependent transitions" OR "network inference" OR "molecular network" OR "molecular networks" OR "signaling motifs" OR "signalling motifs" OR "response motifs" OR "Systems Biology"[Mesh] OR "Neural Networks (Computer)"[Mesh]	Systems biology
7	"chemical specific adjustment factor" OR "chemical specific adjustment factors" OR CSAF OR CSAFs OR "data derived uncertainty factors" OR "data derived safety factor" OR "data derived safety factors" OR "data derived factor" OR "data derived factors" OR "kinetic components" OR "dynamic components" OR ADAF OR HKAF OR "kinetic adjustment factor" OR "kinetic uncertainty factor" OR "toxicokinetic uncertainty factor" OR "composite factor" OR "composite factors"	CSAF
8	"benchmark dose" OR "benchmark doses" OR BMD OR "BD approach" OR "BD model" OR "mantel-bryan procedure" OR "benchmark value" OR "benchmark values" OR "benchmark concentration" OR "benchmark concentrations"	BMD
9	"categorical regression" OR CatReg OR "ordinal regression" OR "categorical response" OR "categorical responses" OR "dose-category"	Categorical regression
10	"lifestage specific" OR "life stage specific" OR "child specific" OR lifestage OR lifestages OR lifecourse OR "life course" OR "life courses" OR "children's risk" OR "children's health risk assessment" OR "children's health risk assessments" OR "children's risk assessment" OR "early life sensitivity" OR "age-related differences" OR "age-related variability" OR "age-related changes" OR "critical windows" OR "developmental life stages" OR "children's health risk" OR "children's health risks" OR "child health risk" OR "individual variability" OR "individual variabilities" OR "individual heterogeneity" OR "physiologic differences" OR "age specific differences" OR "age specific changes" OR "altered susceptibility" OR "aging-related changes" OR "age-related changes" OR "age-related differences" OR "age-related variability" OR "susceptible population" OR "susceptible populations" OR "susceptible subpopulation" OR "susceptible subpopulations" OR "susceptible sub-population" OR "susceptible sub-populations" OR "susceptible persons" OR "susceptible individual" OR "sensitive individual" OR "sensitive individuals" OR "sensitive population" OR "sensitive populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub-populations" OR "sensitive people" OR "sensitive persons" OR "interindividual variation" OR "interindividual variations" OR "interindividual variability" OR "interindividual variabilities" OR "inter-individual variability" OR "inter-individual differences" OR "interindividual heterogeneity" OR "inter-individual heterogeneity" OR "interindividual sensitivity" OR "inter-individual susceptibility" OR "susceptible sub-population" OR "susceptible sub-populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub-populations" OR "extreme sensitivity" OR "vulnerable sub-populations" OR "intraspecies variability" OR "intraspecies variation" OR "intraspecies variations" OR "intraspecies differences" OR "intraspecies sensitivity" OR "intra-species variability" OR "intra-species difference" OR "intra-species differences" OR "human variability" OR "human differences" OR "human susceptibility" OR "human sensitivity" OR "sensitive human" OR "sensitive humans" OR "susceptible human" OR "population variability" OR "population heterogeneity" OR "population susceptibility" OR "population sensitivity" OR "population risk" OR "population risks" OR "intrapopulation variability" OR "pharmacokinetic difference" OR "pharmacokinetic differences" OR "pharmacokinetic variability" OR "pharmacokinetic variations" OR "toxicokinetic differences" OR "toxicokinetic variability" OR "kinetic differences" OR "kinetic variability" OR "kinetic changes" OR "dynamic variability" OR "dynamic variation" OR "population specific" OR "subpopulation specific" OR "biological variability" OR "biological differences" OR "biological variations" OR "biological changes" OR "variability distributions" OR "individual susceptibility" OR "individual susceptibilities" OR "individual sensitivity" OR "individual sensitivities" OR "genetic variability" OR "genetic variabilities" OR "genetic variations" OR "genetic changes" OR "heterogeneous population" OR "heterogeneous populations" OR "heterogeneous subpopulations"	Population variability/ sensitivity
11	"dose addition" OR "cumulative effect" OR "cumulative effects" OR "cumulative risk" OR "cumulative risks" OR "cumulative exposures" OR "cumulative assessment" OR "cumulative assessments" OR "aggregate effect" OR "aggregate risk" OR "aggregate exposure" OR "aggregate exposures" OR "aggregate assessments" OR "combined risk" OR "combined risks" OR "combined exposures" OR "multiple chemicals" OR "multiple chemical effects" OR "multiple chemical exposures" OR "multiple chemical exposure" OR "mixture risk" OR "mixtures assessment" OR "mixture effect" OR "mixture effects" OR "mixtures effects" OR "combined prediction model" OR "toxic equivalency factor" OR "toxic equivalence factors" OR "toxicity equivalency factor" OR "toxicity equivalency factors" OR "toxicity equivalence factor" OR "toxicity equivalence factors" OR "toxic equivalent factor" OR "toxic equivalent factors" OR "toxicity equivalent factor" OR "toxicity equivalent factors" OR "toxic equivalency quotient" OR "toxic equivalency quotients" OR "toxic equivalent quotient" OR "relative potency factor" OR "relative potency factors" OR "mixture model" OR "mixture models" OR "mixtures model" OR "chemical mixture" OR "chemical mixtures" OR "relative toxicity" OR "relative toxicities"	Combined/ cumulative risks
12	"Uncertainty"[Mesh] OR "probability tree" OR "probability trees" OR "probability distribution" OR "probability distributions" OR "uncertainty analysis" OR "uncertainty analyses" OR "uncertainty distribution" OR "uncertainty distributions" OR "judgmental probabilities" OR "subjective probability" OR "subjective probabilities" OR "statistical uncertainty" OR "statistical uncertainties" OR "model uncertainty" OR "model uncertainties" OR "assessment uncertainty" OR "assessment uncertainties" OR "analysis uncertainty" OR "risk distribution" OR "risk distributions" OR "distribution function" OR "distribution functions" OR "uncertainty estimate" OR "uncertainty estimates" OR "uncertainty estimation" OR "uncertainty estimations" OR "uncertainty characterization" OR "characterizing uncertainty"	Uncertainty analysis
13	"extrapolation methodology" OR "extrapolation methodologies" OR "extrapolation method" OR "extrapolation methods" OR "extrapolation factor" OR "extrapolation factors" OR "dose equivalence" OR "dose equivalency" OR "dose extrapolation" OR "dose extrapolations" OR "route extrapolation" OR "route extrapolations" OR "route-to-route extrapolation" OR "route-to-route extrapolations" OR "rtr extrapolation" OR "species extrapolation" OR "species extrapolations" OR "animal to human extrapolation" OR "cross-species extrapolation" OR "cross-species extrapolations" OR "interspecies extrapolation" OR "interspecies extrapolations" OR "inter-species extrapolation" OR "allometric relationship" OR "allometric relationships" OR "allometric scaling" OR "allometrically scaled" OR "allometric adjustment" OR allometry OR "species difference" OR "species differences" OR "species variability" OR "species variation" OR "species variations" OR "dose extrapolation" OR "dose extrapolations" OR "low-dose extrapolation" OR "low-dose extrapolations" OR "linear effect" OR "linear effects" OR "non-threshold effects" OR "nonthreshold effects" OR "no-threshold assumption" OR "low dose linearity" OR "linear dose-response	Extrapolation (generic)

	relationships" OR "linear exposure-response relationship" OR "linear exposure-response relationships" OR "no threshold relationship" OR "no threshold relationships" OR "non-threshold dose-response relationship" OR "nonthreshold model" OR "nonthreshold models" OR "non-threshold model" OR "non-threshold models"	
14	"problem formulation" OR "problem formulations" OR "fit-for-purpose" OR "hypothesis based weight of evidence" OR HBWoE OR "data-informed" OR "multicriteria decision analysis" OR "MCDA" OR "decision analysis"	General terms / frameworks
15	"dosimetry modeling" OR "dosimetry model" OR "dosimetry models" OR "inhalation reference doses" OR RfDi OR "dosimetric adjustment factor" OR "deposited doses" OR "retained dose" OR "dosimetry adjustments" OR "dosimetric adjustment" OR "dosimetric adjustments" OR "human equivalent concentration" OR "human equivalent concentrations" OR HECs OR "particle deposition model" OR "particle deposition models" OR "category 1 gases"	Dosimetry modelling
16	"unusual workshift" OR "unusual workshifts" OR "unusual work schedules" OR "unusual schedules" OR "altered work schedules" OR "adjusting occupational exposure limits" OR "adjusted exposure limits" OR "Haber's law" OR "Haber's rule" OR "novel work schedules" OR "novel schedule" OR "novel schedules" OR "complex exposure scenarios" OR "long shifts" OR "long work schedules" OR "extended work schedule" OR "adjusted exposure limits" OR "long exposure durations"	Duration adjustment
17	#3 OR #4 OR #5 OR #6 OR #7 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	All (except BMD)
18	#1 AND #2 AND #3	Final: MOA
19	#18 with filters (Date: 1983–2015; Language: English; French)	
20	#1 AND #2 AND #4	Final: non-chemical stressors
21	#20 with filters (Date: 1983–2015; Language: English; French)	
22	#1 AND #2 AND #5	Final: PBPK and BBDR modelling
23	#22 with filters (Date: 1983–2015; Language: English; French)	
24	#1 AND #2 AND #6	Final: systems biology
25	#24 with filters (Date: 1983–2015; Language: English; French)	
26	#1 AND #2 AND #7	Final: CSAF
27	#26 with filters (Date: 1983–2015; Language: English; French)	
28	#1 AND #2 AND #8	**Final: BMD**
29	**#28 with filters (Date: 1983–2015; Language: English; French)**	
30	#1 AND #2 AND #9	Final: categorical regression
31	#30 with filters (Date: 1983–2015; Language: English; French)	
32	#1 AND #2 AND #10	Final: pop. variability/ sensitivity
33	#32 with filters (Date: 1983–2015; Language: English; French)	
34	#1 AND #2 AND #11	Final: Combined/ cumulative risks
35	#34 with filters (Date: 1983–2015; Language: English; French)	
36	#1 AND #2 AND #12	Final: Uncertainty analysis
37	#36 with filters (Date: 1983–2015; Language: English; French)	
38	#1 AND #2 AND #13	Final: Extrapolation (generic)
39	#38 with filters (Date: 1983–2015; Language: English; French)	
40	#1 AND #2 AND #14	Final: General terms / frameworks
41	#40 with filters (Date: 1983–2015; Language: English; French)	
42	#1 AND #2 AND #15	Final: Dosimetry modelling
43	#42 with filters (Date: 1983–2015; Language: English; French)	
44	#1 AND #2 AND #16	Final: Duration adjustment
45	#44 with filters (Date: 1983–2015; Language: English; French)	
46	#1 AND #2 AND #17	**Final: All (except BMD)**
47	**#46 with filters (Date: 1983–2015; Language: English; French)**	

Table A.2 – Search queries for MEDLINE (Ovid)

Search #	Query	Category
1	(risk* adj2 (assess* or analy* or estimat*)).tw.	Risk assessments
2	(dose response relation* or exposure response relation* or concentration response relation* or ("dose response" adj2 (analy* or assess* or model* or curve*)) or ("exposure response" adj2 (analy* or assess* or model* or curve*)) or ("concentration response" adj2 (analy* or assess* or model* or curve*)) or hazard assessment*).tw.	
3	((exposure adj2 (limit* or guideline* or standard* or recommendation* or margin*)) or reference level* or limit value* or (margin* adj2 safety) or ((air quality or water quality or food quality or soil quality) adj2 (guideline* or standard* or limit* or recommendation*))).tw.	
4	(reference dose* or RfD* or reference concentration* or allowable daily intake* or acceptable daily intake or tolerable daily intake* or toxicological reference value* or maximum allowable concentration* or maximum acceptable concentration* or soil quality guideline* or SQG* or maximum contaminant level* or mclg* or health advisor* or health based value* or acute exposure guideline* or (AEGL or AEGLs) or threshold limit value* or tlv* or workplace environmental exposure level* or WEEL* or (permissible exposure and (limit* or level*)) or (recommended exposure and (limit* or level*)) or ((binding or indicative) and occupational exposure limit*) or (BOELV* or IOELV*) or derived no effect level* or derived minimal effect level or (DNEL or DNELs or DMEL or DMELs) or cancer slope factor* or (biomonitoring equivalent* or biological exposure ind* or BEIs or ((biological environmental exposure or biological equivalent exposure or biological-based environmental exposure or biological exposure) adj2 (level* or limit*)) or biological limit value* or BLVs or (risk-specific adj1 (dose* or concentration* or exposure*)))).tw.	
5	(health canada or (health adj2 welfare canada) or pest management regulatory agency or PMRA or environmental protection agency or ((food and drug) adj3 (administration or agency)) or FDA or (world health adj2 (organization or organisation)) or ((programme or program) adj2 on chemical safety) or meeting on pesticide residues or jmpr or expert committee on food additives or jecfa or european commission or european chemicals agency or echa or (registration evaluation authorization and restriction of chemicals) or (registration evaluation authorisation and restriction of chemicals) or european food safety authority or efsa or scientific committee on occupational exposure limits or scoel or american conference of governmental industrial hygienists or ACGIH or american industrial hygiene association or occupational alliance for risk science or (occupational safety adj2 health administration) or osha or (national institute for occupational safety and health) or niosh or (agency for toxic substances adj2 disease registry) or ATSDR or (((food adj2 agriculture) or (food adj2 agricultural)) adj1 (organization or organisation)) or committee on toxicology or (board on environmental studies adj2 toxicology) or committee on acute exposure guideline levels or science advisory board or clean air scientific advisory committee or (national academ* adj1 of science*) or institute of medicine).tw.	
6	exp Risk Assessment/ or exp Dose-Response Relationship, Drug/ or exp "Threshold Limit Values"/ or exp Maximum Allowable Concentration/ or exp "United States Environmental Protection Agency"/ or exp "United States Food and Drug Administration"/ or exp "World Health Organization"/ or exp "United States Occupational Safety and Health Administration"/ or exp "National Institute for Occupational Safety and Health (U.S.)"/	
7	1 or 2 or 3 or 4 or 5 or 6	
8	(toxicant or toxicants or toxin or toxins or chemical or chemicals or ((chemical or toxic or hazardous) adj3 (substance* or compound*)) or (cytotox* or hepatotox* or nephrotox* or renotox* or cardiotox* or skeletotox* or neurotox* or genotox* or mutagen* or teratogen* or fetotox* or clastogen* or carcinogen* or leukemogen* or leukaemogen* or reprotox* or teratogen* or tumorigen* or non-cancer* or noncancer* or non-carcinogen* or noncarcinogen* or non-mutagen* or nonmutagen* or immunotox* or hematotox* or haematotox* or dermatotox* or sensitization* or sensitisation* or sensitizer* or sensitiser* or sensitized* or sensitised*) or ((cyto* or cell* or hepato* or hepatic* or liver* or nephro* or nephron* or reno* or renal* or kidney* or cardio* or heart* or cardiac* or cardiopulmo* or pulmo* or lung* or respirator* or skelet* or bone* or osteo* or neuro* or brain* or geno* or genetic* or feto* or fetal* or fetus* or embryo* or chromosom* or blood* or reproductiv* or development* or immun* or spleno* or splenic* or spleen* or thymus* or thymi* or thyma* or thyro* or hemato* or haemato* or dermato* or dermal* or dermi* or epiderm* or skin* or endocrin*) adj3 (toxic* or toxin* or effect* or tumor* or tumour* or adenoma* or carcinoma* or cancer* or sarcoma*)) or osteoma* or leukemia* or inhaled material* or toxicity or toxicities or adverse health effect* or ((tissue or cellular) adj3 response*) or ((toxicological or induced) adj2 (effect* or outcome*)) or (endocrin* adj3 (disrupt* or toxic* or toxin*)) or ((inhalat* or oral* or diet*) adj2 toxic*) or ((water* or air* or soil* or food* or environment*) adj3 (quality or pollut* or contamina* or expos*)) or (exposure* adj3 (environment* or occupation* or work* or take home or paraoccupation*)) or exposome* or ((chemical or oral or dietary or inhalation or ambient) adj3 (exposure* or intake*))).tw.	Toxicity from environmental chemicals
9	exp Hazardous Substances/ or exp Chemical Safety/ or exp Drug-Induced Liver Injury/ or exp Mutagens/ or exp Carcinogens/ or exp Abnormalities, Drug-Induced/ or exp Teratogens/ or exp toxic actions/ or exp Drinking Water/ or exp Water Quality/ or exp Air Pollution/ or exp Environmental Pollutants/ or exp Environmental pollution/ or exp Food Quality/ or exp Legislation, Food/ or exp "Specialty Uses of Chemicals"/ or exp Neoplasms/ or exp Cardiotoxins/ or exp Neurotoxicity Syndromes/ or exp Mutagenesis/ or exp Teratogens/ or exp Teratogenesis/ or exp Hypersensitivity/ or exp Endocrine Disruptors/	
10	8 or 9	
11	((mode of action adj3 (analys* or assess* or evaluat*)) or (MOA or MOAs or adverse outcome pathway*) or (human* adj3 relevan*) or species concordance or (mode of action adj7 (framework* or relevan*)) or (molecular initiating event or pathway based toxicology) or (level* adj3 (biological organization or biological organisation)) or ((IPCS or ILSI or HESI) and mode of action) or (pathway* adj3 perturbation*)).tw.	MOA
12	(((nonchemical* or non-chemical* or non chemical* or psychosocial* or social*) adj3 stress*) or risk modifying factor* or (non-chemical interaction* or nonchemical interaction*) or allostatic load* or social indicator or environmental justice).tw.	Non-chemical stressors
13	((physiologically based adj2 (pharmacokinetic* or toxicokinetic* or kinetic* or dynamic*)) or (PBPK* or PBTK* or PBK* or PBPD* or PBTD* or PBD or PB-PK or PB-PD or PB-TK or PB-TD) or (biologically based dose response or BBDR) or physiological pharmacokinetic* or flow limited model* or ((pharmacodynamic* or pharmacokinetic*) adj2 model*) or physiologically based model* or ((mathematical* or biomathematical* or biologic*) adj10 (physiological* or pharmacokinetic* or toxicokinetic* or pharmacodynamic* or toxicodynamic* or kinetic* or dynamic* or carcinogen* or cancer*) adj10 model*) or (biologically based adj10 (risk assessment* or risk analys*)) or BBRA or mechanistic model* or dosimetric model* or (biologically motivated adj5 model*) or dose metric*).tw.	PBPK and BBDR modelling
14	(((chemical specific or data derived) adj4 (adjustment factor* or uncertainty factor* or safety factor* or (factor or factors))) or CSAF* or ((kinetic* or dynamic*) adj2 component*) or (ADUF or AKUF or HDUF or HKUF or ADAF or AKAF or HDAF or HKAF) or ((human* or animal* or kinetic* or dynamic* or toxicokinetic* or toxicodynamic* or pharmacokinetic* or pharmacodynamic*) adj5 (adjustment factor* or uncertainty factor* or safety factor*)) or composite factor*).tw.	CSAF
15	(categorical regression or CatReg or ordinal regression or categorical response* or dose-categor* or dose categor*).tw.	Categorical regression
16	(((lifestage* or life stage* or lifecourse* or life course* or child*) adj5 (specific or risk assessment* or risk analys* or approach* or framework* or focus*)) or (FQPA adj 5 factor) or (((early life or age-related or lifestage* or life stage* or lifecourse* or life course* or subpopulation* or sub-population* or interindividual* or inter-individual* or intraspecies* or intra-species* or intrapopulation* or intra-population* or pharmacokinetic* or toxicokinetic* or kinetic* or pharmacodynamic* or toxicodynamic* or dynamic*) adj3 (susceptib* or sensitiv* or vulnerab* or differ* or varia* or change* or heterogen* or risk*)) and (risk assessment* or risk analys* or dose-response)) or critical window* or (development* adj3 (lifestage* or life stage*)) or (child* adj2 health risk*) or ((individual adj2 (variabilit* or differen* or heterogen*)) and (risk analys* or risk assessment* or dose-response)) or physiological difference* or ((age adj2 (difference* or change*)) and (risk analys* or risk assessment* or dose-response)) or (altered adj2 (susceptibilit* or vulnerab*)) or (extreme* adj2 sensitiv*) or ((variab* adj2 (individual risk* or distribution* or model*)) and (risk assessment* or risk analys* or dose-response)) or (((population* or subpopulation* or sub-population*) adj2 specific) and (risk assessment* or risk analys* or dose-response)) or (((genetic* or gene) adj2 (variabilit* or variation* or change*)) and (risk assessment* or risk analys* or dose-response))).tw.	Population variability/ sensitivity
17	(dose addition* or ((cumulative* or aggregate*) adj2 (effect* or risk* or assessment*)) or (aggregate* adj2 cumulative*) or multiple chemical* or (mixture* adj2 (risk* or assessment* or effect* or model*)) or combined prediction model* or (toxic* adj2 equivalen* adj2 (factor* or quotient*)) or relative potency factor* or chemical mixture* or relative toxicit* or (common adj2 (mechanism* or mode of action* or modes of action*) adj2 group*)).tw.	Combined/ cumulative risks
18	((extrapolation adj2 (method* or factor*)) or ((dose* or exposure* or route* or species* or animal to human or cross species* or cross-species* or crossspecies* or inter species* or interspecies* or inter-species* or lowdose* or low-dose* or low-exposure*) adj1 (equivalen* or extrapolat* or adjust*)) or (allometric* adj1 (scal* or adjust*)) or allometry or linear effect* or (linear* adj2 (low dose* or low exposure* or lowdose* or dose-response* or exposure-response*))).tw.	Extrapolation (generic)
19	((probability adj2 (tree* or distribution*)) or (uncertain* adj3 (analys* or distribution* or assessment* or measure* or estimat* or characteri*)) or ((judgment* or judgement* or subjective*) adj1 probabilit*) or ((statistical* or model*) adj1 uncertain*) or ((risk* or hazard*) adj2 distribution*) or distribution function*).tw.	Uncertainty analysis
20	exp Uncertainty/	
21	(dosimetry model* or (inhalation reference dose* or RfDi*) or (dosimetric adj2 (adjustment factor* or uncertainty factor* or scaling factor* or extrapolation*)) or scaling factor* or (dosimetric adj1 (extrapolation* or calculation* or difference*)) or deposited dose* or dosimetric difference* or (regional deposition pattern* or regional deposited dose*) or retained dose* or (dosimetr* adj2 adjust*) or deposition fraction* or (HEC adj1 Ca adj2 ratio*) or computational fluid dynamic* or nasal flux pattern* or flux bin* or (cfd adj1 model*) or mass flux pattern* or inspiratory airflow pattern* or nasal surface area* or (flux* adj2 (value* or variation* or nasal* or gradient*)) or (local adj1 dosimetr*) or aerosol deposition* or human equivalent concentration* or (particle deposition* adj2 model*) or (category adj2 gas*)).tw.	Dosimetry modelling

22	(((unusual or altered or novel or extraordinary or conventional or long or extended or short* or lengthen* or nonstandard or non-standard) adj3 (workshift* or work shift* or shift* or schedule* or work schedule* or exposure period*)) or ((adjust* or modif*) adj3 (exposure limit* or threshold limit value* or TLV or TLVs or OEL or OELs or exposure guideline* or time weighted average* or TWA or TWAs)) or prolonged hour* or (Haber* adj1 (law* or rule* or model*)) or OSHA model* or (Brief and Scala*) or (Hickey and Reist*) or Veng-Penderson* or overtime or correction factor* or complex exposure scenario* or various exposure scenario* or ((10* or 12* or ten or twelve) adj1 hour* adj3 (shift* or work shift* or workshift* or schedule* or exposure period*)) or (Roach* adj5 model*) or ((daily or weekly) adj2 adjustment*) or Quebec model* or (compress* adj2 (workweek* or work week*)) or ((OEL or OELs or occupational exposure limit* or TWA or TWAs or time weighted average* or TLV or TLVs or threshold limit value*) adj3 (reduc* or special)) or reduction factor* or (maximum adjustment adj2 (halflife or half life)) or averaging time*).tw.	Duration adjustment
23	((pathway* adj2 (toxicit* or approach* or model* or risk assessment)) or (network* adj2 biology) or (computational adj2 (toxicology or systems biology or systems toxicology or method* or approach or approaches)) or ((system or systems) adj3 toxicology) or ((next generation or NexGen) adj2 risk assessment*) or (in vitro to in vivo adj2 extrapolat*) or (QVIVE or QIVIVE or IVIVE) or ((forward* or reverse*) adj2 dosimetry) or (network* adj4 (model* or analy* or structure* or scale-free or motif* or cluster* or centralit* or bayesian or approach* or dose-response* or inference* or molecular or neural)) or global network structure* or (computational adj2 pathway model*) or bayesian network* or bn model* or pathway response dynamic* or ((signaling or signalling or response) adj2 motif*) or (computational adj3 pathway adj3 model*)).tw.	Systems biology
24	exp Systems Biology/ or exp "neural networks (computer)"/	
25	(problem formulation* or (fit-for-purpose or fit for purpose) or (hypothesis based weight of evidence or HBWoE) or biologically based predictive or (data-informed or data-derived or chemical-specific or multicriteria decision analysis or MCDA or decision analysis)).tw.	General terms / frameworks
26	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	All (except BMD)
27	(benchmark dose* or BMD or BMDS or benchmark concentration* or mantel-bryan procedure or (BD adj2 (approach or model*)) or benchmark value*).tw.	BMD
28	7 and 10 and 11	Final: MOA
29	28 with filters (Date: 1983–2015; Language: English; French)	
30	7 and 10 and 12	Final: non-chemical stressors
31	30 with filters (Date: 1983–2015; Language: English; French)	
32	7 and 10 and 13	Final: PBPK and BBDR modelling
33	32 with filters (Date: 1983–2015; Language: English; French)	
34	7 and 10 and 14	Final: CSAF
35	34 with filters (Date: 1983–2015; Language: English; French)	
36	7 and 10 and 15	Final: categorical regression
37	36 with filters (Date: 1983–2015; Language: English; French)	
38	7 and 10 and 16	Final: pop. Variability/ sensitivity
39	38 with filters (Date: 1983–2015; Language: English; French)	
40	7 and 10 and 17	Final: combined/ cumulative risks
41	40 with filters (Date: 1983–2015; Language: English; French)	
42	7 and 10 and 18	Final: Extrapolation (generic)
43	42 with filters (Date: 1983–2015; Language: English; French)	
44	19 or 20	Final: Uncertainty analysis
45	7 and 10 and 45	
46	45 with filters (Date: 1983–2015; Language: English; French)	
47	7 and 10 and 21	Final: Dosimetry modelling
48	47 with filters (Date: 1983–2015; Language: English; French)	
49	7 and 10 and 22	Final: Duration adjustment
50	49 with filters (Date: 1983–2015; Language: English; French)	
51	23 or 24	Final: Systems toxicology
52	7 and 10 and 51	
53	52 with filters (Date: 1983–2015; Language: English; French)	
54	7 and 10 and 25	Final: General terms / frameworks
55	54 with filters (Date: 1983–2015; Language: English; French)	
56	7 and 10 and 26	**Final: All (except BMD)**
57	56 with filters (Date: 1983–2015; Language: English; French)	
58	7 and 10 and 27	**Final: BMD**
59	58 with filters (Date: 1983–2015; Language: English; French)	

Table A.3 – Search queries for Embase (Ovid)

Search #	Query	Category
1	(risk* adj2 (assess* or analy* or estimat*)).tw.	Risk assessments
2	(dose response relation* or exposure response relation* or concentration response relation* or ("dose response" adj2 (analy* or assess* or model* or curve*)) or ("exposure response" adj2 (analy* or assess* or model* or curve*)) or ("concentration response" adj2 (analy* or assess* or model* or curve*)) or hazard assessment*).tw.	
3	((exposure adj2 (limit* or guideline* or standard* or recommendation* or margin*)) or reference level* or limit value* or (margin* adj2 safety) or ((air quality or water quality or food quality or soil quality) adj2 (guideline* or standard* or limit* or recommendation*))).tw.	
4	(reference dose* or RfD* or reference concentration* or allowable daily intake* or acceptable daily intake or tolerable daily intake* or toxicological reference value* or maximum allowable concentration* or maximum acceptable concentration* or soil quality guideline* or SQG* or maximum contaminant level* or mclg* or health advisor* or health based value* or acute exposure guideline* or (AEGL or AEGLs) or threshold limit value* or tlv* or workplace environmental exposure level* or WEEL* or (permissible exposure and (limit* or level*)) or (recommended exposure and (limit* or level*)) or ((binding or indicative) and occupational exposure limit*) or (BOELV* or IOELV*) or derived no effect level* or derived minimal effect level or (DNEL or DNELs or DMEL or DMELs) or cancer slope factor* or (biomonitoring equivalent* or biological exposure ind* or BEIs or ((biological environmental exposure or biological equivalent exposure or biological-based environmental exposure or biological exposure) adj2 (level* or limit*)) or biological limit value* or BLVs or (risk-specific adj1 (dose* or concentration* or exposure*)))).tw.	
5	(health canada or (health adj2 welfare canada) or pest management regulatory agency or PMRA or environmental protection agency or ((food and drug) adj3 (administration or agency)) or FDA or (world health adj2 (organization or organisation)) or ((programme or program) adj2 on chemical safety) or meeting on pesticide residues or jmpr or expert committee on food additives or jecfa or european commission or european chemicals agency or echa or (registration evaluation authorization and restriction of chemicals) or (registration evaluation authorisation and restriction of chemicals) or european food safety authority or efsa or scientific committee on occupational exposure limits or scoel or american conference of governmental industrial hygienists or ACGIH or american industrial hygiene association or occupational alliance for risk science or (occupational safety adj2 health administration) or osha or (national institute for occupational safety and health) or niosh or (agency for toxic substances adj2 disease registry) or ATSDR or (((food adj2 agriculture) or (food adj2 agricultural)) adj1 (organization or organisation)) or committee on toxicology or (board on environmental studies adj2 toxicology) or committee on acute exposure guideline levels or science advisory board or clean air scientific advisory committee or (national academ* adj1 of science*) or institute of medicine).tw.	
6	exp risk assessment/ or exp dose response/ or exp hazard assessment/ or exp maximum allowable concentration/ or exp maximum permissible dose/ or exp air quality standard/ or exp water standard/ or exp "food and drug administration"/ or exp world health organization/ or exp occupational health service/	
7	1 or 2 or 3 or 4 or 5 or 6	
8	(toxicant or toxicants or toxin or toxins or chemical or chemicals or ((chemical or toxic or hazardous) adj3 (substance* or compound*)) or (cytotox* or hepatotox* or nephrotox* or renotox* or cardiotox* or skeletotox* or neurotox* or genotox* or mutagen* or teratogen* or fetotox* or clastogen* or carcinogen* or leukemogen* or leukaemogen* or reprotox* or teratogen* or tumorigen* or non-cancer* or noncancer* or non-carcinogen* or noncarcinogen* or non-mutagen* or nonmutagen* or immunotox* or hematotox* or haematotox* or dermatotox* or sensitization* or sensitisation* or sensitizer* or sensitiser* or sensitized* or sensitised*) or ((cyto* or cell* or hepato* or hepatic* or liver* or nephro* or nephron* or reno* or renal* or kidney* or cardio* or heart* or cardiac* or cardiopulmo* or pulmo* or lung* or respirator* or skelet* or bone* or osteo* or neuro* or brain* or geno* or genetic* or feto* or fetal* or fetus* or embryo* or chromosom* or blood* or reproductiv* or development* or immun* or spleno* or splenic* or spleen* or thymus* or thymi* or thyma* or thyro* or hemato* or haemato* or dermato* or dermal* or dermi* or epiderm* or skin* or endocrin*) adj3 (toxic* or toxin* or effect* or tumor* or tumour* or adenoma* or carcinoma* or cancer* or sarcoma*)) or osteoma* or leukemia* or inhaled material* or toxicity or toxicities or adverse health effect* or ((tissue or cellular) adj3 response*) or ((toxicological or induced) adj2 (effect* or outcome*)) or (endocrin* adj3 (disrupt* or toxic* or toxin*)) or ((inhalat* or oral* or diet*) adj2 toxic*) or ((water* or air* or soil* or food* or environment*) adj3 (quality or pollut* or contamina* or expos*)) or (exposure* adj3 (environment* or occupation* or work* or take home or paraoccupation*)) or exposome* or ((chemical or oral or dietary or inhalation or ambient) adj3 (exposure* or intake*))).tw.	Toxicity from environmental chemicals
9	exp chemical compound/ or exp toxic substance/ or exp dangerous goods/ or exp chemical safety/ or exp chemically induced disorder/ or exp liver toxicity/ or exp nephrotoxicity/ or exp cardiotoxicity/ or exp lung toxicity/ or exp neurotoxicity/ or exp neurotoxin/ or exp genotoxicity/ or exp mutagenicity/ or exp mutagenic agent/ or exp teratogenicity/ or exp teratogenic agent/ or exp chemical teratogenesis/ or exp fetotoxicity/ or exp embryotoxicity/ or exp clastogen/ or exp carcinogenicity/ or exp carcinogen/ or exp leukemogenesis/ or exp cancer risk/ or exp blood toxicity/ or exp reproductive toxicity/ or exp developmental toxicity/ or exp immunotoxicity/ or exp skin toxicity/ or exp chemosensitization/ or exp endocrine disruptor/ or exp water pollutant/ or exp drinking water/ or exp water quality/ or exp water pollution/ or exp tap water/ or exp water contamination/ or exp air pollutant/ or exp indoor air pollution/ or exp air pollution/ or exp air quality/ or exp soil pollution/ or exp soil pollutant/ or exp soil quality/ or exp food quality/ or exp food safety/ or exp food contamination/ or exp environmental exposure/ or exp occupational exposure/	
10	8 or 9	
11	((mode of action adj3 (analys* or assess* or evaluat*)) or (MOA or MOAs or adverse outcome pathway*) or (human* adj3 relevan*) or species concordance or (mode of action adj7 (framework* or relevan*)) or (molecular initiating event or pathway based toxicology) or (level* adj3 (biological organization or biological organisation)) or ((IPCS or ILSI or HESI) and mode of action) or (pathway* adj3 perturbation*)).tw.	MOA
12	(((nonchemical* or non-chemical* or non chemical* or psychosocial* or social*) adj3 stress*) or risk modifying factor* or (non-chemical interaction* or nonchemical interaction*) or allostatic load* or social indicator or environmental justice).tw.	Non-chemical stressors
13	exp allostasis/ or exp mental stress/ or exp social stress/	
14	((physiologically based adj2 (pharmacokinetic* or toxicokinetic* or kinetic* or dynamic*)) or (PBPK* or PBTK* or PBK* or PBPD* or PBTD* or PBD or PB-PK or PB-PD or PB-TK or PB-TD) or (biologically based dose response or BBDR) or physiological pharmacokinetic* or flow limited model* or ((pharmacodynamic* or pharmacokinetic*) adj2 model*) or physiologically based model* or ((mathematical* or biomathematical* or biologic*) adj10 (physiological* or pharmacokinetic* or toxicokinetic* or pharmacodynamic* or toxicodynamic* or kinetic* or dynamic* or carcinogen* or cancer*) adj10 model*) or (biologically based adj10 (risk assessment* or risk analys*)) or BBRA or mechanistic model* or dosimetric model* or (biologically motivated adj5 model*) or dose metric*).tw.	PBPK and BBDR modelling
15	(((chemical specific or data derived) adj4 (adjustment factor* or uncertainty factor* or safety factor* or (factor or factors))) or CSAF* or ((kinetic* or dynamic*) adj2 component*) or (ADUF or AKUF or HDUF or HKUF or ADAF or AKAF or HDAF or HKAF) or ((human* or animal* or kinetic* or dynamic* or toxicokinetic* or toxicodynamic* or pharmacokinetic* or pharmacodynamic*) adj5 (adjustment factor* or uncertainty factor* or safety factor*)) or composite factor*).tw.	CSAF
16	(categorical regression or CatReg or ordinal regression or categorical response* or dose-categor* or dose categor*).tw.	Categorical regression
17	(((lifestage* or life stage* or lifecourse* or life course* or child*) adj5 (specific or risk assessment* or risk analys* or approach* or framework* or focus*)) or (FQPA adj 5 factor) or (((early life or age-related or lifestage* or life stage* or lifecourse* or life course* or subpopulation* or sub-population* or interindividual* or inter-individual* or intraspecies* or intra-species* or intrapopulation* or intra-population* or pharmacokinetic* or toxicokinetic* or kinetic* or pharmacodynamic* or toxicodynamic* or dynamic*) adj3 (susceptib* or sensitiv* or vulnerab* or differ* or varia* or change* or heterogen* or risk*)) and (risk assessment* or risk analys* or dose-response)) or critical window* or (development* adj3 (lifestage* or life stage*)) or (child* adj2 health risk*) or ((individual adj2 (variabilit* or differen* or heterogen*)) and (risk analys* or risk assessment* or dose-response)) or physiological difference* or ((age adj2 (difference* or change*)) and (risk analys* or risk assessment* or dose-response)) or (altered adj2 (susceptibilit* or vulnerab*)) or (extreme* adj2 sensitiv*) or ((variab* adj2 (individual risk* or distribution* or model*)) and (risk assessment* or risk analys* or dose-response)) or (((population* or subpopulation* or sub-population*) adj2 specific) and (risk assessment* or risk analys* or dose-response)) or (((genetic* or gene) adj2 (variabilit* or variation* or change*)) and (risk assessment* or risk analys* or dose-response))).tw.	Population variability/ sensitivity
18	(dose addition* or ((cumulative* or aggregate*) adj2 (effect* or risk* or assessment*)) or (aggregate* adj2 cumulative*) or multiple chemical* or (mixture* adj2 (risk* or assessment* or effect* or model*)) or combined prediction model* or (toxic* adj2 equivalen* adj2 (factor* or quotient*)) or relative potency factor* or chemical mixture* or relative toxicit* or (common adj2 (mechanism* or mode of action* or modes of action*) adj2 group*)).tw.	Combined/ cumulative risks
19	((extrapolation adj2 (method* or factor*)) or ((dose* or exposure* or route* or species* or animal to human or cross species* or cross-species* or crossspecies* or inter species* or interspecies* or inter-species* or lowdose* or low-dose* or low-exposure*) adj1 (equivalen* or extrapolat* or adjust*)) or (allometric* adj1 (scal* or adjust*)) or allometry or linear effect* or (linear* adj2 (low dose* or low exposure* or lowdose* or dose-response* or exposure-response*))).tw.	Extrapolation (generic)
20	((probability adj2 (tree* or distribution*)) or (uncertain* adj3 (analys* or distribution* or assessment* or measure* or estimat* or characteri*)) or ((judgment* or judgement* or subjective*) adj1 probabilit*) or ((statistical* or model*) adj1 uncertain*) or ((risk* or hazard*) adj2 distribution*) or distribution function*).tw. or exp uncertainty/	Uncertainty analysis
21	(dosimetry model* or (inhalation reference dose* or RfDi*) or (dosimetric adj2 (adjustment factor* or uncertainty factor* or scaling factor* or extrapolation*)) or scaling factor* or (dosimetric adj1 (extrapolation* or calculation* or difference*)) or deposited dose* or dosimetric difference* or (regional deposition pattern* or regional deposited dose*) or retained dose* or (dosimetr* adj2 adjust*) or deposition fraction* or (HEC adj1 Ca adj2 ratio*) or computational fluid dynamic* or nasal flux pattern* or flux bin* or (cfd adj1 model*) or mass flux pattern* or inspiratory airflow pattern* or nasal surface area* or (flux* adj2 (value* or variation* or nasal* or gradient*)) or (local adj1 dosimetr*) or aerosol deposition* or human equivalent concentration* or (particle deposition* adj2 model*) or (category adj2 gas*)).tw.	Dosimetry modelling

22	exp dosimetry/	
23	(((unusual or altered or novel or extraordinary or conventional or long or extended or short* or lengthen* or nonstandard or non-standard) adj3 (workshift* or work shift* or shift* or schedule* or work schedule* or exposure period*)) or ((adjust* or modif*) adj3 (exposure limit* or threshold limit value* or TLV or TLVs or OEL or OELs or exposure guideline* or time weighted average* or TWA or TWAs)) or prolonged hour* or (Haber* adj1 (law* or rule* or model*)) or OSHA model* or (Brief and Scala*) or (Hickey and Reist*) or Veng-Penderson* or overtime or correction factor* or complex exposure scenario* or various exposure scenario* or ((10* or 12* or ten or twelve) adj1 hour* adj3 (shift* or work shift* or workshift* or schedule* or exposure period*)) or (Roach* adj5 model*) or ((daily or weekly) adj2 adjustment*) or Quebec model* or (compress* adj2 (workweek* or work week*)) or ((OEL or OELs or occupational exposure limit* or TWA or TWAs or time weighted average* or TLV or TLVs or threshold limit value*) adj3 (reduc* or special)) or reduction factor* or (maximum adjustment adj2 (halflife or half life)) or averaging time*).tw.	Duration adjustment
24	((pathway* adj2 (toxicit* or approach* or model* or risk assessment)) or (network* adj2 biology) or (computational adj2 (toxicology or systems biology or systems toxicology or method* or approach or approaches)) or ((system or systems) adj3 toxicology) or ((next generation or NexGen) adj2 risk assessment*) or (in vitro to in vivo adj2 extrapolat*) or (QVIVE or QIVIVE or IVIVE) or ((forward* or reverse*) adj2 dosimetry) or (network* adj4 (model* or analy* or structure* or scale-free or motif* or cluster* or centralit* or bayesian or approach* or dose-response* or inference* or molecular or neural)) or global network structure* or (computational adj2 pathway model*) or bayesian network* or bn model* or pathway response dynamic* or ((signaling or signalling or response) adj2 motif*) or (computational adj3 pathway adj3 model*)).tw.	Systems biology
25	exp artificial neural network/	
26	(problem formulation* or (fit-for-purpose or fit for purpose) or (hypothesis based weight of evidence or HBWoE) or biologically based predictive or (data-informed or data-derived or chemical-specific or multicriteria decision analysis or MCDA or decision analysis)).tw.	General terms / frameworks
27	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	All (except BMD)
28	(benchmark dose* or BMD or BMDS or benchmark concentration* or mantel-bryan procedure or (BD adj2 (approach or model*)) or benchmark value*).tw.	BMD
29	7 and 10 and 11	Final: MOA
30	30 with filters (Date: 1983–2015; Language: English; French)	
31	12 or 13	Final: non-chemical stressors
32	7 and 10 and 31	
33	32 with filters (Date: 1983–2015; Language: English; French)	
34	7 and 10 and 14	Final: PBPK and BBDR modelling
35	34 with filters (Date: 1983–2015; Language: English; French)	
36	7 and 10 and 15	Final: CSAF
37	36 with filters (Date: 1983–2015; Language: English; French)	
38	7 and 10 and 16	Final: categorical regression
39	38 with filters (Date: 1983–2015; Language: English; French)	
40	7 and 10 and 17	Final: pop. Variability/ sensitivity
41	40 with filters (Date: 1983–2015; Language: English; French)	
42	7 and 10 and 18	Final: combined/ cumulative risks
43	42 with filters (Date: 1983–2015; Language: English; French)	
44	7 and 10 and 19	Final: Extrapolation (generic)
45	44 with filters (Date: 1983–2015; Language: English; French)	
46	7 and 10 and 20	Final: Uncertainty analysis
47	46 with filters (Date: 1983–2015; Language: English; French)	
48	21 or 22	Final: Dosimetry modelling
49	7 and 10 and 48	
50	49 with filters (Date: 1983–2015; Language: English; French)	
51	7 and 10 and 23	Final: Duration adjustment
52	51 with filters (Date: 1983–2015; Language: English; French)	
53	24 or 25	Final: Systems toxicology
54	7 and 10 and 53	
55	54 with filters (Date: 1983–2015; Language: English; French)	
56	7 and 10 and 26	Final: General terms / frameworks
57	56 with filters (Date: 1983–2015; Language: English; French)	
58	7 and 10 and 27	**Final: All (except BMD)**
59	58 with filters (Date: 1983–2015; Language: English; French)	
60	7 and 10 and 28	**Final: BMD**
61	60 with filters (Date: 1983–2015; Language: English; French)	

Table A.4 – Search queries for Web of Science (Web of Knowledge)

Search #	Query	Category
1	TS=("risk assessment" OR "risk assessments" OR "risk analyses" OR "risk analysis" OR "risk estimate" OR "risk estimates" OR "risk estimation" OR "risk estimations" OR "dose response relationship" OR "exposure response relationship" OR "dose response assessment" OR "exposure response assessment" OR "dose response analysis" OR "dose response analyses" OR "exposure response analyses" OR "exposure response analysis" OR "dose response modelling" OR "dose response modeling" OR "dose response model" OR "dose response models" OR "exposure response modelling" OR "exposure response modeling" OR "exposure response model" OR "exposure response models" OR "hazard assessment" OR "dose response relationships" OR "exposure response relationships" OR "concentration response relationship" OR "concentration response relationships" OR "dose response assessments" OR "concentration response assessment" OR "concentration response analysis" OR "concentration response analyses" OR "concentration response modeling" OR "concentration response model" OR "concentration response models" OR "dose response curve" OR "dose response curves" OR "exposure response curve" OR "exposure response curves" OR "concentration response curve" OR "concentration response curves" OR "exposure limit" OR "exposure limits" OR "exposure guideline" OR "exposure guidelines" OR "margin of exposure" OR "margins of exposure" OR "limit value" OR "limit values" OR "margin of safety" OR "margins of safety" OR "reference dose" OR "reference doses" OR RfD OR RfDs OR "reference concentration" OR "reference concentrations" OR "allowable daily intake" OR "allowable daily intakes" OR "acceptable daily intake" OR "acceptable daily intakes" OR "tolerable daily intake" OR "tolerable daily intakes" OR "toxicological reference value" OR "toxicological reference values" OR "maximum allowable concentration" OR "maximum allowable concentrations" OR "maximum acceptable concentration" OR "maximum acceptable concentrations" OR "soil quality guidelines" OR sqg OR sqgs OR "maximum contaminant level" OR "maximum contaminant levels" OR MCLG OR "health advisory" OR "health advisories" OR "health based value" OR "health based values" OR "acute exposure guideline" OR "acute exposure guidelines" OR AEGL OR AEGLs OR "Threshold limit value" OR "threshold limit values" OR TLV OR TLVs OR "Workplace environmental exposure level" OR WEELs OR "permissible exposure level" OR "permissible exposure levels" OR "permissible exposure limit" OR "permissible exposure limits" OR "recommended exposure limit" OR "recommended exposure limits" OR RELs OR IOELV OR IOELVs OR "derived no effect level" OR "derived no effect levels" OR DNEL OR DNELS OR DMEL OR "cancer slope factor" OR "cancer slope factors" OR "biomonitoring equivalent" OR "biomonitoring equivalents" OR "biological exposure index" OR "biological exposure indices" OR "biological equivalent exposure limit" OR "biological exposure limit" OR "biological exposure limits" OR "biological limit value" OR "biological limit values" OR BLVs OR "risk-specific dose" OR "risk-specific doses" OR "air quality guideline" OR "air quality guidelines" OR "air quality standard" OR "air quality standards" OR "air quality limit" OR "air quality limits" OR "water quality guideline" OR "water quality guidelines" OR "water quality standard" OR "water quality standards" OR "water quality limits" OR "food quality standard" OR "food quality standards" OR "soil quality standard" OR "soil quality standards" OR "exposure guideline" OR "exposure guidelines" OR "exposure standard" OR "exposure standards" OR "exposure limit" OR "exposure limits" OR "exposure recommendations" OR "reference level" OR "reference levels" OR "health canada" OR "health and welfare canada" OR "pest management regulatory agency" OR "environmental protection agency" OR "food and drug administration" OR "food and drug agency" OR "world health organization" OR "world health organisation" OR "international programme on chemical safety" OR "international program on chemical safety" OR IPCS OR JMPR OR "Joint FAO/WHO Expert Committee on Food Additives" OR JECFA OR "European Commission" OR "European Chemicals Agency" OR ECHA OR "Registration, Evaluation, Authorisation and Restriction of Chemicals" OR "Registration, Evaluation, Authorization and Restriction of Chemicals" OR "European Food Safety Authority" OR EFSA OR SCOEL OR "american conference of governmental industrial hygienists" OR ACGIH OR "american industrial hygiene association" OR AIHA OR "occupational safety and health administration" OR "OSHA" OR "national institute for occupational safety and health" OR "NIOSH" OR "Agency for toxic substances and disease registry" OR ATSDR OR "food and agriculture organization" OR "food and agricultural organization" OR "food and agriculture organisation" OR FAO OR "Committee on toxicology" OR "board on environmental studies and toxicology" OR "science advisory board" OR "clean air scientific advisory committee" OR "national academy of science" OR "national academy of sciences" OR "national academies of science" OR "national academies of sciences" OR "institute of medicine" OR "institutes of medicine")	Risk assessments
2	TS=("toxicants" OR "toxins" OR "toxicant" OR "toxin" OR "chemicals" OR "chemical" OR "chemical substance" OR "chemical substances" OR "chemical compounds" OR "chemical compound" OR "toxic substances" OR "toxic substance" OR "toxic compounds" OR "toxic compound" OR "toxic chemicals" OR "toxic chemical" OR "hazardous substances" OR "hazardous substance" OR "hazardous compounds" OR "hazardous compound" OR cytotoxicity OR cytotoxi* OR cytotoxicant OR cytotoxicants OR cytotoxic OR cytotoxin OR cytotoxins OR "cell toxic" OR "cell toxicity" OR "cellular toxicity" OR "cell toxicant" OR "cell toxicants" OR "cell toxin" OR "cell toxins" OR "cellular toxin" OR "cellular toxins" OR hepatotoxic OR hepatotoxicity OR hepatotoxi* OR hepatotoxin OR hepatotoxins OR hepatotoxicant OR hepatotoxicants OR "liver toxic" OR "liver toxicity" OR "liver toxicants" OR "liver toxin" OR "liver toxins" OR nephrotoxicity OR nephrotoxi* OR nephrotoxicant OR nephrotoxicants OR nephrotoxin OR nephrotoxins OR nephrotoxic OR renotoxic OR renotoxicity OR renotoxi* OR "kidney toxic" OR "kidney toxicity" OR "kidney toxicants" OR "kidney toxin" OR cardiotoxic OR cardiotoxicity OR cardiotoxicant OR cardiotoxicants OR cardiotoxin OR cardiotoxins OR cardiotoxi* OR "heart toxicity" OR "pulmonary toxic" OR "pulmonary toxicants" OR "pulmonary toxin" OR "pulmonary toxins" OR "pulmonary toxicity" OR "lung toxic" OR "lung toxicity" OR "lung toxicants" OR "lung toxin" OR "lung toxins" OR "cardiopulmonary toxicity" OR "bone toxicity" OR "bone toxic" OR "neurotoxicity" OR neurotoxi* OR neurotoxic OR neurotoxicant OR neurotoxicants OR neurotoxin OR neurotoxins OR "neurological toxicity" OR genotoxicity OR genotoxi* OR genotoxic OR genotoxicant OR genotoxicants OR genotoxin OR genotoxins OR "genetic toxicity" OR "genetic toxin" OR "genetic toxins" OR "mutagenicity" OR mutagen* OR teratogenicity OR teratogen* OR fetotoxicity OR fetotoxi* OR fetotoxic OR fetotoxicants OR "fetal toxicity" OR "fetal toxic" OR clastogenicity OR clastogen* OR carcinogenicity OR carcinogen* OR leukemogenicity OR leukaemogenicity OR leukemogen* OR leukaemogen* OR "blood toxicity" OR "blood toxin" OR "reprotoxicants" OR reprotoxi* OR "reproductive toxicity" OR "reproductive toxic" OR "reproductive toxicant" OR "reproductive toxicants" OR "reproductive toxin" OR "reproductive toxins" OR reprotoxic OR reprotoxicity OR reprotoxin OR reprotoxins OR "developmental toxicity" OR "developmental toxicant" OR "developmental toxicants" OR "developmental toxin" OR "developmental toxins" OR teratogenicity OR teratogen* OR immunotoxicity OR immunotoxi* OR immunotoxic OR immunotoxicant OR immunotoxicants OR immunotoxin OR immunotoxins OR "immune toxic" OR "immune toxicity" OR hematotoxicity OR haematotoxicity OR hematotoxi* OR haematotoxi* OR haematotoxic OR hematotoxic OR haematotoxin OR hematotoxin OR hematotoxins OR haematotoxins OR hematotoxicant OR hematotoxicants OR dermatotoxicity OR dermatotoxi* OR "dermal toxicity" OR dermatotoxic OR dermatotoxicants OR dermatotoxin OR "skin toxicity" OR "skin toxin" OR "skin toxins" OR sensitized OR sensitised OR sensitization OR sensitisation OR sensitizer OR sensitizers OR sensitiser OR sensitisers OR "endocrine toxicity" OR "endocrine toxic" OR "endocrine toxicants" OR "endocrine disruptor" OR "endocrine disruptors" OR "endocrine disrupter" OR "endocrine disrupters" OR "endocrine disruption" OR "respiratory toxicants" OR "respiratory toxin" OR "respiratory toxins" OR "respiratory toxicity" OR "inhalation toxicity" OR "inhalation toxic" OR "oral toxicity" OR "oral toxin" OR "oral toxins" OR "dietary toxicity" OR "dietary toxicants" OR "dietary toxin" OR "dietary toxins" OR "cell effect" OR "cell effects" OR "cellular effect" OR "cellular effects" OR "hepatic effect" OR "hepatic effects" OR "hepatic tumor" OR "hepatic tumors" OR "hepatic tumour" OR "hepatic tumours" OR "hepatic cancer" OR "hepatic cancers" OR "hepatocellular effect" OR "hepatocellular effects" OR "hepatocellular tumor" OR "hepatocellular tumors" OR "hepatocellular tumour" OR "hepatocellular tumours" OR "hepatocellular cancer" OR "hepatocellular cancers" OR "hepatocellular adenoma" OR "hepatocellular adenomas" OR "hepatocellular carcinoma" OR "hepatocellular carcinomas" OR "effects on liver" OR "liver effect" OR "liver effects" OR "liver tumor" OR "liver tumour" OR "liver tumors" OR "liver tumours" OR "liver cancer" OR "liver cancers" OR "nephron effect" OR "renal effect" OR "renal effects" OR "renal cancer" OR "renal cancers" OR "renal tumor" OR "renal tumors" OR "renal tumour" OR "renal tumours" OR "kidney effect" OR "kidney effects" OR "kidney tumor" OR "kidney tumors" OR "kidney tumour" OR "kidney tumours" OR "kidney cancer" OR "kidney cancers" OR "cardiac effect" OR "cardiac effects" OR "heart effect" OR "heart effects" OR "pulmonary effect" OR "pulmonary effects" OR "pulmonary cancer" OR "pulmonary cancers" OR "pulmonary tumor" OR "pulmonary tumors" OR "pulmonary tumour" OR "pulmonary tumours" OR "lung effect" OR "lung effects" OR "lung cancer" OR "lung cancers" OR "lung tumor" OR "lung tumors" OR "lung tumour" OR "lung tumours" OR "respiratory effect" OR "respiratory effects" OR "respiratory cancer" OR "respiratory cancers" OR "respiratory tumors" OR "respiratory tumours" OR "cardiopulmonary effect" OR "cardiopulmonary effects" OR "skeletal effect" OR "skeletal effects" OR "skeletal cancer" OR "skeletal cancers" OR "skeletal tumor" OR "skeletal tumors" OR "skeletal tumour" OR "skeletal tumours" OR "bone effect" OR "bone effects" OR "bone cancer" OR "bone cancers" OR "bone tumor" OR "bone tumors" OR "bone tumour" OR "bone tumours" OR osteosarcoma OR osteosarcomas OR osteoma OR osteomas OR sarcoma OR sarcomas OR "neurological effect" OR "neurological effects" OR "brain effect" OR "brain effects" OR "effects on brain" OR "neurological cancer" OR "neurological cancers" OR "neurological tumor" OR "neurological tumors" OR "neurological tumours" OR "brain cancer" OR "brain cancers" OR "brain tumor" OR "brain tumors" OR "brain tumour" OR "brain tumours" OR "genetic effect" OR "genetic effects" OR "fetal effect" OR "fetal effects" OR "effects on fetus" OR embryotoxicity OR embryotoxic OR embryotoxicant OR embryotoxicants OR embryotoxin OR "embryo toxicity" OR "embryo toxic" OR "embryo effects" OR mutagenic OR clastogenic OR "chromosomal effect" OR "chromosomal effects" OR "chromosome effect" OR "chromosome effects" OR tumorigen* OR tumorigenicity OR tumorigenic OR tumourigenicity OR tumourigenic OR carcinogenic OR leukemogenic OR leukaemogenic OR "blood effect" OR "blood effects" OR "effect on blood" OR "effects on blood" OR "blood cancer" OR "blood cancers" OR "blood tumor" OR "blood tumors" OR "blood tumour" OR leukemia OR leukemias OR "effect on the reproductive system" OR "reproductive effect" OR "reproductive effects" OR "developmental effect" OR "developmental effects" OR "immune effect" OR "immune effects" OR splenotoxicity OR splenotoxic* OR splenotoxic OR splenotoxin OR "spleen toxicity" OR "spleen effects" OR "splenic effect" OR "splenic effects" OR thymotoxicity OR thymotoxic* OR thymotoxic OR "thymus toxicity" OR thyrotoxicity OR thyrotoxic* OR thyrotoxic OR thyrotoxicant OR thyrotoxicants OR thyrotoxin OR thyrotoxins OR "thyroid toxic" OR "thyroid toxicity" OR "thyroid toxicants" OR "thyroid effect" OR "thyroid effects" OR "effect on thyroid" OR "effects on thyroid" OR "dermal effect" OR "dermal effects" OR "dermal cancer" OR "tumor of the dermis" OR "dermal tumor" OR "dermal tumors" OR "dermal tumour" OR "dermal tumours" OR "epidermal effect" OR "epidermal effects" OR "skin effect" OR "skin effects" OR "endocrine effect" OR "endocrine effects" OR "inhaled material" OR "inhaled materials" OR toxicity OR toxicities OR "adverse health effect" OR "adverse health effects" OR "tissue response" OR "tissue responses" OR "cellular response" OR "cellular responses" OR "toxicological effect" OR "toxicological effects" OR "toxicological outcome" OR "toxicological outcomes" OR "induced effect" OR "induced effects" OR non-cancer OR noncancer OR non-carcinogen OR noncarcinogen OR non-carcinogens OR noncarcinogens OR non-carcinogenic OR noncarcinogenic OR non-mutagen OR nonmutagen OR non-mutagens OR nonmutagens OR non-mutagenic OR nonmutagenic OR "water" OR "water quality" OR "drinking water" OR "water pollution" OR "water pollutant" OR "water pollutants" OR "water contamination" OR "water contaminant" OR "water contaminants" OR "water exposure" OR "water exposures" OR "air" OR "air quality" OR "air pollution" OR "air pollutant" OR "air pollutants" OR "air contamination" OR "air contaminant" OR "air contaminants" OR "air exposure" OR "air exposures" OR soil OR "soil quality" OR "soil pollution" OR "soil pollutant" OR "soil pollutants" OR "soil contamination" OR "soil contaminant" OR "soil contaminants" OR "soil exposure" OR "soil exposures" OR "food" OR "food quality" OR "food pollution" OR "food pollutant" OR "food pollutants" OR "food contamination" OR "food contaminant" OR "food contaminants" OR "food exposure" OR "food exposures" OR "environmental exposure" OR "environmental exposures" OR "occupational exposure" OR "occupational exposures" OR "workplace exposure" OR "workplace exposures" OR "work exposure" OR "work exposures" OR "take home exposure" OR "take home exposures" OR "para-occupational exposure" OR "para-occupational exposures" OR "paraoccupational exposure" OR	Toxicity from environmental chemicals

	"paraoccupational exposures" OR exposome OR exposomes OR "chemical exposure" OR "chemical exposures" OR "chemical intake" OR "chemical intakes" OR "oral exposure" OR "oral exposures" OR "oral intake" OR "oral intakes" OR "dietary exposure" OR "dietary exposures" OR "dietary intake" OR "dietary intakes" OR "inhalation intake" OR "inhalation intakes" OR "inhalation exposure" OR "inhalation exposures" OR "ambient exposure" OR "ambient exposures")	
3	TS=(MOA OR MOAs OR "mode of action analysis" OR "mode of action analyses" OR "mode of action evaluation" OR "MOA analysis" OR "adverse outcome pathway" OR "adverse outcome pathways" OR AOP OR AOPs OR "human relevance" OR "mode of action framework" OR "MOA framework" OR "species concordance" OR "molecular initiating event" OR "pathway perturbation" OR "pathway perturbations")	MOA
4	TS=("non-chemical stressors" OR "risk-modifying factors" OR "psychosocial stress" OR "psychosocial stressors" OR "physical stressor" OR "social stressors" OR "allostatic load" OR "social indicators" OR "environmental justice")	Non-chemical stressors
5	TS=("physiologically based pharmacokinetic" OR "physiologically based pharmacokinetics" OR PBPK OR "physiologically based toxicokinetic" OR "physiologically based toxicokinetics" OR PBTK OR "physiologically based kinetic" OR PBK OR PBPK/PD OR PBTK/TD OR "biologically based dose response" OR BBDR OR "physiological pharmacokinetic" OR "physiological pharmacokinetics" OR "flow-limited model" OR "pharmacodynamic modeling" OR "pharmacodynamic modelling" OR "pharmacodynamic model" OR "pharmacodynamic models" OR "physiologically based model" OR "physiologically based models" OR "physiologically based modelling" OR "physiologically based modeling" OR "mathematical model" OR "biologically based risk assessment" OR "biologically based risk assessments" OR BBRA OR "biomathematical modeling" OR "biological model" OR "biological modeling" OR "biologic model" OR "mathematical translation" OR "mechanistic model" OR "mechanistic models" OR "mechanistic modeling" OR "mechanistic modelling" OR "biologically motivated mathematical models" OR "biologically motivated model" OR "biologically motivated models" OR "dose metric" OR "dose metrics" OR "dosimetric model" OR "dosimetric models" OR "dosimetric modeling" OR "dosimetric modelling" OR PB-PK OR PB-TK OR PB-PD)	PBPK and BBDR modelling
6	TS=("pathways of toxicity" OR "network biology" OR "computational toxicology" OR "computational systems biology" OR "systems toxicology" OR "computational method" OR "computational methods" OR "computational approach" OR "computational approaches" OR "NexGen" OR "QIVIVE" OR "IVIVE" OR "reverse dosimetry" OR "exposure reconstruction" OR "exposure reconstructions" OR "toxicity pathway" OR "toxicity pathways" OR "network model" OR "network models" OR "network modeling" OR "network modelling" OR "network analysis" OR "network analyses" OR "network structure" OR "network structures" OR "scale-free network" OR "scale-free networks" OR "network motifs" OR "network centrality" OR "network centralities" OR "pathway approach" OR "pathway approaches" OR "pathway model" OR "pathway models" OR "pathway modeling" OR "bayesian network" OR "bayesian networks" OR "BN model" OR "BN models" OR "network based approach" OR "network approach" OR "dose-dependent transition" OR "dose-dependent transitions" OR "network inference" OR "molecular network" OR "molecular networks" OR "signaling motifs" OR "signalling motifs" OR "response motifs")	Systems biology
7	TS=("chemical specific adjustment factor" OR "chemical specific adjustment factors" OR CSAF OR CSAFs OR "data derived uncertainty factors" OR "data derived safety factor" OR "data derived safety factors" OR "data derived factor" OR "data derived factors" OR "kinetic components" OR "dynamic components" OR ADAF OR HKAF OR "kinetic adjustment factor" OR "kinetic uncertainty factor" OR "toxicokinetic uncertainty factor" OR "composite factor" OR "composite factors")	CSAF
8	TS=("categorical regression" OR CatReg OR "ordinal regression" OR "categorical response" OR "categorical responses" OR "dose-category")	Categorical regression
9	TS=("lifestage specific" OR "life stage specific" OR "child specific" OR lifestage OR lifestages OR lifecourse OR "life course" OR "life courses" OR "children's risk" OR "children's health risk assessment" OR "children's health risk assessments" OR "children's risk assessment" OR "early life sensitivity" OR "age-related differences" OR "age-related variability" OR "age-related changes" OR "critical windows" OR "developmental life stages" OR "children's health risk" OR "children's health risks" OR "child health risk" OR "individual variability" OR "individual variabilities" OR "individual heterogeneity" OR "physiologic differences" OR "age specific differences" OR "age specific changes" OR "altered susceptibility" OR "aging-related changes" OR "age-related changes" OR "age-related differences" OR "age-related variability" OR "susceptible population" OR "susceptible populations" OR "susceptible subpopulation" OR "susceptible subpopulations" OR "susceptible sub-population" OR "susceptible sub-populations" OR "susceptible persons" OR "susceptible individual" OR "sensitive individual" OR "sensitive individuals" OR "sensitive population" OR "sensitive populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub-populations" OR "sensitive people" OR "sensitive persons" OR "interindividual variation" OR "interindividual variations" OR "interindividual variability" OR "interindividual variabilities" OR "inter-individual variability" OR "inter-individual differences" OR "interindividual heterogeneity" OR "inter-individual heterogeneity" OR "interindividual sensitivity" OR "inter-individual susceptibility" OR "susceptible sub-population" OR "susceptible sub-populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub-populations" OR "extreme sensitivity" OR "vulnerable sub-populations" OR "intraspecies variability" OR "intraspecies variation" OR "intraspecies variations" OR "intraspecies differences" OR "intraspecies sensitivity" OR "intra-species variability" OR "intra-species difference" OR "intra-species differences" OR "human variability" OR "human differences" OR "human susceptibility" OR "human sensitivity" OR "sensitive human" OR "sensitive humans" OR "susceptible human" OR "population variability" OR "population heterogeneity" OR "population susceptibility" OR "population sensitivity" OR "population risk" OR "population risks" OR "intrapopulation variability" OR "pharmacokinetic difference" OR "pharmacokinetic differences" OR "pharmacokinetic variability" OR "pharmacokinetic variations" OR "toxicokinetic differences" OR "toxicokinetic variability" OR "kinetic differences" OR "kinetic variability" OR "kinetic changes" OR "dynamic variability" OR "dynamic variation" OR "population specific" OR "subpopulation specific" OR "biological variability" OR "biological differences" OR "biological variations" OR "biological changes" OR "variability distributions" OR "individual susceptibility" OR "individual susceptibilities" OR "individual sensitivity" OR "individual sensitivities" OR "genetic variability" OR "genetic variabilities" OR "genetic variations" OR "genetic changes" OR "heterogeneous population" OR "heterogeneous populations" OR "heterogeneous subpopulations")	Population variability/ sensitivity
10	TS=("dose addition" OR "cumulative effect" OR "cumulative effects" OR "cumulative risk" OR "cumulative risks" OR "cumulative exposures" OR "cumulative assessment" OR "cumulative assessments" OR "aggregate effect" OR "aggregate risk" OR "aggregate exposure" OR "aggregate exposures" OR "aggregate assessments" OR "combined risk" OR "combined risks" OR "combined exposures" OR "multiple chemicals" OR "multiple chemical effects" OR "multiple chemical exposures" OR "multiple chemical exposure" OR "mixture risk" OR "mixtures assessment" OR "mixture effect" OR "mixture effects" OR "mixtures effects" OR "combined prediction model" OR "toxic equivalency factor" OR "toxic equivalence factors" OR "toxicity equivalency factor" OR "toxicity equivalency factors" OR "toxicity equivalence factor" OR "toxicity equivalence factors" OR "toxic equivalent factor" OR "toxic equivalent factors" OR "toxicity equivalent factor" OR "toxicity equivalent factors" OR "toxic equivalency quotient" OR "toxic equivalency quotients" OR "toxic equivalent quotient" OR "relative potency factor" OR "relative potency factors" OR "mixture model" OR "mixture models" OR "mixtures model" OR "chemical mixture" OR "chemical mixtures" OR "relative toxicity" OR "relative toxicities")	Combined/ cumulative risks
11	TS=("extrapolation methodology" OR "extrapolation methodologies" OR "extrapolation method" OR "extrapolation methods" OR "extrapolation factor" OR "extrapolation factors" OR "dose equivalence" OR "dose equivalency" OR "dose extrapolation" OR "dose extrapolations" OR "route extrapolation" OR "route extrapolations" OR "route-to-route extrapolation" OR "route-to-route extrapolations" OR "rtr extrapolation" OR "species extrapolation" OR "species extrapolations" OR "animal to human extrapolation" OR "cross-species extrapolation" OR "cross-species extrapolations" OR "interspecies extrapolation" OR "interspecies extrapolations" OR "inter-species extrapolation" OR "allometric relationship" OR "allometric relationships" OR "allometric scaling" OR "allometrically scaled" OR "allometric adjustment" OR allometry OR "species difference" OR "species differences" OR "species variability" OR "species variation" OR "species variations" OR "dose extrapolation" OR "dose extrapolations" OR "low-dose extrapolation" OR "low-dose extrapolations" OR "linear effect" OR "linear effects" OR "non-threshold effects" OR "nonthreshold effects" OR "no-threshold assumption" OR "low dose linearity" OR "linear dose-response relationships" OR "linear exposure-response relationship" OR "linear exposure-response relationships" OR "no threshold relationship" OR "no threshold relationships" OR "non-threshold dose-response relationship" OR "nonthreshold model" OR "nonthreshold models" OR "non-threshold model" OR "non-threshold models")	Extrapolation (generic)
12	TS=("probability tree" OR "probability trees" OR "probability distribution" OR "probability distributions" OR "uncertainty analysis" OR "uncertainty analyses" OR "uncertainty distribution" OR "uncertainty distributions" OR "judgmental probabilities" OR "subjective probability" OR "subjective probabilities" OR "statistical uncertainty" OR "statistical uncertainties" OR "model uncertainty" OR "model uncertainties" OR "assessment uncertainty" OR "assessment uncertainties" OR "analysis uncertainty" OR "risk distribution" OR "risk distributions" OR "distribution function" OR "distribution functions" OR "uncertainty estimate" OR "uncertainty estimates" OR "uncertainty estimation" OR "uncertainty estimations" OR "uncertainty characterization" OR "characterizing uncertainty")	Uncertainty analysis
13	TS=("problem formulation" OR "problem formulations" OR "fit-for-purpose" OR "hypothesis based weight of evidence" OR HBWoE OR "data-informed" OR "multicriteria decision analysis" OR "MCDA" OR "decision analysis")	General terms / frameworks
14	TS=("dosimetry modeling" OR "dosimetry model" OR "dosimetry models" OR "inhalation reference doses" OR RfDi OR "dosimetric adjustment factor" OR "deposited doses" OR "retained dose" OR "dosimetry adjustments" OR "dosimetric adjustment" OR "dosimetric adjustments" OR "human equivalent concentration" OR "human equivalent concentrations" OR HECs OR "particle deposition model" OR "particle deposition models" OR "category 1 gases")	Dosimetry modelling
15	TS=("unusual workshift" OR "unusual workshifts" OR "unusual work schedules" OR "unusual schedules" OR "altered work schedules" OR "adjusting occupational exposure limits" OR "adjusted exposure limits" OR "Haber's law" OR "Haber's rule" OR "novel work schedules" OR "novel schedule" OR "novel schedules" OR "complex exposure scenarios" OR "long shifts" OR "long work schedules" OR "extended work schedule" OR "adjusted exposure limits" OR "long exposure durations")	Duration adjustment
16	TS=("benchmark dose" OR "benchmark doses" OR BMD OR "benchmark concentration" OR "benchmark concentrations" OR "BD approach" OR "BD model" OR "mantel-bryan procedure" OR "benchmark value" OR "benchmark values")	BMD
17	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	All (except BMD)
18	#1 AND #2 AND #3	Final: MOA
19	#1 AND #2 AND #4	Final: Non-chemical stressors

20	#1 AND #2 AND #5	Final: PBPK and BBDR modelling
21	#1 AND #2 AND #6	Final: Systems biology
22	#1 AND #2 AND #7	Final: CSAF
23	#1 AND #2 AND #8	Final: Categorical regression
24	#1 AND #2 AND #9	Final: Population variability/ sensitivity
25	#1 AND #2 AND #10	Final: Combined/ cumulative risks
26	#1 AND #2 AND #11	Final: Extrapolation (generic)
27	#1 AND #2 AND #12	Final: Uncertainty analysis
28	#1 AND #2 AND #13	Final: General terms / frameworks
29	#1 AND #2 AND #14	Final: Dosimetry modelling
30	#1 AND #2 AND #15	Final: Duration adjustment
31	#1 AND #2 AND #16	Final: BMD
32	#1 AND #2 AND #17	Final: All (except BMD)

Table A.5 – Search queries for Toxline (NLM)

Search #	Query	Category
1	"risk assessment" OR "risk assessments" OR "risk analyses" OR "risk analysis" OR "risk estimate" OR "risk estimates" OR "risk estimation" OR "risk estimations"	Risk assessments
2	"dose response relationship" OR "exposure response relationship" OR "dose response assessment" OR "exposure response assessment" OR "dose response analysis" OR "dose response analyses" OR "exposure response analyses" OR "exposure response analysis" OR "dose response modelling" OR "dose response modeling" OR "dose response model" OR "dose response models" OR "exposure response modelling" OR "exposure response modeling" OR "exposure response model" OR "exposure response models" OR "hazard assessment" OR "dose response relationships" OR "exposure response relationships" OR "concentration response relationship" OR "concentration response relationships" OR "dose response assessments" OR "concentration response assessment" OR "concentration response analysis" OR "concentration response analyses" OR "concentration response modeling" OR "concentration response model" OR "concentration response models" OR "dose response curve" OR "dose response curves" OR "exposure response curve" OR "exposure response curves" OR "concentration response curve" OR "concentration response curves"	
3	"exposure limit" OR "exposure limits" OR "exposure guideline" OR "exposure guidelines" OR "margin of exposure" OR "margins of exposure" OR "limit value" OR "limit values" OR "margin of safety" OR "margins of safety"	
4	"reference dose" OR "reference doses" OR rfd OR rfds OR "reference concentration" OR "reference concentrations" OR "allowable daily intake" OR "allowable daily intakes" OR "acceptable daily intake" OR "acceptable daily intakes" OR "tolerable daily intake" OR "tolerable daily intakes" OR "toxicological reference value" OR "toxicological reference values" OR "maximum allowable concentration" OR "maximum allowable concentrations" OR "maximum acceptable concentration" OR "maximum acceptable concentrations" OR "soil quality guidelines" OR sqg OR sqgs OR "maximum contaminant level" OR "maximum contaminant levels" OR mclg OR "health advisory" OR "health advisories" OR "health based value" OR "health based values" OR "acute exposure guideline" OR "acute exposure guidelines" OR aegl OR aegls OR "threshold limit value" OR "threshold limit values" OR tlv OR tlvs OR "workplace environmental exposure level" OR weels OR "permissible exposure level" OR "permissible exposure levels" OR "permissible exposure limit" OR "permissible exposure limits" OR "recommended exposure limit" OR "recommended exposure limits" OR rels OR ioelv OR ioelvs OR "derived no effect level" OR "derived no effect levels" OR dnel OR dnels OR dmel OR "cancer slope factor" OR "cancer slope factors" OR "biomonitoring equivalent" OR "biomonitoring equivalents" OR "biological exposure index" OR "biological exposure indices" OR "biological equivalent exposure limit" OR "biological exposure limit" OR "biological exposure limits" OR "biological limit value" OR "biological limit values" OR blvs OR "risk specific dose" OR "risk specific doses" OR "air quality guideline" OR "air quality guidelines" OR "air quality standard" OR "air quality standards" OR "air quality limit" OR "air quality limits" OR "water quality guideline" OR "water quality guidelines" OR "water quality standard" OR "water quality standards" OR "water quality limits" OR "food quality standard" OR "food quality standards" OR "soil quality standard" OR "soil quality standards" OR "exposure guideline" OR "exposure guidelines" OR "exposure standard" OR "exposure standards" OR "exposure limit" OR "exposure limits" OR "exposure recommendations" OR "reference level" OR "reference levels"	
5	"health canada" OR "health AND welfare canada" OR "pest management regulatory agency" OR "environmental protection agency" OR "food AND drug administration" OR "food AND drug agency" OR "world health organization" OR "world health organisation" OR "international programme on chemical safety" OR "international program on chemical safety" OR ipcs OR jmpr OR "joint fao who expert committee on food additives" OR jecfa OR "european commission" OR "european chemicals agency" OR echa OR "registration evaluation authorisation AND restriction of chemicals" OR "registration evaluation authorization AND restriction of chemicals" OR "european food safety authority" OR efsa OR scoel OR "american conference of governmental industrial hygienists" OR acgih OR "american industrial hygiene association" OR aiha OR "occupational safety AND health administration" OR "osha" OR "national institute for occupational safety AND health" OR "niosh" OR "agency for toxic substances AND disease registry" OR atsdr OR "food AND agriculture organization" OR "food AND agricultural organization" OR "food AND agriculture organisation" OR fao OR "committee on toxicology" OR "board on environmental studies AND toxicology" OR "science advisory board" OR "clean air scientific advisory committee" OR "national academy of science" OR "national academy of sciences" OR "national academies of science" OR "national academies of sciences" OR "institute of medicine" OR "institutes of medicine"	
6	#1 OR #2 OR #3 OR #4 OR #5	
7	"dermal effect" OR "dermal effects" OR "dermal cancer" OR "tumor of the dermis" OR "dermal tumor" OR "dermal tumors" OR "dermal tumour" OR "dermal tumours" OR "epidermal effect" OR "epidermal effects" OR "skin effect" OR "skin effects" OR "endocrine effect" OR "endocrine effects" OR "inhaled material" OR "inhaled materials" OR "adverse health effect" OR "adverse health effects" OR "tissue response" OR "tissue responses" OR "cellular response" OR "cellular responses" OR "toxicological effect" OR "toxicological effects" OR "toxicological outcome" OR "toxicological outcomes" OR "induced effect" OR "induced effects" OR non cancer OR noncancer OR non carcinogen OR noncarcinogen OR non (carcinogens OR D002273000 [rn]) OR noncarcinogens OR non carcinogenic OR noncarcinogenic OR non mutagen OR nonmutagen OR non mutagens OR nonmutagens OR non mutagenic OR nonmutagenic OR "endocrine toxicity" OR "endocrine toxic" OR "endocrine toxicants" OR "endocrine disruptor" OR "endocrine disruptors" OR "endocrine disrupter" OR "endocrine disrupters" OR "endocrine disruption" OR "cell effect" OR "cell effects" OR "cellular effect" OR "cellular effects" OR "hepatic effect" OR "hepatic effects" OR "hepatic tumor" OR "hepatic tumors" OR "hepatic tumour" OR "hepatic tumours" OR "hepatic cancer" OR "hepatic cancers" OR "hepatocellular effect" OR "hepatocellular effects" OR "hepatocellular tumor" OR "hepatocellular tumors" OR "hepatocellular tumour" OR "hepatocellular tumours" OR "hepatocellular cancer" OR "hepatocellular cancers" OR "hepatocellular adenoma" OR "hepatocellular adenomas" OR "hepatocellular carcinoma" OR "hepatocellular carcinomas" OR "effects on liver" OR "liver effect" OR "liver effects" OR "liver tumor" OR "liver tumour" OR "liver tumors" OR "liver tumours" OR "liver cancer" OR "liver cancers"	Toxicity from environmental chemicals
8	toxicity OR "respiratory toxicants" OR "respiratory toxin" OR "respiratory toxins" OR "respiratory toxicity" OR "inhalation toxicity" OR "inhalation toxic" OR "oral toxicity" OR "oral toxin" OR "oral toxins" OR "dietary toxicity" OR "dietary toxicants" OR "dietary toxin" OR "dietary toxins" OR cardiotoxic OR cardiotoxicity OR cardiotoxicant OR cardiotoxicants OR cardiotoxin OR cardiotoxins OR cardiotoxi* OR "heart toxicity" OR "pulmonary toxic" OR "pulmonary toxicants" OR "pulmonary toxin" OR "pulmonary toxins" OR "pulmonary toxicity" OR "lung toxic" OR "lung toxicity" OR "lung toxicants" OR "lung toxin" OR "lung toxins" OR "cardiopulmonary toxicity" OR nephrotoxicity OR nephrotoxi* OR nephrotoxicant OR nephrotoxicants OR nephrotoxin OR nephrotoxins OR nephrotoxic OR renotoxic OR renotoxicity OR renotoxi* OR "kidney toxic" OR "kidney toxicity" OR "kidney toxicants" OR "kidney toxin" OR hepatotoxic OR hepatotoxicity OR hepatotoxi* OR hepatotoxin OR hepatotoxins OR hepatotoxicant OR hepatotoxicants OR "liver toxic" OR "liver toxicity" OR "liver toxicants" OR "liver toxin" OR "liver toxins"	
9	"bone toxicity" OR "bone toxic" OR "neurotoxicity" OR neurotoxi* OR neurotoxic OR neurotoxicant OR neurotoxicants OR neurotoxin OR neurotoxins OR "neurological toxicity" OR genotoxicity OR genotoxi* OR genotoxic OR genotoxicant OR genotoxicants OR genotoxin OR genotoxins OR "genetic toxicity" OR "genetic toxin" OR "genetic toxins" OR "mutagenicity" OR mutagen* OR immunotoxicity OR immunotoxi* OR immunotoxic OR immunotoxicant OR immunotoxicants OR immunotoxin OR immunotoxins OR "immune toxic" OR "immune toxicity" OR hematotoxicity OR haematotoxicity OR hematotoxi* OR haematotoxi* OR haematotoxic OR hematotoxic OR haematotoxin OR hematotoxin OR hematotoxins OR haematotoxins OR hematotoxicant OR hematotoxicants OR dermatotoxicity OR dermatotoxi* OR "dermal toxicity" OR dermatotoxic OR dermatotoxicants OR dermatotoxin OR "skin toxicity" OR "skin toxin" OR "skin toxins" OR sensitized OR sensitised OR sensitization OR sensitisation OR sensitizer OR sensitizers OR sensitiser OR sensitisers	
10	teratogenicity OR teratogen* OR fetotoxicity OR fetotoxi* OR fetotoxic OR fetotoxicants OR "fetal toxicity" OR "fetal toxic" OR clastogenicity OR clastogen* OR carcinogenicity OR carcinogen* OR leukemogenicity OR leukaemogenicity OR leukemogen* OR leukaemogen* OR "blood toxicity" OR "blood toxin" OR "nephron effect" OR "renal effect" OR "renal effects" OR "renal cancer" OR "renal cancers" OR "renal tumor" OR "renal tumors" OR "renal tumour" OR "renal tumours" OR "kidney effect" OR "kidney effects" OR "kidney tumor" OR "kidney tumors" OR "kidney tumour" OR "kidney tumours" OR "kidney cancer" OR "kidney cancers" OR "cardiac effect" OR "cardiac effects" OR "heart effect" OR "heart effects" OR "pulmonary effect" OR "pulmonary effects" OR "pulmonary cancer" OR "pulmonary cancers" OR "pulmonary tumor" OR "pulmonary tumors" OR "pulmonary tumour" OR "pulmonary tumours" OR "lung effect" OR "lung effects" OR "lung cancer" OR "lung cancers" OR "lung tumor" OR "lung tumors" OR "lung tumour" OR "lung tumours" OR "respiratory effect" OR "respiratory effects" OR "respiratory cancer" OR "respiratory cancers" OR "respiratory tumor" OR "respiratory tumours" OR "cardiopulmonary effect" OR "cardiopulmonary effects" OR "skeletal effect" OR "skeletal effects" OR "skeletal cancer"	
11	"neurological effect" OR "neurological effects" OR "brain effect" OR "brain effects" OR "effects on brain" OR "neurological cancer" OR "neurological cancers" OR "neurological tumor" OR "neurological tumors" OR "neurological tumours" OR "brain cancer" OR "brain cancers" OR "brain tumor" OR "brain tumors" OR "brain tumour" OR "brain tumours" OR "genetic effect" OR "genetic effects" OR "fetal effect" OR "fetal effects" OR "effects on fetus" OR embryotoxicity OR embryotoxic OR embryotoxicant OR embryotoxicants OR embryotoxin OR "embryo toxicity" OR "embryo toxic" OR "embryo effects" OR mutagenic OR clastogenic OR "chromosomal effect" OR "chromosomal effects" OR "chromosome effect" OR "chromosome effects" OR tumorigen* OR tumorigenicity OR tumorigenic OR tumourigenicity OR tumourigenic OR carcinogenic OR leukemogenic OR leukaemogenic OR "blood effect" OR "blood effects" OR "effect on blood" OR "effects on blood" OR "blood cancer" OR "blood cancers" OR "blood tumor" OR "blood tumors" OR "blood tumour" OR leukemia OR leukemias OR "effect on the reproductive system" OR "reproductive effect" OR "reproductive effects" OR "developmental effect" OR "developmental effects" OR "immune effect" OR "immune effects" OR splenotoxicity OR splenotoxic* OR splenotoxic OR splenotoxin OR "spleen toxicity" OR "spleen effects" OR "splenic effect" OR "splenic effects" OR thymotoxicity OR thymotoxic* OR thymotoxic OR "thymus toxicity" OR thyrotoxicity OR thyrotoxic* OR thyrotoxic OR thyrotoxicant OR thyrotoxicants OR thyrotoxin OR thyrotoxins OR "thyroid toxic" OR "thyroid toxicity" OR "thyroid toxicants" OR "thyroid effect" OR "thyroid effects" OR "effect on thyroid" OR "effects on thyroid" OR "reprotoxicants" OR reprotoxi* OR "reproductive toxicity" OR "reproductive toxic" OR "reproductive toxicant" OR "reproductive toxicants" OR "reproductive toxin" OR "reproductive toxins" OR reprotoxic OR reprotoxicity OR reprotoxin OR reprotoxins OR "developmental toxicity" OR "developmental toxicant" OR "developmental toxicants" OR "developmental toxin" OR "developmental toxins"	
12	"toxicants" OR "toxins" OR "toxicant" OR "toxin" OR "toxic substances" OR "toxic substance" OR "toxic compounds" OR "toxic compound" OR "toxic chemicals" OR "toxic chemical" OR "hazardous substances" OR "hazardous substance" OR "hazardous compounds" OR "hazardous compound" OR "chemical substance" OR "chemical substances" OR "chemical compounds" OR "chemical compound" OR "chemical exposure" OR "chemical exposures" OR "chemical intake" OR "chemical intakes" OR "oral exposure" OR "oral exposures" OR "oral intake" OR "oral intakes" OR "dietary exposure" OR "dietary exposures" OR "dietary intake" OR "dietary intakes" OR "inhalation intake" OR "inhalation intakes" OR "inhalation exposure" OR "inhalation exposures" OR "ambient exposure" OR "ambient exposures" OR cytotoxicity OR cytotoxi* OR cytotoxicant OR cytotoxicants OR cytotoxic	

	OR cytotoxin OR (cytotoxins OR D003603000 [rn]) OR "cell toxic" OR "cell toxicity" OR "cellular toxicity" OR "cell toxicant" OR "cell toxicants" OR "cell toxin" OR "cell toxins" OR "cellular toxin" OR "cellular toxins" OR "skeletal cancers" OR "skeletal tumor" OR "skeletal tumors" OR "skeletal tumour" OR "skeletal tumours" OR "bone effect" OR "bone effects" OR "bone cancer" OR "bone cancers" OR "bone tumor" OR "bone tumors" OR "bone tumour" OR "bone tumours" OR osteosarcoma OR osteosarcomas OR osteoma OR osteomas OR sarcoma OR sarcomas	
13	"water" OR "water quality" OR "drinking water" OR "water pollution" OR "water pollutant" OR "water pollutants" OR "water contamination" OR "water contaminant" OR "water contaminants" OR "water exposure" OR "water exposures" OR "air" OR "air quality" OR "air pollution" OR "air pollutant" OR "air pollutants" OR "air contamination" OR "air contaminant" OR "air contaminants" OR "air exposure" OR "air exposures"	
14	soil OR "soil quality" OR "soil pollution" OR "soil pollutant" OR "soil pollutants" OR "soil contamination" OR "soil contaminant" OR "soil contaminants" OR "soil exposure" OR "soil exposures" OR "food" OR "food quality" OR "food pollution" OR "food pollutant" OR "food pollutants" OR "food contamination" OR "food contaminant" OR "food contaminants" OR "food exposure" OR "food exposures" OR "environmental exposure" OR "environmental exposures" OR "occupational exposure" OR "occupational exposures" OR "workplace exposure" OR "workplace exposures" OR "work exposure" OR "work exposures" OR "take home exposure" OR "take home exposures" OR "para occupational exposure" OR "para occupational exposures" OR "paraoccupational exposure" OR "paraoccupational exposures" OR exposome OR exposomes	
15	moa OR moas OR "mode of action analysis" OR "mode of action analyses" OR "mode of action evaluation" OR "moa analysis" OR "adverse outcome pathway" OR "adverse outcome pathways" OR aop OR aops OR "human relevance" OR "mode of action framework" OR "moa framework" OR "species concordance" OR "molecular initiating event" OR "pathway perturbation" OR "pathway perturbations"	MOA
16	"non chemical stressors" OR "risk modifying factors" OR "psychosocial stress" OR "psychosocial stressors" OR "physical stressor" OR "social stressors" OR "allostatic load" OR "social indicators" OR "environmental justice"	Non-chemical stressors
17	"physiologically based pharmacokinetic" OR "physiologically based pharmacokinetics" OR PBPK OR "physiologically based toxicokinetic" OR "physiologically based toxicokinetics" OR PBTK OR "physiologically based kinetic" OR PBK OR PBPK/PD OR PBTK/TD OR "biologically based dose response" OR BBDR OR "physiological pharmacokinetic" OR "physiological pharmacokinetics" OR "flow-limited model" OR "pharmacodynamic modeling" OR "pharmacodynamic modelling" OR "pharmacodynamic model" OR "pharmacodynamic models" OR "physiologically based model" OR "physiologically based models" OR "physiologically based modelling" OR "physiologically based modeling" OR "mathematical model" OR "biologically based risk assessment" OR "biologically based risk assessments" OR BBRA OR "biomathematical modeling" OR "biological model" OR "biological modeling" OR "biologic model" OR "mathematical translation" OR "mechanistic model" OR "mechanistic models" OR "mechanistic modeling" OR "mechanistic modelling" OR "biologically motivated mathematical models" OR "biologically motivated model" OR "biologically motivated models" OR "dose metric" OR "dose metrics" OR "dosimetric model" OR "dosimetric models" OR "dosimetric modeling" OR "dosimetric modelling" OR PB-PK OR PB-TK OR PB-PD	PBPK and BBDR modelling
18	"pathways of toxicity" OR "network biology" OR "computational toxicology" OR "computational systems biology" OR "systems toxicology" OR "computational method" OR "computational methods" OR "computational approach" OR "computational approaches" OR "nexgen" OR "qivive" OR "ivive" OR "reverse dosimetry" OR "exposure reconstruction" OR "exposure reconstructions" OR "toxicity pathway" OR "toxicity pathways" OR "network model" OR "network models" OR "network modeling" OR "network modelling" OR "network analysis" OR "network analyses" OR "network structure" OR "network structures" OR "scale free network" OR "scale free networks" OR "network motifs" OR "network centrality" OR "network centralities" OR "pathway approach" OR "pathway approaches" OR "pathway model" OR "pathway models" OR "pathway modeling" OR "bayesian network" OR "bayesian networks" OR "bn model" OR "bn models" OR "network based approach" OR "network approach" OR "dose dependent transition" OR "dose dependent transitions" OR "network inference" OR "molecular network" OR "molecular networks" OR "signaling motifs" OR "signalling motifs" OR "response motifs"	Systems biology
19	"chemical specific adjustment factor" OR "chemical specific adjustment factors" OR csaf OR csafs OR "data derived uncertainty factors" OR "data derived safety factor" OR "data derived safety factors" OR "data derived factor" OR "data derived factors" OR "kinetic components" OR "dynamic components" OR adaf OR hkaf OR "kinetic adjustment factor" OR "kinetic uncertainty factor" OR "toxicokinetic uncertainty factor" OR "composite factor" OR "composite factors"	CSAF
20	"categorical regression" OR catreg OR "ordinal regression" OR "categorical response" OR "categorical responses" OR "dose category"	Categorical regression
21	"lifestage specific" OR "life stage specific" OR "child specific" OR lifestage OR lifestages OR lifecourse OR "life course" OR "life courses" OR "children's risk" OR "children's health risk assessment" OR "children's health risk assessments" OR "children's risk assessment" OR "early life sensitivity" OR "age related differences" OR "age related variability" OR "age related changes" OR "critical windows" OR "developmental life stages" OR "children's health risk" OR "children's health risks" OR "child health risk" OR "individual variability" OR "individual variabilities" OR "individual heterogeneity" OR "physiologic differences" OR "age specific differences" OR "age specific changes" OR "altered susceptibility" OR "aging related changes" OR "age related changes" OR "age related differences" OR "age related variability"	Population variability/ sensitivity
22	"susceptible population" OR "susceptible populations" OR "susceptible subpopulation" OR "susceptible subpopulations" OR "susceptible sub population" OR "susceptible sub populations" OR "susceptible persons" OR "susceptible individual" OR "sensitive individual" OR "sensitive individuals" OR "sensitive population" OR "sensitive populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub populations" OR "sensitive people" OR "sensitive persons"	
23	"interindividual variation" OR "interindividual variations" OR "interindividual variability" OR "interindividual variabilities" OR "inter individual variability" OR "inter individual differences" OR "interindividual heterogeneity" OR "inter individual heterogeneity" OR "interindividual sensitivity" OR "inter individual susceptibility" OR "susceptible sub population" OR "susceptible sub populations" OR "sensitive subpopulation" OR "sensitive subpopulations" OR "sensitive sub populations" OR "extreme sensitivity" OR "vulnerable sub populations" OR "intraspecies variability" OR "intraspecies variation" OR "intraspecies variations" OR "intraspecies differences" OR "intraspecies sensitivity" OR "intra species variability" OR "intra species difference" OR "intra species differences" OR "human variability" OR "human differences" OR "human susceptibility" OR "human sensitivity" OR "sensitive human" OR "sensitive humans" OR "susceptible human" OR "population variability" OR "population heterogeneity" OR "population susceptibility" OR "population sensitivity" OR "population risk" OR "population risks" OR "intrapopulation variability" OR "pharmacokinetic difference" OR "pharmacokinetic differences" OR "pharmacokinetic variability" OR "pharmacokinetic variations" OR "toxicokinetic differences" OR "toxicokinetic variability" OR "kinetic differences" OR "kinetic variability" OR "kinetic changes" OR "dynamic variability" OR "dynamic variation" OR "population specific" OR "subpopulation specific" OR "biological variability" OR "biological differences" OR "biological variations" OR "biological changes" OR "variability distributions" OR "individual susceptibility" OR "individual susceptibilities" OR "individual sensitivity" OR "individual sensitivities" OR "genetic variability" OR "genetic variabilities" OR "genetic variations" OR "genetic changes" OR "heterogeneous population" OR "heterogeneous populations" OR "heterogeneous subpopulations"	
24	#21 OR #22 OR #23	
25	"dose addition" OR "cumulative effect" OR "cumulative effects" OR "cumulative risk" OR "cumulative risks" OR "cumulative exposures" OR "cumulative assessment" OR "cumulative assessments" OR "aggregate effect" OR "aggregate risk" OR "aggregate exposure" OR "aggregate exposures" OR "aggregate assessments" OR "combined risk" OR "combined risks" OR "combined exposures" OR "multiple chemicals" OR "multiple chemical effects" OR "multiple chemical exposures" OR "multiple chemical exposure" OR "mixture risk" OR "mixtures assessment" OR "mixture effect" OR "mixture effects" OR "mixtures effects" OR "combined prediction model" OR "toxic equivalency factor" OR "toxic equivalence factors" OR "toxicity equivalency factor" OR "toxicity equivalency factors" OR "toxicity equivalence factor" OR "toxicity equivalence factors" OR "toxic equivalent factor" OR "toxic equivalent factors" OR "toxicity equivalent factor" OR "toxicity equivalent factors" OR "toxic equivalency quotient" OR "toxic equivalency quotients" OR "toxic equivalent quotient" OR "relative potency factor" OR "relative potency factors" OR "mixture model" OR "mixture models" OR "mixtures model" OR "chemical mixture" OR "chemical mixtures" OR "relative toxicity" OR "relative toxicities"	Combined/ cumulative risks
26	"extrapolation methodology" OR "extrapolation methodologies" OR "extrapolation method" OR "extrapolation methods" OR "extrapolation factor" OR "extrapolation factors" OR "dose equivalence" OR "dose equivalency" OR "dose extrapolation" OR "dose extrapolations" OR "route extrapolation" OR "route extrapolations" OR "route to route extrapolation" OR "route to route extrapolations" OR "rtr extrapolation" OR "species extrapolation" OR "species extrapolations" OR "animal to human extrapolation" OR "cross species extrapolation" OR "cross species extrapolations" OR "interspecies extrapolation" OR "interspecies extrapolations" OR "inter species extrapolation" OR "allometric relationship" OR "allometric relationships" OR "allometric scaling" OR "allometrically scaled" OR "allometric adjustment" OR allometry OR "species difference" OR "species differences" OR "species variability" OR "species variation" OR "species variations" OR "dose extrapolation" OR "dose extrapolations" OR "low dose extrapolation" OR "low dose extrapolations" OR "linear effect" OR "linear effects" OR "non threshold effects" OR "nonthreshold effects" OR "no threshold assumption" OR "low dose linearity" OR "linear dose response relationships" OR "linear exposure response relationship" OR "linear exposure response relationships" OR "no threshold relationship" OR "no threshold relationships" OR "non threshold dose response relationship" OR "nonthreshold model" OR "nonthreshold models" OR "non threshold model" OR "non threshold models"	Extrapolation (generic)
27	"problem formulation" OR "problem formulations" OR "fit for purpose" OR "hypothesis based weight of evidence" OR hbwoe OR "data informed" OR "multicriteria decision analysis" OR "mcda" OR "decision analysis"	General terms / frameworks
28	"probability tree" OR "probability trees" OR "probability distribution" OR "probability distributions" OR "uncertainty analysis" OR "uncertainty analyses" OR "uncertainty distribution" OR "uncertainty distributions" OR "judgmental probabilities" OR "subjective probability" OR "subjective probabilities" OR "statistical uncertainty" OR "statistical uncertainties" OR "model uncertainty" OR "model uncertainties" OR "assessment uncertainty" OR "assessment uncertainties" OR "analysis uncertainty" OR "risk distribution" OR "risk distributions" OR "distribution function" OR "distribution functions" OR "uncertainty estimate" OR "uncertainty estimates" OR "uncertainty estimation" OR "uncertainty estimations" OR "uncertainty characterization" OR "characterizing uncertainty"	Uncertainty analysis
29	"dosimetry modeling" OR "dosimetry model" OR "dosimetry models" OR "inhalation reference doses" OR rfdi OR "dosimetric adjustment factor" OR "deposited doses" OR "retained dose" OR "dosimetry adjustments" OR "dosimetric adjustment" OR "dosimetric adjustments" OR "human equivalent concentration" OR "human equivalent concentrations" OR hecs OR "particle deposition model" OR "particle deposition models" OR "category 1 gases"	Dosimetry modelling
30	"unusual workshift" OR "unusual workshifts" OR "unusual work schedules" OR "unusual schedules" OR "altered work schedules" OR "adjusting occupational exposure limits" OR "adjusted exposure limits" OR "haber's law" OR "haber's rule" OR "novel work schedules" OR "novel schedule" OR "novel schedules" OR "complex exposure scenarios" OR "long shifts" OR "long work schedules" OR "extended work schedule" OR "adjusted exposure limits" OR "long exposure durations"	Duration adjustment

31	"benchmark dose" OR "benchmark doses" OR "bmd" OR "benchmark concentration" OR "benchmark concentrations" OR "bd approach" OR "bd model" OR "mantel bryan procedure" OR "benchmark value" OR "benchmark values"	BMD
32	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	All (except BMD)
33	#6 AND #15 AND #7	Final: MOA
34	#6 AND #15 AND #8	
35	#6 AND #15 AND #9	
36	#6 AND #15 AND #10	
37	#6 AND #15 AND #11	
38	#6 AND #15 AND #12	
39	#6 AND #15 AND #13	
40	#6 AND #15 AND #14	
41	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	
42	#6 AND #16 AND #7	Final: Non-chemical stressors
43	#6 AND #16 AND #8	
44	#6 AND #16 AND #9	
45	#6 AND #16 AND #10	
46	#6 AND #16 AND #11	
47	#6 AND #16 AND #12	
48	#6 AND #16 AND #13	
49	#6 AND #16 AND #14	
50	Error in query (individual query lines cannot be cleared in Toxline NLM platform); error was corrected on query #52	
52	#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	
51	#6 AND #17 AND #7	Final: PBPK and BBDR modelling
53	#6 AND #17 AND #8	
54	#6 AND #17 AND #9	
55	#6 AND #17 AND #10	
56	#6 AND #17 AND #11	
57	#6 AND #17 AND #12	
58	#6 AND #17 AND #13	
59	#6 AND #17 AND #14	
60	#51 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	
61	#6 AND #18 AND #7	Final: Systems biology
62	#6 AND #18 AND #8	
63	#6 AND #18 AND #9	
64	#6 AND #18 AND #10	
65	#6 AND #18 AND #11	
66	#6 AND #18 AND #12	
67	#6 AND #18 AND #13	
68	#6 AND #18 AND #14	
69	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	
70	#6 AND #19 AND #7	Final: CSAF
71	#6 AND #19 AND #8	
72	#6 AND #19 AND #9	
73	#6 AND #19 AND #10	
74	#6 AND #19 AND #11	

75	#6 AND #19 AND #12	
76	#6 AND #19 AND #13	
77	#6 AND #19 AND #14	
78	#70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	
79	#6 AND #20 AND #7	Final: Categorical regression
80	#6 AND #20 AND #8	
81	#6 AND #20 AND #9	
82	#6 AND #20 AND #10	
83	#6 AND #20 AND #11	
84	#6 AND #20 AND #12	
85	#6 AND #20 AND #13	
86	#6 AND #20 AND #14	
87	#79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86	
88	#6 AND #24 AND #7	Final: Population variability/ sensitivity
89	#6 AND #24 AND #8	
90	#6 AND #24 AND #9	
91	#6 AND #24 AND #10	
92	#6 AND #24 AND #11	
93	#6 AND #24 AND #12	
94	#6 AND #24 AND #13	
95	#6 AND #24 AND #14	
96	#88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95	
97	#6 AND #25 AND #7	Final: Combined/ cumulative risks
98	#6 AND #25 AND #8	
99	#6 AND #25 AND #9	
100	#6 AND #25 AND #10	
101	#6 AND #25 AND #11	
102	#6 AND #25 AND #12	
103	#6 AND #25 AND #13	
104	#6 AND #25 AND #14	
105	#97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104	
106	#6 AND #26 AND #7	Final: Extrapolation (generic)
107	#6 AND #26 AND #8	
108	#6 AND #26 AND #9	
109	#6 AND #26 AND #10	
110	#6 AND #26 AND #11	
111	#6 AND #26 AND #12	
112	#6 AND #26 AND #13	
113	#6 AND #26 AND #14	
114	#106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113	
115	#6 AND #27 AND #7	Final: General terms/ frameworks
116	#6 AND #27 AND #8	
117	#6 AND #27 AND #9	
118	#6 AND #27 AND #10	

119	#6 AND #27 AND #11	
120	#6 AND #27 AND #12	
121	#6 AND #27 AND #13	
122	#6 AND #27 AND #14	
123	#115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122	
124	#6 AND #28 AND #7	Final: Uncertainty analysis
125	#6 AND #28 AND #8	
126	#6 AND #28 AND #9	
127	#6 AND #28 AND #10	
128	#6 AND #28 AND #11	
129	#6 AND #28 AND #12	
130	#6 AND #28 AND #13	
131	#6 AND #28 AND #14	
132	#124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131	
133	#6 AND #29 AND #7	Final: Dosimetry modelling
134	#6 AND #29 AND #8	
135	#6 AND #29 AND #9	
136	#6 AND #29 AND #10	
137	#6 AND #29 AND #11	
138	#6 AND #29 AND #12	
139	#6 AND #29 AND #13	
140	#6 AND #29 AND #14	
141	#133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140	
142	#6 AND #30 AND #7	Final: Duration adjustment
143	History could not be accessed after 0 result in NLM platform; random search was run to be able to view history	
144	#6 AND #30 AND #8	
145	#6 AND #30 AND #9	
146	#6 AND #30 AND #10	
147	#6 AND #30 AND #11	
148	History could not be accessed after 0 result in NLM platform; random search was run to be able to view history	
149	#6 AND #30 AND #12	
150	#6 AND #30 AND #13	
151	#6 AND #30 AND #14	
152	#144 OR #145 OR #146 OR #149 OR #150 OR #151	
153	#6 AND #31 AND #7	**Final: BMD**
154	#6 AND #31 AND #8	
155	#6 AND #31 AND #9	
156	#6 AND #31 AND #10	
157	#6 AND #31 AND #11	
158	#6 AND #31 AND #12	
159	#6 AND #31 AND #13	
160	#6 AND #31 AND #14	
161	#153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160	
162	#6 AND #32 AND #7	

163	#6 AND #32 AND #8	**Final: All (except BMD)**
164	#6 AND #32 AND #9	
165	#6 AND #32 AND #10	
166	#6 AND #32 AND #11	
167	#6 AND #32 AND #12	
168	#6 AND #32 AND #13	
169	#6 AND #32 AND #14	
170	#162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169	

Chapter 3 – The application of physiologically based kinetic and dynamic models in regulatory dose–response assessments

ABSTRACT

Physiological kinetic and dynamic models have been used since the late 1980s to refine dose–response analyses in chemical risk assessments published by governmental organizations. To better understand the evolution of dose–response applications of physiological models, and to identify whether model use varied among organizations, an analysis of regulatory assessment reports was performed. After the first uses of physiological models in regulatory assessments in 1986 and 1987, dose–response application was sporadic for the next decade, but at least one such application was identified every year beginning in 1999. Physiological model use peaked in 2010 and 2011 at 10 dose–response applications in each year, with an average of 8.5 regulatory reports per year using these (predominantly physiologically based pharmacokinetic) models in the 2010s. Differences among organizations were noted in the dates when models were first used, frequency of application, and methods by which model results were incorporated into dose–response assessments. Analyses of certain chemicals also identified that some organizations opted not to use available physiological models, whereas others incorporated these same models into their dose–response assessments. Physiological models were most commonly used by organizations evaluating risks in the general environment, and were only applied much later in assessments of pesticides and environmental contaminants in food. US regulatory organizations also used the models most frequently and earlier than those in other countries. Although the models were most frequently used *de novo* to refine dose–response assessments, some programs—particularly those evaluating occupational exposures to chemicals—instead relied on published model results. Although results of the analysis identify differences among regulatory organizations in the adoption of physiologically-based models for dose–response analyses, their acceptance has increased over time, and appears to be similar to the evolution of dose–response applications of the models in the general scientific literature.

1.0 Introduction

Physiological kinetic and dynamic models used for dose–response assessments of chemicals in the general and occupational environment have been published in scientific literature databases since 1986, as outlined in Chapter 2. These physiological models include physiologically based pharmacokinetic or toxicokinetic (PBPK/TK) models, physiologically based pharmacodynamic or toxicodynamic (PBPD/TD) models, dosimetry models, and biologically-based dose–response (BBDR) models, as defined in Table 1 of Chapter 2. Development and application of the models falls along a continuum, with dose–response analysis being one of several application approaches along the continuum. When used in dose–response analyses, physiological models can reduce the need for default assumptions and approaches, as they allow for biologically realistic extrapolations between species, human subpopulations, exposure routes, dose levels, and dose durations (1-3).

The previous chapter explored the publication of dose–response analyses using physiological kinetic and dynamic models in scientific literature databases. Bibliometric reviews of physiological models demonstrated a steady increase over time in the number of publications related to physiological models overall; however, publications using these models for dose–response purposes formed only a small subset of all physiological model publications, with only a comparatively modest increase in their use over time. Although many publications identified in the literature were from authors at regulatory organizations, few of those publications appeared to represent summaries of dose–response analyses that formed the basis of agency exposure guidelines or margin of exposure assessments. Reports representing official policies and risk assessments by regulatory organizations were only very rarely indexed in the literature databases; therefore, to obtain a complete picture of the use of physiological kinetic and dynamic models in dose–response assessments, documents prepared by regulatory agencies needed to be evaluated.

The objective of this chapter is to quantify the evolution of the use of physiological models in dose–response analyses presented in publications and reports from regulatory organizations. This objective was achieved by systematically evaluating documents published by a variety of regulatory risk assessment programs addressing exposures to chemicals in the domains of the general environment, including pesticides and environmental contaminants in food, and the occupational environment. Results from these documents are compared with

publications in the literature database outlined in Chapter 2, to identify similarities and differences in the use of physiological models in dose–response assessments in regulatory reports versus those in the general scientific literature.

2.0 Methods

A list of all organizations and their associated risk assessments that were initially gathered in the analysis are listed in Table 1. Organizations that were considered in this research were primarily regulatory agencies that perform dose–response assessments for derivation of exposure guidelines or margin of exposure assessments for human health. Agency selection was limited to those that are at the national level in Canada and US, the regional level in Europe, and the international level. The American Conference of Governmental Industrial Hygienists (ACGIH) was also considered even though it is not a governmental organization, as Threshold Limit Values® (TLVs®) are sometimes incorporated into legislation, including the Canadian Occupational Health and Safety Regulations (4); although less likely to influence legislative guidelines, the American Industrial Hygiene Association (AIHA)/Occupational Alliance for Risk Sciences (OARS) Workplace Environmental Exposure Levels (WEELs) were also included because they are a similar committee-based organization. Regulatory programs were not included if they derived exposure guidelines for special environments or occupations (e.g., space, submarine, and military environments). Within each included agency, multiple relevant risk assessment programs were identified if more than one met the inclusion criteria. Documents were primarily downloaded from organizations' websites, although some attempts were made to obtain documents that were not available online. Documents were limited to those published during 1983 to 2018, and included draft documents if the final versions could not be obtained or had not been published by 2018. If an assessment using a physiological model was identified, and had been preceded by earlier assessments of the same chemical, the earlier assessments were also examined to identify the earliest point in time at which the physiological model was given regulatory consideration. Further searches were also performed using keywords related to PBPK, inhalation dosimetry, and PBPD/BBDR models in relevant databases, including Government of Canada Publications (5), the Canada.ca search function, the US Federal Register (6), the US National Technical Reports Library (7), United States Environmental Protection Agency (US EPA) National Environmental Publications Information System (8), European Food Safety

Authority (EFSA) Journal (9), and World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) INCHEM (10). Documents were excluded if they were the summary of a workshop or meeting, were peer or public review comments or responses with no new dose–response analyses performed by the agency, or a duplication or adoption of a dose–response analysis performed in another assessment already included in this study. As an organization's publication of a contractor report demonstrated their willingness to consider the use of physiological models, published contractor reports were also included in the analysis. Derived No-Effect Levels (DNELs) derived by industry for submissions under Registration, Evaluation, Authorisation and Restriction of Chemical (REACH) regulations were not evaluated as they do not reflect regulatory application; however, DNELs directly derived or supported by the European Chemicals Agency (ECHA) were included for evaluation.

Documents were considered to have used a dose–response application of an approach if models quantitatively, semi-quantitatively, or qualitatively affected the selection of points of departure (PODs) or uncertainty factors (UFs). An assessment was included if physiological model results were used in any dose–response assessment in the document, even if it was not applied for the final selected value (e.g., if it was used as an alternative assessment approach).

Table 1 – Description of assessment documents gathered, by region

Canada Health Canada Chemicals Management Plan Assessments Health Canada Guidelines for Canadian Drinking Water Quality Health Canada Priority Substance List assessments Health Canada Residential Indoor Air Quality Guidelines Pest Management Regulatory Agency
United States Agency for Toxic Substances and Disease Registry Minimal Risk Levels American Conference of Governmental Industrial Hygienists Threshold Limit Values and Biological Exposure Indices American Industrial Hygiene Association/Occupational Alliance for Risk Science Workplace Environmental Exposure Levels Environmental Protection Agency Acute Exposure Guideline Levels Environmental Protection Agency Integrated Risk Information System Environmental Protection Agency assessments by Office of Pesticide Programs Environmental Protection Agency Provisional Peer Reviewed Toxicity Values Environmental Protection Agency assessments under Toxic Substances Control Act National Institute for Occupational Safety and Health Recommended Exposure Limits Occupational Safety and Health Administration Permissible Exposure Limits
Europe European Chemicals Agency Risk Assessment Committee Occupational Exposure Limits, Derived No Effect Levels, and Derived Minimal Effect Levels European Chemicals Agency Scientific Committee on Occupational Exposure Limits Indicative Occupational Exposure Limit Values European Chemicals Bureau Risk Assessment Reports European Food Safety Agency Panel on Contaminants in the Food Chain assessments European Food Safety Agency Panel on Plant Protection Products and their Residues assessments World Health Organization Regional Office for Europe Air Quality Guidelines for Europe and World Health Organization Guidelines for Indoor Air Quality
International International Programme on Chemical Safety Concise International Chemical Assessment Documents, Environmental Health Criteria, and Harmonization Project documents Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives evaluations Joint Food and Agricultural Organization/World Health Organization Meeting on Pesticide Residues Evaluations of Pesticide residue in food World Health Organization Guidelines for Drinking-Water Quality

3.0 Results

A list of the assessments that used physiological models in dose–response assessments is presented in Appendix A. Appendix B includes a list of guidance documents mentioning the potential for dose–response applications of the models.

The first part of the results section discusses the timeline of application of physiological models. Narrative descriptions of the applications of each type of model are presented. The PBPK modelling section is further subdivided to allow for discussions of dose–response applications of the models by exposure domain and organization; because few dosimetry and BBDR models used in regulatory dose–response assessments, these assessments are discussed collectively rather than by exposure domain or organization. Discussion of the timeline is followed by a more detailed analysis of the overall database, comparing how the models were used in regulatory dose–response assessments between exposure domains and over time.

3.1 Timeline of physiological model application

A total of 122 regulatory reports were identified that used physiological models in dose–response assessments between 1983 and 2018. As demonstrated in Figure 1a, the first uses of a physiological model in a regulatory dose–response assessment were in 1986 and 1987, and were sporadic in the decade thereafter. Beginning in 1999, at least one regulatory document was published every year that included a dose–response application of a physiological model. The highest rates of dose–response application of physiological models in any year was 10, which occurred in 2006, 2010, and 2011. In 2006, the increase in the number of regulatory uses of physiological dose–response modelling was sudden, and most years that followed had a higher rate of application than pre-2006. Dose–response uses of the models in regulatory documents increased in each decade, with an average of 0.57 reports per year in the 1980s, 0.8 per year in the 1990s, 4.0 per year in the 2000s, and 7.8 per study year in the 2010s.

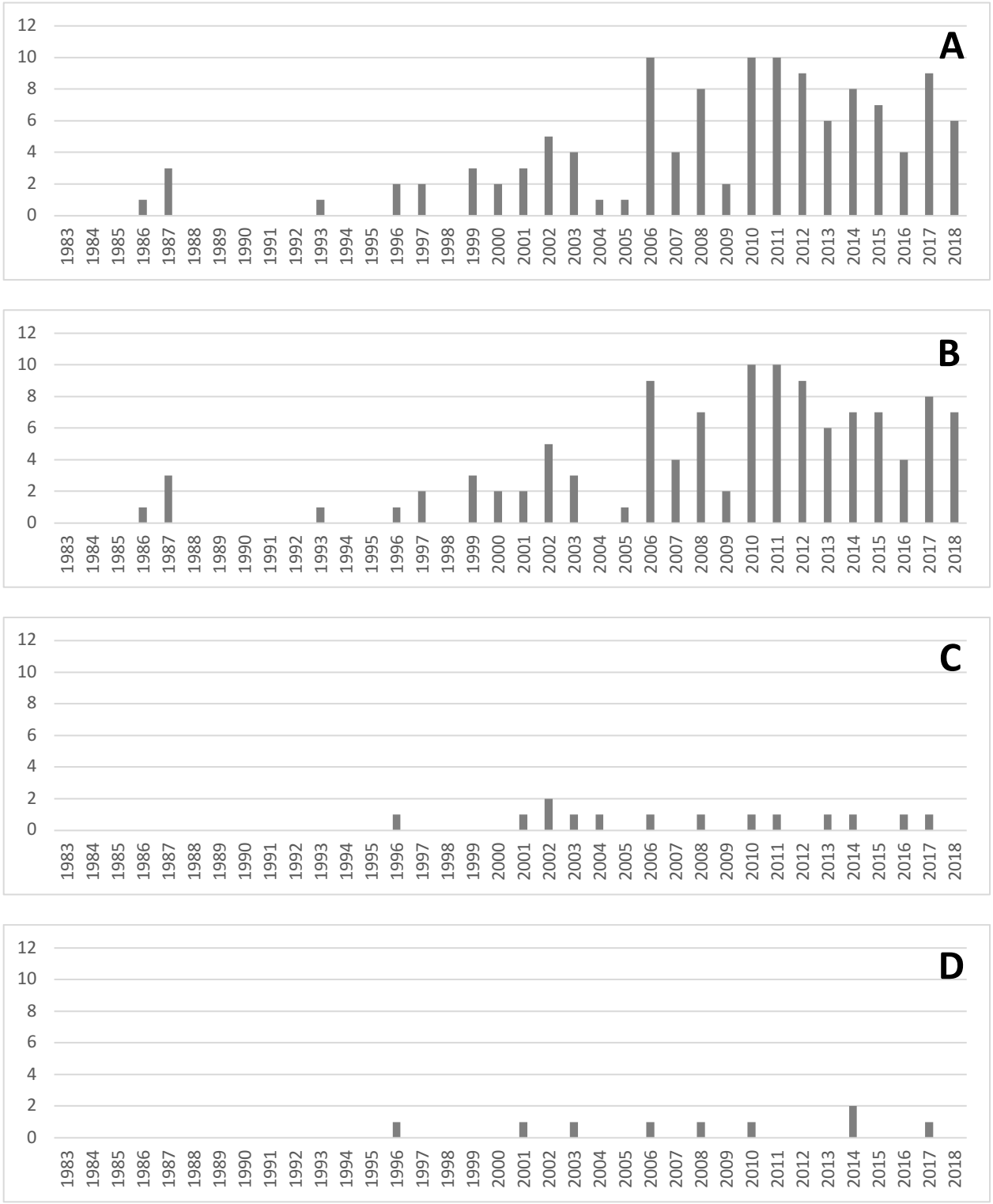
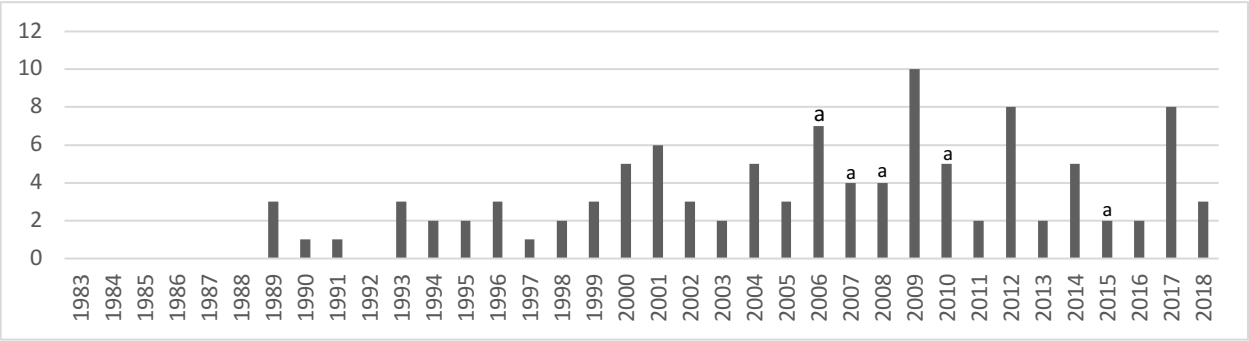


Figure 1. Reports applying physiological models in dose–response analyses by year
A) All included model types; B) Physiologically-based pharmacokinetic models; C) Inhalation dosimetry models; D) PBPD/BBDR models

Many of the organizations included in this study also developed guidance documents that mentioned the possible uses of physiological models in dose–response assessments. A total of 107 guidance documents are presented in Figure 2, the majority of which were published in the 2000s and 2010s, albeit with a slight decline in the last decade. The first guidance documents discussing physiological models emerged in 1989, and were published in every subsequent year except 1992. The models were typically presented as alternative dose–response methods to replace default approaches, whenever data existed. However, many of the guidance documents indicated that although the use of physiological models was the preferred dose–response approach, model availability precluded their regular use in risk assessments. The majority of the identified guidance documents discussed PBPK modelling (92%; data not shown). Guidance mentioning physiological models was mostly related to general risk assessment approaches, but also included documents on other specific risk assessment refinements (e.g., benchmark dose modelling and cumulative risk assessment) that mentioned ways in which physiological model results could be incorporated into the more refined processes. In the 2000s and 2010s, six guidance documents specifically focused on the development and application of PBPK models. Only one of these documents—published in 2015—discussed PBPK-PD models throughout the document; none of the other guidance documents published by any organization focused specifically on chemical-specific dosimetry or BBDR modelling.



[a]Guidance document focused specifically on physiological modelling (N = 2 in 2010)

Figure 2. Guidance documents discussing physiological models in dose–response assessments, by year

3.1.1 PBPK modelling

In general, all organizations included in this study appeared to be open to considering the use of PBPK models to some degree. Even if the models were not applied in dose–response assessments, summaries of the models were often included in assessment reports, particularly in

sections on pharmacokinetics. However, for present purposes, PBPK models are not considered to be used unless they either directly or indirectly influenced dose–response assessments. Moreover, discussions providing justification for not using the PBPK models in the evaluation[1] are not included as an application of the model. Finally, for evaluations of some compounds with non-existent PBPK models, organizations would also often discuss why types of extrapolations could not be performed in the absence of a PBPK model; comments of this nature are not reflected in the analysis.

The first guidance documents that referred to potential dose–response applications of PBPK models were published in 1989. After 1989, at least one guidance document mentioning potential uses of PBPK models was published in most years, with exceptions in 1991, 1992, and 1997. A total of 98 guidance documents mentioning dose–response applications of PBPK models were identified, but only six of these guidance documents focused specifically on PBPK modelling, the first of which was published in 2006 (see Figure 2).

The first identified application of a PBPK model in a dose–response assessment by included organizations was in 1986, for tetrachloroethylene (details are provided in Section 3.1.1.1.3). This was followed by three dose–response applications in 1987, two of which were for dichloromethane (methylene chloride), which is frequently discussed as the earliest application of a PBPK in a dose–response assessment published by a regulatory organization. No other dose–response applications were identified until 1993, followed by another gap until 1996. After 1996, at least one relevant use of a PBPK model was published in almost every year, with 1998 and 2004 being the only exceptions. The number of publications in which PBPK models influenced dose–response has increased with each decade, with 4 in the 1980s, 7 in the 1990s, 35 in the 2000s, and 68 in the 2010s. Most of the years with the highest frequency of publications of dose–responses including these models occurred in the 2010s, with 10 publications in each of 2010 and 2011, 9 in 2006 and 2012, 8 in 2017, and 7 in 2008, 2014, 2015, and 2018.

3.1.1.1 Environmental programs

The use of PBPK models in dose–response assessments performed by regulatory organizations responsible for environmental programs predated the mention of the models in

[1] Justification for not using the models in risk assessment was commonly that the model was not developed or fully evaluated for relevant target species (including humans and the species from which the POD was obtained) or target route of exposure.

guidance documents, as the first guidance documents to suggest potential uses of PBPK models were published in 1989. Environmental programs also developed guidance documents specific to PBPK modelling methods in 2006, 2007, 2008, and 2010, with two documents published in the latter year.

The first applications of PBPK models in dose–response assessments in this exploration were in environmental assessments, beginning in 1986 and 1987. Following these initial evaluations, no further use of PBPK models by environmental programs was published until 1993. Beginning in 1997, at least one relevant use of a PBPK model in an environmental assessment was published every year, except 1998 and 2004.

3.1.1.1.1 Health Canada

No Health Canada documents were identified that provided guidance on the use of PBPK models in dose–response assessments. Applications of PBPK models were identified in four different types of assessments. In general, Guidelines for Canadian Drinking Water Quality (GCDWQ) and Priority Substances List (PSL) assessments performed their own PBPK modelling, whereas other assessments used published PBPK model results.

The first Health Canada assessment to incorporate a PBPK model was a GCDWQ for dichloromethane, which used the model in deriving a cancer risk estimate in the 1987 assessment of dichloromethane (11). No other GCDWQs used PBPK models until the 2011 update of the dichloromethane assessment (12), which also applied the model for cancer risk estimation. In subsequent years, GCDWQs for 1,2-dichloroethane (2013) (13), vinyl chloride (2013) (14), tetrachloroethylene (2015) (15), toluene, ethylbenzene, and xylenes (2015) (16), and chromium (2016) (17) applied PBPK models to derive PODs, including PODs for cancer risk assessments. An evaluation of bromate published in 2016 (18) applied the PBPK approach alongside a traditional approach, as the human bromate PBPK model was not validated. In 2017, a draft GCDWQ for lead (19) was used to extrapolate from a POD based on a blood concentration to an oral concentration. Finally, as no fully validated human models were available for the 2018 evaluations of perfluorooctanesulfonic acid (PFOS) (20) and perfluorooctanoic acid (PFOA) (21), the models were used only for the derivation of chemical-specific adjustment factors (CSAFs).

PSL assessments for four compounds used PBPK models in their dose–response assessments. The 1993 dichloromethane assessment (22) and 2001 chloroform assessment (23)

used PBPK models to derive PODs, and a PBPK model was used to derive CSAFs in the 2002 2-butoxyethanol assessment (24). A PSL follow-up for ethylene glycol that was published in 2010 (25) used PBPK model results to support a non-toxic conclusion, as model results indicated that blood concentrations associated with adverse effects in rats were unlikely to be achieved in humans.

PBPK models were also used in margin of exposure (MOE) assessments under the Chemicals Management Plan (CMP). A POD in the 2017 draft assessment of N-methyl-2-pyrrolidone (NMP) and N-ethyl-2-pyrrolidone (NEP) (26) was obtained from model results published elsewhere. It is not clear whether PBPK model results discussed in the human health characterization section were used to influence UF selection for the MOE in a 2011 assessment of ethyl acrylate (27), as detailed discussions of sufficient MOEs were not presented. A Science Approach Document on biomonitoring equivalents for various metals (28) summarized the use of a PBPK model to derive a BE for silver; however, this evaluation is not considered in the present analysis as the derivation was performed in the scientific literature rather than in the regulatory document.

One further application of a PBPK model in a Health Canada dose–response assessment was identified in the Residential Indoor Air Quality Guideline (RIAQG) for acetaldehyde (29), published in 2017. In that evaluation, a POD was obtained from PBPK model results published in peer reviewed literature.

3.1.1.1.2 Agency for Toxic Substances and Disease Registry

An undated[2] draft guidance document (30) (and similar 2018 draft (31)) outlining the development of Agency for Toxic Substances and Disease Registry's (ATSDR) Toxicological Profiles asks writers to consider the potential for PBPK-PD models to be used in extrapolations. Guidance on the derivation of interaction profiles published in 2001 (32) also discusses the use of PBPK-PD models in the context of dose–response assessment.

ATSDR's general approach for the use of PBPK models in deriving Minimal Risk Levels (MRLs) was typically to apply PBPK models *de novo* to derive human equivalent concentrations (HECs) and human equivalent doses (HEDs). The first such application was in the 2000

[2] The undated guidance document was downloaded in 2014. The 2018 version of the draft guidance document was discusses PBPK-PD models similarly to the older draft.

methylene chloride assessment (33), which was followed by vinyl chloride (2006) (34), ethylbenzene (2010) (35), acrylamide (2012) (36), RDX (2012) (37), and a draft tetrachloroethylene assessment (2014) (38). The mercury MRL (39) was also compared with a PBPK approach, and draft trichloroethylene MRLs (40) were based on PBPK results, but neither document is included in this analysis as ATSDR only summarized dose–response assessments performed elsewhere. No original dose–response assessments published in interaction profiles used PBPK models.

3.1.1.1.3 US EPA

As early as 1989, PBPK modelling was mentioned in US EPA guidance documents, beginning with inhalation reference dose guidance (41). Beginning in the mid-1990s, PBPK modelling was regularly mentioned in guidance documents developed by various programs at US EPA as a gold standard approach to refine inter- and intraspecies extrapolations, duration adjustments, and other dose–response applications; these documents are listed in Appendix B. US EPA also developed PBPK-specific guidance beginning in the mid-2000s, with five different documents (42-46) developed by three different US EPA programs.

The earliest uses of PBPK models in dose–response assessments at US EPA were in the Integrated Risk Information System (IRIS) program. IRIS assessments always involved running models *de novo* for the derivation of human equivalent concentrations or doses. The first application of a PBPK model that was used as the basis of a final risk value was in the 1987 draft update to the dichloromethane assessment (47); however, in a 1986 draft addendum to the tetrachlorethylene assessment (48), an alternative approach that was presented—but not selected—used a PBPK model to derive a cancer risk value. After these initial applications, no other uses of PBPK models in dose–response analyses for IRIS assessments were identified until 1999, when a PBPK model was applied for ethylene glycol monobutyl ether (49). Throughout the 2000s, three IRIS assessments used PBPK models to derive HECs or HEDs—vinyl chloride in 2000 (50), xylenes in 2003 (51), and 1,1,1-trichloroethane in 2007 (52). The use of PBPK models in the IRIS program increased in the 2010s, with Reference Concentrations (RfCs), Reference Doses (RfDs), or cancer risk estimates derived using the models in nine final assessments (53-61) and six draft assessments (62-67). The 2013 inhalation assessment of 1,4-dioxane (68) also used PBPK model results indirectly, as the weight of evidence from models

was used to support the use of a dosimetric adjustment factor (DAF) of 1, rather than using a DAF derived using default approaches.

The US EPA Acute Exposure Guideline Level (AEGL) program first published final assessments that incorporated PBPK model results into the dose–response assessment process in 2010; however, draft assessments (that were never finalized) from 2008 and 2009 also applied such models. PBPK model results published elsewhere were used to either influence the selection of default UFs (1,2-dibromoethane (69), styrene (70), ethylene oxide (71), furan (72) and chloroform (73)) or to calculate a data-derived UF (acrylonitrile (74) and carbon tetrachloride (75)). Models run specifically for AEGL assessments were used to derive PODs (methylene chloride (76), ethylbenzene (77), xylenes (78), and toluene (79)). Although the trichloroethylene model appears to be run *de novo* for the assessment, results appear to have influenced the default UF selection (80). PBPK models were also used for dose duration extrapolations for five assessments (methylene chloride (76), trichloroethylene (80), ethylbenzene (77), xylenes (78), and toluene (79)); however, the default duration extrapolation approach (i.e., use of the ten Berge equation) was still applied in assessments where PBPK models were not run *de novo*.

Two Provisional Peer Reviewed Toxicity Value (PPRTV) assessments published in 2007 (4-chlorobenzotrifluoride and hexachlorobutadiene) used PBPK model results to support the use of a DAF of 1 (81) or a lower interspecies UF of 3 (82). Several documents stated that route-to-route extrapolation could not be performed without a PBPK model, and standard wording in many documents indicated that bodyweight scaling was used due to an absence of PBPK models for interspecies extrapolation. However, a 2014 evaluation of isopropanol (83) stated that despite the availability of a PBPK model for interspecies extrapolation, HECs or HEDs were not derived using the model because it was beyond the scope of a PPRTV assessment.

Several National Center for Environmental Assessment assessments other than those presented for IRIS and PPRTV ran PBPK models for dose–response purposes. These included a tetrachloroethylene BMD value derived using internal dose metrics in 1997 (84), and a draft perchlorate RfD in 2002 (85). The 2002 diesel assessment (86) used a model that was referred to as a PBPK model to derive the POD used in an RfC; the model mainly described lung dosimetry, but also included transport to lung-associated lymph nodes. An ethylene glycol monobutyl ether assessment in 2005 (87) also used a PBPK model to derive an HED and HEC, which were used

to ensure that the existing RfC and RfD were sufficient to prevent gastrointestinal hyperplastic effects.

Three US EPA research reports that employed PBPK models for dose–response assessments were found in government document repositories. A 2003 report used PBPK models to derive relative potency factors for drinking water disinfection by-products (88). Two 2006 reports describing the development of PBPK models also applied models for dose–response assessments—one derived a human NOAEL for carbofuran using an Exposure Related Dose Estimating Model that contained a PBPK-PD component (89), and the other derived an RfC for chloroform that incorporated quantitative human variability (90).

The only use of a PBPK model use to derive risk values in TSCA assessments that was not obtained from an IRIS assessment was for n-methylpyrrolidone in 2015 (91). In a scoping assessment (referred to as a workplan assessment), PBPK model results published elsewhere were used to derive a human equivalent concentration used in a margin of exposure assessment.

Although US EPA's air program published guidance documents from 1993 to 2006 stating that PBPK models could be used for extrapolating from animals to humans (92-96), no dose–response applications of the model were identified in air assessments. The air program began developing the Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in 1985 and published a draft in 1989, with guidance on using the IEUBK model published in 1994 (97). Although assessments using the IEUBK model in dose–response assessments (typically to extrapolate from a blood-based POD to an external exposure) have been published by many organizations, documents identified within the US EPA air program only used the model for exposure assessments.

Two original dose–response applications of PBPK models were identified in US EPA's water program. The 2001 Water Quality Criterion for methylmercury (98) used PBPK model results published elsewhere indirectly, to inform UF selection. An interim Drinking Water Health Advisory for perchlorate from 2008 (99) used a PBPK-PD model to compare age-related differences in iodide inhibition levels at the proposed Health Advisory level (derived within the assessment document using traditional approaches without the use of a PBPK model), to ensure that iodide inhibition levels were not of concern even in susceptible subpopulations. HEDs derived from PBPK models were also used as the basis for Human Health Ambient Water Quality Criteria; however, as the dose–response assessments for these values were initially

presented in IRIS RfDs or Health Canada GCDWQs, the assessments were not considered in the present analysis.

3.1.1.1.4 European Chemicals Bureau

No guidance document was located for European Chemicals Bureau (ECB) Risk Assessment Report (RAR) evaluations. PBPK models influenced dose–response processes in four assessments. For 2-butoxyethanol (100) and 2-butoxyethyl acetate (101), both published in 2006, the PBPK model was used to derive an HED. PBPK models indirectly influenced dose–response assessments of two compounds, as models were used to eliminate the need for adjusting the POD for humans (acrylic acid, 2002 (102)) or reducing the interspecies UF in the reference margin of safety (vinyl acetate, 2008 (103)).

3.1.1.1.5 ECHA Risk Assessment Committee

ECHA guidance (104, 105) provides details on using PBPK models in Derived No-Effect Level (DNEL) derivation, including route-to-route extrapolation and calculation of assessment factors. One Risk Assessment Committee (RAC) assessment in 2011 specifically addressing exposures in the general population reported Derived Minimal Effect Levels (DMELs) for lead exposures in children, using a PBPK model to extrapolate between blood concentrations and intake estimates.

3.1.1.1.6 WHO and IPCS

Many IPCS guidance documents have discussed PBPK models, the first of which were published in the mid-1990s, considering extrapolations in biomarker-based risk assessments in 1993 (106) and general risk assessments in 1994 (107). Four additional Environmental Health Criteria documents mentioning the use of PBPK models were published between 1999 and 2009 (108-111). Harmonization projects first discussed the use of PBPK modelling in CSAF guidance (2005 (112)), with a guidance document focusing specifically on PBPK modelling in 2010 (113). A 2012 harmonization project report on immunotoxicity only briefly mentioned PBPK models (114), but the potential role of PBPK model use was discussed more thoroughly in a document guiding uncertainty characterization in hazard assessments (115). PBPK approaches were also recommended when greater refinement is required in cumulative risk assessments in a 2009 harmonization document (116); however, as this document only presented a summary of

workshop results, with final guidance being published later in peer reviewed literature (117), the guidance document is not included in the present analysis.

Guidance on risk assessment approaches for drinking water also mentioned potential uses of PBPK models. Beginning with the third edition of the Guidelines for Drinking-water Quality (2004 (118)), and continuing with their fourth edition (2017 (119)), WHO began discussing PBPK models in CSAF derivation, which was presented as an alternative risk assessment approach. PBPK models were also proposed for use in higher tiers of assessments of chemical mixtures in water (120).

Several WHO and IPCS risk assessments had final risk values that were based on PBPK model results, but most were duplications from assessments published by other organizations and were therefore excluded from the analysis. Although the Concise International Chemical Assessment Document for tetrachloroethylene from 2006 (121) was based on other assessments, it was included in this analysis because it did not present a duplication of results, as the derived oral tolerable daily intake was performed from an assessment that was not otherwise included in this analysis. Similarly, the only WHO drinking-water guidelines that were based on PBPK model extrapolations were not included in this analysis as they used assessments performed elsewhere. No PBPK models were used to derive WHO Air Quality Guidelines for Europe.

3.1.1.2 Occupational programs

Only six guidance documents mentioning the use of PBPK models have been published by occupational organizations (104, 105, 122-125), the first of which appeared in 2008. Occupational dose–response assessments, however, still incorporated PBPK data into dose–response assessments, some as early as two decades prior to the publication of the first guidance document mentioning the use of models.

A total of 23 occupational dose–response assessments published by the programs included in this analysis used PBPK models in some manner; the publications are described throughout the following subsections. The first published application was in the 1980s (126), but was a contractor report that does not appear to have been incorporated into official agency evaluations. PBPK models were used in dose–response assessments by the included agencies 4 times in the 1990s, increasing to 11 in the 2000s, then declining to 7 in the 2010s.

3.1.1.2.1 ACGIH

No direct mentions of PBPK models were identified in discussions of the overall TLV/Biological Exposure Indices® (BEI®) development process used by ACGIH (127). In guidance provided to users on the consideration of unusual work schedules, one mathematical model was discussed as providing adjusted exposure limits that were similar to those adjusted using PBPK models; however, neither PBPK models nor the mathematical model were used directly by ACGIH for duration adjustment.

ACGIH has not developed or run their own PBPK models, but published results from PBPK models have been used in the derivation of their TLVs and BEIs. PBPK models were discussed in the TLV Recommendations section for several compounds, and might therefore have been factored into the weight of evidence evaluations; however, a lack of detailed description of UF use precluded the ability to determine whether these models quantitatively affected the outcome of any TLVs. The carbon tetrachloride TLV derived in 1996 (128) clearly incorporated PBPK modelling in a quantitative manner, as the POD for the TLV was obtained from PBPK model results published in a peer-reviewed journal. Other uses of PBPK model results in the TLV derivation process included the discussions that metabolite concentrations would be insufficient to produce renal effects observed in rodents exposed to ethylene glycol (129) or hemolysis subsequent to dermal exposure for both 2-butoxyethanol (130) and 2-butoxyethyl acetate (131); this evidence was used to support excluding renal effects as a POD for ethylene glycol and the absence of a need for a skin notation for the latter two compounds. However, for many of the other compounds that mentioned PBPK models in the TLV Recommendations section (1-methoxy-2-propanol (132), 2-methoxyethanol (133), 2-metoxyethyl acetate (134), cyclohexane (135), and vinylidene chloride (136)), the results were typically discussed in the context of comparative pharmacokinetics and therefore might have been used to influence, calculate, or eliminate inter- and intraspecies UFs. However, as the TLV Recommendations only typically indicate the POD and the final TLV, it is not possible to determine the extent to which model results may have influenced the final selection of UFs for these chemicals.

BEIs for three compounds were derived using forward dosimetry. PBPK models for 2-butoxyethanol (137), tetrahydrofuran (138), and acetone (139) were used to estimate urinary concentrations after exposure to the TLV; these concentrations formed the basis of the BEIs derived in 2007, 2008, and 2015, respectively. Model results were obtained from publications in

peer-reviewed journals, with the tetrahydrofuran publication possibly having been developed specifically for the BEI committee.

3.1.1.2.2 AIHA/OARS

No mention of PBPK models was identified in operating procedures or white papers developed by the WEEL Committee, which currently operates under OARS, and was formerly housed under AIHA. PBPK models were discussed in the rationale section for only two WEELs, 2,3,3,3-tetrafluoropropene (140) and trans-1-Chloro-3,3,3-Trifluoropropene (1233zd(E)) (141), derived in 2009 and 2013, respectively. PBPK model results were discussed in the context of comparing internal concentrations in animals and humans. Although the interspecies differences in internal tissue concentrations might have potentially affected the selection of UFs, this is not clear because UF selection is not described.

3.1.1.2.3 National Institute for Occupational Health and Safety

Two Current Intelligence Bulletins (CIBs) outline quantitative processes for derivation of exposure guidelines at the National Institute of Occupational Health and Safety (NIOSH). Both a 2014 CIB outlining derivation processes for Immediately Dangerous to Life and Health values (122) and a 2018 draft CIB presenting approaches for NIOSH's occupational risk assessments in general (123) discuss PBPK modelling as an ideal extrapolation approach.

PBPK models were used to provide supporting dose–response data in three evaluations performed or sponsored by NIOSH. In 1987, a contractor report used a PBPK model to derive cancer risk estimates for butadiene, for comparison with a US EPA-proposed cancer risk assessment that was based on a default approach (126); however, the results of this report do not appear to have been used directly to derive a NIOSH Recommended Exposure Limit (REL). A PBPK-computational fluid dynamics (CFD) model was used in the assessment of animal data to extrapolate from rodent BMCs to HECs in the 2016 diacetyl assessment (142); however, the final REL was based on PODs from human studies. Finally, in the 2018 draft of the silver nanomaterials assessment (143), a PBPK model was used to eliminate argyria as a potential POD, as PBPK-derived PODs for the different particulate sizes were all greater than the existing REL for total silver.

3.1.1.2.4 Occupational Health and Safety Administration

The only published guidance document that discussed physiological models was developed in 2008 to outline methods for occupational risk assessments for agencies under the Department of Labor (including Occupational Health and Safety Administration [OSHA]) (124). The guidance sets out minimal requirements for applying physiologically based models (PBPK models are not specifically mentioned) in assessments.

The 1997 Final Rule for methylene chloride exposure (144) used a PBPK model to extrapolate from animals to humans in its cancer risk assessment. Within the Final Rule publication, a set of 11 criteria that allow for evaluation of adequacy of PBPK models for estimating human equivalent concentrations was stated. These criteria were also used to identify that PBPK models for 1,3-butadiene were not sufficient for the derivation of a Permissible Exposure Limit (145).

3.1.1.2.5 ECB

As the ECB RAR evaluations were mode of action analyses performed using data for both environmental and occupational exposure scenarios, the use of PBPK models in RARs has already been discussed in Section 3.1.1.1.4. Briefly, PBPK models were used to derive an HED for two assessments published in 2006 (2-butoxyethanol (100) and 2-butoxyethyl acetate (101)), and were used indirectly in interspecies extrapolation considerations in 2002 (acrylic acid) (102) and 2008 (vinyl acetate) (103).

3.1.1.2.6 ECHA Scientific Committee on Occupational Exposure Limits and RAC

Scientific Committee on Occupational Exposure Limits (SCOEL) methodology developed in 2017 (125) discusses potential uses for PBPK models as a means for extrapolating from animals to humans (including for deriving interspecies UFs) and transforming OELs into biological limit values (BLVs). However, no applications of PBPK models in the derivation of SCOEL Indicative Occupational Exposure Limit Values (IOELVs) or BLVs were identified.

ECHA guidance (104, 105) provides details on using PBPK models in DNEL derivation, as discussed in Section 3.1.1.1.5; however, no guidance specific to the derivation of OELs could be identified, so it is not clear whether the worker DNEL-derivation guidance is consistent with RAC's derivation of OELs. The 2018 OEL for acrylonitrile (146) was based on a PBPK-derived human equivalent concentration obtained from peer-reviewed literature.

3.1.1.3 Foods

The first document providing guidance for assessment of contaminants in foods that mentioned potential dose–response applications of PBPK models was published in 2009 (147). In total, 10 guidance documents mentioned potential uses of PBPK models in food dose–response assessments, as will be described in the subsequent subsections. The first identified application of a PBPK model in a dose–response assessment for environmental contaminants in food was in 2010 (148); PBPK models were used to derive risk values in five additional food assessments between 2011 and 2018 (149-153).

3.1.1.3.1 EFSA Panel on Contaminants in the Food Chain

EFSA has not derived guidance specifically focused on PBPK modelling; however, in several documents guiding various aspects of their risk assessments, EFSA has discussed the role of PBPK models as tools to refine risk assessments. When considering overall EFSA guidance—as no guidance was authored through the Panel on Contaminants in the Food Chain (CONTAM panel)—the first guidance document mentioning PBPK modelling was published in 2009 (147). Additional guidance documents referring to PBPK models were published nearly every year thereafter (154-160).

The CONTAM panel first applied PBPK models in an assessment in 2010, as a method of extrapolating from an internal POD for lead to an oral concentration that formed the basis of their guideline (148); a similar approach was used in 2018 to extrapolate from an internal POD for PFOS and PFOA (152). PBPK model results were also used to influence the selection of default UFs in the 2014 assessment of perchlorate (149). PBPK models were used to derive human equivalent dose factors in two assessments in 2015, which were employed to determine a sufficient MOE for acrylamide (151) and applied to a POD obtained from an animal study prior to applying UFs for BPA (150).

3.1.1.3.2 Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives

The Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives (JECFA) published a guidance document outlining the development of food additive monographs in 2017 (161), which discussed potential uses of PBPK models for various types of extrapolation. One application of a PBPK model for dose–

response analysis was identified in JECFA assessments. PBPK models were used to derive PODs in a MOE analysis for acrylamide in 2011 (153); the models used in the analysis were published after the previous 2006 acrylamide assessment that identified that PBPK models were not sufficient.

3.1.1.4 Pesticides

Guidance documents discussing potential dose–response applications of PBPK models in assessments of pesticides were first published in 1999. In total, 12 guidance documents mentioning PBPK models were identified (45, 162-172), one of which specifically focused on PBPK models.

Dose–response applications of PBPK models by pesticide assessment programs were only identified from one organization (US EPA). The first use of a PBPK model was in 2006, with all other dose–response assessments published between 2012 and 2018; these models are described in Section 3.1.1.4.2.

3.1.1.4.1 Pest Management Regulatory Agency

Pest Management Regulatory Agency (PMRA) published one guidance document that briefly mentioned PBPK models. A 2008 guidance document on UFs (162) discussed the potential future role of PBPK models of placental and lactational transfer in lifestage-specific risk assessments.

Two PMRA assessments mentioned the consideration of PBPK models, but neither assessment appeared to use the model to affect the dose–response assessment. Although results of a PBPK model were used to indicate pharmacokinetic similarities between rats and humans for halauxifen-methyl, no changes were made to interspecies UFs used to derive an acute RfD or used as the target MOE in a 2014 assessment (173). PMRA also considered a PBPK model for a surrogate compound that was submitted by a registrant in the 2018 evaluation of sodium omadine (174); however, PBPK model results were not used to reduce the interspecies UF as recommended by the registrant, as PMRA stated insufficient data for model evaluation were provided by the registrant.

3.1.1.4.2 US EPA Office of Pesticide Programs

As US EPA guidance mentioned in Section 3.1.1.1.3—such as documents produced by the Risk Assessment Forum—is developed for the entire agency, these documents also likely

guide the risk assessments performed in the US EPA Office of Pesticide Programs (OPP). Additional guidance specifically derived by OPP has also been produced, with a total of five documents published between 1999 and 2016 (45, 163-166). Most of the documents briefly mention PBPK modelling as an optimal approach, but a 2015 document was specifically developed to provide guidance for the development and application of PBPK and PBPK-PD models for pesticides (45).

OPP has developed and run PBPK models for dose–response applications in 13 different assessments. The first identified application was in the 2006 propylene oxide risk assessment (175), which states that an alternative cancer slope factor was derived using a PBPK model; no further details on model application were provided. In 2011, a cumulative risk assessment on pyrethroids (176, 177) used PBPK model results to justify the selection of Food Quality Protection Act (FQPA) factors. The use of an age-dependent model for deltamethrin identified that no FQPA factor was required for women of child-bearing age or children older than 6 years, but a data-derived FQPA factor of 3 was calculated for children younger than 6 years. This data-derived FQPA factor was then applied in several subsequent assessments of individual pyrethroid pesticides, in 2012 (bifenthrin (178), zeta-permethrin (179), alpha-permethrin (180), tefluthrin (181), fenpropathrin (182)), 2014 (prallethrin (183)), 2015 (deltamethrin (184)), and 2017 (lambda- & gamma-cyhalothrin (185)); the 2017 draft pyrethrins assessment (186) also proposed a similar approach. The most recent (2014) assessment of chlorpyrifos (187) used a PBPK-PD model to derive PODs associated with 10% inhibition in acetylcholinesterase in red blood cells, as well as to calculate an intraspecies DDEF using adult:human ratios for model-estimated ED10 levels. The 2018 atrazine assessment (188) also used a PBPK model to derive human-equivalent doses for extrapolation from rats to humans.

OPP has also published reports of PBPK model evaluation for carbaryl and malathion (189) and deltamethrin, permethrin, carbaryl, malathion, dimethoate, and acibenzolar (190), which is a potential indication of the program's interest in considering these models in future assessments. However, the evaluation of PBPK models does not necessarily mean they will be applied in future assessments; for example, a 2003 report discussed progress on the development of a PBPK model for n-methyl carbamate pesticides (191), but the 2007 cumulative risk assessment for this class of pesticides (192) did not use the PBPK models, as there was no model for certain pesticides that were important contributors to exposure.

3.1.1.4.3 EFSA Scientific Panel on Plant Protection products and their Residues

General EFSA guidance discussed in Section 3.1.1.3.1 is also applicable to pesticide evaluations; in addition, guidance developed by the Scientific Panel on Plant Protection Products and their Residues (PPR panel) began mentioning PBPK modelling earlier than other EFSA guidance. In general, in the six identified guidance documents that discussed PBPK models (published by PPR in 2006 to 2013) (167-172), the models were mentioned as an approach to explore the toxicological relevance of metabolites, to extrapolate from animals to humans and investigate human variability, and as a tool for refinement in the highest tier of cumulative risk assessments. In a number of instances, the guidance stated the models could be used on a case-by-case basis, but that routine use of the models was not appropriate because they were data-intensive.

No use of PBPK models was identified in assessments published by the PPR panel.

3.1.1.4.4 Joint Food and Agricultural Organization/World Health Organization Meeting on Pesticide Residues

No mentions of PBPK models were identified in guidance documents published by the Joint Food and Agricultural Organization/World Health Organization Meeting on Pesticide Residues (JMPR). Furthermore, no PBPK models were used in deriving acceptable daily intakes or acute RfDs in readily available JMPR assessments.

3.1.2 Inhalation dosimetry modelling

Some organizations used categorical adjustment approaches to perform species extrapolations, including various US EPA programs (IRIS, PPRTV, pesticides, AEGLs, and other assessments) and NIOSH. However, as categorical approaches were not within the scope of this study, no further discussion of these approaches is included.

Most guidance documents mentioning dosimetry discussed categorical dosimetry approaches; however, eight guidance documents specifically recommended consideration of chemical-specific dosimetry models (41, 42, 95, 123, 193-196), the first of which was published in 1989. All of the guidance documents also mentioned PBPK modelling. Seven of the guidance documents were published by different US EPA programs, and the eighth was published by NIOSH.

Chemical-specific dosimetry models were used in dose–response assessments in 14 evaluations, with the first evaluation published in 1996. Dosimetry models were combined with PBPK models for 6 assessments, and the remaining 8 were inhalation dosimetry models that considered only the respiratory tract without systemic uptake.

PBPK models mentioned in the previous section that were also combined with inhalation dosimetry models, such as CFD models, included ECB's 2002 RARs for acrylic acid (102), US EPA's draft formaldehyde IRIS assessment in 2010 (62), US EPA's 2013 inhalation IRIS assessment for 1,4-dioxane (68), and NIOSH's 2016 diacetyl REL (142). The aforementioned Health Canada 2011 CMP assessment for ethyl acrylate (27) and US EPA assessment for diesel (86) also referred to the use of a PBPK model, but the described model was used for interspecies comparison of olfactory epithelium tissue, and was therefore what this study would consider an inhalation dosimetry model, rather than a PBPK model.

Chemical-specific dosimetry models without PBPK models were used in environmental and occupational assessments. The models were used to derive human equivalent PODs that reflected species-related differences in lung physiology for a 1996 IPCS assessment of diesel fuel (197), a 2001 Health Canada Priority Substances List assessment of formaldehyde (198), National Emission Standards for Hazardous Air Pollutants (NESHAP) assessments of formaldehyde published beginning in 2003 (199), and a 2006 NIOSH REL for refractory ceramic fiber (200). Two AEGL assessments—for acrylic acid in 2004 (201) and methyl methacrylate in 2008 (202)—used model results published elsewhere to support the reduction of toxicokinetic components of interspecies UFs. Finally, dosimetry models were discussed within the context of ACGIH TLV derivation for propylene oxide in 2014 (203) and formaldehyde in 2017 (204) and potentially played a role in POD or UF selection decisions, but an absence of details precludes confirmation of the influence of model results.

3.1.3 PBPK-PD or BBDR modelling

The potential use of BBDR modelling in dose–response assessments was discussed in 40 different guidance documents, which are listed in Appendix B. The general theme of discussions in the guidance documents was that BBDR modelling was a gold standard approach, and should be considered whenever possible, but that very few such models existed because the data to develop the models were not often available; however, one guidance document by US EPA's

OPP was specifically focused on PBPK and PBPK-PD models (45). Most of the guidance documents discussed BBDR modelling together with PBPK modelling, but 9 specifically mentioned BBDR modelling without discussing PBPK models (205-213).

Few assessments used a BBDR model, reflecting the guidance document discussions. A BBDR model was used in nine assessments included in the analysis. All of the models contained either a PBPK or dosimetry component in addition to the pharmacodynamic component; therefore, they have already been discussed in previous sections.

Most of the assessments using a BBDR model were published by environmental programs. The first use was in the 1996 IPCS diesel assessment (197), followed by the 2001 Health Canada PSL inhalation assessment of formaldehyde (198). The remaining assessments by environmental programs that included BBDR models were all performed by US EPA. In the 2000s, NESHAP regulations for formaldehyde were based on an original assessment using a BBDR model; the earliest NESHAP rule that was identified was published in 2003 (199). This was followed by three additional publications: a report from a US EPA research program that derived a NOAEL for carbofuran in 2006 (89), an interim drinking water health advisory for perchlorate in 2008 (99), and a draft IRIS RfC for formaldehyde published in 2010 (62).

BBDR models have also been developed and considered for use by US EPA in diesel and dioxin assessments, but not applied in final versions of the assessments. US EPA considered using a BBDR model in a diesel inhalation assessment, and did so for unit risk estimates of cancer in the 1998 draft (62); however, the risk estimate based on animal cancers was removed from the final publication in 2002 (86) due to non-relevance of the mode of action for human lung tumours. Similarly, a draft dioxin IRIS assessment (214) used a BBDR model in a dose–response assessment of animal data. A later reanalysis published in 2012 used only a PBPK model for the animal dose–response (65). The animal assessments of dioxin provided only supporting data, as the final RfD derivation in both documents was based on human data.

Three dose–response applications of BBDR models were identified in programs other than those evaluating the general environment. A CFD-BBDR model was discussed as supporting data for ACGIH's 2017 formaldehyde TLV (204), but insufficient information was provided in documentation to conclusively determine its use. Both uses of BBDR models in foods (EFSA's perchlorate assessment (149)) and pesticides (US EPA's Office of Pesticide Programs assessment of chlorpyrifos (187)) were published in 2014.

3.2 Analysis of the overall use of physiological models

Figure 1, which provides separate timelines for each type of physiological model, demonstrates that PBPK models were the most common physiological models used in regulatory dose–response assessments. During the study period, 114 regulatory reports used PBPK modelling in dose–response analyses, comprising 93% of the entire database. The first use of both chemical-specific inhalation dosimetry models and PBPK-PD or BBDR models was in 1996, approximately a decade after PBPK models made their debut in dose-response applications. Dosimetry models were identified in 14 assessments (11%), in which 6 were combined with PBPK models (5%). PBPK-PD or BBDR models were used in 9 assessments (7%), with toxicokinetic components of the models described by PBPK models and inhalation dosimetry models in 5 (4%) assessments each.

Overall dose–response use of physiological models varied by exposure domain, as presented in Figure 3. Physiological models were applied only by environmental and occupational programs in the 1980s and 1990s, with 75% of uses in environmental programs in the 1980s and evenly split between the two domains in the 1990s. The 2000s continued to see most applications in evaluations of exposures in the general environment (78%), with an additional 30% from occupational exposures and 3% from programs evaluating pesticide exposures (total of greater than 100% because four assessments were both environmental and occupational). The 2010s saw an increase in the contribution of food and pesticide assessments (9% and 17%, respectively), and a decrease in the fraction of occupational assessments (13%), with general environmental assessments at 61%.

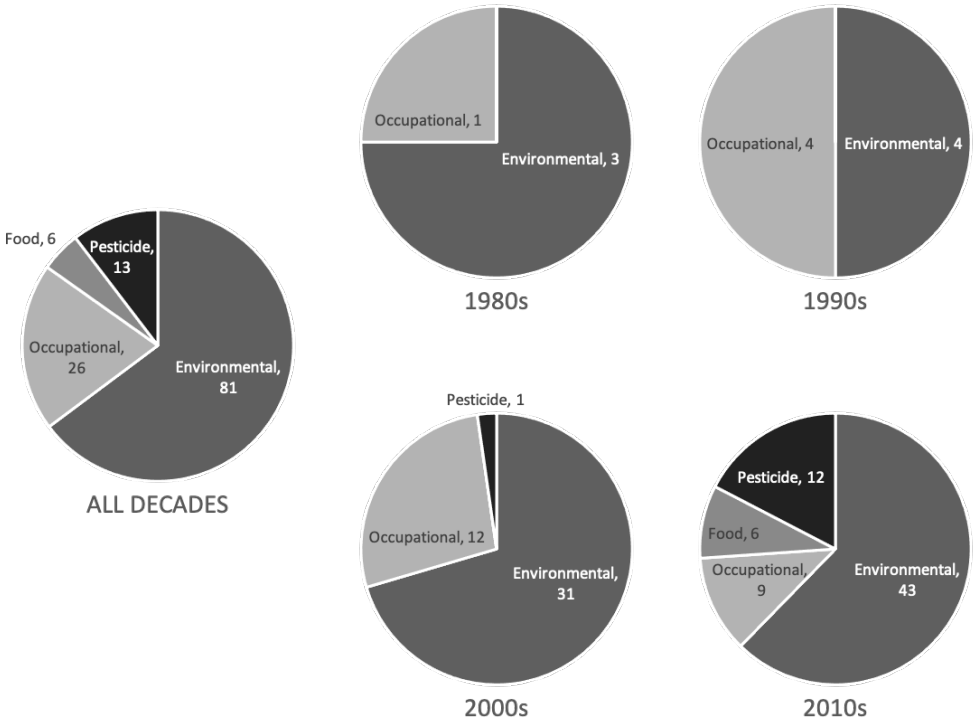


Figure 3. Use of physiological models in dose–response assessments by exposure domain, by decade

Guidance documents discussing physiological models were also predominantly produced by environmental organizations (74%), as presented in Figure 4. The first guidance document mentioning physiological models published by an environmental organization was in 1989, compared with 1999 for pesticide, 2006 for food, and 2008 for occupational organizations. Five guidance documents specifically focused on physiological modelling were written by environmental agencies, with the sixth physiological model-specific guidance document published by a pesticide organization.

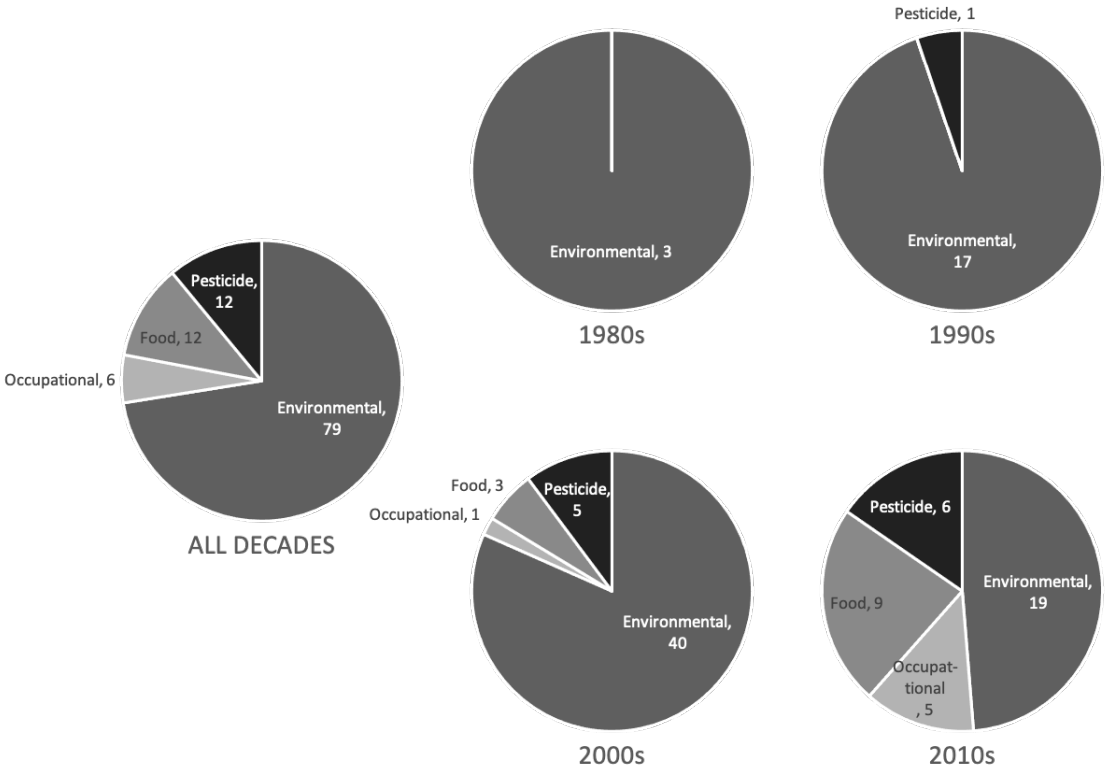


Figure 4. Availability of guidance documents mentioning dose–response uses of physiological modelling by exposure domain, by decade

Dose–response applications of physiological models were performed for 72 chemicals or chemical groupings (for example, for cumulative risk assessments of disinfection byproducts, pyrethroids, or pyrethrins), as presented in Table 2. Dichloromethane was the chemical that was most commonly evaluated using physiological dose–response modelling with eight assessments, followed by 2-butoxyethanol (ethylene glycol monobutyl ether) with seven and tetrachloroethylene with six, and four applications each for 2-butoxyethanol and acrylamide. For most chemicals, a physiological model was used for dose–response purposes in only one regulatory risk assessment.

Table 2 – Number of assessments per chemical

Number of Applications	8	7	6	5	4	3	2	1	Total Chemicals
Number of Chemicals	1	1	1	0	2	9	9	49	72

As demonstrated in Figure 5, the use of physiological models in dose–response analyses occurred predominantly in US organizations: overall, 73% of the assessments included in this study were from US programs. This observation was consistent over time—the highest proportion reached by non-US organizations in any of the decades was less than one third. This was despite the earliest dose–response uses of physiological models occurring around the same time both in US (1986) and internationally (1987).

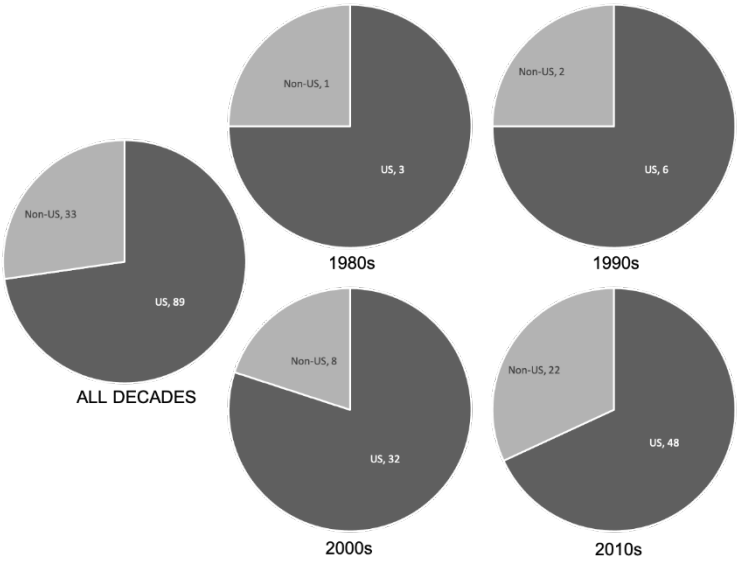


Figure 5. US vs. non-US uses of physiological models in dose–response analyses, by decade

Figure 6 outlines how physiological models were typically used in regulatory assessments. The models were primarily used to derive HECs or HEDs, which was the approach used in 56% of assessments. A smaller subset (15%) of reports used the models to calculate data-derived UFs, and a further 12% of assessments used the models to influence UF selection in a more qualitative manner. An additional 15% of documents used PBPK models in some other way in the dose–response assessment (details on the approaches used are discussed throughout the preceding sections). In 8% of assessments, it was not possible to tell whether PBPK models

influenced the dose–response analysis due to insufficient documentation. Some variation in these overall trends occurred when considering exposure domain. In evaluations published by occupational programs, only 31% of model uses were confirmed to directly derive HECs, as 27% of models were used in some other way and it was not possible to identify the use of models in 35% of assessments. In assessments performed by pesticide programs, the models were predominantly (85%) used for data-derived UFs.

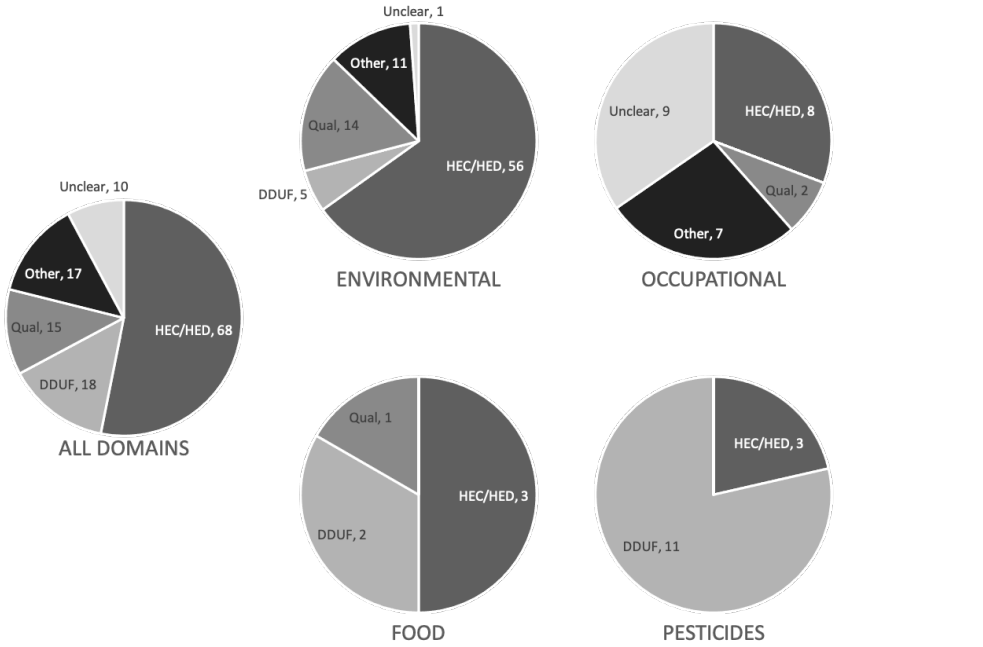


Figure 6. Methods of application of physiological models in regulatory dose–response assessments, by exposure domain

Only 61% of regulatory applications were confirmed to have run a physiological model *de novo* (see Figure 7). A third of the publications relied on published model results, while 6% of reports did not provide sufficient details to determine if the model was run specifically for the assessment. Publications from programs deriving occupational exposure limits differed from programs evaluating other sources of exposure, as 77% of occupational assessments relied on model results published elsewhere (versus 23% for environmental, 0% for pesticides, and 50% for foods).

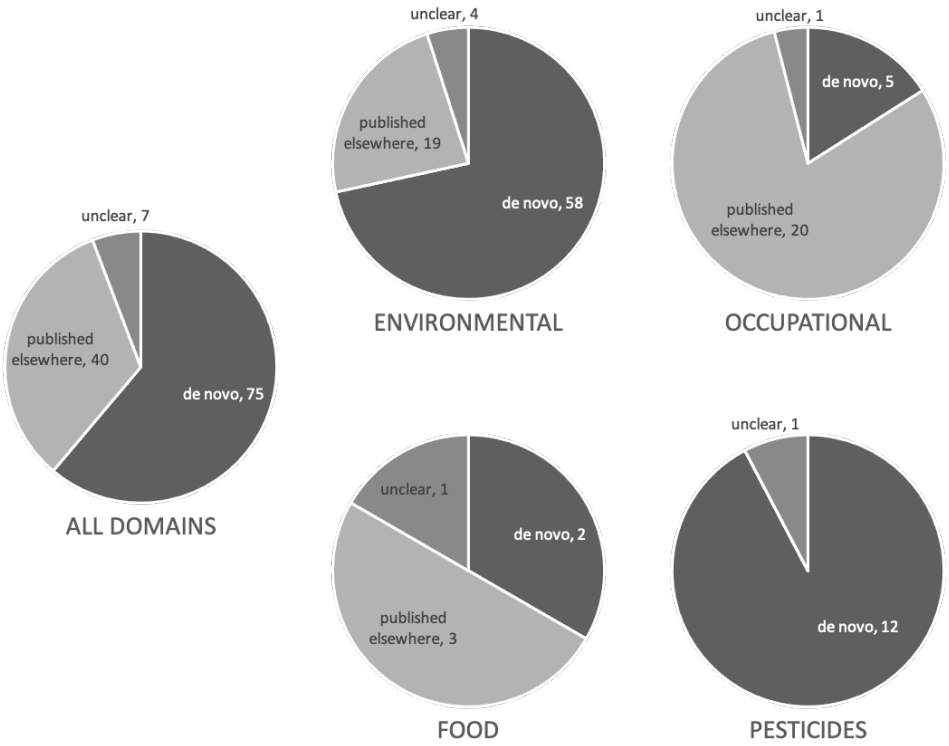


Figure 7. Source of physiological model data, by exposure domain

Seven compounds were selected for analysis of consistency of use of physiological models on a chemical-by-chemical basis. Dichloromethane, tetrachloroethylene, and 2-butoxyethanol (ethylene glycol monobutyl ether) were selected because they were the most commonly used PBPK models in regulatory dose–response assessments. Trichloroethylene was selected as it was the chemical for which dose–response applications of a PBPK model were identified in the scientific literature (see Chapter 2). Acrylamide and deltamethrin were selected because they were the most commonly used models in food and pesticide assessments, respectively. Formaldehyde was selected as it was an example of a combined dosimetry and PBPD model that was used in multiple regulatory assessments.

Analysis of the use of physiological models on a chemical-by-chemical basis indicates inconsistencies among regulatory organizations in decisions to apply physiological models in dose–response assessments. The first dichloromethane assessments using a PBPK model were published in 1987 (11, 47), and although most subsequent dichloromethane evaluations incorporated a PBPK model, the model was not used in the 1993 ATSDR MRL (215), 2009 ECHA SCOEL IOELV (216), and ACGIH TLV (which initially quantitatively derived in 1989,

but listed as having been last updated in 1999) (217). The tetrachloroethylene PBPK model was first used as an alternative approach in a draft IRIS addendum published in 1986 (48), followed by a 1997 US EPA contractor report (84), with other organizations only using the model beginning in the 2000s (15, 38, 58, 121); however, no tetrachloroethylene model was used in assessments published in 1993 (218, 219), 1997 (220), 2005 (221), or 2009 (222, 223). The PBPK model for 2-butoxyethanol was first used in the 1999 IRIS assessment (49), and in the 1999 ACGIH TLV (130); although all subsequently published assessments used a PBPK model, the earlier ECHA SCOEL (224) and ATSDR (225) assessments would have had access to the model publications used for the US EPA and ACGIH (226, 227) application of the PBPK model. Use of trichloroethylene PBPK models in dose–response assessments in the scientific literature occurred as early as the 1980s (see Chapter 2), but the US EPA AEGL was the first identified regulatory assessment to use the model, using a 2000 model (228) in its 2008 assessment (80). PBPK modelling was used in a 2011 IRIS assessment for trichloroethylene (57), but no other dose–response application was identified in assessments published after the 2000 model (229-231) or 2008 AEGL assessment (232, 233). An acrylamide PBPK model was first used in a 2010 IRIS assessment (54); all subsequent assessments also used the PBPK model (36, 151, 153), but a 2009 evaluation (234) did not use the 2007 model used in the IRIS assessment. The deltamethrin PBPK models developed by US EPA in 2006 (235) and 2010 (236) were used in 2011 (176) and draft 2017 (186) US EPA pyrethrin assessments, as well as a 2015 US EPA deltamethrin assessment (184), but were not used in a recent PMRA deltamethrin reevaluation (237). Deltamethrin evaluations in 2015 by EFSA (238) and 2016 by JMPR (239) also did not use a PBPK model, but the assessments relied on Acceptable Daily Intakes first derived in 2000 and 2002, respectively. The formaldehyde CFD-PBPD model was first used in a 2001 Health Canada PSL assessment (198) and appeared to potentially influence the 2017 ACGIH TLV (204), but was not used in some other subsequent evaluations (240-242).

4.0 Discussion

Chemical-specific and scenario-specific data can be incorporated into dose–response assessments to replace default assumptions when refinement of risk estimates is warranted. The use of physiological kinetic and dynamic modelling is one of the more common approaches that government organizations use to produce increasingly data-informed exposure guidelines or

margin of exposure assessments. This chapter described the evolution of the use of physiological models by organizations from different geographical regions and that address chemicals from different exposure domains.

Most of the organizations considered in this analysis either used physiological models in some of their assessments or discussed the potential dose–response applications of physiological models in guidance documents. Even when the models were not used for a particular chemical, documentation tended to discuss available models but often stated that the models were not applied because they were not appropriate. The most common justifications for not using a model were absence of models for the route or species involved in the extrapolation; documentation frequently mentioned the absence of a validated human model.

Despite the general support for the use of physiological models in dose–response assessments among organizations, there were differences in adoption date and application frequency. A few organizations began to use the models in dose–response assessments in the 1980s: physiological models were used in US EPA's tetrachloroethylene addendum, dichloromethane assessments by US EPA and Health Canada, and a NIOSH contract on butadiene. Limited additional uses were identified in the 1990s (three by ACGIH, two by US EPA, and one each by OSHA, Health Canada, and IPCS). In the 2000s, the US EPA used the models in 22 dose–response assessments, with at least one application every year except 2001; although some other organizations used the models in their assessments, the occurrence was less frequent (six for ACGIH, four in EU, three by Health Canada, ATSDR with two, and NIOSH, AIHA, and IPCS using one each). More organizations tended to use the models in the 2010s, with an increase in frequency in many of the programs that had used such models in previous decades, and uptake in pesticide and food assessments began to occur. The variability in uptake was also observed when looking at use of the models for specific chemicals—for all of the chemicals included in the chemical-by-chemical analysis, assessments were identified in which a physiological model could have been used in dose–response, but was not applied. In some of these instances, particularly in occupational assessments, one potential justification for not using a model could have been that the organizations selected a POD based on human data, reducing the need to apply the model for extrapolation purposes; however, there were still many assessments in which a model could have refined a dose–response assessment but was not used by the organization.

Even within organizations, various programs demonstrated differences in the adoption of the models in dose–response assessments. For example, a 1987 Health Canada drinking water guideline incorporated dichloromethane PBPK model results, but no further drinking water assessments used physiological models until the 2010s, when they were used in ten publications. Three PSL assessments in the 1990s and 2000s used physiological models (along with one additional application in a 2010 PSL update), but only two Screening Assessment Reports of the hundreds published under CMP considered physiological models. Only one additional use of a physiological model was identified by any other Health Canada program. Reasons for this might have at least partially related to data availability—many of the PSL and drinking water assessments were for chemicals that had more robust datasets and validated physiological models when compared with the chemicals evaluated under CMP. Moreover, problem formulation drives the use of fit-for-purpose risk assessments, which might contribute to a decreased need for the refinement provided by physiological models in the screening margin-of-exposure assessments performed under CMP.

Reasons for variability in the adoption of the approaches among and within organizations might be related to data and resource availability: this is a potential factor influencing the different methods of applying the models in dose–response assessments. Some organizations typically performed physiological modelling *de novo*, either using in-house resources or contracting the modelling. Other organizations tended to use model results published elsewhere, either directly as PODs or UFs, or indirectly by influencing the selection of UFs or providing qualitative support for POD selection. As the latter approach can reduce the cost and time of applying the models, as well as the need for expertise on modelling approaches, it could potentially increase the adoption of physiological models by some organizations. Programs that used this approach included ACGIH, US EPA's AEGL program, Health Canada's Indoor Air Contaminant Assessment Section, and EFSA's CONTAM panel. However, for PODs to be obtained directly from peer reviewed literature without the need for additional modelling, requires PBPK modellers to present results for species, tissues, doses, dose metrics, and studies that would be selected as PODs by government organizations. This would require more effort and risk assessment expertise by PBPK modellers, as well as increased collaboration between modellers and the risk assessment community, and could be complicated by the fact that PODs selected could vary among organizations, depending on the purpose of their risk assessments.

Moreover, potential new key studies published subsequent to the PBPK models would result in published model outputs that again would not be relevant. One approach PBPK modellers could use to resolve some of these issues is to publish a regression equation for portions of the model output that are linear, such as was performed by Teeguarden et al. (243), which was later used to derive the POD for Health Canada's RIAQG for acetaldehyde (29). However, this could only be performed if kinetics are linear in the ranges of concentrations relevant for human exposures. Therefore, although the use of published PBPK model results can simplify the adoption of physiological models in regulatory dose–response assessments, organizations reliant on this approach might be limited in their ability to refine their assessments if model publications do not include sufficient details to allow for a full evaluation of results.

When comparing the exposure source categories of organizations (environmental, occupational, pesticides, and food) that developed the assessments, environmental programs had a much higher frequency of adoption of physiological models in dose–response assessments, as demonstrated both in the development of guidance documents discussing physiological models (Figure 4) and use of the models in deriving exposure guidelines or in MOE assessments (Figure 3). This could be due in part to the fact that there are more environmental programs performing dose–response assessments; for example, US EPA and Health Canada had at least 5 and 4 different programs, respectively, that used physiological models in dose–response assessments. However, adoption of physiological models was also performed earliest in environmental and occupational dose–response assessments (in 1986 and 1987, respectively), followed only by pesticides beginning in 2006 and foods in 2010. As demonstrated in Figure 3, the use of physiological models in dose–response assessments in occupational and environmental categories was similar in the 1980s and 1990s, but was much higher in environmental assessments in the 2000s and 2010s. The frequency of adoption of physiological models in pesticide and food assessments was lower than other categories in the first three decades considered in the study, but in the 2010s was consistent with or higher than use in occupational dose–response assessments. This pattern was similar to that observed in dose–response assessment applications of physiological models in peer-reviewed scientific literature, and may therefore be related to model availability for the compounds of interest. However, other factors might also affect this, as discussed in the previous chapter, such as food and pesticide assessments being restricted to risk assessment methods outlined in legislation that might be

older or less flexible. Moreover, as early acceptance of physiological models in dose–response assessments occurred for environmental and occupational programs, programs in these domains might have been motivated to explore use of the models in order to keep abreast of innovative practices adopted by other organizations.

For ten of the assessments, the use of physiological models in dose–response assessment cannot be confirmed, but it is assumed they have either influenced POD selection or UF selection as the outcomes of models were discussed from this perspective when summarizing the derivation. Removing the unclear uses of the models would remove nine occupational applications (one in 1990s, four in 2000s, and four in 2010s) and one environmental use (in 2010s). The reason for this lack of clarity is due to an absence of details in the documentation of these assessments, as the selected UFs were not presented. To address this lack of detail, it is recommended that organizations ensure sufficient transparency for readers to clearly understand the basis of both PODs and UFs, as good risk assessment practice.

Producing guidance referring to the use of physiological modelling in dose–response assessments can indicate an organization's support for the approach. The degree to which guidance documents discussed physiological modelling varied—some guidance documents fully focused on physiological modelling, while others only briefly mentioned that the models were approaches that can be used in dose–response assessments. However, even a mere mention of the potential use of a physiological model could be helpful as it is still an indication of support for the approach, and might also normalize the consideration of physiological models in future risk assessments. Several organizations had no guidance mentioning the potential use of physiological models in dose–response assessments, yet still used the models in their assessments. Therefore, the absence of relevant guidance documents is not necessarily an indication of an absence of support for the use of an approach. Conversely, other organizations indicated their support for the approaches in guidance documents, but had few or no such applications. For example, foods assessment programs published more guidance discussing the models than applications, and pesticides programs had an equal number of publications of guidance documents and dose–response assessment applications. This is likely an indication that the lower frequency of application in these domains is affected by factors other than support for the use of the models.

Many similarities can be observed when comparing the timeline of physiological model use in dose–response assessments from regulatory reports (presented in this chapter) with publications in the scientific literature (presented in Chapter 2). The earliest dose–response uses of the models in both sources were in 1986 and 1987. While physiological model applications in dose–response assessments in the scientific literature continued to be published during the remainder of the 1980s, there were no further regulatory uses in the decade; however, relevant publications in the scientific literature also declined in the early 1990s. The dose–response applications of physiological models began to increase in both venues in the mid- to late-1990s. Although the increase was higher earlier in the scientific literature in the 2000s—resulting in an average of 5.9 relevant publications per year in the scientific literature vs. 4 per year in government reports—the average publications per year in the regulatory database in the 2010s (7.8 per year) exceeded the averages in any decade in scientific literature. The maximum annual number of dose–response applications of physiological models in government reports also slightly exceeded that of scientific publications (10 vs. 8 per year). Although the decline in average relevant publications per year that was observed in the 2010s in the scientific literature did not occur in government publications, Figure 1a demonstrates the possibility of a slight downward trend in regulatory applications throughout the last decade. For both sources of dose–response assessments, PBPK models were the predominant type of physiological models used, and heavily influenced the timeline of overall physiological model use, with dosimetry and BBDR models playing only a minor role in comparison. The first dose–response application of a BBDR model was earlier in scientific literature than in regulatory assessments (1990 vs. 1996); however, chemical-specific dosimetry models were applied earlier in regulatory publications (1996 vs. 1999).

Other commonalities can be observed when comparing the use of models in dose–response assessments in government reports with that in the scientific literature, as outlined in Chapter 2. In assessments published both in scientific literature and government reports, the models used were primarily PBPK models (96% and 93%, respectively). The publications included in both chapters were also primarily developed by US authors or organizations (77% in the scientific database and 73% of government assessments for all decades). Although non-US authored assessments increased in the last decade, they comprised almost half of the scientific publications, versus only approximately one-third of government assessments. In both sources,

dose–response applications of models were only performed once for the majority of chemicals. Dose–response assessments published in both literature and government sources were most common for dichloromethane (16 in the scientific literature and eight in government reports) and tetrachloroethylene (eight in the scientific literature and six in government publications). Large differences between the two sources of dose–response assessments were identified for trichloroethylene and 2-butoxyethanol. Publications of original trichloroethylene model applications were common in the scientific literature (N = 17) versus only two in regulatory documents, and seven government assessments of 2-butoxyethanol were identified (versus one in the scientific literature).

A main limitation of the study is that not all regulatory dose–response applications of the models were identified. Due to resource limitations, the inclusion of organizations was restricted to the national level in Canada and US, regional level in Europe, and international level in other regions. This means that organizations that perform dose–response assessments in Canadian provinces and US states, as well as countries around the world—many of which perform excellent risk assessment work—were not reflected in the results of this assessment. Moreover, the analysis was restricted by the accessibility of reports. Some organizations did not publish older documents that had been superseded by newer assessments; therefore, some older applications of the models might have been overlooked. Some organizations were excluded as their entire database of risk assessment work was unpublished; notably, food assessments were only available from EFSA and JECFA, meaning that use of physiological models from other foods organizations were not included in totals in the documents. The limited accessibility to older documents and the need to search in document repositories specifically using physiological model-related keywords meant that for some programs incomplete information was obtained. Although most relevant documents were likely obtained using these methods, non-relevant documents were not gathered, which restricted quantification of model use to frequency counts; therefore, the analyses could not reliably evaluate the proportion of published documents using physiological models.

In conclusion, organizations included in this assessment tended to indicate support for the use of physiological models in dose–response assessments. Most organizations either discussed the benefits and potential dose–response applications of the models in guidance documents, or used the models to derive exposure guidelines or perform margin of exposure assessments.

Nearly as many regulatory examples of physiological model use were identified from the subset of organizations included in this analysis, compared with the number of publications with dose–response applications of the models in scientific literature. The number of government examples would presumably be even higher if other organizations—such as at the Canadian provincial and U.S. state level, or different countries internationally—were included. This is an indication that the use of physiological models might be limited due to an absence of available models and data. However, despite the potential implications of data limitations on the adoption of physiological model use in regulatory dose–response assessments, there are indications that other factors might affect the regulatory uptake of models. As discussed earlier, incorporation of the models into dose–response analyses occurred more frequently in some organizations than others, and even among programs within the same organization. Physiological models tended to be used much more frequently by environmental programs than those assessing risks of exposures from workplaces, foods, or pesticides. The analysis also indicated that some organizations would determine a physiological model as not fit for use in dose–response assessment, even if other regulatory programs had already adopted it.

To better identify factors other than data availability that affect the regulatory uptake of physiological models, the results of a survey of regulatory risk assessors is presented in Chapter 4. The chapter will examine the barriers and facilitators that impede or encourage the adoption of physiological models and other increasingly data-informed approaches.

REFERENCES

1. Tan YM, Worley RR, Leonard JA, Fisher JW. Challenges associated with applying physiologically based pharmacokinetic modeling for public health decision-making. Toxicological Sciences. 2018;162(2):341-8.

2. McLanahan ED, El-Masri HA, Sweeney LM, Kopylev LY, Clewell HJ, Wambaugh JF, et al. Physiologically Based Pharmacokinetic Model Use in Risk Assessment-Why Being Published Is Not Enough. Toxicological Sciences. 2012;126(1):5-15.

3. Andersen ME. Toxicokinetic modeling and its applications in chemical risk assessment. Toxicology Letters. 2003;138(1-2):9-27.

4. Barn P, Keefe AR, Slot N, Jardine KJ, Ziembicki S, Telfer J, et al. Canada should move toward adopting harmonized evidence-based OELs to consistently and adequately protect workers. Annals of Work Exposures and Health. 2020.

5. Government of Canada. Government of Canada Publications 2021 [Available from: http://publications.gc.ca/site/eng/search/search.html.

6. National Archives and Records Administration. Federal Register: The Daily Journal of the United States Government 2021 [Available from: https://www.federalregister.gov/.

7. US Department of Commerce. National Technical Reports Library 2021 [Available from: https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml.

8. US EPA. National Service Center for Environmental Publications (NSCEP) Simple Search 2021 [Available from: https://nepis.epa.gov/.

9. EFSA. EFSA Journal 2021 [Available from: https://efsa.onlinelibrary.wiley.com/journal/18314732.

10. WHO. INCHEM: Internationally Peer Reviewed Chemical Safety Information 2021 [Available from: http://www.inchem.org/#/search.

11. Health Canada. Dichloromethane (Guidelines for Canadian Drinking Water Quality). Ottawa, ON; 1987.

12. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Dichloromethane. Ottawa, ON; 2011.

13. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – 1,2–Dichloroethane. Ottawa, ON; 2013.

14. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Vinyl Chloride. Ottawa, ON; 2013.

15. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Tetrachloroethylene. Ottawa, ON; 2015.

16. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Toluene, Ethylbenzene and the Xylenes. Ottawa, ON; 2015.

17. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chromium. Ottawa, ON; 2016.

18. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Bromate. Ottawa, ON; 2016.

19. Health Canada. Lead in Drinking Water: Document for Public Consultation. Ottawa, ON; 2017.

20. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctane Sulfonate (PFOS). Ottawa, ON; 2018.

21. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctanoic Acid (PFOA). Ottawa, ON; 2018.

22. Environment Canada and Health Canada. Canadian Environmental Protection Act, Priority Substances List Assessment Report - Dichloromethane. Ottawa, ON; 1993.

23. Environment Canada and Health Canada. Priority Substances List Assessment Report - Chloroform. Ottawa, ON; 2001.

24. Environment Canada and Health Canada. Priority Substances List Assessment Report - 2-butoxyethanol. Ottawa, ON; 2002.

25. Environment Canada and Health Canada. Follow-up to the State of Science Report, 2000 Ethylene Glycol. Ottawa, ON; 2010.

26. Environment Canada and Health Canada. Draft screening assessment - 2-Pyrrolidinone, 1-methyl- (NMP) and 2-Pyrrolidinone, 1-ethyl- (NEP); Chemical Abstracts Service Registry Numbers (872-50-4 and 2687-91-4). Ottawa, ON; 2017.

27. Environment Canada and Health Canada. Screening Assessment for the Challenge: 2-Propenoic acid, ethyl ester (Ethyl acrylate); Chemical Abstracts Service Registry Number 140-88-5. Ottawa, ON; 2011.

28. Environment Canada and Health Canada. Science Approach Document Biomonitoring-based Approach 2 for Barium-containing Substances; Molybdenum-containing Substances; Silver-containing Substances; Thallium-containing Substances; Inorganic Tin-containing Substances. Ottawa, ON; 2016.

29. Health Canada. Residential Indoor Air Quality Guideline: Science Assessment Document – Acetaldehyde. Ottawa, ON; 2017.

30. ATSDR. Guidance for the Preparation of Toxicological Profiles. Atlanta, GA.

31. ATSDR. Guidance for the Preparation of Toxicological Profiles. Atlanta, GA; 2018.

32. ATSDR. Guidance for the Preparation of an Interaction Profile. Atlanta, GA; 2001.

33. ATSDR. Toxicological Profile for Methylene Chloride. Atlanta, GA; 2000.

34. ATSDR. Toxicological Profile for Vinyl Chloride. Atlanta, GA; 2006.

35. ATSDR. Toxicological Profile for Ethylbenzene. Atlanta, GA; 2010.

36. ATSDR. Toxicological Profile for Acrylamide. Atlanta, GA; 2012.

37. ATSDR. Toxicological Profile for RDX. Atlanta, GA; 2012.

38. ATSDR. Draft Toxicological Profile for Tetrachloroethylene. Atlanta, GA; 2014.

39. ATSDR. Toxicological Profile for Mercury. Atlanta, GA; 1999.

40. ATSDR. Draft Toxicological Profile for Trichloroethylene. Atlanta, GA; 2014.

41. US EPA. Interim Methods for Development of Inhalation Reference Doses Washington, DC; 1989. Report No.: EPA 600 8-88 066F.

42. US EPA. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. Washington, DC; 2006. Report No.: EPA/600/R-05/043F.

43. US EPA. Considerations for Developing a Dosimetry-Based Cumulative Risk Assessment Approach for Mixtures of Environmental Contaminants. Cincinnati, OH; 2007. Report No.: EPA/600/R-07/064.

44. US EPA. Uncertainty and Variability in Physiologically Based Pharmacokinetic Models: Key Issues and Case Studies. Washington, DC; 2008. Report No.: EPA/600/R-08/090.

45. US EPA. Proposed Approach to Efficiently Develop Physiologically Based Pharmacokinetic (PBPK) & Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK-PD) Models for Pesticides. Washington, DC; 2015.

46. NRC Committee on AEGLs. PBPK Modeling White Paper: Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9. Washington, DC: National Academies Press; 2010. p. 381-438.

47. US EPA. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action, and Epidemiology. Washington, D.C.; 1987. Report No.: EPA/600/8-87/030A.

48. US EPA. Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene): Updated Carcinogenicity Assessment for Tetrachloroethylene (Perchloroethylene,
PERC,PCE). Washington, DC; 1986. Report No.: EPA/600/8-82/005FA.

49. US EPA. Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE) (CAS No. 111-76-2) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 1999.

50. US EPA. Toxicological Review of Vinyl Chloride (CAS No. 75-01-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2000. Report No.: EPA/635R-00/004.

51. US EPA. Toxicological Review of Xylenes (CAS No. 1330-20-7) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2003. Report No.: EPA 635/R-03/001.

52. US EPA. Toxicological Review of 1,1,1-Trichloroethane (CAS No. 71-55-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2007. Report No.: EPA/635/R-03/013.

53. US EPA. Toxicological Review of Carbon Tetrachloride (CAS No. 56-23-5) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2010. Report No.: EPA/635/R-08/005F.

54. US EPA. Toxicological Review of Acrylamide (CAS No. 79-06-1) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2010. Report No.: EPA/635/R-07/009F.

55. US EPA. Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE) (CAS No. 111-76-2) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2010. Report No.: EPA/635/R-08/006F.

56. US EPA. Toxicological Review of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2011. Report No.: EPA/635/R-10/003F.

57. US EPA. Toxicological Review of Trichloroethylene (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2011. Report No.: EPA/635/R-09/011F.

58. US EPA. Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2012. Report No.: EPA/635/R-08/011F.

59. US EPA. Toxicological Review of Methanol (Non-cancer) (CAS No. 67-56-1) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2013. Report No.: EPA/635/R-11/001Fa.

60. US EPA. Toxicological Review of Trimethylbenzenes [CASRNs 25551-13-7, 95-63-6, 526-73-8, and 108-67-8]. Washington, DC; 2016. Report No.: EPA/635/R-16/161Fa.

61. US EPA. Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) (CASRN 121-82-4). Washington, DC; 2018. Report No.: EPA/635/R-18/211Fa.

62. US EPA. Toxicological Review of Formaldehyde - Inhalation Assessment (CAS No. 50-00-0) In Support of Summary Information on the Integrated Risk Information System (IRIS). Draft. Washington, DC; 2010. Report No.: EPA/635/R-10/002A.

63. US EPA. Toxicological Review of n-Butanol (CAS No. 71-36-3) In Support of Summary Information on the Integrated Risk Information System (IRIS). Draft. Washington, DC; 2011. Report No.: EPA/635/R-11/081A.

64. US EPA. Toxicological Review of Acrylonitrile (CAS No. 107-13-1) In Support of Summary Information on the Integrated Risk Information System (IRIS). Draft. Washington, DC; 2011. Report No.: EPA/635/R-08/013A.

65. US EPA. EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1. Draft. Washington, DC; 2011. Report No.: EPA/600/R-10/038D.

66. US EPA. Toxicological Review of tert-Butyl Alcohol (tert-Butanol) (CAS No. 75-65-0). Draft. Washington, DC; 2017. Report No.: EPA/635/R-16/079a.

67. US EPA. Toxicological Review of Ethyl Tertiary Butyl Ether (CASRN 637-92-3). Draft. Washington, DC; 2017. Report No.: EPA/635/R-17/016a.

68. US EPA. Toxicological Review of 1,4-Dioxane (With Inhalation Update) (CAS No. 123-91-1) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2013. Report No.: EPA/635/R-11/003F.

69. NRC Committee on AEGLs. Interim Acute Exposure Guideline Levels (AEGLs) for 1,2-Dibromoethane (CAS Reg. No. 106-93-4). Washington, DC; 2008.

70. NRC Committee on AEGLs. Styrene (CAS Reg. No. 100-42-5) Interim Acute Exposure Guideline Levels (AEGLs). Washington, DC; 2008.

71. NRC Committee on AEGLs. Ethylene Oxide Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9. Washington, DC: National Academies Press; 2010. p. 46-135.

72. NRC Committee on AEGLs. Furan Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9. Washington, DC: National Academies Press; 2010. p. 136-72.

73. NRC Committee on AEGLs. Chloroform Acute Exposure Guidelines. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 12. Washington, DC: National Academies Press; 2012. p. 120-70.

74. NRC Committee on AEGLs. Acrylonitrile Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 17. Washington, DC: National Academies Press; 2014. p. 13-95.

75. NRC Committee on AEGLs. Carbon Tetrachloride Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 17. Washington, DC: National Academies Press; 2014. p. 96-159.

76. NRC Committee on AEGLs. Methylene chloride (CAS Reg. No. 75-09-2) CH2Cl2 Interim Acute Exposure Guideline Levels (AEGLs) for NAS/COT Subcommittee for AEGLS. Washington, DC; 2009.

77. NRC Committee on AEGLs. Interim Acute Exposure Guideline Levels (AEGLs) for Ethylbenzene (CAS Reg. No. 100-41-4) C8H10. Washington, DC; 2009.

78. NRC Committee on AEGLs. Xylenes Acute Exposure Guideline Level. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9. Washington, DC: National Academies Press; 2010. p. 293-380.

79. NRC Committee on AEGLs. Toluene Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 17. Washington, DC: National Academies Press; 2014. p. 289-413.

80. NRC Committee on AEGLs. Trichloroethylene (CAS Reg. No. 79-01-6) Interim Acute Exposure Guideline Levels (AEGLs) for NAS/COT Subcommittee for AEGLs. Washington, DC; 2009.

81. US EPA. Provisional Peer Reviewed Toxicity Values for 4-Chlorobenzotrifluoride (CASRN 98-56-6). Cincinnati, OH; 2007.

82. US EPA. Provisional Peer Reviewed Toxicity Values for Hexachlorobutadiene (CASRN 87-68-3). Cincinnati, OH; 2007.

83. US EPA. Provisional Peer-Reviewed Toxicity Values for Isopropanol (CASRN 67-63-0). Cincinnati, OH; 2014.

84. US EPA. Application of Benchmark Dose Methodology to a Variety of Endpoints and Exposures. Washington, DC; 1997. Report No.: EPA/600/R-97/138.

85. US EPA. Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. External review draft. Washington, DC; 2002. Report No.: NCEA-1-0503.

86. US EPA. Health Asssessment Document for Diesel Engine Exhaust. Washington, DC; 2002. Report No.: EPA/600/8-90/057F.

87. US EPA. An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether. 2005. Report No.: EPA 600/R-04/123.

88. US EPA. The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water. Cincinnati, OH; 2003. Report No.: EPA/600/R-03/051.

89. US EPA. Construction of a Physiologically Based Pharmacokinetic/ Pharmacodynamic (PBPK/PD) Model for Carbofuran Using the Exposure Related Dose Estimating Model (ERDEM). Washington, DC; 2006. Report No.: EPA/600/R-06/135.

90. US EPA. Use of Physiologically Based Pharmacokinetic Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk. 2006. Report No.: EPA/600/R-06/014A.

91. US EPA. TSCA Work Plan Chemical Risk Assessment, N-Methylpyrrolidone: Paint Stripper Use CASRN: 872-50-4. 2015. Report No.: 740-R1-5002.

92. US EPA. Air Toxics Risk Assessment Reference Library Volume 1 Technical Resource Manual. Research Triangle Park, NC; 2004. Report No.: EPA-453-K-04-001A.

93. US EPA. Air Toxics Risk Assessment Reference Library Volume 2 Facility-Specific Assessment. Research Triangle Park; 2004. Report No.: EP A-453-K-04-001B.

94. US EPA. Air Toxics Risk Assessment Reference Library Volume 3 Community Scale Assessment. Research Triangle Park, NC; 2006. Report No.: EPA-452/K-06-001C.

95. US EPA. A Descriptive Guide to Risk Assessment Methodologies for Toxic Air Pollutants. Research Triangle Park, NC; 1993. Report No.: EPA-453/R-93-038.

96. US EPA. Study of Hazardous Air Pollutant Emissions from Electric Utility Steam Generating Units—Interim Final Report. Volume 1. Research Triangle Park, NC; 1996. Report No.: EPA-453/R-96-013a.

97. US EPA. Guidance Manual for the Integrated Exposure Uptake Biokinetic Model for Lead in Children. Research Triangle Park; 1994. Report No.: 540-R-93-081.

98. US EPA. Water Quality Criterion for the Protection of Human Health: Methylmercury. Washington, DC; 2001. Report No.: EPA-823-R-01-001.

99. US EPA. Interim Drinking Water Health Advisory For Perchlorate. Washington, DC; 2008. Report No.: EPA 822-R-08-025.

100. ECB. European Union Risk Assessment Report 2-Butoxyethanol CAS No: 111-76-2 EINECS No: 203-905-0. Luxembourg: European Commission; 2006.

101. ECB. European Union Risk Assessment Report 2-Butoxyethyl Acetate (EGBEA) CAS No: 112-07-2 EINECS No: 203-933-3. Luxembourg: European Commission; 2006.

102. ECB. European Union Risk Assessment Report Acrylic Acid CAS No: 79-10-7 EINECS No: 201-177-9. Luxembourg: European Commission; 2002.

103. ECB. Vinyl acetate CAS No.: 108-05-4 EINECS No.: 203-545-4. Luxembourg: European Commission; 2008.

104. ECHA. Chapter R.8: Characterisation of dose [concentration]-response for human health. Guidance on information requirements and chemical safety assessment. Helsinki, Finland: ECHA; 2012.

105. ECHA. Chapter R.7c: Endpoint specific guidance. Guidance on information requirements and chemical safety assessment. Helsinki, Finland: ECHA; 2012.

106. IPCS. Biomarkers and Risk Assessment: Concepts and Principles. Geneva, Switzerland; 1993. Report No.: Environmental Health Criteria 155.

107. IPCS. Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits. Geneva, Switzerland; 1994. Report No.: Environmental Health Criteria 170.

108. IPCS. Principles for the Assessment of Risks to Human Health from Exposure to Chemicals Geneva, Switzerland; 1999. Report No.: Environmental Health Criteria 210.

109. IPCS. Biomarkers In Risk Assessment: Validity And Validation. Geneva, Switzerland; 2001. Report No.: Environmental Health Criteria 222.

110. IPCS. Principles for Evaluated Health Risks in Children Associated with Exposure to Chemicals Geneva, Switzerland; 2006. Report No.: Environmental Health Criteria 237.

111. IPCS. Principles and Methods for the Risk Assessment of Chemicals in Food. Geneva, Switzerland; 2009. Report No.: Environmental Health Criteria 240.

112. IPCS. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration–Response Assessment. Geneva; 2005. Report No.: Harmonization Project Document No. 2.

113. IPCS. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva; 2010. Report No.: IPCS Harmonization Project No. 9.

114. IPCS. Guidance for Immunotoxicity Risk Assessment for Chemicals. Geneva, Switzerland; 2012. Report No.: Harmonization Project Document No. 10.

115. IPCS. Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. Geneva; 2017. Report No.: Harmonization Project Document No. 11.

116. IPCS. Assessment of Combined Exposure to Multiple Chemicals: Report of a WHO/IPCS International Workshop. 2009. Report No.: IPCS Harmonization Project Document No. 7.

117. Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Van Raaij M, Vickers C. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regulatory Toxicology and Pharmacology. 2011;60(2):S1-S14.

118. WHO. Guidelines for Drinking-water Quality, Third Edition. Geneva, Switzerland: WHO; 2004.

119. WHO. Guidelines for Drinking-water Quality, Fourth Edition incorporating the first addendum. Geneva, Switzerland: WHO; 2017.

120. WHO. Chemical mixtures in source water and drinking-water. Geneva: WHO; 2017.

121. WHO. Tetrachloroethylene. Geneva, Switzerland: WHO; 2006.

122. NIOSH. Derivation of Immediately Dangerous to Life or Health (IDLH) Values. Cincinnati, OH; 2014. Report No.: 2014-100.

123. NIOSH. Current Intelligence Bulletin: NIOSH Practices in Occupational Risk Assessment External Review Draft. Cincinnati, OH; 2018.

124. Requirements for DOL Agencies' Assessment of Occupational Health Risks, Stat. 29 CFR Part 2 (2008).

125. SCOEL. Methodology for derivation of occupational exposure limitsof chemical agents: The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL). Brussels, Belgium: European Commission; 2017.

126. Hattis D, Wasson J. A Pharmacokinetic/Mechanism-Based Analysis of the Carcinogenic Risk of Butadiene. Cambridge, MA: NIOSH; 1987. Report No.: PB88-20 2817.

127. ACGIH. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2020.

128. ACGIH. Carbon tetrachloride. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2001.

129. ACGIH. Ethylene glycol. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2017.

130. ACGIH. 2-butoxyethanol. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2003.

131. ACGIH. 2-butoxyethyl acetate. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2003.

132. ACGIH. 1-methoxy-2-propanol. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2013.

133. ACGIH. 2-metoxyethanol. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2006.

134. ACGIH. 2-metoxyethyl acetate. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2006.

135. ACGIH. Cyclohexane. 2015 TLVs(R) and BEIs(R) with 7th Edition Documentation. Cincinnati, OH; 2002.

136. ACGIH. Vinylidene chloride. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2001.

137. ACGIH. 2-butoxyethanol [BEI]. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2007.

138. ACGIH. Tetrahydrofuran [BEI]. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2008.

139. ACGIH. Acetone [BEI]. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2015.

140. AIHA. 2,3,3,3-Tetrafluoropropene. 2009 WEEL Update Set. Fairfax, VA; 2009.

141. OARS. trans-1-Chloro-3,3,3-Trifluoropropene (1233zd(E)). Cincinnati, OH; 2013.

142. NIOSH. Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione. Cincinnati, OH; 2016. Report No.: 2016-111.

143. NIOSH. Current Intelligence Bulletin: Health Effects of Occupational Exposure to Silver Nanomaterials. Revised External Review Draft. Cincinnati, OH; 2018.

144. Occupational Exposure to Methylene Chloride, Stat. 29 CFR Parts 1910, 1915 and 1926 (1997).

145. Occupational Exposure to 1,3-Butadiene, Stat. 29 CFR Parts 1910, 1915 and 1926 (1996).

146. ECHA RAC. Committee for Risk Assessment (RAC) Opinion on scientific evaluation of occupational exposure limits for Acrylonitrile. Helsinki, Finland: ECHA; 2018. Report No.: ECHA/RAC/O-0000001412-86-188/F.

147. EFSA. Existing approaches incorporating replacement, reduction and refinement of animal testing: applicability in food and feed risk assessment. Efsa J. 2009;7(6):1052.

148. EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on Lead in Food. Efsa J. 2010;8(4):1570.

149. EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables. Efsa J. 2014;12(10):3869.

150. Husoy T, Hart A, Pirow R, Mennes WC, Wolfle D, Fowler PA, et al. The EFSA assessment of the risks to public health associated with bisphenol A (BPA) exposure. Toxicology Letters. 2015;1):S76.

151. EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on acrylamide in food. Efsa J. 2015;13(6):4104.

152. EFSA Panel on Contaminants in the Food Chain, Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, et al. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. Efsa J. 2018;16(12):e05194.

153. JECFA. Acrylamide (addendum). Safety Evaluation of Certain Contaminants in Food: prepared by the seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, Switzerland; 2011. p. 1-151.

154. EFSA Scientific Committee. Guidance on human health risk-benefit assessment of foods. Efsa J. 2010;8(7):1673.

155. European Commission Joint Research Centre. Applicability of QSAR analysis to the evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances for dietary risk assessment. EFSA Supporting Publications. 2010;7(5):50E.

156. EFSA Scientific Committee. Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. Efsa J. 2013;11(3):3132.

157. EFSA. Modern methodologies and tools for human hazard assessment of chemicals. Efsa J. 2014;12(4):3638.

158. EFSA. Principles and process for dealing with data and evidence in scientific assessments. Efsa J. 2015;13(6):4121.

159. EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, et al. Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. Efsa J. 2017;15(5):e04849.

160. Alexander J, Benford D, Boobis A, Eskola M, Fink-Gremmels J, Fürst P, et al. Risk assessment of contaminants in food and feed. Efsa J. 2012;10(10):s1004.

161. JECFA. Guidance document for WHO monographers and reviewers evaluating contaminants in food and feed. Geneva; 2017.

162. PMRA. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides. Ottawa, ON; 2008. Report No.: SPN2008-01.

163. US EPA. Draft Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health Washington, DC; 1999.

164. US EPA. Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. Washington, DC; 2002.

165. US EPA. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. Washington, DC; 2016.

166. US EPA. Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose. Washington, DC; 2016.

167. EFSA. Panel on plant protection products and their residues on the Guidance Document (GD) for the establishment of acceptable operator exposure levels (AOELs). Efsa J. 2006;4(4):345.

168. EFSA. Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. Efsa J. 2008;6(5):705.

169. EFSA Panel on Plant Protection Products and their Residues. Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health. Efsa J. 2009;7(9):1167.

170. EFSA Panel on Plant Protection Products and their Residues. Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment. Efsa J. 2012;10(7):2799.

171. EFSA Panel on Plant Protection Products and their Residues. Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. Efsa J. 2012;10(10):2839.

172. Chemicals Regulation Directorate, Health Safety Executive UK. Investigation of the state of the art on identification of appropriate reference points for the derivation of health-based guidance values (ADI, AOEL and AAOEL) for pesticides and on the derivation of uncertainty factors to be used in human risk assessment. EFSA Supporting Publications. 2013;10(4):413E.

173. PMRA. Halauxifen-methyl. Ottawa, ON; 2014. Report No.: PRD2014-12.

174. PMRA. Sodium Omadine. Ottawa, ON; 2016. Report No.: PRVD2016-12.

175. US EPA. Reregistration Eligibility Decision for Propylene Oxide. Washington, DC; 2006. Report No.: EPA 738-R-06-029.

176. US EPA. Pyrethrins/Pyrethroid Cumulative Risk Assessment. Washington, DC; 2011.

177. US EPA. Re-Evaluation of the FQPA Safety Factor for Pyrethroid Pesticides. Washington, DC; 2011.

178. US EPA. Bifenthrin: Human Health Risk Assessment to Support Section 3 New Uses for a Bed Bug Treatment, Grass Grown for Seed, Tolerances for Imported Tea, and a Section 18 Emergency Exemption Use on Apple, Nectarine, and Peach. Washington, DC; 2012.

179. US EPA. Zeta-permethrin - Human Health Risk Assessment for New Poultry House Use and Agricultural Uses on Tropical Fruit, Artichoke, Barley, Oat, Rye, Buckwheat, and Pistachio. Washington, DC; 2012.

180. US EPA. Alpha-Cypermethrin - Human Health Risk Assessment for the New Active Ingredient. Washington, DC; 2012. Report No.: DP No. D376098.

181. US EPA. Tefluthrin: Human Health Risk Assessment for Proposed Section 3 Registration on Sugar Beet Seed (Non-Food Use). Washington, DC; 2012.

182. US EPA. Fenpropathrin. Human Health Risk Assessment for Section 3 Registration on Tropical Fruit and a Request for a Tolerance Without U.S. Registration on Tea. Washington, DC; 2012.

183. US EPA. Prallethrin. Human Health Risk Assessment for the Tolerance Petition to Amend the Section 3 Mosquito Adulticide Registration to Include Use of the Insecticide Over All Crops. Washington, DC; 2014.

184. US EPA. Deltamethrin. Human Health Risk Assessment for the Proposed Use of Deltamethrin as a Mosquito Adulticide over Agricultural Crops. Washington, DC; 2015.

185. US EPA. Lambda- & Gamma-Cyhalothrin: Human Health Draft Risk Assessment for Registration Review. Washington, DC; 2017.

186. US EPA. Pyrethrins. Preliminary Draft Human Health Risk Assessment for Registration Review. Washington, DC; 2017.

187. US EPA. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Washington, DC; 2014.

188. US EPA. Atrazine. Draft Human Health Risk Assessment for Registration Review. Washington, DC; 2018. Report No.: D418316.

189. US EPA. Evaluation of Carbaryl and Malathion Human Studies For Their Proposed Application in a Physiologically-Based Pharmacokinetic Model for Risk Assessment. Washington, DC; 2016.

190. US EPA. EPA's Office of Pesticide Programs' Review of the Status of Six PBPK Models in Preparation for the FIFRA SAP for the October 24-27, 2017. Washington, DC; 2017.

191. US EPA. Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling: Preliminary Evaluation and Case Study for the N-Methyl Carbamate Pesticides. Washington, DC; 2003.

192. US EPA. Revised N-Methyl Carbamate Cumulative Risk Assessment. Washington, DC; 2007.

193. US EPA. STATUS REPORT: Advances in Inhalation Dosimetry of Gases and Vapors with Portal of Entry Effects in the Upper Respiratory Tract. Washington, DC; 2009. Report No.: EPA/600/R-09/072.

194. US EPA. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. Washington, DC; 2012. Report No.: EPA/600/R-12/044.

195. NRC Committee on AEGLs. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC; 2001.

196. EPA U. STATUS REPORT: Advances in Inhalation Dosimetry for Gases with Lower Respiratory Tract and Systemic Effects. Washington, DC; 2011. Report No.: EPA/600/R-11/067.

197. IPCS. Diesel fuel and exhaust emissions. Geneva, Switzerland; 1996. Report No.: Environmental Health Criteria 171.

198. Environment Canada and Health Canada. Priority Substances List Assessment Report: Formaldehyde. Ottawa, ON; 2001.

199. National Emission Standards for Hazardous Air Pollutants for Stationary Combustion Turbines, Stat. 40 CFR Part 63 (2003).

200. NIOSH. Occupational Exposure to Refractory Ceramic Fibers. Cincinnati, OH; 2006. Report No.: 2006-123.

201. US EPA. Interim Acute Exposure Guideline Levels (AEGLs): Acrylic Acid. 2004.

202. US EPA. Methyl Methacrylate Interim Acute Exposure Guideline Levels (AEGLs). 2008.

203. ACGIH. Propylene oxide. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2014.

204. ACGIH. Formaldehyde. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2017.

205. US EPA. Guidelines for Developmental Toxicity Risk Assessment. Washington, DC; 1991. Report No.: EPA/600/FR-91/001.

206. US EPA. Guidelines for Reproductive Toxicity Risk Assessment. Washington, DC; 1996. Report No.: EPA/630/R-96/009.

207. US EPA. Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis. Washington, DC; 1997. Report No.: EPA/630/R-96/012.

208. US EPA. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories; Volume 2: Risk Assessment and Fish Consumption Limits. Third Edition. Washington, DC; 2000. Report No.: EPA 823-8-00-008.

209. JECFA. Annex 4 - The formulation of advice on compounds that are both genotoxic and carcinogenic. Safety evaluation of certain contaminants in food: Prepared by the Sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, Switzerland; 2006. p. 765-8.

210. US EPA. An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study. Washington, DC; 2009. Report No.: EPA/600/R-09/028F.

211. IPCS. Principles for Modelling Dose–Response for the Risk Assessment of Chemicals Geneva, Switzerland; 2009. Report No.: Environmental Health Criteria 239.

212. US EPA. Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision-Making With Case Study Examples. Washington, DC; 2009. Report No.: EPA/100/R-09/001.

213. EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, et al. Update: use of the benchmark dose approach in risk assessment. Efsa J. 2017;15(1):e04658.

214. US EPA. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds; Part II: Health Assessment for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds. Washington, DC; 2003.

215. ATSDR. Toxicological Profile for Methylene Chloride. Atlanta, GA; 1993.

216. SCOEL. Recommendation from the Scientific Committee on Occupational Exposure Limits for Methylene Chloride (Dichloromethane). Brussels, Belgium: European Commission; 2009. Report No.: SCOEL/SUM/130.

217. ACGIH. Dichloromethane. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2001.

218. Environment Canada and Health Canada. Priority Substances List Assessment Report - Tetrachloroethylene. Ottawa, ON; 1993.

219. ACGIH. Tetrachloroethylene. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2001.

220. ATSDR. Toxicological Profile for Tetrachloroethylene. Atlanta, GA; 1997.

221. ECB. European Union Risk Assessment Report TETRACHLOROETHYLENE CAS No: 127-18-4 EINECS No: 204-825-9. Luxembourg: European Commission; 2005. Report No.: EUR 21680 EN.

222. SCOEL. Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene (Perchloroethylene). Brussels, Belgium: European Commission; 2009. Report No.: SCOEL/SUM/133.

223. NRC Committee on AEGLs. Tetrachloroethylene (CAS Reg. No. 127-18-4) Interim Acute Exposure Guideline Levels (AEGLs). Washington, DC; 2009.

224. SCOEL. Recommendation from the Scientific Expert Group on Occupational Exposure Limits for 2-butoxyethanol. Brussels, Belgium: European Commission; 1996. Report No.: SCOEL/SUM/70.

225. ATSDR. Toxicological Profile for 2-butoxyethanol and 2-butoxyethanol acetate Atlanta, GA; 1998.

226. Corley RA, Bormett GA, Ghanayem BI. Physiologically Based Pharmacokinetics of 2-Butoxyethanol and Its Major Metabolite, 2-Butoxyacetic Acid, in Rats and Humans. Toxicology and Applied Pharmacology. 1994;129(1):61-79.

227. Corley RA. Assessing the risk of hemolysis in humans exposed to 2-butoxyethanol using a physiologically-based pharmacokinetic model. Occupational Hygiene. 1996;2:45-55.

228. Boyes WK, Bushnell PJ, Crofton KM, Evans M, Simmons JE. Neurotoxic and pharmacokinetic responses to trichloroethylene as a function of exposure scenario. Environmental Health Perspectives. 2000;108 Suppl 2:317-22.

229. ECB. European Union Risk Assessment Report Trichloroethylene CAS No: 79-01-6 EINECS No: 201-167-4. Luxembourg: European Commission; 2004. Report No.: EUR 21057 EN.

230. Health Canada. Guidelines for Canadian Drinking Water Quality: Supporting Documentation — Trichloroethylene. Ottawa, ON; 2005.

231. ACGIH. Trichloroethylene. 2020 TLVs(R) and BEIs(R) with 8th Edition Documentation. Cincinnati, OH; 2007.

232. SCOEL. Recommendation of the Scientific Committee on Occupational Exposure Limits for Trichloroethylene. Brussels, Belgium: European Commission; 2009. Report No.: SCOEL/SUM/142.

233. ECHA RAC. Trichloroethylene - Carcinogenicity dose-response analysis. 2014. Report No.: ECHA project SR13.

234. Environment Canada and Health Canada. Screening Assessment for the Challenge: 2-Propenamide (Acrylamide); Chemical Abstracts Service Registry Number 79-06-1. Ottawa, ON; 2009.

235. Mirfazaelian A, Kim KB, Anand SS, Kim HJ, Tornero-Velez R, Bruckner JV, et al. Development of a physiologically based pharmacokinetic model for deltamethrin in the adult male Sprague-Dawley rat. Toxicological Sciences. 2006;93(2):432-42.

236. Godin SJ, DeVito MJ, Hughes MF, Ross DG, Scollon EJ, Starr JM, et al. Physiologically Based Pharmacokinetic Modeling of Deltamethrin: Development of a Rat and Human Diffusion-Limited Model. Toxicological Sciences. 2010;115(2):330-43.

237. PMRA. Deltamethrin. Ottawa, ON; 2015. Report No.: PRVD2015-07.

238. EFSA. Review of the existing maximum residue levels for deltamethrin according to Article 12 of Regulation (EC) No 396/2005. Efsa J. 2015;13(11):4309.

239. JMPR. Deltamethrin (135). Pesticide residues in food 2016; Evaluations; Part I - Residues. Rome: WHO and FAO; 2017. p. 301-12.

240. Health Canada. Residential Indoor Air Quality Guideline: Formaldehyde. Ottawa, ON: Government of Canada; 2006.

241. NRC Committee on AEGLs. Interim Acute Exposure Guideline Levels (AEGLs) for Formaldehyde (CAS Reg. No. 50-00-0). Washington, DC; 2008.

242. SCOEL. Formaldehyde: Recommendation from the Scientific Committee on Occupational Exposure Limits. Brussels, Belgium: European Commission; 2017. Report No.: SCOEL/REC/125.

243. Teeguarden JG, Bogdanffy MS, Covington TR, Tan C, Jarabek AM. A PBPK Model for Evaluating the Impact of Aldehyde Dehydrogenase Polymorphisms on Comparative Rat and Human Nasal Tissue Acetaldehyde Dosimetry. Inhalation Toxicology. 2008;20(4):375-90.

Appendix A

This appendix includes a list of all of the identified assessments from the included organizations that used PBPK, dosimetry, or PBPK-PD or BBDR modelling.

Table A.1 – Regulatory assessments using a physiological model to inform dose–response analyses

Evaluation	PBPK	Dosi-metry	BBDR	Year
Environmental programs				
Health Canada Guidelines for Canadian Drinking Water Quality				
Dichloromethane	x			1987
Dichloromethane	x			2011
1,2-dichloroethane	x			2013
Vinyl chloride	x			2013
Tetrachloroethylene	x			2015
Toluene, ethylbenzene, and xylenes	x			2015
Bromate	x			2016
Chromium	x			2016
Lead (draft)	x			2017
PFOS	x			2018
PFOA	x			2018
Health Canada Priority Substance List Assessments				
Dichloromethane	x			1993
Chloroform	x			2001
Formaldehyde		x	x	2001
2-butoxyethanol	x			2002
Ethylene glycol follow-up	x			2010
Health Canada Chemicals Management Plan Assessments				
2-propenoic acid, ethyl ester (ethyl acrylate)	x	x		2011
NMP & NEP (draft)	x			2017
Health Canada Residential Indoor Air Quality Guidelines				
Acetaldehyde	x			2017
Agency for Toxic Substances and Disease Registry Minimal Risk Levels				
Methylene chloride	x			2000
Vinyl chloride	x			2006
Ethylbenzene	x			2010
Acrylamide	x			2012
RDX	x			2012
Tetrachloroethylene (draft)	x			2014
United States Environmental Protection Agency (US EPA) Integrated Risk Information System Assessments				
Tetrachloroethylene	x			1986
Dichloromethane (draft)	x			1987
Ethylene glycol monobutyl ether	x			1999

Evaluation	PBPK	Dosi-metry	BBDR	Year
Vinyl chloride	x			2000
Xylenes	x			2003
1,1,1-trichloroethane	x			2007
Carbon tetrachloride	x			2010
Acrylamide	x			2010
Ethylene glycol monobutyl ether	x			2010
Formaldehyde (draft)	x	x	x	2010
Acrylonitrile (draft)	x			2011
Dichloromethane	x			2011
Dioxin (draft)	x			2011
Trichloroethylene	x			2011
n-Butanol (draft)	x			2011
Tetrachloroethylene	x			2012
Methanol	x			2013
1,4-dioxane	x	x		2013
Trimethylbenzenes	x			2016
Ethyl tertiary butyl ether (draft)	x			2017
Tert-butyl alcohol (draft)	x			2017
RDX	x			2018
US EPA Acute Exposure Guideline Levels				
Acrylic acid (draft)		x		2004
1,2-dibromoethane (draft)	x			2008
Methylene chloride (draft)	x			2008
Styrene (draft)	x			2008
Trichloroethylene (draft)	x			2008
Methyl methacrylate (draft)		x		2008
Ethylbenzene (draft)	x			2009
Ethylene oxide	x			2010
Furan	x			2010
Xylenes	x			2010
Chloroform	x			2012
Acrylonitrile	x			2014
Carbon tetrachloride	x			2014
Toluene	x			2014
US EPA Provisional Peer Reviewed Toxicity Values				
4-chlorobenzotrifluoride	x			2007
Hexachlorobenzene	x			2007
US EPA Toxic Substances Control Act Assessments				
n-methylpyrrolidone	x			2015
US EPA water programs				
Methylmercury	x			2001
Perchlorate	x		x	2008
US EPA National Emission Standards for Hazardous Air Pollutants				

Evaluation	PBPK	Dosi-metry	BBDR	Year
Formaldehyde		x	x	2003
Other US EPA assessments				
Tetrachloroethylene (benchmark dose)	x			1997
Perchlorate (draft)	x			2002
Diesel	x	x		2002
Drinking water disinfection by-products (mixture)	x			2003
Ethylene glycol monobutyl ether	x			2005
Carbofuran	x		x	2006
Chloroform	x			2006
European Chemicals Bureau Risk Assessment Reports				
Acrylic acid	x	x		2002
2-butoxyethanol	x			2006
2-butoxyethyl acetate	x			2006
Vinyl acetate	x			2008
European Chemicals Agency Risk Assessment Committee Assessments				
Lead and its compounds in jewellery	x			2011
International Programme on Chemical Safety				
Diesel fuel		x	x	1996
Tetrachloroethylene	x			2006
Occupational				
American Conference of Governmental Industrial Hygienists Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs)				
Carbon tetrachloride TLV	x			1996
Vinylidene chloride TLV	x			1999
2-Butoxyethanol TLV	x			1999
Cyclohexane TLV	x			2002
2-Butoxyethyl acetate TLV	x			2003
2-Methoxyethanol TLV	x			2006
2-Methoxyethyl acetate TLV	x			2006
2-butoxyethanol BEI	x			2007
Tetrahydrofuran BEI	x			2008
1-Methoxy-2-propanol TLV	x			2013
Propylene oxide TLV		x		2014
Acetone BEI	x			2015
Ethylene glycol TLV	x			2017
Formaldehyde TLV		x	x	2017
American Industrial Hygiene Association and Occupational Alliance for Risk Science Workplace Environmental Exposure Levels				
2,3,3,3-tetrafluoropropene	x			2009
trans-1-Chloro-3,3,3-Trifluoropropene (1233zd(E))	x			2013
National Institute for Occupational Safety and Health Recommended Exposure Limits				
Butadiene	x			1987
Refractory ceramic fibers		x		2006

Evaluation	PBPK	Dosi-metry	BBDR	Year
Diacetyl and 2,3-pentanedione	x	x		2016
Silver nanomaterials (draft)	x			2018
Occupational Safety and Health Administration Permissible Exposure Limits				
Methylene chloride	x			1997
European Chemicals Bureau				
Refer to the four risk assessment reports listed under the environmental section				
European Chemicals Agency Risk Assessment Committee				
Acrylonitrile	x			2018
Foods				
European Food Safety Authority Panel on Contaminants in the Food Chain assessments				
Lead	x			2010
Perchlorate	x		x	2014
Acrylamide	x			2015
Bisphenol A	x			2015
PFOS and PFOA	x			2018
Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives assessments				
Acrylamide	x			2011
Pesticides				
US EPA assessments				
Propylene oxide	x			2006
Pyrethroid	x			2011
Bifenthrin	x			2012
Zeta-cypermethrin	x			2012
Alpha-cypermethrin	x			2012
Tefluthrin	x			2012
Fenpropathrin	x			2012
Prallethrin	x			2014
Chlorpyrifos	x		x	2014
Deltamethrin	x			2015
Lambda- & gamma-cyhalothrin	x			2017
Pyrethrins (draft)	x			2017
Atrazine	x			2018

Appendix B

This appendix presents a list of guidance documents identified from included organizations that mentioned the potential use of PBPK, dosimetry, or PBPK-PD or BBDR modelling.

Table A.2 – Regulatory guidance documents describing potential dose–response applications of physiological models

Guidance document title	Year	PBPK	Dosi-metry	BBDR
Environmental				
Agency for Toxic Substances and Disease Registry (ATSDR)				
Interaction Profile Guidance	2001	x		x
Profile development guidance (Unable to identify when original undated version was published; downloaded in 2014)	Undated & 2018	x		x
ATSDR and United States Environmental Protection Agency (US EPA)				
Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances	1993	x		
US EPA Risk Assessment Forum				
Guidelines for Developmental Toxicity Risk Assessment	1991			x
The Use of the Benchmark Dose Approach in Health Risk Assessment	1995	x		
Guidelines for Reproductive Toxicity Risk Assessment	1996			x
Proposed Guidelines for Carcinogen Risk Assessment (draft)	1996	x		x
Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis	1997			x
Assessment of Thyroid Follicular Cell Tumors	1998	x		x
Guideline for Carcinogen Risk Assessment (draft)	1999	x		
Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures	2000	x		x
Exploration of Perinatal Pharmacokinetic Issues	2001	x		
A Review of the Reference Dose and Reference Concentration Processes	2002	x		x
Framework for Cumulative Risk Assessment	2003	x		
Methods for Identifying a Default Cross-Species Scaling Factor	2004	x		
Guidelines for Carcinogen Risk Assessment	2005	x		x
Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (draft)	2007	x		
Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision-Making With Case Study Examples	2009			x
Advances in Inhalation Dosimetry of Gases and Vapors with Portal of Entry Effects	2009	x	x	
Advances in Inhalation Dosimetry for Gases with Lower Respiratory Tract and Systemic Effects	2011	x	x	

Guidance document title	Year	PBPK	Dosi-metry	BBDR
Recommended Use of Body Weight3/4 as the Default Method in Derivation of the Oral Reference Dose	2011	x		x
Benchmark Dose Technical Guidance	2012	x		
Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment	2012	x	x	x
Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation	2014	x		x
US EPA Integrated Risk Information System				
Interim Methods for Development of Inhalation Reference Doses	1989	x		
Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry	1994	x		
US EPA Acute Exposure Guideline Levels (AEGLs)				
SOPs for deriving AEGLs	2001	x	x	
PBPK Modeling White Paper: Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels	2010	x[a]		x
US EPA Office of Research and Development				
Development of Risk Assessment Methodology for Land Application and Distribution and Marketing of Municipal Sludge	1989	x		
Development of Risk Assessment Methodology for Municipal Sludge Landfilling	1989	x		
Computational Methods for Sensitivity and Uncertainty Analysis for Environmental and Biological Models	2001	x		
US EPA Office of Solid Waste and Emergency Response				
Risk Assessment Guidance for Superfund: Volume III - Part A, Process for Conducting Probabilistic Risk Assessment	2001	x		
US EPA Office of Pollution Prevention and Toxics				
Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations Under the Toxic Substances Control Act	2017	x		
Application of Systematic Review in TSCA Risk Evaluations	2018	x		
US EPA Water				
Draft water quality criteria methodology: human health	1998	x		
Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories Volume 2 Risk Assessment and Fish Consumption Limits Third Edition	2000			x
Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Technical Support Document Volume 1: Risk Assessment	2000	x		x
Drinking Water Contaminant Candidate List 3—Final	2009	x		
US EPA Air				
A Descriptive Guide to Risk Assessment Methodologies for Toxic Air Pollutants	1993	x	x	
Study Of Hazardous Air Pollutant Emissions From Electric Utility Steam Generating Units Interim Final Report, Volume 1	1996	x		
Protection of Stratospheric Ozone: Removal of Restrictions on Certain Fire Suppression Substitutes for Ozone-Depleting Substances; and Listing of Substitutes	2002	x		

Guidance document title	Year	PBPK	Dosi-metry	BBDR
Air Toxics Risk Assessment Reference Library Volume 1 Technical Resource Manual	2004	x		
Air Toxics Risk Assessment Reference Library Volume 2 Facility-Specific Assessment	2004	x		
Air Toxics Risk Assessment Reference Library Volume 3 Community-Scale Assessment	2006	x		
US EPA National Center for Environmental Assessment				
Principles of Developmental Toxicity Risk Assessment	1995	x		
Characterization of Data Uncertainty and Variability in IRIS Assessments Pre-pilot vs Pilot/Post-pilot	2000	x		
Research report: Conducting a Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems	2000	x		x
Developing Relative Potency Factors for Pesticide Mixtures: Biostatistical Analyses of Joint Dose-Response	2003	x		x
A Cross-Species Mode of Action Information Assessment: A Case Study of Bisphenol A	2005	x		
A framework for assessing health risks of environmental exposures to children	2006	x		x
Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects	2006	x		
Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment	2006	x[a]	x	x
Considerations for Developing a Dosimetry-Based Cumulative Risk Assessment Approach for Mixtures of Environmental Contaminants	2007	x[a]		x
Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document	2007	x		x
Uncertainty and Variability in Physiologically Based Pharmacokinetic Models: Key Issues and Case Studies	2008	x[a]		
An Approach to Using Toxicogenomic Data In U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study	2009			x
US EPA Other				
Developmental Toxicology: Risk Assessment and the Future	1990	x		
Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA	2004	x		x
Framework for Metals Risk Assessment	2007	x		x
Guidance on the Development, Evaluation, and Application of Environmental Models	2009	x		
Potential for Incorporation of Genetic Polymorphism Data in Human Health Risk Assessment	2010	x		
Next Generation Risk Assessment: Recent Advances in Molecular, Computational, and Systems Biology	2014	x		
Non-monotonic dose-response (draft)	2014	x		
European Chemicals Agency (ECHA) Risk Assessment Committee (RAC)				

Guidance document title	Year	PBPK	Dosi-metry	BBDR
Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health V2.1	2012	x		x
Guidance on information requirements and chemical safety assessment Chapter R.7c: Endpoint specific guidance	2012	x		
International Programme on Chemical Safety				
Biomarkers and Risk Assessment: Concepts and Principles	1993	x		
EHC 170 Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits	1994	x		
EHC 210 Principles for the assessment of risks to human health from exposure to chemicals	1999	x		
Biomarkers In Risk Assessment: Validity And Validation	2001	x		
Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration–Response Assessment	2005	x		x
EHC 237 Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals	2006	x		x
Environmental Health Criteria 239 Principles for Modelling Dose–Response for the Risk Assessment of Chemicals	2009			x
Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food. Chapter 5 – Dose–Response Assessment and Derivation of Health-Based Guidance Values	2009	x		
Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment	2010	x[a]		x
Guidance for Immunotoxicity Risk Assessment for Chemicals	2012	x		
Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization	2017	x		
World Health Organization Water				
Guidelines for Drinking-water Quality, Third Edition; Volume 1: Recommendations	2004	x		
Chemical mixtures in source water and drinking-water	2017	x		x
Guidelines for Drinking-water Quality, Fourth Edition Incorporating the First Addendum	2017	x		
Occupational				
National Institute for Occupational Safety and Health				
Derivation of IDLH values	2014	x		x
NIOSH Practices in Occupational Risk Assessment (draft)	2018	x	x	
Occupational Safety and Health Administration				
Requirements for DOL Agencies' Assessment of Occupational Health Risks (Proposed rule)	2008	x		
ECHA Scientific Committee on Occupational Exposure Limits				
Methodology for derivation of occupational exposure limits of chemical agents	2017	x		

Guidance document title	Year	PBPK	Dosi-metry	BBDR
ECHA RAC				
Refer to the four risk assessment reports listed under the environmental section				
Foods				
European Food Safety Authority				
Existing approaches incorporating replacement, reduction and refinement of animal testing: applicability in food and feed risk assessment	2009	x		
Guidance on human health risk-benefit assessment of foods	2010	x		x
Applicability of QSAR analysis to the evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances for dietary risk assessment	2010	x		
Risk assessment of contaminants in food and feed	2012	x		
Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment	2013	x		
Modern methodologies and tools for human hazard assessment of chemicals	2014	x		x
Principles and process for dealing with data and evidence in scientific assessments	2015	x		
Update: use of the benchmark dose approach in risk assessment	2017			x
Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age	2017	x		
International Programme on Chemical Safety				
Refer to Environmental Health Criteria 240 listed in the environmental section				
Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives				
Annex 4 - The formulation of advice on compounds that are both genotoxic and carcinogenic	2006			x
Guidance document for WHO monographers and reviewers evaluating contaminants in food and feed	2017	x		
Pesticides				
Pest Management Regulatory Agency				
The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides	2008	x		
US EPA				
Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health (draft)	1999	x		
Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity	2002	x		
Proposed Approach to Efficiently Develop Physiologically Based Pharmacokinetic (PBPK) & Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK-PD) Models for Pesticides	2015	x[a]		x[a]

Guidance document title	Year	PBPK	Dosi-metry	BBDR
Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides	2016	x		
Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose	2016	x		
European Food Safety Authority Scientific Panel on Plant health, Plant protection products and their Residues				
Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from the Commission on the Guidance Document (GD) for the establishment of acceptable operator exposure levels (AOELs)	2006	x		
Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/20051	2008	x		x
Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health	2009	x		x
Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment	2012	x		
Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues	2012	x		x
Investigation of the state of the art on identification of appropriate reference points for the derivation of health-based guidance values (ADI, AOEL and AAOEL) for pesticides and on the derivation of uncertainty factors to be used in human risk assessment	2013	x		

[a]Guidance document was focused on PBPK or BBDR modelling

Chapter 4 – Contextual Factors Influencing Incorporation of Chemical- and Scenario-Specific Data in Regulatory Dose–Response Assessments

ABSTRACT

Various dose–response approaches can be used to incorporate chemical- and scenario-specific data to allow for refinement over default assumptions including: physiologically-based modelling, quantitative incorporation of human variability, data-derived extrapolation factors, mode of action or adverse outcome pathway analysis, cumulative risk assessments with multiple chemicals or non-chemical stressors, chemical-specific duration adjustment, and quantitative uncertainty analysis. The implementation of these methods varies among—and even within—regulatory organizations, suggesting that data and model availability is not the only factor influencing their adoption. This study surveyed risk assessors in regulatory programs involved in evaluating chemicals in the general environment, including pesticides and food contaminants, and in the occupational environment, to explore factors that might promote or hinder the use of increasingly data-informed approaches. Analysis of survey responses was guided by a conceptual framework developed to describe contextual influences of evidence-based decision making in regulatory policy. Although the availability and accessibility of data was discussed as a major barrier to incorporation of increasingly data-informed approaches, other contextual factors were described as influencing their adoption. External contextual factors with implications on uptake included the regulatory environment, domestic and international alignment, expertise of external participants such as peer reviewers and stakeholders, characteristics of software and tools, and chemical-dependent factors. The internal context influenced adoption through problem formulation, availability of resources such as time and money, organizational and management support, and training. All of these factors converged to affect policy decisions regarding the effectiveness, appropriateness, and ability to implement of an approach. The conceptual framework was updated based on survey results, which will help to facilitate the consideration of contextual factors when developing recommendations for enhancing uptake of increasingly data-informed approaches in regulatory dose–response assessments.

1.0 INTRODUCTION

Dose–response analysis is a critical stage in human health risk assessment for chemicals in the general and occupational environments (1, 2). Outputs of dose–response analyses—including exposure guidelines or benchmarks for margin of exposure assessments—are targets against which human exposures can be compared, with a goal of protecting population health. Traditional dose–response assessments rely on defaults that are effectively generic assumptions based on broader knowledge of chemicals: one such example is the application of 10-fold uncertainty factors to reflect potential pharmacokinetic and pharmacodynamic variability when extrapolating from animals to humans and to the broader human population (3-5). Chemical- and scenario-specific data can be incorporated into dose–response analyses to allow for refinement of risk assessments (6-17). The various dose–response methodologies fall along a data-informed continuum, with the use of defaults having lower refinement (but presumed to be protective), whereas increasingly biologically-based approaches incorporating greater chemical- and scenario-specific data reflective of a chemical's mode of action are considered to be more predictive (5).

The adoption of methodologies to incorporate greater chemical- and scenario-specific data into dose–response assessments is variable among regulatory organizations. As discussed in Chapter 3, using the example of physiologically based models as a means of refining regulatory dose–response assessments, some organizations regularly considered the potential to incorporate chemical- and scenario-specific data and had higher rates of adoption, whereas other organizations had limited or inconsistent use of the approaches. As data and model availability was not sufficient to explain the variability among organizations, other factors are also expected to influence rates of adoption of dose–response refinements.

The objective of this study was to investigate various factors that can promote or hinder a regulatory organization's uptake of methods to incorporate chemical- and scenario-specific data into the dose–response assessment process. This was performed by surveying individuals from regulatory organizations who perform risk assessments or manage risk assessors. The methods that participants were asked to consider in the survey are listed in Table 1. Survey analysis was guided using a previously-developed conceptual framework that describes contextual influences of evidence-based decision making in policy (18, 19). The framework was then updated based on survey results, to generate a conceptual framework that can be used to

guide recommendations for increasing uptake of increasingly data-informed approaches in regulatory dose–response assessments.

Table 1. Chemical-specific and scenario-specific data-informed dose–response approaches for consideration in this study

Approach	Description of relevant applications for dose–response
BMD modelling	Statistical approach to derive a POD that can be used instead of a NOAEL or LOAEL in an assessment. NOTE: although this method is statistical modelling rather than incorporating chemical-specific data, it is being included for comparison as it has gained widespread uptake in the risk assessment community.
PBPK, PBPD, BBDR, and dosimetry modelling	Quantitative application of chemical-specific PBPK/PBPD/BBDR/ dosimetry models for interspecies, intraspecies, route, high-to-low dose, and/or duration extrapolations. Models are used to estimate of tissue dose and/or response, through adjustment of PODs and/or UFs. Generic or categorical models or equations (e.g. regional gas dose ratios, regional deposited dose ratio, allometric scaling factors) are excluded for the purpose of this evaluation.
Quantitative evaluation of sensitive subpopulations/ human variability	Quantitative approaches to addressing biological aspects of human variability (including sensitive subpopulations and lifestages) in the derivation of a POD or application of uncertainty factors. Can include probabilistic methods, application of CSAFs or other data-derived adjustment factors, or application of PBPK, PBPD, BBDR, or dosimetry models. Excludes assessments limited to the incorporation of exposure characteristics of sensitive subpopulations (or probabilistic modelling restricted to exposure data), and the application of additional default UFs to address sensitive subpopulations or lifestages.
CSAFs and other data-derived UFs	Derivation of CSAFs or other chemical-specific data-derived UFs, or application of probabilistic methods using chemical-specific data to derive uncertainty factors. Excludes categorical or pathway-specific adjustment factors.
MOA/AOP pathway analysis	Application of frameworks for the analysis of MOAs or AOPs to systematically evaluate appropriateness of PODs and dose–response approaches (e.g., linear vs. non-linear).
Combined exposures to multiple chemicals / cumulative risk assessment (including non-chemical stressors)	Application of dose–response analyses to address the combined risk of exposure to multiple hazards (including multiple chemicals, or may also include non-chemical hazards, including social determinants of health). Includes only approaches that result in new dose–response derivations for the scenario (e.g. application of PBPK, PBPD or BBDR models). Excludes methods that rely on existing dose–response assessments (e.g. application of hazard index or use of TEF/TEQ without original dose–response analysis).

Table 1 continued

Approach	Description of relevant applications for dose–response
Chemical-specific duration adjustment	Chemical-specific adjustments for duration that incorporate toxicokinetics or other hazard data in dose-response assessments to extrapolate duration for the point of departure (e.g. extrapolating from a subchronic study for a chronic duration assessment, to address intermittent exposure, or to address workshifts of non-standard durations). Can include chemical-specific extrapolation approaches such as PBPK, PBPD, BBDR, or dosimetry modelling. Excludes linear extrapolations that are not chemical specific (e.g. Haber, Brief & Scala, power model or ten Berge equations, or other equations relying on concentration x time).
Quantitative uncertainty analysis	Incorporation of quantitative analysis of uncertainty in various aspects of the dose–response that result in a range for the POD, UFs, and/or overall assessment values. Uncertainty analyses that do not directly quantitatively impact the final assessment are excluded.
Other	Any other similar approach an organization might have used to quantitatively incorporate chemical-specific data into dose–response assessments.

BMD: benchmark dose; POD: point of departure; NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level; PBPK: physiologically based pharmacokinetic; PBPD: physiologically based pharmacodynamic; BBDR: biologically based dose–response; UF: uncertainty factor; CSAF: chemical-specific adjustment factor; MOA: mode of action; AOP: adverse outcome pathway; TEF: toxic equivalency factor; TEQ: toxic equivalency quotient.

1.1 Conceptual framework guiding research

To help guide analysis and interpretation of survey results, an existing conceptual framework was used. As stated above, the research objective for this chapter is to identify the factors that promote and hinder risk assessors' decisions to include data-informed approaches in dose–response assessments. This nature of inquiry can be likened to the types of decisions that are made in evidence-based decision making in medicine. A conceptual framework was previously developed by Dobrow and colleagues to identify the influence that context can have on evidence-based decision making when moving away from clinical decision making and towards the complex and uncertain decisions made at the population policy level (18, 19). The framework, illustrated in Figure 1, was used to investigate how contextual factors impact the incorporation of increasingly data-derived approaches into the dose–response assessment process.

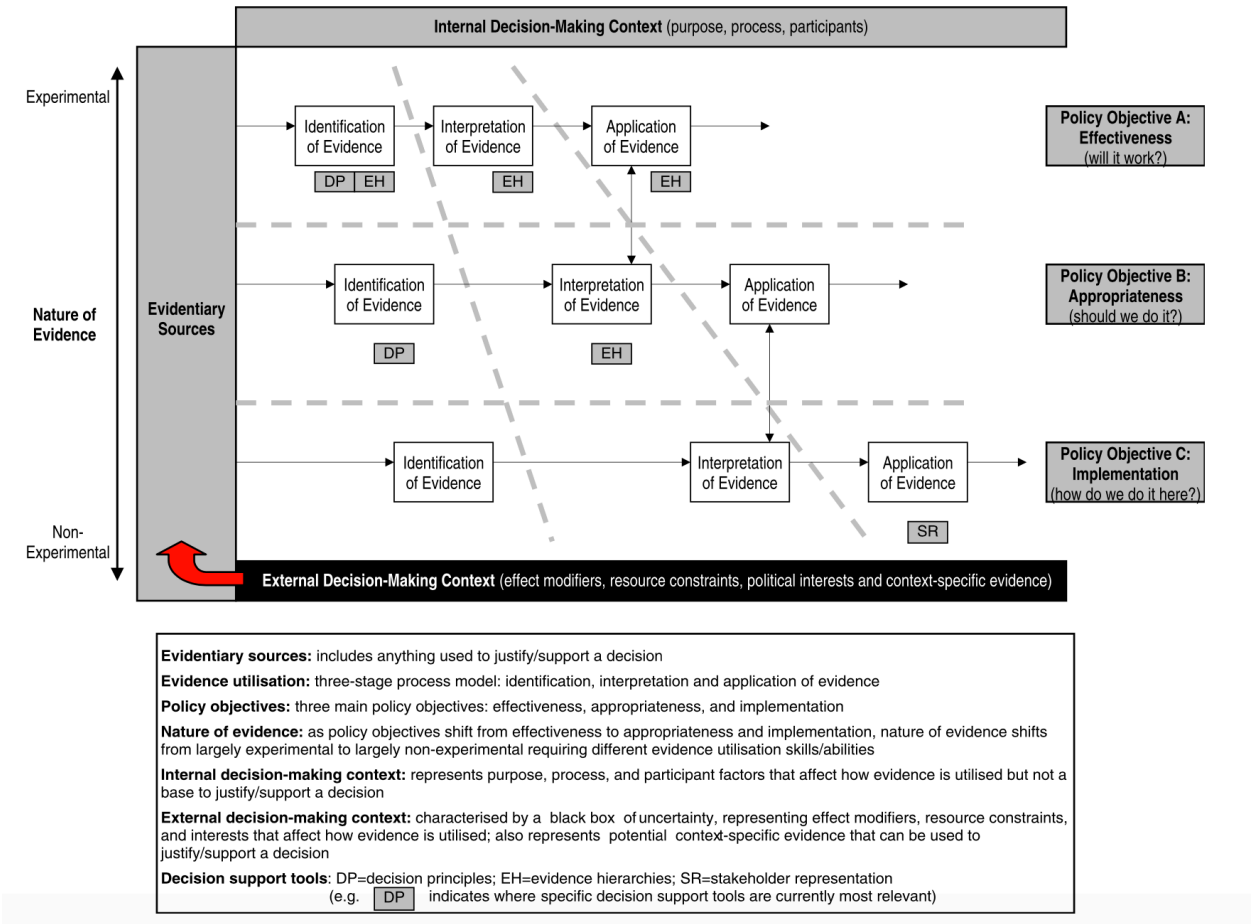


Figure 1. Conceptual framework for consideration of evidence and context in development of health policy recommendations.
Reproduced with permission from Elsevier, from Dobrow et al. (19).

The conceptual framework for context-based evidence-based decision making consists of three major components: evidence, context, and utilisation. Each of these components, and how they relate to the present research, is described in the following paragraphs.

Dobrow et al. describe two orientations for evidence, a philosophical-normative orientation and the practical-operational orientation. The former orientation of evidence is context-free and deals with the most ideal data that could be used in the decision-making process, focusing on aspects such as validity and reliability. In this project, this type of evidence can be represented by the body of toxicological (including pharmacokinetic and mechanistic) and epidemiological data that is available and could potentially be considered for a given dose–response assessment. The practical-operational orientation of evidence does consider evidence to be contextual, influencing whether specific data sources are considered to be important for

decision making. To properly consider the factors affecting whether certain types of data are considered to be useful for dose–response assessment, the issue of context must be explored.

The Dobrow framework posits that both internal and external context have influence even in evidence-based decision-making processes. Despite the scientific nature of dose–response analyses, various non-scientific factors can affect the decision-making process. Although availability of scientific evidence can affect the likelihood that a particular approach is adopted by the risk assessment community, internal and external contextual barriers and facilitators are also likely to be important factors influencing incorporation of chemical- and scenario-specific data in dose–response assessments.

In the Dobrow framework, evidence and context interact to influence how data will be used in decision-making processes. For dose–response assessments, this can be seen in the way that the same data can be interpreted and applied differently among various organizations, resulting in different exposure guidelines (4, 20). The conceptual framework identifies three main stages of evidence utilisation: identification of evidence, interpretation of evidence, and application of evidence. Using the authors' descriptions of each of the stages, they can be applied to the dose–response assessment component of risk assessment. Identification of evidence encompasses the gathering and selection of studies to be considered within the dose–response assessment process. Interpretation of evidence refers to the evaluation of each of the studies included in the original database for their quality, relevance, and utility for decision making for the dose–response assessment. Finally, in the application of evidence stage, the data that were obtained and interpreted are used in the decision-making process, of which weight of evidence and dose–response analyses are critical components, but are potentially influenced by various internal and external contextual factors. In the refined conceptual framework (19), Dobrow and colleagues overlaid three policy objectives over the stages of identification, interpretation, and application of evidence. These policy objectives were effectiveness (i.e., will the approach work?), appropriateness (i.e. should we apply the approach?), and implementation (i.e., how should the approach be applied for our assessment?). The model demonstrates a continuum of the nature of evidence that corresponds to the policy decisions, with the evidentiary sources being most empirical for effectiveness, and least empirical for implementation.

2.0 METHODS

Key informant surveys were used to obtain data from participants. A pilot phase was performed to evaluate the clarity of the survey questions and instructions. Pilot surveys were sent to three former risk assessors from government organizations, and updates were made post-pilot based on participants' responses and an accompanying evaluation. The final survey included the two open-ended questions given in Table 2, which were designed to encourage fulsome discussions by respondents. Participants were also given the list of approaches to incorporate chemical- and scenario-specific data and their corresponding descriptions presented in Table 1 to guide their discussions.

Table 2 – Questions completed by survey participants

Q1. Many factors might hinder or prevent the application of data-informed approaches, whereas others might encourage their application. In your experiences in performing dose–response assessments, which factors act or have acted as barriers to the application of the data-informed approaches, and which have encouraged their application?
Q2. Please provide any other comments related to your or [organization name]'s experiences with the application of data-informed approaches that you think might be useful or relevant. If your organization has any experience with overcoming the barriers discussed above or encouraging the use of the data-informed approaches, discussions related to this would be useful for inclusion.

To gain an understanding of the application of dose–response assessments in a variety of settings, the organizations that were contacted varied by chemical exposure domain (environmental, occupational, pesticide, and food contaminant exposures) and geographical area (Canada, United States, European Union, and international). For each geographical region considered in the study, one or two governmental programs for each category of exposure were contacted. In total, 17 programs were initially contacted. For each program, requests were made to obtain the names of two to three individuals who perform dose–response assessments (hereafter referred to as "risk assessors") and one to two individuals who manage risk assessors (hereafter referred to as "managers"). For programs in which risk assessments are performed by expert committee members that are external to the organization, the names of two to three external committee members and one to two program secretariat representatives were requested. Surveys were sent directly between the research team and potential participants.

Organizations were contacted from January to May 2020, and all completed surveys were received by July 2020.

Surveys were evaluated using qualitative coding methods, in which three levels of coding were used for both descriptive and interpretive analysis. One author (MD) performed all coding. Initial coding was performed using line-by-line coding of the surveys, in which one or more phrases or keywords that summarized the discussion theme were attributed to each line of text from survey responses. Next, the initial codes were grouped into related themes. Finally, the themes were categorized using concept-driven coding, with high-level concepts derived from the Dobrow conceptual framework for context-based evidence-based decision-making described earlier. In the interest of confidentiality, and due to the small sample size, only a narrative presentation of survey analysis is presented collectively, without explicit comparison among exposure categories or geographical regions.

Approval for the study was obtained from both the University of Ottawa Research Ethics Board and Health Canada and the Public Health Agency of Canada's Research Ethics Board, and all participants provided written informed consent prior to completing the surveys.

3.0 RESULTS

Seven programs participated in the surveys, with nine programs declining to participate; one additional program initially agreed to participate but did not provide names of potential respondents. Participating programs provided names of one to four potential survey respondents. In total, 14 completed surveys were received from the 19 contacts provided by participating organizations (participation rate of 74% of contacted individuals), with seven responses from risk assessors and seven from individuals who manage risk assessors. Multiple completed surveys were received from each of the exposure domains. Completed surveys were received three of the four geographic regions, with all international level organizations declining to participate in the survey. The sample size of responses received was sufficient to reach saturation, as there was much overlap in the contextual factors described in survey responses.

Results of the analysis of survey results are presented throughout this section as a narrative, with sections divided according to the components of the Dobrow framework.

3.1 Non-contextual evidentiary sources

3.1.1 Data availability

A major barrier that was mentioned by nearly all respondents was data availability. Respondents frequently mentioned that the absence of empirical data prevented them from using the various chemical-specific data-informed approaches. Most respondents mentioned data limitations and data-poor chemicals in general; however, some specific areas where data were frequently lacking were mentioned. These examples included: studies with a sufficient number of doses or group sizes; data to identify the most sensitive lifestages for chemical exposure; studies of combined exposures of chemicals with non-chemical stressors; data for the development of PBPK models; and human data including pharmacokinetic data to validate human PBPK models. As one respondent stated, "All the frameworks, guidelines, evidence grading systems and the like do not make up for less than ideal data." Some of the participants also stated that the availability of data required for a compound was a facilitator to the incorporation of chemical-specific data in a dose–response assessment. In the words of one respondent, "Availability of well-conducted, clearly applicable studies showing the link between the data collected and the outcome of interest to the risk assessor" facilitated the application of the approaches. The incorporation of chemical-specific data was described as being helpful for the assessment of data-rich compounds, as it allowed for the maximization of use of available information.

3.1.2 Availability of models

The availability of models was mentioned as a factor that could act as either a barrier or facilitator to the application of the models for risk assessment, particularly in reference to PBPK modelling. However, respondents mentioned that models not only needed to be available, but also sufficiently robust; as one participant stated, "…confidence related to input parameters and modelling algorithms are primary barriers, aside from lack of availability, to using PBPK modelling…" Moreover, respondents stated that the model results should be reproducible by others seeking to verify and extend the original findings.

3.1.3 Availability of guidance, frameworks, decision-support tools

Many of the respondents identified the availability of guidance and frameworks as a factor that could either be either a barrier or a facilitator. In some cases, respondents stated that a lack of guidance on the approaches was a barrier, whereas in other cases respondents stated this was not a major barrier due to guidance being readily available. Some respondents indicated the availability of guidance and frameworks varied by approach; for example, benchmark dose modelling was mentioned as having available guidance, whereas PBPK modelling, cumulative assessment of chemical and non-chemical stressors, and incorporation of adverse outcome pathways into risk assessments were mentioned as not having available standard operating procedures. However, some participants discussed that the guidance needs not only to be available, but to be presented in a manner that is user-friendly. As stated by one participant, "Even if guidance is available it is too dense…" and that there is a need for "…easily accessible 'cheat sheets,' flow charts, decision trees, etc." Moreover, it was stated that if guidance is too prescriptive, it can inhibit innovation in risk assessment. The use of case studies and examples of application, which are often incorporated into guidance documents, was also presented by some respondents as a helpful way of demonstrating how the approaches could be applied, how to perform quality assessments, and the benefits of their application.

3.2 External context

3.2.1 Domestic and international alignment/harmonization/support

Many participants discussed the level of acceptance of increasingly data-informed approaches by other programs and organizations as a factor that either encouraged or prevented adoption of the methods. If some organizations around the world are incorporating chemical- and scenario-specific data, it can encourage other agencies to do the same; as one respondent stated, "We want to modernize and align with other international regulatory agencies." Respondents noted that support can come as simply as providing additional confidence to management, stakeholders, and others that a particular method is valid because it has been accepted and used by other organizations. Respondents further noted that if other organizations have also developed guidance on an approach, their documents can be consulted in the absence of any in-house guidance. Survey responses also suggested that relationships between organizations can be

simpler, such as an organization with less experience consulting with an organization that is more proficient with the application of chemical- and scenario-specific data. Individual risk assessors may also seek insight and input from colleagues of other organizations while attending conferences and workshops. Respondents considered that more elaborate relationships can also develop, which results in beneficial outcomes: as in one example provided by a participant, "sustained collaboration between…organizations has resulted in some harmonization of methods."

Conversely, some respondents discussed examples of how the need to align or harmonize with other organizations can impede adoption of novel approaches. For example, there can be a desire to maintain consistency with risk assessments from other internal programs or external organizations, and if those programs and organizations did not incorporate chemical- or scenario-specific data, it might prevent another program from doing so in a new assessment. As one participant stated about the impact of harmonization, "It can take a long time for even 'better science' to be universally adopted and, as we move towards greater international cooperation, the more complex and longer it can take." Moreover, as in the past there has often been limited harmonization between organizations, "diverging views" have resulted in different ways of applying the approaches, which can create confusion for assessors from organizations with less experience attempting to identify which methods to use.

3.2.2 Regulatory environment

The regulatory environment can also place some restrictions on the ability to incorporate chemical- or scenario-specific data in dose–response assessments. For example, the regulatory environment can affect the availability data and models. In programs with prescribed data requirements for applicants that is codified in legislation, applicants are sometimes not willing to incur the cost of performing additional studies outside of those required in legislation. Moreover, the data or models might not be transparent or accessible despite having been generated if they are proprietary information, which can preclude their evaluation and further application. In certain programs, legislation can also be prescriptive regarding risk assessment methods, which can prevent or majorly delay the adoption of approaches in these programs. As stated by one participant, "…there is a natural lag between the development of a new approach, publication of new methods in the scientific literature, their application in the science literature to specific

chemicals or chemical mixtures, their evaluation and acceptance in the science assessment community as 'improvements' over current practice and the revision of environmental laws or agency guidance." The regulatory environment was also mentioned as imposing time restrictions on risk assessments, as there might be regulatory requirements for completion of an assessment (or a certain number thereof) within a given time period.

3.2.3 Software and tools

Software and other tools are often required to apply increasingly data-informed approaches. Participants mentioned that difficulty in obtaining access to software was a barrier, and having access to the software was mentioned as a facilitator. For benchmark dose (BMD) and physiologically based pharmacokinetic (PBPK) modelling, multiple software types are available; however, differences in the modelling methods and non-interchangeabilities sometimes resulted in the need to have access to multiple software types. In certain cases, software is not easily accessible, and requires potentially costly third-party licenses. Organizational policies about information technology can also present challenges to using the software. For example, organizational processes can require lengthy approval processes for purchase or installation of relevant software. Restrictions in access to software affect not only the risk assessment organizations, but also can limit reviewers' and stakeholders' access to the software.

3.2.4 External stakeholders

The degree to which stakeholders understand and support the use of chemical- and scenario-specific data can affect organizations' ability to incorporate such data in dose–response assessments. Some respondents mentioned that stakeholders have accepted or encouraged increasingly data-informed approaches as they can result in transparency and refinement of hazard and risk assessments. Conversely, other statements from participants highlighted the difficulties and time requirements in communicating the methods and the advantages of their application to stakeholders. One participant also mentioned that some stakeholders "may be motivated to challenge a novel 'data-informed dose-response approach' in the court system," which would result in delays to an assessment. Furthermore, a respondent mentioned that even the fear that public stakeholders or industry groups might oppose an approach might prevent its

application; however, the participant stated "…I think this fear is overblown as the reviews from those groups are often oppositional no matter what methods are used."

3.2.5 External peer reviewers and science panels

Most discussions of peer reviewers and science panels presented these groups as encouraging the use of increasingly data-informed approaches. A basis for this as stated by one participant is that the external reviewers are not "tied to organizational constraints" in the same way that other internal reviewers might be. External reviewers and panels were also presented as a potential source of guidance, as their feedback might help to better explain a method and convey uncertainty. However, the backgrounds of peer reviewers might affect the level of support provided, as others might discourage application of the approaches; as one participant stated: "…even with a detailed MOA assessment, some peer reviewers prefer an abundance of caution, although this climate is changing."

3.2.6 Access to external expertise

Participants expressed that the availability of external expertise, through contracts or *ad hoc* presentations by invited experts, can facilitate incorporation of chemical- or scenario-specific data. However, many factors can be barriers to accessing such expertise. Although availability of external expertise is an external contextual factor, all of the challenges discussed by participants were internal contextual factors. Training can help assessors to identify whether there is a need to hire an external expert, identify relevant experts, and evaluate the validity and value of results. As hiring experts can be costly, availability of financial resources can affect access to external expertise. Time resources are also required; as stated by one respondent, there is still a need when hiring external expertise to "…develop and manage a contract, assess the quality of the work, and incorporate the data if useful…" However, the use of problem formulation was mentioned as a way to facilitate access to external expertise, as "Problem formulation is helpful to identify needs and potential strategies that can be used for risk assessment early on, and to set aside money in a budget for expert help that may be required."

3.2.7 Chemical-dependent factors

Some participants stated that the use of chemical-specific data could sometimes be encouraged by characteristics of the chemicals under assessment. Several respondents mentioned this was more likely to occur for higher profile or controversial chemicals. As stated by one participant, the approaches "…are very often reserved for assessment of high complexity and for controversial topics with high 'political' sensitivity." Participants also mentioned that the methods tend to be applied more often for suspected threshold carcinogens. A participant also provided an example where an increasingly data-informed approach was applied specifically because the estimated exposure levels approached concentrations associated with toxicity, which warranted greater refinement of the assessment.

3.3 Internal context

3.3.1 Problem formulation

Problem formulation is performed prior to embarking on a risk assessment to identify the questions to be answered and set the scope for the process. The problem formulation phase is informed by many other contextual factors, as the scope and objectives are dependent on the regulatory environment, chemical-dependent factors, organizational support, availability of resources, and risk assessors' expertise. Participants commented that well-designed problem formulations that "clearly state how information will be used to impact risk assessment methods" can facilitate the use of increasingly data-informed approaches. For example, in the problem formulation phase, it would be possible to identify the potential need to incorporate chemical- or scenario-specific data; as identified by participants, which can increase the likelihood of adoption of methods, as the resources necessary to perform such processes can be allotted in advance. The problem formulation might also identify a reason why a particular data-informed approach is not necessary to answer a specific risk assessment question. Participants noted that risk assessments need to be fit-for-purpose; therefore, an important question during the problem formulation stage, as noted by a participant, is "Do we have enough precision to make a decision?" In cases where a thorough scientific review is not required, or if there is a sufficiently wide margin between exposure and toxicity, participants stated that use of the methods might not provide any added benefit to the risk assessment. However, a barrier to the application of

approaches that might arise in the problem formulation phase is if there is a "lack of clarity in the risk assessment questions that are under investigation."

3.3.2 Organizational and management support

Participants discussed various aspects of organizational and management support that can facilitate or hinder the incorporation of chemical- and scenario-specific data. Organizations that encourage use of the methods—or innovation in general—at multiple levels of the organization, including in programs other than those directly involved in risk assessment, were stated as more likely to adopt the approaches. As stated by one participant, "Some groups are more daring I think to use methods that are in the published literature or to publish methods themselves in order have a basis for methods applied in an assessment." Support for innovation includes allowing for the publication of guidance documents or applications of the approaches; as one respondent described, "Organizations that allow their scientists and risk assessors to publish methods or applications of methods are more likely to adopt those methods." Organizations that encourage risk assessor participation in discussion forums, both within the organization and externally—with partnerships with other international organizations, or in participation at conferences and workshops—facilitate the adoption of advanced methods in risk assessments. As application of the methods can potentially delay the risk assessment process, especially when risk assessors have less experience in applying the approaches or analyses are particularly complex, management accommodation of flexibility in deadlines, when permitted under the regulatory program, can increase the likelihood of adoption. Organizational structure was also mentioned as a factor that impacted support for innovation, particularly for committees performing risk assessments. One participant's experiences identified that committee environments were more conducive to adoption of novel approaches when the majority of the technical risk assessment work was performed by government programs, with expert committee members serving to discuss the proposed methods; the participant contrasted this with workloads falling to committee members with minimal technical support from the government program, which allowed little time for innovation. Participants also explained that management's level of understanding of the importance of data-driven decisions could impact the likelihood of support.

3.3.3 Time, financial, and human resources

Resource availability was frequently mentioned as a factor that can strongly affect the implementation of increasingly data-informed approaches in risk assessments. Respondents asserted that the amount of time allotted to an assessment could affect the ability to generate or gather data, apply complex methods to interpret new data, develop and manage contracts with external experts, obtain training, properly explain and communicate the approaches to management and stakeholders, develop and publish guidance, and change a program's traditional processes. Therefore, participants stated that it may not be possible to apply a data-informed approach, particularly one that is less familiar to an organization or that has less guidance available, and still meet deadlines. As one participant stated, "time…seems to be an obstacle lately, as there is an expectation for more output in less time…" The availability of time can also be affected by human resources, particularly regarding whether there are sufficient staff and the appropriate expertise to do the work. Financial resources were mentioned as being required for obtaining training and participating in conferences and workshops, hiring sufficient or additional staff, contracting external expertise, and obtaining licenses for software. Participants stated that identifying the need to adopt a method early in a risk process is helpful as it can allow for forecasting of budget needs for external expertise.

3.3.4 Training of risk assessors

Most participants identified training of risk assessors as critical to increasing incorporation of chemical- and scenario-specific data in dose–response assessments. Increasing an assessor's confidence in incorporating such data increases the likelihood that an assessor will consider applying an approach over more traditional default methods. As described by one participant, "Getting people comfortable with the theoretical underpinning of a data-derived/informed approach as well as the application of the approach is critical to getting people to actually use it. If a person doesn't know how to drive, they won't use a Ferrari." Necessary aspects of training include identifying when, why, and how the methods could be used, the advantages provided by the approaches, how to evaluate whether results are valid, and how to identify that external expertise. Many participants mentioned that the training must be ongoing and evolving to reflect scientific evolution, and that continued support is required. Discussions by respondents reflected the need for management and organizational support for training, in the

form of providing time and funding for the training itself and practical opportunities for the application of the methods.

3.3.5 Risk assessor background

A minority of participants mentioned aspects of a risk assessor's background other than training that can influence the likelihood that an assessor might push for the implementation increasingly data-informed approaches. Familiarity with and use of the methods can vary by organization, or between programs evaluating different sources of exposure, which can affect an assessor's experience in applying the approaches. Participants stated that engaging risk assessors from varying backgrounds might provide not only a broader expertise in the program, but might also encourage change to existing processes. For example, assessors new to a program might be more likely to identify a need to adopt the methods, if assessors with longer tenure in the program are more entrenched in the traditional approaches used in the program.

3.4 Utilization of evidence

As discussed throughout the previous sections, internal and external contextual factors can impact the ability of risk assessors to consider and use increasingly data-informed approaches. A summary of how these factors can affect three main stages in the decision-making process, identification, interpretation, and application of evidence, is presented below.

3.4.1 Identification of evidence

A main focus of the identification of evidence stage is whether there is sufficient data to support the decision-making process. Availability of data in the absence of context was discussed previously in the Evidentiary Sources section. Survey participants frequently stated that major barriers to their application of relevant approaches included the availability of chemical-specific data, of models (particularly for PBPK modelling), and of guidance, frameworks, and decision-support tools. However, contextual factors can also play a role in the availability and accessibility of relevant data. Information provided by respondents provided insight into contextual factors that impact the quantity and quality (and perceptions thereof) of available and accessible evidence.

Two of the external contextual factors described by respondents that can impact the availability of chemical-specific data are chemical-dependent factors and the regulatory environment. Participants mentioned that the approaches were more likely to be applied for chemicals with a higher profile or associated controversy; although participants did not mention the reasons for this, it could result at least in part from higher availability of data for these chemicals. Moreover, as mentioned earlier, the regulatory environment can affect data availability. This was particularly mentioned for scenarios when regulatory programs provide approvals for chemicals or products, as prescriptiveness of legislation on data requirements for applicants may reduce their willingness to produce data other than the mandatory minimal data.

Although risk assessors are not typically directly involved in the generation of the data used in the risk assessment process, they still can have some influence over the availability of data. Members of the regulatory risk assessment community can communicate data gaps or data needs to researchers. However, as mentioned by participants, collaborations with researchers require time and resources that might not always be available, and are dependent on management and organizational support. However, the need to maintain such relationships with programs generating data relevant to the application of increasingly data-informed approaches is important; as stated by one participant, "…we should implement as far as possible to encourage and develop data pipelines to support [the applications]." These relationships might need to be formed with researchers from multiple sectors, as the data can be generated by many different organizations. This was noted by a respondent's statement that "Since risk assessments are driven by data and all data are considered for adequacy and relevance, availability of relevant substance-specific data (whether provided by applicants or generated by industry, government, or academia) would encourage the probability of an approach being applied."

One of the important aspects of data availability that can be influenced by the contextual environment is data accessibility. As discussed earlier, even when data are available, they are not always accessible. The regulatory environment can influence data accessibility, as data or models developed with commercial interests might be deemed as proprietary information, which might limit their accessibility or transparency. The ability to obtain access to software and tools can also affect accessibility to the available data, particularly since it may require access to multiple software platforms, depending on the chemical and approaches being applied. In turn, the ability to obtain the software can be limited by constraints imposed by the internal context, such as

organizational informational technology processes and availability of funding to obtain access to the software. Furthermore, risk assessors' training on and comfort with the requisite software tools can affect the ability to access data using the appropriate tools; these factors are in turn impacted by the level of organizational support, which can also affect the necessary time and financial resources to gain training and experience with the tools. The availability and accessibility of software and tools can also impact reviewer or stakeholder opinions on the application of increasingly data-informed approaches, particularly if their ability to evaluate or replicate the models or their output is limited, which can be magnified if there is a lack of transparency due to proprietary information.

The data-gathering process is another aspect of identification of evidence considered relevant in the Dobrow framework, but no participants described related issues with data-gathering. Therefore, although access to and knowledge of use of literature databases and subscription-based peer reviewed journals could theoretically impact accessibility of data, it was not of sufficient importance to warrant mentioning by the individuals who completed the surveys.

Another aspect of data availability within the contextual lens is risk assessors' judgements of what they consider to be sufficient levels of data for the application of the increasingly data-informed approaches. Respondents noted that different individuals and organizations may have varying levels of comfort with the same available data. As noted in earlier sections, survey responses indicated that factors such as domestic and international alignment, external stakeholders' support, organizational and management factors, and the training, expertise, and background of risk assessors can all play a role in shaping comfort with data availability. In many of the potential applications of relevant methods, there might be a need to use assumptions to fill data gaps; the resulting comfort with the level of uncertainty associated with such assumptions might vary among risk assessors, management, organizations, and stakeholders. As discussed by a participant, "I think people are more comfortable with the uncertainty they are familiar with"; some individuals and organizations may therefore be more accepting of the level of uncertainty in traditional defaults than in the newer, less familiar data-informed approaches. The respondent continued the discussion by stating "An example would be the use of [pharmacokinetic] data to derive a chemical-specific dosimetric adjustment factor. There may be (and assuredly is) uncertainty in its derivation and some organizations may opt to

default to older, accepted approaches. But, under careful consideration, the uncertainty in the data-derived approach almost certainly has less uncertainty over a default approach meant to be applied in all situations."

One aspect that should also be considered in the identification of evidence is tools for evaluating sufficiency of weight of evidence. No participants directly discussed the availability of such tools. Although participants mentioned that the availability of guidance, frameworks, and decision-support tools—which is affected by international acceptance of the approaches—can impact their ability to incorporate chemical- and scenario-specific data, specific aspects of their application for evaluation of sufficient quantity of data were not stated.

3.4.2 Interpretation of evidence

Evaluation of the quality, relevance, and applicability of individual sources of evidence (individual studies and models) is performed in the interpretation of evidence stage. Although all participants stated that the lack of suitable data impacted their abilities to incorporate chemical- and scenario-specific data in dose–response assessments, they did not directly discuss factors that affected evaluation of quality. However, several lines of discussion embedded in the survey responses provided indirect information on the contextual factors that impact the interpretation of evidence.

As discussed earlier, the availability and consistency of guidelines on risk assessment from around the world can impact application of increasingly data-informed approaches. One aspect that can be discussed in the guidelines is how to evaluate individual studies or models for robustness. The absence of such guidance or conflicts among the different sources of guidance can therefore impede the evaluation of studies or models, or result in discrepancies in conclusions among risk assessors or organizations.

Comfort in the robustness of a study or model for a particular chemical can also vary among individuals and organizations. As one participant stated, there is a "…changing landscape of data available for risk assessment. Regardless of what risk assessors would prefer to work with, the facts are that fewer and fewer large, longitudinal occupational cohorts and chronic rodent bioassays are being conducted. This forces us to examine less ideal data for making determinations of risk." Working within the evolving landscape of data availability, participants stated the need to evaluate the uncertainty of and confidence in input parameters, modelling

algorithms, and other available data. However, as noted by participants, these decisions are often made based on conflicting data, and it is difficult to weigh evidence when there are studies with which the protocols are less familiar. Therefore, internal and external contextual factors such as risk assessors' training and expertise, input of peer reviewers and external stakeholders, and the ability to consult external experts, could impact an assessor's level of comfort with individual studies or models.

An additional factor that could impact a risk assessor's evaluation of an individual study or model is the source of the evidence, as, for example, whether a study or model was produced or funded by industry versus government. However, participants did not directly discuss this aspect in their responses, with one exception. As discussed earlier, industry's generation of proprietary data or models based on such data can limit the ability to evaluate the data due to transparency issues. This factor is dependent on the regulatory context of the risk assessment, and can also be impacted by the ability of risk assessors, peer reviewers, and external stakeholders to obtain the necessary software to evaluate the models.

3.4.3 Application of evidence

The final stage in the Dobrow model is application of evidence, wherein the weight of evidence for a particular assessment is evaluated, and all contextual factors and evidentiary sources combine to influence the decision outcome. Two main decision outcomes at this stage were discussed by participants: the decision whether increasingly data-informed approaches should be applied, and the decision on how they should be applied.

3.4.3.1 Should an increasingly data-informed approach be applied?

The first decision outcome that is influenced by contextual factors is whether a data-informed approach would be useful for a particular situation. As discussed previously, the problem formulation phase of a risk assessment is a contextual factor that influences the remaining phases of the risk assessment process; therefore, even if confidence in application of a relevant method is high, it might not always provide an added value to the risk assessment, if additional precision is not necessary. The chemical context can also influence the need for an approach; as discussed earlier, incorporating chemical-specific data may be more important for controversial chemicals. An additional aspect mentioned by one respondent is that for more data-rich substances, there might not be a need for extrapolations. For example, when the point of

departure is based on robust, population-representative data in humans, "…additional potential refinement of the point of departure (e.g., through PBPK modelling or chemical-specific adjustment factors) would not be expected to change the conclusion…" In these cases, the additional effort and resources required to perform the extrapolations would be difficult to justify.

For an approach to be considered useful for a particular assessment, benefits of its application must outweigh the challenges. Survey respondents discussed many benefits of applying increasingly data-informed approaches. Participants stated that their use allowed for maximization and improvement of use of available data, resulting in more robust estimates of point of departure and more refined estimates of risk. This in turn increased transparency, by "minimiz[ing] the subjective judgment of the assessors" and by "better identify[ing] and quantify[ing] the uncertainties." For example, one participant stated that "…calculating a chemical-specific uncertainty factor and reporting all inputs is more transparent than saying you'll apply a 10-fold value because 'that's what the guidance says to do'."

One challenge to the benefits of the increasingly data-informed approaches is the long-standing acceptance of defaults in risk assessment. One question often asked, as stated by one respondent, is: "why [do] we need a new approach, since the consolidated approach has shown to work well for decades…?" It can be very difficult to change a process that has become engrained in practice and defended for decades, and that has long been considered "good enough." For this reason, many risk assessors, organizations, or stakeholders might hold an increasingly data-informed approach to a much higher standard than a default assumption. As noted by one participant, "There is often a 'the perfect being the enemy of the good' situation going on in that some will discount a method if it doesn't solve ALL the short-comings of [an] alternative approach."

As noted by respondents, one reason why risk assessors may tend to continue to use default methods is a potential perception of the increasingly data-informed approaches being difficult or complicated. Participants mentioned that training is key to reducing misperceptions of difficulty. However, sufficient time and financial resources are required to be able to obtain necessary training. As stated by one participant, "…time for training seems to be an obstacle lately, as there is an expectation for more output in less time (i.e. busy with work and meeting timelines for deliverables), so fitting training in as much as I would like is difficult." In turn,

management and organizational support of the approaches or of innovation in general will impact the amount of time and resources provided for risk assessors to obtain the required training.

However, even if a risk assessor has gained the expertise to incorporate chemical- or scenario-specific data, a further barrier can be to convince others of the benefits over traditional assumptions. As worded by one participant, "Often, with any newer type of approach, the evaluator is required to go 'above and beyond' to convince the reader/peer reviewer/management that it is a strong and valid approach to use." Contextual factors such as risk assessors' expertise, training, and time can allow for better communication of the advantages of a more complex method over the default when trying to convince management, peer reviewers, and external stakeholders of the need for such an approach. However, if groups have little experience (or negative experience) with the methods, this may reduce the likelihood that they can be convinced of their utility. Conversely, if other organizations internationally or domestically have already adopted the approaches, this can increase confidence of management and stakeholders in their application.

The availability of well-designed guidance can also provide support for organizations' adoption of increasingly data-informed approaches, but the availability of guidance might be limited without sufficient acceptance by an organization. As one respondent stated, "…some organizations have shown a lack of desire to use new methods without guidance. This is pretty short-sighted and paradoxical in a sense because there guidance typically wouldn't be developed unless a method is being used and there's a need to make sure it's applied consistently." An organization's development of guidance or mentioning an approach in risk assessment standard operating procedures can also help normalize its consideration in every risk assessment. However, formalizing such methods could be difficult. As discussed by one participant, "…current practice is considered easy enough to implement and provides a reliable enough answer that regulatory organizations will be reluctant to undergo such an arduous and sometime costly (both in terms of [money] but also in terms of [risk assessor and organization] time) process to change it."

3.4.3.2 How should an increasingly data-informed approach be applied?

A second decision outcome that is influenced by contextual factors is the method by which an increasingly data-informed approach will be applied. Even if two individuals or

organizations decide that a method is worth applying for a given dose–response assessment, their implementation methods might vary. As stated by a participant, there is a "lack of clarity in how to apply data-driven approaches appropriately for given risk assessment situations due to conflicting rationales and approaches in the literature." As discussed earlier, harmonization of methods among different organizations internationally can help to encourage application, with the caveat that the need to gain agreement from too many organizations can delay the process, and that guidelines that are too prescriptive may actually limit the ability to apply approaches. However, well-designed guidance can help with not only a risk assessor's application, but also with communicating the applied methods to others. As mentioned by a respondent, "Thoughtful frameworks that organize and simplify the evaluation of the data for applicability and to clarify the decision process, to ease the communications to stakeholders."

As discussed earlier, level of comfort with uncertainty can vary among individuals and organizations. This varying level of comfort could also result in different decisions being made during the application of the increasingly data-informed approaches. For example, some participants discussed differences among organizations in the selection of the appropriate benchmark response level when performing BMD modelling. Organizations and individuals who are less comfortable with uncertainty might have tendencies to make more conservative decisions at the various decision points when applying the approaches, or might be less likely to reduce or eliminate the use of uncertainty factors.

4.0 DISCUSSION

The goal of the research presented in this chapter was to build upon the previous chapters' investigations that were rooted solely in quantifying the evolution of evidentiary aspects of the Dobrow et al. (18, 19) framework for evidence-based decision making, particularly interpretation and application of evidence. As discussed in Chapter 3, although many physiological models exist and are considered in regulatory dose–response assessments, they are often deemed as inappropriate for use in decision making. However, the availability of data is only one factor influencing the decisions behind interpretation and application of evidence.

Barriers that hinder risk assessors from incorporating chemical- and scenario-specific data are complex, multifactorial, and occurring at multiple contextual levels. Although insufficient data was the factor that was mentioned most commonly and stated by many as being

the biggest barrier, many other more complex contextual issues were identified upon analysis of completed surveys. Some of these factors can impact access to data or models, or perception of sufficiency of the data or models. Other factors may impact risk assessors' ability to apply the approaches, or to convince others of the benefits of such an application. One commonality of all the factors is that they are external to the risk assessor; therefore, risk assessors might have limited ability to apply increasingly data-informed approaches if too many barriers exist. If the application of the methods is dependent on individual risk assessors promoting their use against multiple contextual layers of barriers, the approaches will undergo infrequent adoption. Notably, one aspect that was not discussed by participants was non-technical characteristics of individual risk assessors, such as level of motivation or initiative. Even when risk assessor expertise was mentioned, it was primarily discussed from the context of access to training rather than as an assessor-specific trait. Therefore, traits of individual risk assessors are likely to be less important than other contextual factors, as barriers at other levels can even impede risk assessors with the greatest amount of initiative and motivation.

As the internal context is more proximal to individual risk assessors, there is greater potential for risk assessors to modify and improve this context; however, the ability to make these changes can still be limited. If risk assessors are able to convince their management and organization of the potential benefits of increasingly data-informed approaches over default methods, this will ideally result in greater support in the form of time, financial, and human resources. However, the ability to convince management and other key organizational players requires acquirement of sufficient expertise in the approaches to convey their importance. Convincing others of the importance of changing an engrained dose–response process can also take a lot of a risk assessor's time, which is usually limited by the need to quickly and efficiently produce risk assessments. Therefore, the resources that can be gained by obtaining management and organizational support are the same resources that are required to convince management and others in the organization of the benefits of the approaches.

The risk assessor's ability to influence the external context can vary. Some of the aspects of context, such as regulatory environment and chemical-dependent factors, are relatively immutable. Conversely, risk assessors can have some impact on other aspects of external context. For example, they can participate on committees or in workshops at the international level to contribute to methods, guidance, and harmonization; improve communication with

external stakeholders to increase the likelihood of stakeholder support; identify the external experts who would be best suited to support the targeted approaches; or work with their organization's IT specialists to improve access to various software. However, the risk assessor's path to influencing the external context is through the internal context, as management and organizational support, time, and financial resources are necessary to influence the external context.

One notable observation from the survey responses was that the absence of in-house guidance and written SOPs including the increasingly data-informed approaches was not a barrier to their application. Although organization-specific documentation can be helpful in facilitating application of a method, in its absence, risk assessors instead consulted guidance developed by other organizations. Nonetheless, the presence of internal guidance to support the approaches might be an indicator of management or organizational support. As discussed above, management support can therefore influence the external context. This may be best demonstrated in a quote from one of the survey participants, who stated: "Organizations that allow their scientists and risk assessors to publish methods or applications of methods are more likely to adopt those methods, and there's the downstream result of facilitating other organization's adoption of the methods."

Analysis of survey responses indicates that the Dobrow conceptual framework appropriately describes the contextual environment around decision-making processes in dose–response analysis for environmental and occupational health. Analysis of the survey results indicated that although data availability viewed outside of the contextual lens could impact the ability to use data-informed approaches, the internal and external context also played a large role in the ability to identify, interpret, and apply the data.

The refined conceptual framework by Dobrow and colleagues overlaid three policy objectives (effectiveness, appropriateness, and implementation), forming a three-by-three matrix with the three utilisation stages (identification, interpretation, and application of evidence). Although these policy objectives were not specifically discussed in the results, their questions were implicitly incorporated in decision stages, with effectiveness being most evident in the identification and interpretation stages, appropriateness prevalent across all three stages, and implementation predominantly in the application stage. Therefore, based on the results of the survey, the policy objectives fit better as a continuum, rather than as a matrix. As presented in

Dobrow et al. (19), the policy objectives correspond well with the continuum of the nature of evidence. For data-informed approaches, the availability of empirical data (and models based on such data) is more important for the earlier policy objectives, whereas evidentiary sources such as guidance documents outlining dose–response approaches are more predominant for the later policy objectives.

One key aspect relevant to environmental and occupational dose–response assessments that was not a factor in the Dobrow framework is that risk assessors and their organizations can be actively involved in the development of evidentiary sources. As noted in the results, collaboration of risk assessors with researchers should be encouraged, and is being performed. Moreover, risk assessors from regulatory organizations are often involved in the development of guidance documents that are used by others within or outside of their organizations. However, the relevant internal and external contextual factors also impact risk assessors' abilities to be involved in evidence generation. As a result, to use the conceptual model to explore the application of data-informed approaches in dose–response assessment, it might be useful to add the extra step of generation of evidence before the activities of identification, interpretation, and application of evidence.

The Dobrow framework also presents the external and internal contexts as more separate than was identified from analysis of survey results from risk assessors and their managers. Although the two contextual environments are visually represented in the framework as being completely separate, Dobrow and colleagues do mention the potential for the external context to impact the internal context. Similarly, analysis of survey results described the contextual factors forming a complex web or series of layers that influence each other, with bidirectional flow between each layer.

Because the Dobrow framework was useful in describing the influence of internal and external context on the identification, interpretation, and application of evidence, the framework provides a basis for performing future explorations of increasingly data-informed approaches, and for developing recommendations to improve their uptake by government organizations. However, the inclusion of the generation of evidence step and the layering of external and internal contextual factors improves the model relevance to environmental and occupational health risk assessments performed by regulatory organizations. At the centre of the framework are the risk assessors, who have varying experiences, attitudes, and levels of expertise, which is a

result of the contextual environment surrounding them. These risk assessors are involved with the generation, identification, interpretation, and application of evidence, all of which are therefore influenced by the surrounding contextual layers. The matrix of evidence utilisation vs. policy objective was also adapted, with evidence utilisation presented as linear, and the policy objectives presented as underlying questions implicit to differing degrees in the different stages of evidence utilisation. A framework incorporating these changes is presented in Figure 2.

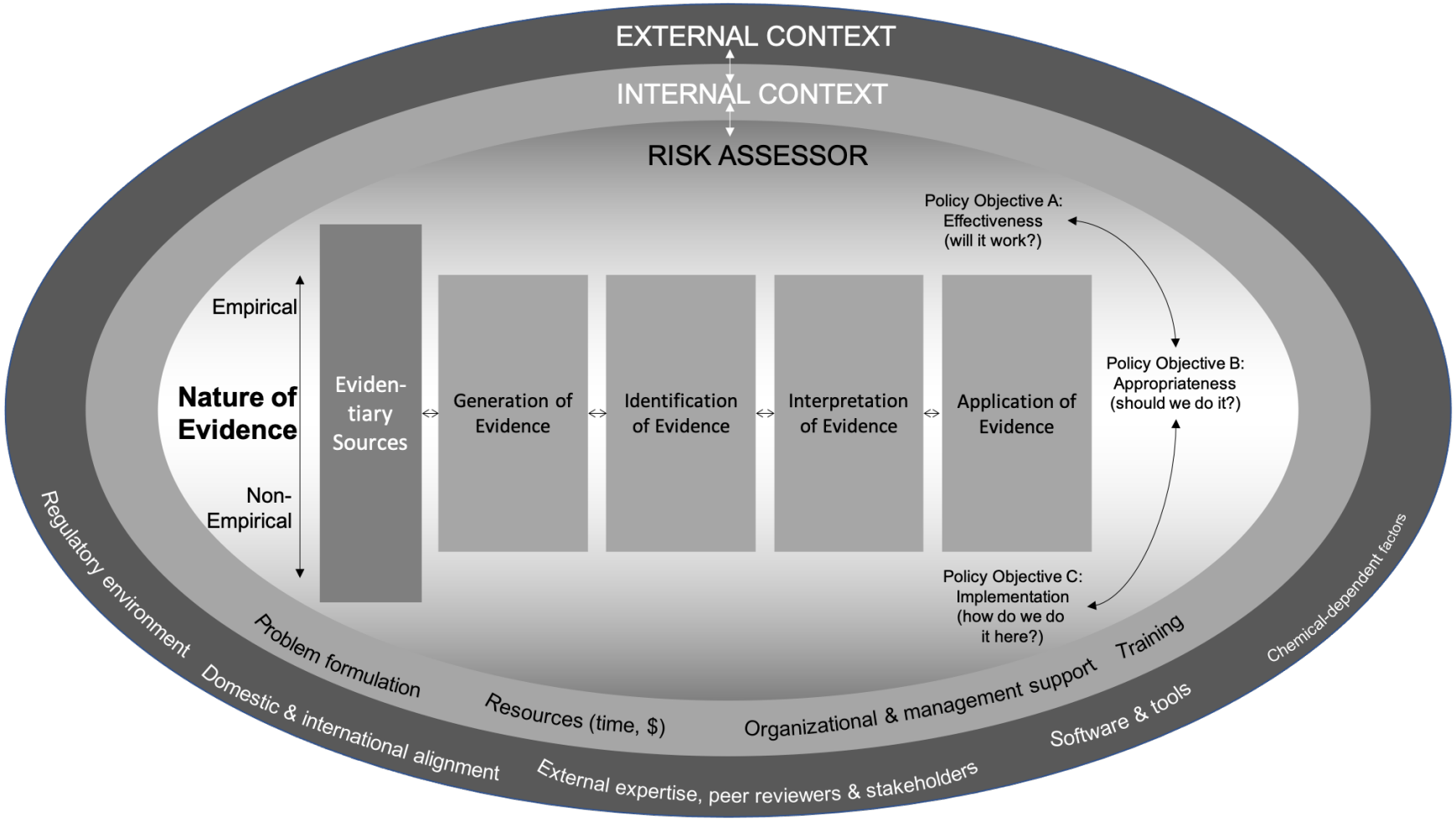


Figure 2. Conceptual framework for consideration of evidence and context in the incorporation of chemical- and scenario-specific data in dose–response assessments.
Adapted from the Dobrow et al. (18, 19) conceptual frameworks for consideration of evidence and context in development of health policy recommendations.

4.1 Recommendations

The resulting framework can be used to guide recommendations of measures that could be taken in an attempt to increase incorporation of chemical- and scenario-specific data into dose–response assessments. The framework provides a lens from which to consider internal and external contextual influences to governments in the ongoing and future activities occurring in the broader risk assessment community.

4.1.1 Improvement of availability of relevant, accessible, and useful evidentiary sources

Although the focus of this study was on the contextual factors that influence the incorporation of chemical- and scenario-specific data into dose–response assessments, respondents seemed to indicate that the biggest limitation they often encountered was within the evidentiary sources component of the framework. The types of evidentiary sources that are sometimes absent include empirical data (primarily physiological, kinetic, and mechanistic data at relevant doses, in relevant species, and for an appropriate distribution of the population), models, and guidance on the use of an approach. However, recommendations regarding the improvement of availability of evidence can be presented through the lens of the contextual factors. For example, improvements should be made to ensure that research activities will meet the needs of risk assessors. This can result from improved collaboration between the regulatory risk assessment and research communities, and requires the involvement of risk assessors throughout the research process, particularly in the planning stage. Improvement in the research–risk assessment interface could also help to ensure that the manner in which their results are published meets the needs of risk assessors even in resource-poor environments; for example, extra steps could be taken to ensure that quantitative dose–response assessment outputs (e.g., points of departure or uncertainty factors) are included in the publication, reducing the need for risk assessors to apply complex models themselves. A more active interface between researchers and regulators could be achieved by researchers identifying regulatory partners. Moreover, government strategies on research grants and funds could

be improved, for example, by ensuring risk assessors are actively involved in identifying research priorities and requiring researchers to include application outputs.

Another context-based recommendation focused on evidentiary sources is to consider more broadly the utility of guidance documents and tools that are developed, particularly for organizations with fewer resources. Guidance documents and tools that are developed from international initiatives should be simple and concise resources that can be quickly referenced and provide guidance even to those with less experience and time. To ensure the practicality of such tools across less developed risk assessment programs, risk assessors from programs with fewer resources should be sought for the piloting and evaluation of draft guidance and tools.

4.1.2 Provision of sufficient resources

As discussed throughout the results section, the availability of time and financial resources is a contextual factor that influences many other barriers and facilitators to the use of increasingly data-informed approaches. Providing sufficient time and resources for risk assessors to learn about and apply the approaches will increase the likelihood of their uptake. Risk assessors should consider the potential need for using the approaches in an assessment as early as possible, ideally in the problem formulation stage, to flag potential time and resource needs to senior management. This can be encouraged by management requiring a problem formulation stage for all assessments, and placing requirements for evaluation of the potential need for incorporation of chemical-specific data within the problem formulation process. However, some general additional time and funding should generally be incorporated into risk assessment activities, to allow for risk assessors to be informed of new developments in the dose–response assessment field, including the ability to participate in workshops and conferences, and collaborate with other governmental programs. One additional way of mitigating the impact of resource availability via the external context is for the broader risk assessment community to develop training and tools that are accessible even for risk assessors with limited time and funding. This could include concise and low- or no-cost training modules that are available on demand so as to be accessible to risk assessors as their own schedules

permit. Similarly, free tools could be developed through accessible and familiar platforms, such as web browsers or spreadsheet software.

4.1.3 Organizational, management, external stakeholder support

Availability of time and financial resources is often a reflection of organizational and management support for the incorporation of chemical- and scenario-specific data into dose–response assessments. As discussed earlier, this can create a "chicken and egg" scenario, as lack of senior management and organizational support can result in low resource availability, which can reduce a risk assessor's ability to convince management of the need to use an approach. Therefore, the availability of resources designed for decision-makers and stakeholders with less advanced risk assessment backgrounds, that provide simple and concise explanations of the methods and their advantages and limitations, could be helpful.

4.1.4 International collaboration efforts

The many existing activities that bring together risk assessors from various international programs are helpful, as they produce tools and case studies that are made available to all risk assessment programs, even those with fewer resources or less support for the incorporation of increasingly data-informed approaches. However, participants in these activities would tend to be from organizations that provide more financial and time resources and therefore already have greater support for the use of the methods. Because of this, tools might be developed based on the needs of programs already adopting the approaches, and might not address the needs of those with fewer resources. Leaders of such collaboration efforts should therefore consider means of involving risk assessors from programs that have less experience with the incorporation of chemical- and scenario-specific data in dose–response assessments. As mentioned in Section 4.1.1, risk assessors from organizations with fewer resources could be involved in the piloting or evaluation of tools to identify the utility of tools for risk assessors less experienced in the approaches.

4.2 Limitations

Several limitations with the study have been identified. Although the participation rate of individual risk assessors and managers who were invited to complete the survey was 74%, there was low organizational participation, with only 7 of 17 (41%) of organizations that were initially contacted agreeing to be involved in the survey. Organizational participation rate was likely decreased due to increased demand on organizations in the early months of the COVID-19 pandemic response. Participating organizations and respondents were also potentially those who were supportive of and had experience in applying increasingly data-informed approaches; additional contextual factors might have been identified if better attempts were made to identify organizations or individuals who were less inclined to apply the approaches. Moreover, only a single survey was sent to a pre-determined number of target organizations and participants; sampling was not purposive, with no attempts made to probe participants further or invite additional participants. This restricted the analysis to the received completed surveys and prevented follow-up on themes that could have been further explored. Finally, many different methods of incorporating chemical- or scenario-specific data into dose–response assessments were explored in the survey, and participants were asked for their input on the collective approaches. As the respondents' experiences vary, their responses might have focused on the methods in which they have most familiarity or experience, which could result in some additional variability in responses. For example, several participants stated the absence of guidance could be a barrier, while others stated that there was no shortage in guidance; the methods they were considering could have influenced the opinion. Moreover, some participants responded to the survey considering data-informed approaches collectively, whereas others looked at each method listed in Table 1 individually.

In conclusion, although the availability of data is a common determinant of the incorporation of chemical- and scenario-specific data in dose–response assessments, there are many additional contextual factors that can act as barriers or facilitators in regulatory settings. Whether an approach becomes applied depends on whether its benefits outweigh the challenges in each individual situation. The presence or absence of these contextual barriers and facilitators can result in inconsistencies in the level of uptake and methods of

application of increasingly data-informed approaches between—and even within—organizations. There are many justifiable reasons why the use of an increasingly data-informed approach might not be appropriate for a particular situation; however, reasons for deciding not to depart from defaults should be communicated just as often as reasons supporting the incorporation of chemical- or scenario-specific data. A final quote from one participant underscores this: "There will always be grey areas and areas where thoughtful scientists disagree. As long as our decision process is clear and transparent, I think this is the best we can do."

ACKNOWLEDGEMENTS

The authors would like to thank the 3 anonymous pilot participants and 14 anonymous survey respondents. The authors would also like to acknowledge the efforts of individuals who were the initial sources of contact at each of the targeted organizations, along with other individuals who were not able to participate in the survey but provided other useful organizational information.

REFERENCES

1. NRC. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: The National Academies Press; 1983.

2. NRC. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press; 2009.

3. Ritter L, Totman C, Krishnan K, Carrier R, Vézina A, Morisset V. Deriving uncertainty factors for threshold chemical contaminants in drinking water. Journal of Toxicology and Environmental Health, Part B. 2007;10(7):527-57.

4. Barnes DG, Dourson M, Dourson M, Preuss P, Barnes DG, Bellin J, et al. Reference dose (RfD): Description and use in health risk assessments. Regulatory Toxicology and Pharmacology. 1988;8(4):471-86.

5. Renwick AG, Dorne J-LCM, Walton K. Pathway-related factors: The potential for human data to improve the scientific basis of risk assessment. Human and Ecological Risk Assessment: An International Journal. 2001;7(1):165-80.

6. IPCS. Part 1: IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans and Case-studies; Part 2: IPCS Framework for Analysing the Relevance of a Non-Cancer Mode of Action for Humans. Geneva; 2007. Report No.: Harmonization Project Document No. 4.

7. IPCS. Assessment of Combined Exposure to Multiple Chemicals: Report of a WHO/IPCS International Workshop. 2009. Report No.: IPCS Harmonization Project Document No. 7.

8. IPCS. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva; 2010. Report No.: IPCS Harmonization Project No. 9.

9. Bhat VS, Meek ME, Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47(9):729-49.

10. IPCS. Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. Geneva; 2017. Report No.: Harmonization Project Document No. 11.

11. IPCS. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration–Response Assessment. Geneva; 2005. Report No.: Harmonization Project Document No. 2.

12. DeWoskin RS, Barone S, Clewell HJ, Setzer RW. Improving the development and use of biologically based dose response models (BBDR) in risk assessment. Human and Ecological Risk Assessment. 2001;7(5):1091-120.

13. Lapare S, Brodeur J, Tardif R. Contribution of toxicokinetic modeling to the adjustment of exposure limits to unusual work schedules. AIHA J (Fairfax, Va). 2003;64(1):17-23.

14. Meek ME, Palermo CM, Bachman AN, North CM, Jeffrey Lewis R. Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. Journal of Applied Toxicology. 2014;34(6):595-606.

15. Wason SC, Smith TJ, Perry MJ, Levy JI. Using physiologically-based pharmacokinetic models to incorporate chemical and non-chemical stressors into cumulative risk assessment: a case study of pesticide exposures. Int J Environ Res Public Health. 2012;9(5):1971-83.

16. Evans JS, Gray GM, Sielken RL, Smith AE, Valdezflores C, Graham JD. Use of probabilistic expert judgment in uncertainty analysis of carcinogenic potency. Regulatory Toxicology and Pharmacology. 1994;20(1):15-36.

17. Small MJ. Methods for assessing uncertainty in fundamental assumptions and associated models for cancer risk assessment. Risk Anal. 2008;28(5):1289-308.

18. Dobrow MJ, Goel V, Upshur REG. Evidence-based health policy: context and utilisation. Social Science & Medicine. 2004;58(1):207-17.

19. Dobrow MJ, Goel V, Lemieux-Charles L, Black NA. The impact of context on evidence utilization: A framework for expert groups developing health policy recommendations. Social Science & Medicine. 2006;63(7):1811-24.

20. Schenk L. Comparison of data used for setting occupational exposure limits. International Journal of Occupational and Environmental Health. 2010;16(3):249-9A.

Chapter 5 – Other Approaches and the Need for an Evaluation and Selection Framework for Occupational Exposure Limits

1.0 Introduction

This brief chapter serves as a link between the two main sections of the thesis. The first part of this chapter outlines preliminary observations on the application of other chemical- and scenario-specific dose–response approaches in regulatory assessments. The second part provides support for the development of a knowledge translation tool that focuses on occupational exposure limits (OELs). The information provided in this section is based on preliminary analyses developed for oral presentations at symposia, along with observations made while gathering data for the work presented in Part I of the thesis.

2.0 Other increasingly data-informed dose–response approaches

2.1 Pilot study

A pilot exploration of the use of increasingly data-informed dose–response approaches was undertaken. The preliminary investigation was performed for a subset of regulatory reports from environmental organizations (Health Canada's assessments associated with the Priority Substance List, Chemicals Management Plan, and Guidelines for Canadian Drinking Water Quality, and the United States Environmental Protection Agency's [US EPA] Integrated Risk Information System [IRIS] assessments) and occupational organizations (American Conference of Governmental Industrial Hygienists [ACGIH] Threshold Limit Values® [TLVs®], American Industrial Hygiene Association and Occupational Alliance for Risk Sciences' Workplace Environmental Exposure Levels [WEELs], and assessments performed by the European Chemicals Agency Scientific Committee on Occupational Exposure Limits). The time period for the evaluation was from 1983 to 2014. The use of the approaches was compared with key milestones, including the earliest relevant publications in scientific literature and targeted guidance documents developed by regulatory organizations. Results of the analysis were

presented at the Society for Risk Analysis annual meeting in 2015, and are demonstrated in Figure 1.

The pilot considered physiological modelling (physiologically based pharmacokinetic [PBPK], dosimetry, and physiologically based pharmacodynamic [PBPD] or biologically based dose–response modelling) and mode of action (MOA) analysis, and used benchmark dose (BMD) modelling as a comparison approach. Although benchmark dose modelling is a departure from the default use of a no (or lowest) observed adverse effect level (NOAEL or LOAEL) as a point of departure (POD), it does not incorporate greater chemical- or scenario-specific data into dose–response assessments. However, it was used for comparison with increasingly data-informed approaches as its application is more complex than relying on NOAELs and LOAELs as PODs, yet does not typically require data beyond what is presented in a well-reported study. Consequently, although uptake might be limited by similar contextual factors to increasingly data-informed approaches, BMD modelling is not as encumbered by data availability. Physiological modelling and mode of action analyses were selected as the two increasingly data-informed approaches to be quantified in the pilot study, as they appeared to be the approaches most commonly used from preliminary readings of the regulatory reports.

Results of the pilot evaluation (Figure 1) indicate that BMD modelling was the most commonly used of the approaches. Because its use was more common, results were also presented as percentages of published reports that used BMD modelling (Figure 1B). The overall number of included regulatory assessments that used BMD modelling increased over time; BMD modelling was used in ≥50% of assessments for several years in the late 1990s through the mid-2000s, but the overall proportion of BMD model use decreased in later years. One contributing factor for this is that beginning in 2008, assessments performed under Health Canada's Chemicals Management Plan were the predominant publications. These assessments rarely used BMD modelling, possibly because they were margin of exposure assessments that did not require more precise PODs.

The years of first adoption identified for physiological modelling and MOA analysis were 1987 and 2001, respectively. After being first adopted, use of both

approaches was sporadic, but their use increased and occurred annually in the 2010s. Although the more regular use of these approaches occurred later than did BMD modelling, the first use of both physiological modelling and mode of action analysis occurred in the same year as the publication of milestone papers, whereas the first identified use of BMD modelling was over a decade after its proposed use, despite lower barriers for use of BMD modelling. One potential reason for the more rapid uptake relative to milestone publication is that regulatory risk assessors were more heavily involved in the earlier stages of PBPK modelling and MOA analysis, potentially indicating a benefit of collaborations between the research and risk assessment communities.

Figure 1 also compares use of the three approaches considered in the pilot in environmental and occupational assessments. All three of the approaches were used much more commonly by environmental programs than occupational programs. Uses of the approaches in occupational assessments were limited to nine applications for BMD modelling and two for physiological modelling; no occupational uses of MOA analysis were identified. The use of BMD modelling by occupational programs was also lower when considering the proportion of assessments that used the approach.

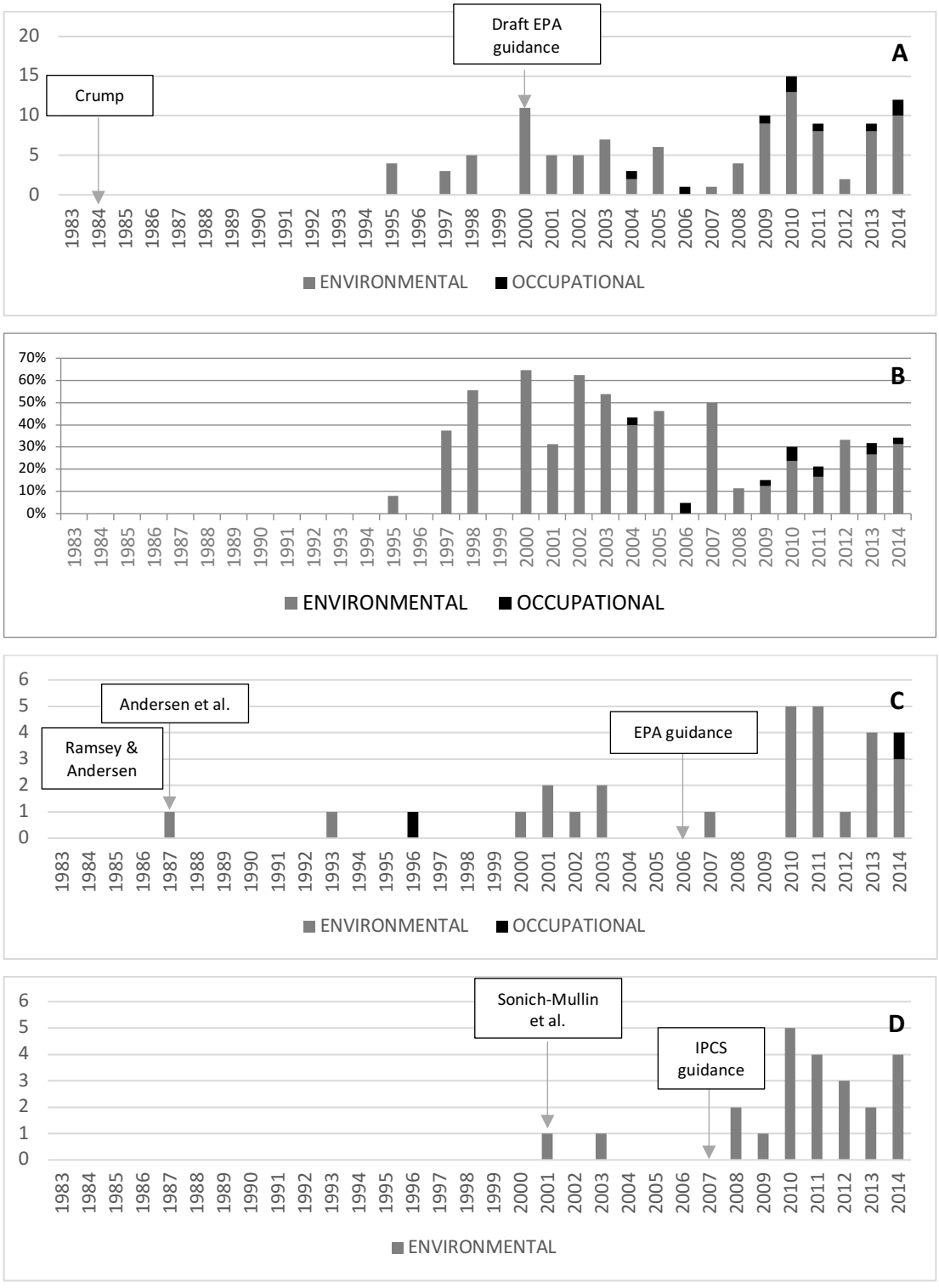


Figure 1. Pilot study results indicating frequency of adoption of approaches in regulatory risk assessments

A) Benchmark dose modelling; B) Benchmark dose modelling by percentage; C) Physiological modelling (PBPK, dosimetry, and PBPK-PD or BBDR); D) Mode of action analysis. Milestone publications are presented in the timeline with arrows.

2.2 Non-pilot approaches

Several additional approaches for incorporation of chemical- or scenario-specific data were initially considered in the thesis, as outlined in Chapters 1 and 4. Although the use of these additional approaches was not evaluated quantitatively, and no additional attempts were made to identify regulatory reports that specifically used the approaches, their use was noted when identified while reviewing documents for physiological model use. Very few applications of the other approaches were identified outside of their incorporation into physiological modelling. Discussion of these observations, albeit preliminary and incomplete as they were not the focus of the evaluations, is given below.

Many different applications of physiological models noted in Chapter 3 used the models to derive chemical-specific adjustment factors (CSAFs). Few additional non-PBPK derivations of CSAFs were noted when reviewing documents; the two identified examples were boron assessments performed by US EPA's IRIS program (1) and by the Agency for Toxic Substances and Disease Registry (ATSDR) (2).

Quantitative incorporation of population variability data in dose–response assessments was primarily noted in the use of physiological models discussed in Chapter 3 and the use of CSAFs outlined above. Examples of this were the incorporation of population distribution values in the parameters incorporated in PBPK modelling for dichloromethane (by US EPA's IRIS program, the US Occupational Safety and Health Administration, and Health Canada's drinking water program)(3-5), and in the PBPK-PD model used by US EPA's Office of Pesticide Programs in their chlorpyrifos assessment (6). Some assessments also explored population variability in dose–response by using physiological models for potentially susceptible subpopulations, including pregnancy and infant models used in perchlorate assessments performed by US EPA (7, 8) and the European Food Safety Authority (9), and a juvenile model for deltamethrin used by US EPA (10-13). One additional assessment that incorporated chemical-specific data on population variability was the 2018 draft of ATSDR's perfluoroalkyls assessment (14), which used probabilistic data in a pharmacokinetic model (not physiologically based) to derive a POD.

Approaches for the consideration of cumulative risk that were identified were mostly limited to approaches that were not considered as incorporating chemical- or

scenario-specific data into dose–response assessments for the purpose of this thesis. These approaches included the use of default dose–response approaches for deriving hazard indices, relative potency factors (RPFs), and organ-specific exposure guidelines to facilitate the evaluation of combined exposures to multiple chemicals. However, in one instance US EPA derived RPFs for mixtures of disinfection byproducts using a PBPK model (15). A physiological modelling approach was also considered for a US EPA assessment of combined exposures to pyrethroids (11), but was not applied because models were only available for two of the pyrethroids. No cumulative dose–response assessments addressing combined effects of chemicals and non-chemical stressors, including consideration of social determinants of health, were identified.

Adjustments of duration of exposure—to extrapolate from dosing regimens in key studies or for the development of exposure guidelines for various durations—were primarily limited to linear adjustments. Some of the physiological models noted in Chapter 3 were used for chemical- and scenario-specific duration adjustments. However, linear duration extrapolations were still performed in some cases where physiological models were used; this was noted in the discussion of US EPA's Acute Exposure Guideline Levels in Chapter 3, in which ten Berge equations were still used for some chemicals for which physiological models had otherwise influenced the dose–response assessment.

The use of in-depth quantitative uncertainty analysis in dose–response assessments was only noted in one assessment. The most recent draft of US EPA's IRIS dioxin reanalysis (16) developed a sensitivity tree, in which the impacts of various visually-depicted decisions in the dose–response process were quantified. In general, however, the presentation of results from alternative decisions was limited only to overarching decisions; for example, by presenting results for two different types of assessments (e.g., cancer vs. non-cancer; human vs. animal PODs), and discussing why one approach was selected over the other.

3.0 Additional support for focusing on occupational exposures

As presented in Figure 1 and discussed in Section 2.1, occupational dose–response assessments had much lower levels of adoption of BMD modelling,

physiological modelling, and MOA analysis than environmental assessments. This is possibly an indication that OELs are less likely to incorporate more modern scientific approaches during their derivation. One factor for this could be the nature of the revision process for two of the occupational organizations considered in the pilot. For the TLVs and WEELs, the committees that derive the values tend to regularly re-evaluate their assessments. If no new studies were identified that would change the value, the literature review might be updated and the assessment considered newer, without changes to the derivation of the value. This can result in what seems to be newer OELs that are actually still based on older approaches.

Observations about the age of a large subset of ACGIH TLVs were first made when evaluating the TLVs for the pilot work described in Section 2.1. While compiling and analyzing TLVs for the pilot study, the dates that an existing TLV was first derived were identified, rather than using the dates that were listed by the TLV committee as the most recent evaluation of the TLV. As the TLV history for each value is published in ACGIH documentation, it is possible to track a value to the date it was originally derived. For many compounds, the date the TLV was initially derived was much older than when the documentation was last updated; in these cases, only qualitative aspects of the TLV had been updated (e.g., updating a literature search that did not influence the derived value, adding or changing of the notations that will be described in Chapter 6) or a short-term exposure limit was removed while leaving the 8-hour time weighted average value unchanged. After identifying dates of quantitative derivation of each TLV, a large proportion of the existing values were excluded from the analysis as they had been derived prior to 1983.

Further exploration of the age of TLVs and the reliability of older values was performed for a presentation given at an Occupational Hygiene Association of Ontario symposium in 2017. For that analysis, the age of TLVs was updated to be current to the 2017 values. Based on the inclusion criteria for my thesis, TLVs were removed from the analysis if they had no quantitative value or were derived based on radiological activity of a compound. A total of 635 TLVs was included in the analysis. The distribution of decade of derivation of TLVs is presented in Figure 2. Although the majority of TLVs

were derived in the 1990s to 2010s, many values were derived earlier. In total, 113 TLVs, representing 18% of the values, were derived prior to 1983.

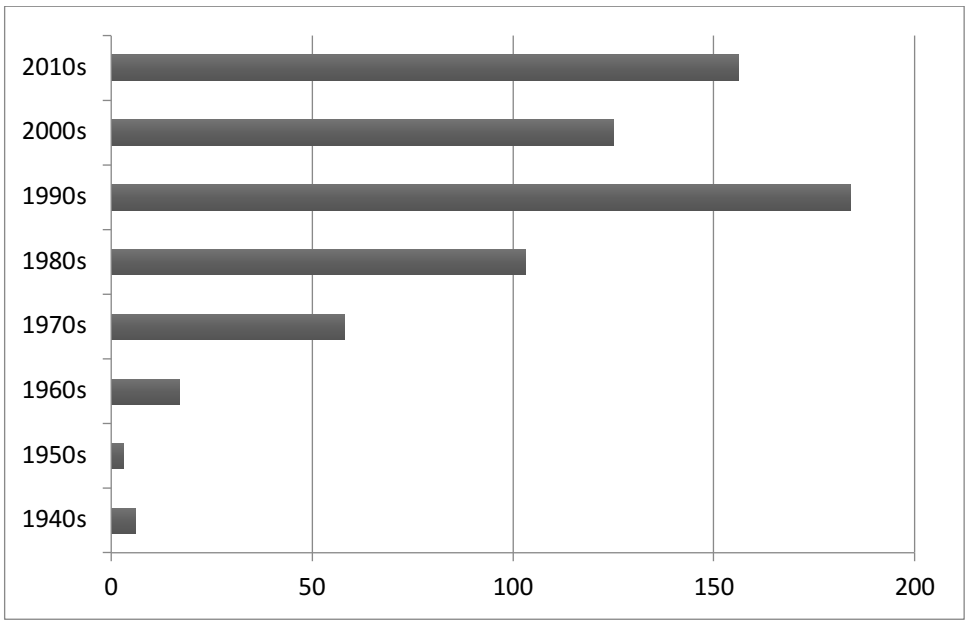


Figure 2. Number of current TLVs by decade in which the TLVs were originally derived

A concern that exists with older values is that they may be based on study data or risk assessment methods that would not be considered appropriate using current standards. Notably, assessments performed prior to 1983 have a lower likelihood of being based on general principles outlined in the 1983 National Academy of Sciences' *Risk Assessment in the Federal Government* (17) ("Red Book"), which sets out risk assessment practices that are still used today. A more detailed exploration of the basis of values was performed for the oldest values—the 6 TLVs initially derived in the 1940s, and the 3 TLVs derived in the 1950s.

A summary of characteristics of the studies that form the basis of the older TLVs is presented in Table 1. Although the documentation for most values had been updated in the 1990s, all TLVs except for nicotine were based on older key studies. Older key studies in animals might represent study protocols and laboratory practices that do not meet current standards. Older human data used as key studies present additional limitations, which are noted in Table 1. Many of the values were based primarily on acute data, even though the derived TLVs were 8-hour time-weighted averages. Older human

studies often relied on self-reporting of subjective symptoms of adverse effects, based solely on the identification of overt effects, rather than attempting to measure more subtle or precursor effects. Industrial experience and case reports were often used to identify PODs. In studies of industrial experience, the POD was based on adverse effects (or lack thereof) reported at typical concentrations to which workers were exposed, which is often in a single workplace and for a small number of workers. When using case reports, PODs were based on data from individual acute poisoning events, either from oral poisoning, or from abnormally high occupational exposure concentrations that were not likely well characterized. The POD was also sometimes used as the TLV, in which case there was no margin of safety.

Table 1 – Factors decreasing confidence in oldest derived TLVs

Chemical	TLV derived	Most recent reassessment	Old data	Acute data	Overt effects	Industrial experience	Case reports
1,2-dichloroethylene	1946	1990	X	X	X	X	
ethyl acetate	1948	1979	X	X	X		
hydrogen selenide	1948	1990	X	X	X	X	
methanol	1948	2008	X	X	X		X
phosphorus yellow	1948	1992	X	X	X		X
tellurium	1948	1992	X	X	X	X	
diborane	1956	1990	X		X		
nicotine	1957	1992					
strychnine	1957	1992	X	X	X		X

The absence of observed health effects in workers exposed to the chemicals over the decades in which the TLVs have existed is sometimes used as support for the protectiveness of the existing values; however, there are weaknesses with that argument. The fact that a TLV is old is an indication that few new studies have been performed, indicating that the chemicals might not be of interest to researchers and have therefore not been investigated in larger epidemiological studies. In this case, observations would be limited to individual companies or worksites, with lower power to measure adverse health effects. Observations of health effects might become even less likely at smaller employers who might not staff occupational hygienists or other health professionals.

Furthermore, the observations may be reliant more on passive self-reporting of crude and subjective health effects.

Despite the uncertainties associated with older OELs, they can still be useful, as they ultimately serve as benchmarks for risk managers who use the values to identify appropriate measures to be taken to reduce populations' risks to chemical exposures. OELs and other outputs of dose–response analyses should not be solely considered as "bright lines," producing a dichotomy in which exposures below the guidelines warrant no actions and those exceeding the guidelines trigger risk management activities. Rather, the approach is more appropriate as incremental interventions, with some action being taken to mitigate risks even below exposure guidelines, but with more immediate, multi-faceted, and intense measures being taken as population exposure is increasingly above the guidelines.

The levels of confidence in and protectiveness of outputs of dose–response assessments should be considered by risk managers when identifying the need to implement mitigation measures below an exposure guideline. However, the general tendency in occupational hygiene is to treat all OELs as having equivalent reliability, using exposure levels relative to an OEL to identify the need for risk management action. A long-standing rule of thumb in occupational hygiene is that exposure levels at half of the OEL should be used as an action level (18). More modern occupational approaches use statistical methods to ensure that the 95th percentile exposures remain below an OEL (19).

The need to develop a knowledge translation tool that could be used by occupational hygienists to evaluate OELs was therefore identified. Such a tool would be helpful in guiding occupational hygienists to identify the need to take risk management actions at lower concentrations when OELs have narrow or non-existent margins of safety, or when they are based on less robust data or dose–response approaches. Moreover, as OELs are produced by many different organizations around the world, each with their own derivation approaches, occupational hygienists are often faced with multiple OELs for each compound. The variability in OELs can present a challenge to occupational hygienists who must select the OEL that is most appropriate for their situation.

The goals for the knowledge translation tool were therefore two-fold. The first objective was to provide guidance on the evaluation of OELs to the risk management end-users, who often have a basic knowledge of toxicology, but might not have more in-depth experience in developing or critiquing OELs. The second aim was to encourage users to seek OELs from multiple organizations, rather than restricting their search to a single organization, allowing them to select the OEL that is the most appropriate from the international body of derived OELs. The second part of this thesis provides background information on OEL derivation and resulting variability in values, presents a framework for evaluating and selecting OELs, and applies the framework to several compounds.

REFERENCES

1. US EPA. Toxicological Review of Boron and Compounds (CAS No. 7440-42-8) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC: US EPA; 2004. Report No.: EPA 635/04/052.

2. ATSDR. Toxicological Profile for Boron. Atlanta, GA; 2010.

3. Health Canada. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Dichloromethane. Ottawa, ON; 2011.

4. US EPA. Toxicological Review of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC; 2011. Report No.: EPA/635/R-10/003F.

5. Occupational Exposure to Methylene Chloride, Stat. 29 CFR Parts 1910, 1915 and 1926 (1997).

6. US EPA. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Washington, DC; 2014.

7. US EPA. Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. External review draft. Washington, DC; 2002. Report No.: NCEA-1-0503.

8. US EPA. Interim Drinking Water Health Advisory For Perchlorate. Washington, DC; 2008. Report No.: EPA 822-R-08-025.

9. EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables. Efsa J. 2014;12(10):3869.

10. US EPA. Deltamethrin. Human Health Risk Assessment for the Proposed Use of Deltamethrin as a Mosquito Adulticide over Agricultural Crops. Washington, DC; 2015.

11. US EPA. Pyrethrins/Pyrethroid Cumulative Risk Assessment. Washington, DC; 2011.

12. US EPA. Re-Evaluation of the FQPA Safety Factor for Pyrethroid Pesticides. Washington, DC; 2011.

13. US EPA. Pyrethrins. Preliminary Draft Human Health Risk Assessment for Registration Review. Washington, DC; 2017.

14. ATSDR. Toxicological Profile for Perfluoroalkyls: Draft for Public Comment. Atlanta, GA: ATSDR; 2018.

15. US EPA. The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water. Cincinnati, OH; 2003. Report No.: EPA/600/R-03/051.

16. US EPA. EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1. Draft. Washington, DC; 2011. Report No.: EPA/600/R-10/038D.

17. NRC. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: The National Academies Press; 1983.

18. Lee JS. An Industrial Hygienist's Perspective On Generic Standards. Ann N Y Acad Sci. 1989;572(1):93-9.

19. Waters M, McKernan L, Maier A, Jayjock M, Schaeffer V, Brosseau L. Exposure Estimation and Interpretation of Occupational Risk: Enhanced Information for the Occupational Risk Manager. J Occup Environ Hyg. 2015;12(sup1):S99-S111.

PART II
DEVELOPMENT OF A TOOL TO EVALUATE THE BASIS OF OELs

Chapter 6 – Derivation of Occupational Exposure Limits

Michelle Deveau, Kenneth R. Still, Andrew Maier, and Daniel Krewski

Reproduced Material

Citation

Deveau, M., Still, K.R., Maier, A., Krewski, D. (2019) Chapter 38 – Derivation of Occupational Exposure Limits. In: Toxicology Principles for the Industrial Hygienist, 2nd Edition. Luttrell, W.E., Still, K.R., Church, J.A., Beyer, L.A. (eds.). American Industrial Hygiene Association: Falls Church, VA.

Outcome Competencies

Upon completion of this chapter, the reader should be able to:

I. Understand the overall process used to develop occupational exposure limit (OEL) values.
II. Suggest specific components necessary to derive an OEL.
III. Critically read OEL documentation to identify strengths and limitations of derived values prior to applying them.

Prerequisite Knowledge Basic understanding of industrial hygiene, toxicology, biochemistry, chemistry, risk and exposure assessment principles is necessary.

Key Terms occupational exposure limit, risk, uncertainty factor, dose–response assessment

Key Topics

1. Overview of history and coverage of OELs
2. Hierarchy of OELs
3. Derivation of OELs
4. Hazard notations
5. Overview of newer techniques in OELs
6. Limitations of OELs
7. Examples of derivations of OELs

BACKGROUND

Occupational exposure limits (OELs) are developed as health-based benchmarks against which measured air concentrations of chemicals in workplace environments are compared. Derivation of OELs is performed based on the principle of preventing occupational disease or other adverse health effects, including irritation and acute neurological effects.[1] OEL values are derived using toxicological or epidemiological data as a starting point, and typically incorporate adjustment (safety or uncertainty) factors that take into account unknowns in the data, variability among humans, and, when animal data are used, differences between animals and humans. OELs are traditionally expressed in the form of 8-hour time weighted averages (TWAs), short-term exposure limits (STELs)—typically 15-minute TWAs—or ceiling values that should never be exceeded, all of which are established to protect workers against chemical risks.[1,2]

OELs are derived by many different organizations around the world. Descriptions of some OEL-deriving entities for many countries can be found on the International Labour Organization (ILO) website (http://www.ilo.org/safework/info/publications/WCMS_151534/lang--en/index.htm). Lists of OELs from various organizations can be found in databases such as the GESTIS International Limit Values database (http://limitvalue.ifa.dguv.de/) and the SER OEL database (https://www.ser.nl/en/oel_database.aspx).

Despite the abundance of OEL-deriving organizations, OELs exist for only a small fraction of chemicals in commerce (see Figure 38.1). The most comprehensive list of published OELs from around the world contains values for about 6,000 chemicals[3], whereas over 100,000 chemicals had been registered as of 2011 under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)[4]—European regulations that require industry to register and perform risk analysis and management on chemicals used, imported, or manufactured in the EU at quantities greater than 10 metric tonnes.[5] Different organizations frequently establish different OELs for the same agent; the OELs often vary quite substantially.[6] A comparative study of OELs from 18 organizations spanning a total of 1,341 different chemical substances found that

approximately two-thirds of these substances had OELs derived by at least two organizations, and that only 25 substances had OELs derived by all organizations in the study.[7]

HIERARCHY OF OELS

In addition to traditional OELs, various other occupational exposure benchmarks are available for consideration by industrial hygienists. Each of these is briefly described in Table 38.1. A "hierarchy of OELs" has been proposed by Laszcz-Davis et al.[8] as a means of demonstrating these various occupational exposure benchmarks available to be used in exposure risk assessments performed by industrial hygienists. The hierarchical structure is used to illustrate differences in data requirements and robustness incorporated into different types of occupational exposure benchmarks, and provides alternative exposure benchmarks for chemicals without traditional OELs (Figure 38.2). Quantitative health-based OELs and traditional OELs encompass the top tiers with the most extensive data requirements; working provisional OELs and prescriptive process-based OELs have moderate data requirements; and hazard banding strategies the fewest data requirements.

DERIVATION OF OELS

Although differences arise in many of the specific approaches used by various OEL-setting organizations, the general framework for the derivation of OELs is similar around the world. A decision logic for OEL development is presented in Figure 38.3. The overall OEL setting process requires: (1) selecting candidate chemicals for the OEL derivation process; (2) collecting a complete data set on the chemical substance of interest; (3) evaluating published peer-reviewed human and animal studies; and, (4) identifying the critical adverse health effect(s). Documentation of the entire process is critical and must include: nomenclature; physiochemical properties; animal data; human use and experience; and the rationale used to derive the OEL. The rationale for the OEL must be clearly documented and should include: (1) a description of the key studies used; (2) the selection of the critical endpoint(s) and why they were selected; (3) the selection of any uncertainty or safety factors used; (4) any uncertainties associated with the derivation; and (5) any other factor that an OEL user should be aware of regarding the derivation.

The OEL process also needs to consider averaging time (i.e. setting a TWA versus a STEL or ceiling) and how to assign appropriate notations for specific hazards (e.g., cancer or sensitization).

Selection of Candidate Chemicals

A first step in developing an OEL is the selection of candidate chemicals. Most OEL-setting organizations use various prioritization schemes to focus their efforts on chemicals lacking appropriate OELs. Thus, a new candidate substance will ideally have no existing and up-to-date authoritative OEL, be handled by a significant number of employees, and/or have the potential to cause adverse health effects or harm to workers as a result of occupational exposure. Existing OELs should also be reviewed periodically to identify new scientific data that might warrant a review and update of an existing OEL.

Literature Review

An early step in deriving an OEL for a specific substance is to perform a literature search to identify as many relevant studies as possible.[9] Information used to support risk assessment includes chemical and physical properties, major uses of the compound, animal toxicity, and human health effects and exposure data (including epidemiological studies, and data from workplaces that describe medical or other health observations in workers exposed to measured or estimated concentrations of the substance of interest).[10,11] If the data available in the scientific literature are insufficient to support an OEL, and cannot be supplemented with proprietary data from chemical manufacturers or other organizations with experience in using the compounds, read-across using compounds of a similar structure and/or nature may be considered as the basis for determining an OEL. If the literature search identifies that data are insufficient, alternative approaches—including hazard banding and threshold of toxicological concern approaches—might be also be considered for OEL derivation (see section entitled Derivation of OELs for Data-Poor Compounds for further discussion).

Selection of Key Studies

After gathering and evaluating the available data, critical effects and key studies are then

selected. The ideal key study is a good quality study demonstrating a dose–response relationship for a chemical-induced adverse effect that is relevant to humans. The key study (or studies, as more than one is sometimes used for a particular substance) provides the dose–response data for the most sensitive adverse effects (i.e., those effects that occur at the lowest exposure levels observed within the gathered database). Protecting against the most sensitive effects is expected to also protect against other adverse effects that might occur at higher exposure levels.[12] A definition of an adverse effect proffered by Lewis et al.[13]—similar versions of which were adopted by organizations such as the International Programme on Chemical Safety (IPCS)[14] and Organization for Economic Cooperation and Development (OECD)[15]—is a "biochemical, morphological, or physiological change (in response to a stimulus) that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge." However, many physiological or morphological changes can reflect adaptive or transient alterations elicited by chemical exposures, and are not necessarily expected to result in adverse health effects. Consequently, organizations evaluate the weight of evidence regarding whether or not observed biological effects may be adverse, and they might not use the most sensitive effect as the critical effect if it is not truly adverse.[13,16,17]

Both animal and human studies are candidates for key studies. Of the 414 American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Values (TLVs®) included in the 1968 publication, 49% were based on human data, 27% on animal toxicity studies, and 24% on chemical analogy.[18] However, current OELs are more often based on animal data.[18,19] Although human studies might be more relevant to occupational exposure scenarios, few well-designed studies with adequate exposure measurements have been performed in humans. Moreover, controlled dosing studies (i.e. studies where researchers expose participants to specific exposure concentrations or to clean air and measure associated health effects) in humans are also limited to due ethical concerns. These factors limit the opportunity for OEL derivation based on human data.

Reliability and relevance of each animal study is assessed prior to its inclusion as a

potential key study for OEL determination. Study reliability can be evaluated by comparing its compliance with relevant research guidelines (e.g. Section 4 of the OECD Guidelines for the Testing of Chemicals[20]), which can be performed by using systematic scoring criteria (such as the Klimisch criteria for evaluating toxicological data quality[21] or Toxicological Data Reliability Assessment Tool [ToxRTool].[22] Adverse effects observed in animal studies are also evaluated for their relevance to humans; one systematic approach to this—mode of action and human relevance analysis—is further described in the section entitled "Advanced Risk Assessment Techniques."

In some cases, several potential key studies are used for the dose–response assessment process allowing qualitative or quantitative comparisons of OELs resulting from the different approaches.

Dose–Response Analysis

A first step in OEL calculation is identifying the point of departure (POD) from the selected key study or studies. Traditionally, the POD is identified by selecting the highest dose at which no adverse effects were observed (the no observed adverse effect level [NOAEL]). If no NOAEL is available in the study, the lowest dose at which adverse effects were observed (lowest observed adverse effect level [LOAEL]) is selected. More recent approaches to dose–response assessment include calculating a benchmark dose to use as a POD. This process is described in the section entitled "Advanced Risk Assessment Techniques." Both traditional and advanced methods for POD estimation are described in greater detail by Wheeler et al.[23]

The OEL is typically calculated by dividing the selected POD by uncertainty factors (UFs) as shown in Eq. 1.

$$\frac{\text{Point of departure}}{\text{Uncertainty (safety) factors}} \quad \text{(Eq. 1)}$$

The uncertainty factors (called safety factors in some contexts) are used to provide a margin of safety between the POD and the OEL, and to reflect uncertainties in data as well as variability between and within species.[1,24] The categories of uncertainty factors

that are most frequently considered are listed in Table 38.2. Very little guidance on quantitative selection of UFs is specified by OEL-deriving organizations[18] (REACH is an exception), with the values typically being assigned on a case-by-case basis.[24] For calculating allowable daily intake (ADI) values for the general public, 10-fold uncertainty factors for each category (first proposed by Lehman and Fitzhugh[25]) are considered sufficient for a wide range of chemicals.[26] Recommended UFs for occupational exposures tend to be lower than for the general population,[1,18,19] but specific values (or ranges thereof) are not typically discussed. Composite UFs applied when deriving OELs typically range between 1 and 100[1,18,24], with the lowest composite value (UF=1) applied when NOAELs are identified in well-conducted human studies.[24] In some cases, organizations do not assign UFs for each subcategory listed in Table 38.2. Instead, they (*e.g.*, the Workplace Environmental Exposure Level [WEEL] committee) only identify a composite UF (or margin of safety between POD and OEL) that considers all of the potential sources of uncertainty.[10] Many organizations do not specify either the selected UFs or the composite UF, although the composite UF can be inferred based on the ratio between the POD(s) and the final OEL.[18,19] Under REACH, the application of UFs (called assessment factors under REACH) when calculating Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs) (see Table 38.2) is more prescriptive; REACH guidance provides an in-depth discussion on selecting appropriate UFs.[27]

Larger uncertainty factors are typically applied for chemicals with weaker data[12], consistent with the idea that these factors account for uncertainties in the database. Although higher uncertainty factors are sometimes suggested for compounds with greater severity,[9,18,24,27] this might not be the case in practice. For example, a study identified that the size of composite uncertainty factors for OELs derived by the Scientific Committee on Occupational Exposure Limits (SCOEL) in Europe did not vary with the type of critical effect.[19]

Depending on data availability, the default uncertainty factors for inter- and intra-species variability can also be replaced by chemical-specific adjustment factors, which are data-

derived uncertainty factors that are further discussed in the section entitled "Advanced Risk Assessment Techniques." The basis for application of traditional and advanced methods for assigning UFs is reviewed in greater detail by Dankovic et al., 2015[28].

Risk Assessment for Carcinogens

The OEL-derivation process described above (i.e., a POD divided by UFs) is thought to be appropriate for deriving OELs for carcinogenic chemicals that are believed to act via non-mutagenic modes of action.[29] This is because cancer is not expected to occur if the early key events in cancer development (e.g., cytotoxicity, cell proliferation, alteration of receptor-induced cell signaling pathways) are prevented by setting an OEL at a dose smaller than the dose required for such key events.

In contrast, direct-acting mutagens are often thought to have some level of risk even at very low levels of exposure.[1,18,30] To allow for the possibility that certain unrepaired mutations occurring from a single exposure to a mutagenic chemical could become fixed upon cell replication, potentially resulting in tumor development according to the "one-hit" model[1], some organizations use approaches other than the traditional OEL-derivation process (i.e. POD divided by UFs) to set OELs for carcinogens that are expected to act via mutagenic mechanisms. One approach – used by organizations such as the DFG in Germany[31] – is to recommend that exposures remain as low as reasonably achievable (ALARA) or as low as reasonably practical (ALARP), without providing any quantitative exposure guidelines for mutagenic chemicals. An alternative approach, linear extrapolation, calculates quantitative OEL values to estimate cancer risk at various exposure levels using mathematical models that are constrained to go through the origin and be linear at low doses. This approach, referred to as linear low-dose extrapolation, is used by organizations in the US (*e.g.*, Occupational Safety and Health Administration [OSHA], National Institute for Occupational Safety and Health [NIOSH]) and internationally (*e.g.*, the European Union, several European countries, and Japan).[30]

The linear extrapolation procedure estimates a risk-specific dose or concentration that can be used as the basis for the OEL. To calculate a risk-specific dose (i.e. the dose

corresponding to a specified level of risk) to use as the basis of an OEL for cancer, downward extrapolations are performed mathematically, using the dose–response curve from the key toxicological or epidemiological study.[12,23] This involves calculating the slope of the dose–response curve, which is described in greater detail in the section entitled "Advanced Risk Assessment Techniques." OELs derived using this approach are typically based on a level of risk that is considered to be *de minimis*—an accepted or tolerable level of risk. Definitions of *de minimis risk* vary among OEL-deriving organizations[30], but typically fall in the range of 10^{-5} (i.e. an estimated probability of the development of 1 excess cancer in a population of 100,000 exposed at a specific dose) to 10^{-3} (i.e., a 1 in 1,000 risk).[30,32,33,34] However, OELs are sometimes set at risk levels even higher than 1 in 1,000, as demonstrated by several OSHA PELs[35] that considered risk management issues in developing the final PEL value. Post hoc analysis also shows that risks might be above 10^{-3} for the 1988–1989 ACGIH® TLVs® when compared to the values derived using EPA-derived cancer unit risk values as a starting point (EPA values were used for comparison as cancer unit risks or similar values were not provided in the TLV® documentation[36]); no newer analyses of this nature could be found in published literature.

Adjustments for Route and Duration of Exposure

Depending on the nature of the key study, additional adjustments might be required to make the POD or OEL relevant to occupational exposure scenarios. Many toxicity studies in which the test agent is administered by ingestion present exposures in units of milligram of test material per kilogram body weight of the test species per day (mg/kg-d) or mg/d, which then are converted to units relevant to inhalation (mg/m^3 or ppm). A default approach is to perform linear adjustments based on assumptions for bodyweight and inhalation in humans (see Eq. 2).

$$\text{POD or OEL } (mg/m^3) = \frac{\text{POD or OEL } (mg/kg \text{ per day}) \times \text{human bodyweight (kg)}}{\text{human inhalation rate } (m^3 \text{ per shift or day})} \quad \text{(Eq. 2)}$$

The use of a POD from ingestion studies is only recommended if the health effects are

expected to be relevant to inhalation routes of exposure. Health effects from ingestion studies are relevant if they are systemic. Conversely, health effects related to the portal of entry are not appropriate for use in route extrapolation. For example, a POD for irritation of the gastrointestinal tract after oral exposure cannot simply be converted to reflect irritation of the respiratory tract for inhalation exposures.

Durations of exposure in key studies might also differ from the typical work shift durations used in the development of the OELs (e.g. 8 hours per day, 5 days per week). Animal inhalation studies are often of a shorter duration than 8 hours per day[20], or daily exposures (such as those often seen in oral studies) could represent effectively continuous exposure (e.g. ingestion studies administering doses via feed or drinking water). Linear extrapolation can be employed for these adjustments, as indicated in Eq. 3.

$$\text{Duration adjusted POD} = \text{Original POD} \times \frac{\text{Hours per day in study}}{\text{Hours per day in shift}} \times \frac{\text{Days per week in study}}{\text{Days per week in shift}} \quad \text{(Eq. 3)}$$

Although the default linear scaling approach might be appropriate for route and duration adjustments of some compounds, kinetic behavior of many chemicals does not follow a linear pattern. To account for non-linear behavior of chemicals, physiologically-based pharmacokinetic (PBPK) modeling can be used for route and duration adjustments. The application of PBPK modeling is further discussed in the section entitled "Advanced Risk Assessment Techniques." PBPK models can also account for the impact of exposure patterns on metabolism and other pharmacokinetic aspects when used to adjust OELs post-hoc for unusual work shifts, as an alternative to linear adjustment approaches (e.g. Brief and Scala)[18].

Finally, OELs for aerosols are typically maintained in units of mg/m^3, whereas those for gases or vapors are converted to units of parts per million (ppm).[1,2] This conversion is performed using a formula similar to Eq. 4, which presents the conversion at 25°C and 1 atmosphere of pressure.

$$\text{OEL (ppm)} = \frac{\text{OEL (mg/m}^3) \times 24.45 \text{ L/mol}}{\text{molecular weight (g/mol)}} \quad \text{(Eq. 4)}$$

Derivation of OELs for Data-Poor Compounds

OELs can sometimes be derived for chemicals lacking sufficient toxicity data, if data exist for chemicals that are homologous or in the same family of compounds.[12] Hazard banding and threshold of toxicological concern techniques (as outlined in Table 38.1) can be used as semi-quantitative, protective benchmarks for exposure comparisons. An alternative approach, which has been used for the derivation of some OELs, is the application of quantitative structure-activity relationship [(Q)SAR] techniques. Using (Q)SAR—a modeling approach that associates molecular structures with the potential for specific chemically-induced effects in humans and animal models—OELs can be derived for data-poor chemicals having structures similar to data-rich compounds (using an approach sometimes referred to as "read across"). For example, OELs for chemicals belonging to classes with similar toxicological function, such as isocyanates, nitriles, and glycidyl ethers, can be derived based on chemicals with the same active group.[37] Another approach, which is not used frequently, is to calculate an OEL based on equations that use LD_{50} or LC_{50} values.[37] As risk assessment evolves to incorporate increased high-throughput data (based on rapid *in vitro* tests using human cells or human cell lines), OELs for data-poor compounds might also increasingly become based on *in vitro* studies.

Adjustments for Feasibility

Many OELs are health-based, and therefore derived based solely on the approaches described above. However, some organizations develop OELs that are "regulatory adjusted", meaning that technical and economic feasibility are considered when setting the final value.[38] After the development of a health-based OEL, organizations that perform feasibility adjustments consider whether air sampling and analysis techniques can measure sufficiently low levels, and whether current engineering or other controls are sufficient to reduce exposure levels below the OEL in a manner that is not cost prohibitive. These technical and economic abilities might vary depending on

geographical region.[39] The OSHA PELs, for example, are developed by considering technical and economic feasibility, in addition to protecting health.

HAZARD NOTATIONS

Many organizations apply one or more qualitative notations to reflect toxicological complexities that might not sufficiently be addressed in the quantitative derivation of the OELs. These notations are used to alert industrial hygienists that increased precautions might be required even if worker airborne exposures are well below the OELs. Some of the notations of particular relevance to toxicology relate to chemicals that are dermally relevant, sensitizers, carcinogens, or reproductive or developmental toxicants. These notations can be combined when required, resulting in OELs with multiple qualitative notations.

Skin Notations

Many OEL-deriving organizations use a qualitative determination of a chemical's potential to cause hazardous health effects via dermal exposure, including ACGIH®[2], NIOSH[40], OARS WEEL Committee [10], Dutch Expert Committee on Occupational Standards (DECOS)[41], Group of Experts for Chemical Agents in Poland[42], and the DFG Commission in Germany.[43,44] These skin notations are typically used to inform industrial hygienists that the OEL might not sufficiently protect workers if dermal exposure occurs to skin-penetrative compounds.[2] Skin notations exist for approximately one quarter to one third of OELs derived by the organizations that apply this approach.[45,46] Criteria for assigning notations are not consistent, leading to differences in application of notations, both among organizations[46,47,48,49] and within organizations.[50] The types of data that might be used to indicate a chemical's potential for dermal absorption and contributions to toxicity include:

- LD_{50} estimates (from acute dermal exposure studies) that are below a certain threshold, which is sometimes 1,000 mg/kg[2,10,42], and other times 2,000 mg/kg[40], or
- Evidence of high potential for dermal penetration. For example, data from *in vivo* or *in vitro* studies of dermal absorption, mathematical models[40,43]

structure-activity relationships[40], or physicochemical properties, such as octanol–water partition coefficients[2], paired with observations of systemic toxicity from any route of exposure.

Moreover, some organizations have developed specific quantitative guidance to consider whether dermal penetration is high enough to contribute to a chemical's toxicity. For example, in the Netherlands, DECOS designated >10% of the 8-hour OEL as a significant exposure level. If the estimated systemic dose from dermal absorption (from combined arms and forearms) from a 1-hour exposure exceeds a systemic dose equivalent to 10% of the OEL, DECOS applies a skin notation.[41,51]

Skin notations are typically used to address the potential for systemic toxicity from dermal penetration, and do not usually address irritation, corrosion, or sensitization of the skin[2]. An exception is Poland's use of separate notations to indicate if a compound is corrosive or an irritant.[52] In 2009, NIOSH introduced a new process for developing and assigning skin notation classifications for a variety of effects, including irritation, corrosion, and sensitization of the skin.[40] These different notations are described in Table 38.3. A Skin Notation Profile is published for each chemical assigned a skin notation by the new process, which provides detailed information on the data supporting the classification.

Sensitizer Notations

Very few quantitative OELs based on sensitization have been developed.[53] Many challenges limit the derivation of sensitization-based OELs, including the typical absence of dose–response data, large intraspecies variability due to differences in individual susceptibility, and difficulties in identifying the appropriate immune-mediated response (i.e., induction vs. elicitation of sensitization) or biomarkers of effect as the basis for the OEL.[53]

In response to the challenges and limitations in setting OELs for sensitizing compounds, many organizations develop OELs based on health endpoints other than allergenic

effects, and use a qualitative notation to alert users to a compound's sensitizing potential. Notations to highlight the potential for respiratory and/or dermal sensitization are applied by various OEL-developing organizations, including the ACGIH® TLV® committee[2], OARS WEEL committee[10], German MAK committee[54] and organizations in Austria, Czech Republic, Poland, and Spain.[52] Organizations often specify whether the compounds are respiratory or dermal sensitizers (i.e. RSENS or DSENS). Although NIOSH applies a notation specific to dermal sensitizers[40] no similar notation exists for chemicals that potentially cause respiratory sensitization.[53]

Cancer Notations

Cancer notations are used by some organizations (e.g. for ACGIH® TLVs®[11] or UK OELs[52]) as qualitative indicators of the weight of evidence for carcinogenicity. The notations can be used in the absence of—or as a supplement to—the application of low-dose linear extrapolation to assess cancer risk. These carcinogen classifications vary among OEL-deriving organizations[55]; those used for the ACGIH® TLVs® are presented in Table 38.4. Some organizations (*e.g.* NIOSH, OSHA) use a binary approach and either consider an agent to be a carcinogen or not, with no additional categories.

Notations for Developmental and/or Reproductive Toxicity

Complexities arise in evaluating occupational exposures to developmental toxicants, as developing fetuses can be at increased risk during "critical windows of exposure" corresponding to organogenesis. To highlight the fact that some OELs might not sufficiently protect developing fetuses, particularly if exposures occur during a critical window of organogenesis, some OEL-developing organizations apply notations for developmental and reproductive toxicity. Examples of some of the countries using these notations, and the specific health effects addressed in the notations, are listed in Table 38.5. Germany also considers the potential for a compound to act as a germ cell mutagen, which could result in genetic disorders or other heritable alterations in future generations.[31]

OVERVIEW OF NEWER TECHNIQUES IN OEL DERIVATION

Industrial hygienists reading documentation for OELs might sometimes encounter quantitative dose–response techniques that may appear to be more complicated than the approaches described in previous sections of this chapter. Some of these approaches include benchmark dose modeling, physiologically-based pharmacokinetic modeling, mode of action analysis, and derivation of chemical-specific adjustment factors. This section focuses on benchmark dose modeling, which is being applied with increasing frequency in deriving OELs.

Benchmark Dose (BMD) Modeling

A benchmark dose (BMD) can be used as an alternative to the LOAEL or NOAEL as a point of departure for calculating an OEL.[23] Whereas LOAELs or NOAELs are dependent on the doses used in animal studies, BMD modeling uses all of the data across the entire dose range in selecting the point of departure.[56-58] The term "benchmark concentration" (BMC) is also sometimes used when exposures occurred via the inhalation route.

BMDs are estimates of the rate of occurrence of a specific adverse effect in the study population. The default occurrence rate used for dichotomous data (i.e. presence or absence of an effect, e.g. hepatocellular tumor vs. no hepatocellular tumor) is 10% (with the corresponding BMD denoted as the BMD_{10}), but incidence levels of 5% or 1% (BMD_{05} or BMD_{01}) can also be used depending on the nature of the available data (e.g., the use of a lower BMR is warranted if the study population size is large, and might be selected if the adverse effect is severe, such as cancer or developmental effects).[59] Lower bounds around the BMD (often referring to a 95% confidence interval) are also calculated, and are referred to as BMDL values. The $BMDL_{10}$ refers to the lower 95% confidence limit on the dose associated with an increase of 10% in the rate of occurrence of an adverse effect above the background rate.

When using continuous data (e.g. levels of biomarkers indicating potential changes in effect, such as levels of liver enzymes), the default occurrence rate is a change of 1

standard deviation in the data (corresponding to the BMD_{1SD} or $BMDL_{1SD}$).[59] For some adverse outcomes, these default values can be replaced with percent changes in clinical measures associated with biological significance, such as clinical benchmarks for disease[59] (e.g. cutoff points used by clinicians for classifying patients as having cholesterolemia, glomerular filtration rates associated with various stages of chronic kidney disease).

The calculation of BMDs and BMDLs is illustrated in Figure 38.4, which contains an output plot from a software package used to calculate BMD values (U.S. Environmental Protection Agency's Benchmark Dose Software, version 2.6). The figure depicts BMD modeling for a hypothetical key study, where study subjects (n=50 per group) were exposed to a chemical at levels of 0 (i.e. control), 5, 10, 15, or 20 ppm, with an incidence of an adverse effect of 2%, 4%, 24%, 70%, and 90%, respectively (as denoted by the ellipses in the figure). Error bars placed around the incidence at each dose reflect the 95% confidence intervals around the fraction affected. The solid curve was calculated by the software as being the best dose–response curve that fit the data, while the dotted curve indicates the 95% confidence interval for the dose–response curve. The selected occurrence rate in this plot is 10% above background levels; because the control group had a 2% incidence of the adverse effect, the BMD_{10} values will be associated with an incidence of effect of 12% (i.e. 10% incidence above background level + 2% incidence at background). To identify BMD_{10} and $BMDL_{10}$ values, a line is drawn from the 0.12 fraction affected on the y-axis; the associated x-axis doses (where that line intersects the dose–response curve and lower confidence curve) are the BMD_{10} and $BMDL_{10}$, respectively. In this scenario, the BMD_{10} was 7.1 ppm and the $BMDL_{10}$ was 5.9 ppm. The $BMDL_{10}$ can be selected as a point of departure for calculating an OEL.

BMD values can be employed to estimate a POD that is then used when performing linear low-dose extrapolation for cancer risks down to relevant risk levels (e.g. incidence of 1 in 1,000 or 1 in 10,000). This approach assumes the drawing of a straight line from the POD (e.g. $BMDL_{10}$) down to a risk of 0 (i.e. intersection of x- and y-axes). The slope

of the linear curve can be calculated by dividing the y-axis by the x-axis, which is demonstrated in Eq. 5.

$$\text{cancer slope factor} = \frac{\text{response rate at POD (e.g. 10\% for BMDL}_{10})}{\text{POD (e.g. BMDL}_{10})} \quad \text{(Eq. 5)}$$

The resulting cancer slope factor will be the inverse of the original dose unit used in the study of interest (e.g. $[\text{ppm}]^{-1}$ or $[\text{mg/kg-d}]^{-1}$). To calculate the risk-specific doses (e.g. the dose associated with an estimated cancer incidence of 1 in 10,000), Eq. 6 is used.

$$\text{risk-specific dose} = \frac{\text{risk level of interest (e.g. } 10^{-4})}{\text{cancer slope factor}} \quad \text{(Eq. 6)}$$

Physiologically-Based Pharmacokinetic (PBPK) Modeling

A PBPK model is a series of interlinked biologically-based compartments – representing individual organs or groups of similar organs – each with mathematical equations to describe the pharmacokinetic behavior of chemicals (i.e. representing absorption, distribution, metabolism, and excretion for each compartment) in humans and animals. These models can be used to estimate concentrations and amounts of a chemical in the blood and various target organs (i.e., referred to as "compartments") over time. PBPK models are useful because the toxicity of chemicals is thought to be most closely related to concentrations of a chemical (or its toxic metabolite, if applicable) at the target organ.

Using PBPK models, concentrations of a chemical in target organs or in blood can be estimated for different external exposure scenarios (e.g. air concentrations), to extrapolate across dose routes, and to adjust animal toxicity doses to human equivalent values. Depending on the data available when the model is developed, internal dose estimates can be made for different species, varying routes and patterns of exposure, or human subpopulations with different physiological characteristics. Although all of these factors could be addressed using linear scaling, the pharmacokinetics of many chemicals are non-linear (i.e. rates of absorption, metabolism, and excretion can all vary at different doses); therefore, linear scaling is not generally an accurate way of addressing differences in exposure scenarios for many chemicals. The modeling of different scenarios allows for

several types of extrapolation that are relevant to workplace exposures to chemicals, in a way that reflects the potential non-linear pharmacokinetics of a chemical. The many different types of extrapolation can be performed concurrently. Some of the types of predictions that can be addressed by PBPK models are outlined in Table 38.6.

The purpose of using a PBPK model to perform these extrapolations in the context of OELs is to estimate the air concentrations of a chemical expected to produce the same tissue doses as the key study, should workers be exposed for typical shift patterns (e.g. 8 hours per day, 5 days per week). The model is first run for relevant exposure levels in the key study scenario (e.g. at the POD or individual doses from the study). The model will provide data on various dose metrics (e.g. peak or average tissue concentrations of the parent compound or its metabolites, or rate of metabolism) for the defined exposure scenario that is related to the observed adverse effects. These internal doses are assumed to also be the relevant levels at which adverse effects would be observed for the occupational exposure scenario, and are therefore the target internal doses. The PBPK model is then run for the occupational exposure scenario, to estimate the air concentrations that would generate these same target internal doses. If the initial value that was run in the model was the POD from the key study, the resulting air concentration from the modeled occupational scenario can be used as the new POD for the OEL. Furthermore, if BMDs are being calculated for the key study, BMDs can also be calculated based on internal doses, which become the new target internal doses for the occupational exposure scenario modeling; this accounts for any potential non-linearity in pharmacokinetics in the key study. A visual representation of these steps is presented in Figure 38.5.

PBPK models can also be used to adjust OELs for different durations of working shifts in a manner that can reflect pharmacokinetic non-linearities. Standard linear methods of extrapolating from an OEL that is an 8-hour TWA to a shift of longer duration (e.g. using the Brief and Scala method[2,18]) might not be sufficient if exposures at the OEL are expected to lead to saturation of pharmacokinetic processes (e.g. of absorption, metabolism, or excretion). Using PBPK modeling, estimates can be made of the air

concentration in a longer shift that would produce the same internal dose levels as the 8-hour exposures.[60,61]

In some cases, steps representing adverse health effects can be incorporated into the models (e.g. binding of the chemical to a receptor on a cell, or other early key events for an adverse outcome that can represent cellular change). These aspects of models are considered to represent pharmacodynamic processes; therefore, models incorporating them might be referred to as physiologically-based pharmacokinetic/pharmacodynamic models, and might be considered one of a type of model called biologically-based dose–response (BBDR) models.

Mode of Action (MOA) Analysis

The International Programme on Chemical Safety (IPCS) has developed a framework to systematically evaluate various potential modes of action for critical effects being considered in risk assessments.[62-66] Mode of action analysis evaluates the human relevance of adverse effects observed in animal studies; effects that are deemed not relevant to humans are not used as the basis for OELs. This approach can also be used to identify whether the development of a chemically induced cancer is likely to occur by a mode of action that is linear but without a clear threshold at low doses (e.g., some mutagenic carcinogens, as described earlier) versus having a threshold (i.e., at some low dose key events such as cytotoxicity that lead to the cancer response do not occur). For carcinogens this distinction of low-dose threshold behavior can help guide decisions on whether to derive an OEL using a linear low-dose risk-based approach or by dividing a POD by UFs. Examples of the use of MOA to guide the selection of dose–response approaches in OEL derivation can be found in the Case Studies section of this chapter (e.g., SCOEL assessments for carbon tetrachloride and formaldehyde assumed threshold MOAs and divided PODs by UFs, whereas SCOEL performed linear extrapolation for vinyl chloride because of an assumed non-threshold MOA).

The IPCS MOA analysis framework is shown in Figure 38.6. The first stage of the process evaluates whether sufficient evidence exists to conclude that a particular MOA

for the critical effect(s) can be demonstrated in the test species from which the POD was derived. In this step, all potentially relevant MOAs are considered. A series of key events—early steps in the development of an adverse effect, which are both measurable and critical, and that can progress into the final adverse outcome—is identified for each hypothesized MOA. Data on positive and negative observations of each key event are arranged in a table by increasing dose and duration. Revised Bradford-Hill criteria (see Table 38.7) can be used to evaluate the data table and assess the likelihood of each MOA. Any MOAs that cannot be reasonably excluded on the basis of qualitative or quantitative differences among species is assumed to be relevant to humans and can be used as a basis for the risk assessment.

The subsequent MOA stages use data about the understanding of human biology to evaluate whether the biological processes for each MOA can occur in humans. The second stage of the analysis identifies whether the MOA is relevant in humans at any exposure level (i.e. do humans have the same toxicity pathways as the test species?), and the third stage of the analysis determines whether the MOA is relevant in humans at typical exposure levels (i.e., are there quantitative differences in sensitivity or toxic responses that preclude effects in humans even at high exposure levels?). If the human relevance of MOAs cannot be eliminated, the critical effect must be considered as relevant for deriving the OEL. Conversely, if the MOA(s) with the greatest weight of evidence are considered irrelevant to humans, the adverse outcome might not be used as the critical effect for an OEL. An example of an effect in animals that is not considered relevant to humans can be found in the decamethylcyclopentasiloxane WEEL (presented in the Case Studies section in this chapter).

Derivation of Chemical-Specific Adjustment Factors (CSAFs)

Chemical-specific adjustment factors (CSAFs) are data-derived uncertainty factors that can more precisely reflect variability in the pharmacokinetics (what the body does to the chemical; i.e. the absorption, distribution, metabolism, and excretion of a chemical) and pharmacodynamics (what the chemical does to the body; i.e. the toxic action of the chemical on cells or molecules of target tissues) between animals and humans, and within

the human population. These values can be used to replace the default interspecies and intraspecies uncertainty factors.[28] Greater variability between species or within the human population results in larger CSAFs, and indications that humans are less sensitive might warrant the removal of some or all of an uncertainty factor.

The International Programme on Chemical Safety developed guidance on deriving CSAFs.[67] Each uncertainty factor is broken down into two components to address pharmacokinetic and pharmacodynamic differences separately, as demonstrated in Figure 38.7. A default animal-to-human UF of 10 is subdivided into components of 2.5 for toxicodynamic variability multiplied by 4.0 for toxicokinetic variability. The default human variability UF of 10 is subdivided into factors of 3.16 for toxicodynamic variability multiplied by 3.16 for toxicokinetic variability. Each of these values can be derived based on chemical-specific data to calculate CSAFs. The interspecies CSAFs are calculated using ratios of data for the animal species relevant to the key study and humans. Intraspecies CSAFs are calculated using ratios of data for average individuals and individuals in the more sensitive tail of a population distribution (e.g. represented by the 5^{th} or 95^{th} percentile of either the healthy population or a sensitive subpopulation depending on the metric being used). Several different types of data can be used to calculate these ratios; however, the metrics must remain consistent for both groups in each calculation. The chemical's cumulative dose (area under the blood concentration–time curve or AUC) or clearance rates (rate at which the chemical is removed from the body) are typical parameters used to calculate the pharmacokinetic CSAFs. Pharmacodynamic CSAFs are based on quantitative *in vitro* or *in vivo* data on biomarkers of toxic response for the critical effect (or a key event preceding the critical effect); therefore, the types of data used for pharmacodynamic values vary by adverse outcome expected for the chemical.

LIMITATIONS OF OELs

The robustness of each OEL is dependent on the data, methods, and assumptions used in its derivation; therefore, industrial hygienists should be familiar with the methods used to develop particular OELs prior to using the values as risk assessment tools.[12] Industrial

hygienists are also encouraged to critically evaluate the basis of each individual OEL prior to applying them. Several factors that industrial hygienists should keep in mind when evaluating an OEL are listed in Table 38.8. If evaluating the OEL raises concerns (such as those listed in the table), and applied uncertainty factors are not sufficient to address the weaknesses in the values, industrial hygienists should consider lowering an organization's action level for a chemical.

An additional recommendation for good industrial hygiene practice related to OELs is to consider values derived from a variety of organizations, rather than referring only to one type of OEL by default. OELs often vary among organizations[7] due to different OEL-derivation practices used by each organization.[68] A framework has been developed to help guide industrial hygienists through the process of selecting the most relevant and reliable OEL for each particular exposure scenario.[68] Considering other OELs is particularly important when the OEL documentation is incomplete, as this can severely limit the industrial hygienist's ability to either evaluate the OEL or conduct a meaningful risk assessment.

EXAMPLES OF DERIVATION OF OELs

Industrial hygienists can gain a better understanding of the principles described throughout the chapter by learning how OELs for various chemicals were developed. The chemicals in this section were selected to cover the breadth of topics discussed in the chapter. Only a small fraction of OEL-deriving organizations are discussed in this section, as documentation in English on the specific processes used for each value is readily available from only a few organizations. Table 38.9 provides an overview of the OEL values discussed in this section.

Vinyl Chloride

The GESTIS Limit Value database[69] identified STELs developed by 6 organizations (ranging from 6–30 mg/m^3, or 2–5 ppm), and 8-hour TWAs developed by 25 organizations (ranging from 1–5 ppm, or 2.5–13 mg/m^3). The methods used to derive

these OELs varied among organizations, and although documentation was readily available for the 8-hour TWAs, it was not available for the STELs.

The ACGIH® TLV® of 1 ppm[70] – established in 1999 – is accompanied by a cancer notation of A1 (Confirmed Human Carcinogen). The TLV® committee did not develop a STEL, as the critical effect for the TLV® was thought to be most closely associated with cumulative exposure. The TLV® is based on an occupational epidemiological study with a large sample size (14,351 subjects), in which the LOAEL of 28.8 ppm was derived from the lowest estimated cumulative exposure in workers with hepatic angiosarcoma (288 ppm–years in an individual who was exposed for 10 years, leading to an estimated annual average concentration of 28.8 ppm of vinyl chloride) prior to developing hepatic angiosarcoma 16 years after exposures commenced. After performing a linear adjustment for exposure duration to extrapolate to a 45-year working lifetime duration (i.e. by multiplying the LOAEL of 28.8 ppm by 10 years divided by 45 years, or 0.22), an adjusted LOAEL of approximately 6.5 ppm was obtained. UFs were not explicitly mentioned, but discussions in the documentation of the key study selection (a robust human study) and of the potential for sensitive individuals (for example, due to the possible potentiation by ethanol of vinyl-chloride induced tumors) provide potential clues to factors considered when establishing a 6.5-fold margin between the LOAEL and the final TLV® of 1 ppm. Although low-dose linear extrapolation was not performed, the documentation discusses other studies that used low-dose linear extrapolation. The TLV® committee mentioned that risk estimates for developing hepatic angiosarcoma at air concentrations of 1 ppb tended to be less than 1 in 1,000,000 when using some types of models. Higher risk levels were estimated using the linearized multistage model, but this was described as being overly conservative because of weight of evidence suggesting a practical threshold for angiosarcoma development.

In their 2004 evaluation, the SCOEL did not establish an 8-hour TWA for vinyl chloride.[71] Instead, the committee provided quantitative estimates of the risk of humans developing angiosarcoma after continuous exposure for a working lifetime (i.e. 14% of total lifetime, assuming a working lifetime of 45 years at 8 hours per day, 240 days per

year, and a lifetime of 70 years or more), using linear low-dose extrapolation (3×10^{-4} for 1 ppm, 6×10^{-4} for 2 ppm, and 9×10^{-4} for 3 ppm). These values were selected based on two existing risk assessments for lifetime exposures to vinyl chloride. The assessments were from the World Health Organization (conducted in 1987 and reaffirmed in 1999 and 2000)[72-74] and Clewell et al.[75]; both were based on epidemiological data, and Clewell et al. incorporated PBPK modeling to account for vinyl chloride metabolism. After SCOEL adjusted these lifetime risk estimates to account for a working lifetime, the estimated risk levels were 3.6×10^{-4} using the WHO data and 2.5×10^{-4} using the Clewell et al. evaluation. SCOEL also concluded that existing risk estimates based on animal data supported the human-derived values, as they were within an order of magnitude.

An 8-hour TWA of 5 ppm has been established by Australia. The value is based on the documentation for the 1991 ACGIH® TLVs®;[76] the 1991 TLV® was first proposed in 1978 and accepted as a new TLV® in 1980.[70] The Australian 8-hour TWA is also accompanied by a carcinogen notation of Category 1 ("established human carcinogen known to be carcinogenic to humans").[76]

Formaldehyde

Various organizations have developed both 8-hour TWAs and 15-minute STELs for formaldehyde. The ranges of the values listed in the GESTIS database were 0.016–2 ppm for the 8-hour values, and 0.1–2 ppm for the STELs.[69] To demonstrate potential differences in the derivation of an OEL, the bases of three values—one value listed in the GESTIS database (NIOSH Recommended Exposure Limit [REL]), and two other commonly used values (ACGIH TLV and SCOEL Indicative Occupational Exposure Limit Value [IOELV])—are described in this section.

ACGIH® developed a TLV®–TWA of 0.1 ppm, along with a STEL of 0.3 ppm, which were adopted in 2017 (the previous TLV® was a ceiling value of 0.3 ppm, which was the quantitative OEL since 1992).[77] The TLV® is based on sensory irritation of eye and upper respiratory tract. Both a TWA and STEL were recommended because LOAELs, which were obtained from a human controlled dosing study (LOAEL of 0.5 ppm from a

4-hour TWA, with peaks of 1 ppm) and a cross-sectional occupational epidemiology study (LOAEL of 0.3 ppm from an 8-hour TWA, with a peak of 0.6 ppm), were based on both continuous and peak exposures. UFs were applied, as the LOAELs were lower than the TLV® values, but the basis for the selection of the UFs was not discussed. Notations for sensitization, both from dermal (DSEN) and respiratory (RSEN) exposure have been added to the TLV®. Moreover, a cancer notation (A1 – confirmed human carcinogen) was applied, due to development of nasopharyngeal tumors in strong or moderately strong epidemiological studies and nasal tumors in animal inhalation studies, concordance of tumor site in animals and humans, and data supporting cancer modes of action (increase in nasal cell proliferation in animals, and genotoxicity in animals and humans). Although the PODs were based on irritation effects, the TLV® is thought to be protective of cancer. The cancer risks are considered negligible below the TLV®, as the MOA likely progresses through a cytotoxicity and cell proliferation (non-linear) MOA, which is prevented by minimizing repeated irritation.[77]

The SCOEL IOELV[78] proffers two values—an 8-hour value of 0.3 ppm, and a 15-minute STEL of 0.6 ppm. The OEL was derived to prevent cell proliferation in the nasal cavity, which is thought to be a necessary key event in the carcinogenic mode of action for formaldehyde—in the absence of cell proliferation, the development of formaldehyde-induced nasal tumors is not expected to occur. A NOAEC of 1 ppm for histological changes and regenerative cell proliferation was obtained from a large database of animal studies. No human studies of nasal cytotoxicity exist, but SCOEL assumed humans were less sensitive than rats because rats were more sensitive than monkeys. A large database of formaldehyde-induced human sensory irritation comprises many controlled dosing and epidemiological studies; these data can be used as a POD because concentrations that do not cause sensory irritation of the eye and upper respiratory tract in humans are protective of cytotoxic irritation. The POD for the IOELV was based on two controlled-dosing studies with objective measures of sensory irritation of the eye[79,80], which indicated a NOAEC of 0.3 ppm with peaks of 0.6 ppm in short-term exposures. The SCOEL considered eye irritation to be a good proxy for nasal irritation. The SCOEL stated that they did not apply UFs because interindividual

variability of the irritation was low in the studies, and the volunteer studies were of high quality and large sample size (62 volunteers combined from both studies). Dividing the animal histological NOAEC of 1 ppm by an interspecies UF would result in a similar OEL, which was used by SCOEL as support for the selected value. A notation was added to indicate that formaldehyde is a skin sensitizer (known dermal contact allergen). No notation was used for respiratory sensitization, as evidence of respiratory sensitization was limited. The SCOEL also classified formaldehyde as a Group C carcinogen (genotoxic carcinogen for which a practical threshold is supported).

The NIOSH REL is 0.016 ppm for an 8-hour TWA and 0.1 ppm for a 15-minute STEL. These values were selected as a quantitative representation of ALARA, because formaldehyde was considered to have no safe exposure level, since it was a carcinogen. The lowest measurable levels of formaldehyde at the time this OEL was derived was 0.1 ppm in a 15-minute sampling period and 0.016 ppm in an 8-hour sample; these values were selected as the 15-minute STEL and 8-hour REL, respectively.[81] More recently, NIOSH produced an updated skin notation profile for formaldehyde.[82] Two notations were applied for the compound—the first was SK:DIR (IRR) (skin irritation), which was based on sufficient animal data of mild to moderate skin irritation after exposure to formaldehyde at ≤37% (above that concentration, increased severity of irritation and incidence of corrosion was observed). The second notation of SK:SEN (skin sensitization) was based on sufficient data in humans (from patch-testing and repeated-application tests) and predictive tests in animals (i.e., Guinea pig maximization tests, Buehler tests, and local lymph node assays).[82]

2,4-Dinitroanisole (DNAN)

DNAN is a compound used in munitions, and in the synthesis of dyes and insect repellants. The only OEL that could be found for the chemical was a WEEL[83]; no other OELs could be identified using the GESTIS and SER databases. The critical effect identified for the WEEL was extramedullary hematopoiesis (EMH) in an oral subchronic study.[84] The study exposed rats to daily doses of 0, 1.25, 5, 20, and 80 mg/kg for 90 days; the incidence of EMH in female rats in these test groups was 0/10, 1/10, 3/10, 4/10,

and 9/10. Because the effect was observed even at the lowest dose in the study, BMD modeling was performed using these data (Figure 38.8) to obtain a $BMDL_{10}$ of 0.93 mg/kg/d, which was used as the POD for the WEEL. This BMDL was converted to an airborne concentration of 6 mg/m^3 (using equation 2 described earlier in the chapter, and the WEEL default assumptions for exposure factors—a bodyweight of 55 kg and breathing rate of 8 m^3 per 8 hour workshift). The final WEEL of 0.1 mg/m^3 was selected. Although the values for each of the potential uncertainty factors were not specified, the lower value was stated as being selected to reflect intraspecies (human) and interpecies (rat-to-human) variability, subchronic to chronic extrapolation (as EMH—which is associated with anemia—is a short-term effect on blood formation, but being used as the basis for a chronic OEL), and database deficiencies (in particular the absence of reproductive studies).

Carbon Tetrachloride

OELs have been derived for carbon tetrachloride by many different organizations. As listed in the GESTIS database, 8-hour TWAs range from 0.1–10 ppm, and STELs range from 1–40 ppm.[69] Two OELs that were derived by organizations that are not listed in the GESTIS database (SCOEL and ACGIH®)—but that fall within the ranges presented in the database—will be described in this section.

The SCOEL IOELV of 1 ppm was derived based on a non-linear analysis for carcinogenicity.[85] SCOEL determined that the MOA for carbon tetrachloride-derived tumors was not genotoxicity—leading to a cancer classification notation of Carcinogen Group D (non-genotoxic carcinogen with threshold)—but hepatotoxicity leading to liver tumor development. The selected POD was a NOAEL of 1 ppm, in which no changes in serum parameters for hepatotoxicity were observed in humans. No UF was applied, as SCOEL stated that a margin of safety had already likely been incorporated into the selected NOAEL, which was the upper end of the range of exposures in a low-dose occupational group. SCOEL also derived a STEL of 5 ppm (based on a LOAEL of 10 ppm), for increased liver serum enzymes in rats exposed for 1 hour. The recommended STEL was two-fold lower than the LOAEL, although the UF was not specifically

discussed. A skin notation accompanies the two OEL values, as dermal exposure can contribute substantially to exposure.

The ACGIH® TLV®-TWA of 5 ppm[86] was derived differently, using results from a PBPK model as the POD. The PBPK model determined that humans exposed to 5 ppm would have a liver tissue dose of carbon tetrachloride—a good predictor of carbon tetrachloride toxicity—that was stated by ACGIH to be "well below" the liver dose in rats exposed to 10 mg/kg, which was the lowest dose demonstrating toxicity.[87] This dose was stated as being protective of carcinogenicity because it does not induce cytotoxicity. Because the PBPK model also demonstrated that the liver tissue dose in humans could reach potentially toxic levels if air concentrations exceeded 10 ppm for 15-minute intervals, 10 ppm was selected as the recommended STEL. UFs for both values were not applied nor further discussed in the documentation. However, ACGIH® stated that these values might not be protective for individuals consuming alcoholic beverages or with compromised liver function. The cancer notation of A2 (suspected human carcinogen) was applied, but with the acknowledgement that carbon tetrachloride was recognized as having a threshold MOA. ACGIH® also applied a skin notation, based on data indicating sufficient potential for dermal absorption.

Decamethylcyclopentasiloxane (D5)

D5 is used in the manufacturing of toiletries, cosmetics, electronics, and siloxane polymers (used in industry and medical fields). The OARS WEEL® of 10 ppm (151 mg/m^3)[88] was the only traditional OEL that could be identified for D5. The WEEL® was based on a NOAEL of 160 ppm, the highest concentration to which rats were exposed to in a chronic bioassay. The applied UFs were not specified, but the WEEL® was selected to be 16-fold lower than the NOAEL to account for the various sources of variability and uncertainty (including human variability and uncertainty related to the upper respiratory tract effects that were still measured at the NOAEL).

Although several health effects (liver weight increases, nasal effects, and uterine tumors) were observed in rats at this high dose, a lower POD was not used because the effects

were determined to be 1) adaptive, rather than adverse; 2) age-related, rather than chemically induced; or 3) developed via a mode of action (MOA) that is not relevant to humans. Liver weight increases were observed, but because no adverse cellular changes in the liver accompanied the weight changes, the effect was identified as an adaptive response typical after chemical exposures and was not adverse. Moreover, nasal cellular changes in the form of hyaline inclusions—which are often observed after exposure to irritants, as well as being age-related (independent of chemical exposure) in rats—were not considered to be adverse because no other indications of irritation to the nasal cavity were observed. Finally, although several different types of uterine tumors were observed at this high dose, the MOA was deemed to not be relevant to humans. Based on an in-depth MOA analysis[89], a likely MOA was identified to be the alteration of the estrus cycle via the dopamine pathway, leading to a decrease in prolactin levels, which leads to decreased progesterone levels. The rodent strain used in the key study (Fischer 344 rats) has a high background rate of age-related uterine tumors, and D5-induced estrus cycle changes resulted in an accelerated aging of the reproductive endocrine system, which caused a slight increase in the age-related tumors. Because the age-related tumors are thought to be a strain-specific susceptibility, the MOA was deemed not relevant to humans.

Although not traditional OELs, DNELs are exposure benchmarks that are on the hierarchy of OELs; these values are derived using rigid, prescribed methods. Two inhalation DNELs for workers for D5 have been derived using REACH guidance—values of 24.2 mg/m^3 for local effects and 97.3 mg/m^3 for systemic effects.[90] To derive the systemic DNEL, the No Observed Adverse Effect Concentration (NOAEC) of 2420 mg/m^3 (for an unspecified adverse effect in a chronic study in rats) was adjusted for exposure duration (from 6 hours per day in the study to 8 hours per day) and inhalation volume (from 6.7 m^3 to 10 m^3) to provide a POD of 1216 mg/m^3. Adjustment factors of 2.5 (for interspecies differences) and 5 (for intraspecies differences) were applied to derive the DNEL of 97.3 mg/m^3. The local effect DNEL of 24.2 mg/m^3 was derived using an unspecified POD from a chronic study in rats, which was divided by the same adjustment factors as the systemic DNEL.

OTHER INHALATION-BASED LIMITS

Additional inhalation-based limits that are not considered as part of the hierarchy of OELs are developed for special exposure scenarios. The values for these special scenarios are also typically derived based on weight of evidence from toxicological and epidemiological studies. These tools can complement the use of OELs, but are developed for different purposes and should therefore not be used interchangeably with OELs.

One such scenario for inhalation-based limits is emergency response applications. For example, NIOSH develops Immediately Dangerous to Life and Health (IDLH) limits[91], which identify the airborne concentration from which a worker could escape from an exposure environment without injury or irreversible health effects in the event of a respirator failure. Although these IDLH values are based on effects that might occur from a period as long as 30 minutes, NIOSH emphasizes that they are not intended to be surrogates for OELs, and workers' exposures should cease immediately at these levels.[91] Values such as EPA's Acute Exposure Guideline Levels (AEGLs)[92] and AIHAs® Emergency Response Planning Guidelines (ERPGs®)[93] are both designed for scenarios of acute exposure of the general population that are rare and unanticipated; these values are also not designed to protect workers who might be regularly exposed to the chemicals. Separate AEGL and ERPG® values can be developed for up to three levels of severity for each chemical – AEGL–1 or ERPG–1 values are associated with mild, transient health effects; AEGL–2 or ERPG–2 values are associated with irreversible and/or severe health effects, which might impair an individual's ability to take protective action; and AEGL–3 or ERPG–3 values are associated with life-threatening health effects or death. The AEGL values can be derived for different durations (depending on data availability) – including 10 and 30 minutes, and 1, 4, and 8 hours—whereas ERPGs are designed for based on one-hour exposures.

Inhalation exposure guidelines are also developed for the general public. Agencies such as EPA[94,95], Health Canada[96-98], ATSDR[99], and WHO[72-74,100,101] develop inhalation guidelines for many chemicals; many of the guidelines are summarized in the International Toxicity Estimates for Risk Assessment (ITER) database.[102,103] As these

values are derived for a broader population – including individuals at increased potential for susceptibility to chemicals, such as children, the elderly, and infirm – and for continuous exposures, they have a different basis than OELs and are often more conservative. However, if these guidelines exist for chemicals with no OEL, they could potentially be useful to industrial hygienists as screening values or as a starting point from which values can be adjusted.[104]

CONCLUSION

OELs are derived by many different organizations around the world. All organizations tend to apply generally similar principles in the OEL-derivation process. However, differences arise because the approaches are not prescriptive. Because of these differences in approaches, as well as variability in the derivation date of assessments, the margin between the POD and resulting OEL values can vary. Industrial hygienists should be aware of the approaches and margins of safety for any OELs that they are applying to become better informed users of the tools; they should also consider lowering action limits for any OELs that appear to be highly uncertain or based on older data or risk assessment approaches, if UFs do not sufficiently address these factors.

Although OELs are developed and efficiently used, there is a movement today to develop and utilize alternative benchmarks for workers' exposure; these approaches are highlighted by the hierarchy of OELs concept. Exposure benchmarks that are lower on the hierarchy can be useful when traditional OELs have not been derived—a situation that is applicable for the vast majority of chemicals in commerce.

This chapter addresses primarily the development of OELs for chemical agents. However, the underlying toxicological principles are similar to those used to develop OELs for physical, pharmaceutical, and biological agents.

REFERENCES

1. **Nielsen, G.D. and S. Ovrebo:** Background, approaches and recent trends for setting health-based occupational exposure limits: a minireview. *Regul. Toxicol. Pharmacol.51(3)*:253–69 (2008).
2. **American Conference of Governmental Industrial Hygienists (ACGIH®):** *2017 TLVs and BEIs.* Cincinnati, OH: ACGIH®, 2017.
3. **Brandys, R.C. and G.M. Brandys:** *Global Occupational Exposure Limits for Over 6,000 Specific Chemicals.* Occupational and Environmental Health Consulting Services Inc., 2008.
4. **European Chemicals Agency (ECHA):** Classification and Labelling Notification Report on January 4, 2011. (2011).
5. **Kreider, M.L. and E.S. Williams:** Interpreting REACH guidance in the determination of the derived no effect level (DNEL). *Regul. Toxicol. Pharmacol.58(2)*:323–29 (2010).
6. **Schenk, L.:** Comparison of data used for setting occupational exposure limits. *Int. J. Occup. Environ. Health16(3)*:249–62 (2010).
7. **Schenk, L., S. O. Hansson, C. Rudén, and M. Gilek:** Occupational exposure limits: A comparative study. *Regul. Toxicol. Pharmacol.50(2)*:261–70 (2008).
8. **Laszcz-Davis, C., A. Maier, and J. Perkins:** The hierarchy of OELs: A new organizing principle for occupational risk assessment. *The Synergist.* March:26-30 (2014).
9. **Cohen, R., C. Steinmaus, P. Quinlan, R. Ku, M. Cooper, and T. Roberts:** Development of permissible exposure limits: The California experience. *Internatl. J. Occup. and Environ. Health 12(3)*:242–47 (2006).
10. **Occupational Alliance for Risk Science (OARS):** Administrative Operating Procedures. (2011).
11. **American Conference of Governmental Industrial Hygienists (ACGIH®):** *2017 TLVs® and BEIs®: Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices with 7th Edition Documentation.* Cincinnati, OH: ACGIH®, 2017.
12. **Galer, D.M., H.W. Leung, R.G. Sussman, and R.J. Trzos:** Scientific and practical considerations for the development of occupational exposure limits (OELs) for chemical substances. *Regul. Toxicol. Pharmacol. 15(3)*:291–306 (1992).
13. **Lewis, R.W., R. Billington, E. Debryune, A. Gamer, B. Lang, and F. Carpanini:** Recognition of adverse and nonadverse effects in toxicity studies. *Toxicol. Pathol.30(1)*:66–74 (2002).
14. **International Programme on Chemical Safety and World Health Organization:** *IPCS Risk Assessment Terminology.* : World Health Organization, 2004.
15. **Organisation for Economic Co-operation and Development (OECD):** Guidance Document on Developing and Assessing Adverse Outcome Pathways. ENV/JM/MONO(2013)6 (2013).
16. **European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC):** Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies. Technical Report No. 85 (2002).

17. **Kerlin, R., B. Bolon, J. Burkhardt, S. Francke, P. Greaves, V. Meador, et al:** Scientific and Regulatory Policy Committee: Recommended ("Best") Practices for Determining, Communicating, and Using Adverse Effect Data from Nonclinical Studies. *Toxicol. Pathol.* (2015).
18. **Paustenbach, D.J., D.M. Cowan, and J. Sahmel:** The history and biological basis of occupational exposure limits for chemical agents. In *Patty's Industrial Hygiene,* R. V and B. Cohrssen (eds.). Hoboken, NJ: John Wiley & Sons Inc, 2011.
19. **Schenk, L. and G. Johanson:** Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit. Rev. Toxicol.*40(9):791-798 (2010).
20. **OECD:** Section 4: Health Effects. In *OECD Guidelines for the Testing of Chemicals,* Anonymous . Paris, France: OECD, 2015.
21. **Klimisch, H.J., M. Andreae, and U. Tillmann:** A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol. 25(1)*:1–5 (1997).
22. **Schneider, K., et al.:** "ToxRTool", a new tool to assess the reliability of toxicological data. *Toxicol. Lett.189(2)*:138–44 (2009).
23. **Wheeler, M., R. Park, A. Bailer, and C. Whittaker:** Historical context and recent advances in exposure-response estimation for deriving occupational exposure limits. *J. Occup. Environ. Hyg. 12(sup1)*:S7–17 (2015).
24. **Fairhurst, S.:** The uncertainty factor in the setting of occupational exposure standards. *Ann. Occup. Hyg. 39(3)*:375–85 (1995).
25. **Lehman, A.J. and O.G. Fitzhugh:** 100-fold margin of safety. *Assoc. Food Drug Off. US Quant. Bull.18*:33–35 (1954).
26. **Dourson, M.L. and J.F. Stara:** Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.3(3)*:224–38 (1983).
27. **European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC):** Guidance on Assessment Factors to Derive a DNEL. Technical Report No. 110 (2010).
28. **Dankovic, D.A., B. Naumann, A. Maier, M. Dourson, and L. Levy:** The scientific basis of uncertainty factors used in setting occupational exposure limits. *J. Occup. Environ. Hyg. 12(sup1)*:S55–68 (2015).
29. **Bolt, H.M. and A. Huici-Montagud:** Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. *Arch. Toxicol. 82(1)*:61–64 (2008).
30. **Ding, Q., L. Schenk, and S.O. Hansson:** Setting risk-based occupational exposure limits for no-threshold carcinogens. *Human and Ecological Risk Assessment: An International Journal 20(5)*:1329–44 (2014).
31. **Deutsche Forschungsgemeinschaft (DFG):** Germ Cell Mutagens. In *List of MAK and BAT Values.* Anonymous. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co., 2014. pp. 211–212.
32. **United States Government Accountability Office (USGAO):** Chemical risk assessment: Selected federal agencies' procedures, assumptions, and policies. No. GAO-01-810 (2001).
33. **Travis, C.C. and H.A. Hattemer-Frey:** Determining an acceptable level of risk. *Environ. Sci. Technol. 22(8)*:873–76 (1988).

34. **National Institute for Occupational Safety and Health (NIOSH):** NIOSH Chemical Carcinogen Policy. Current Intelligence Bulletin 68 (2016).
35. **Rodricks, J.V., S.M. Brett, and G.C. Wrenn:** Significant risk decisions in federal regulatory agencies. *Regul. Toxicol. Pharmacol. 7(3)*:307–20 (1987).
36. **Alavanja, M.C., C. Brown, R. Spirtas, and M. Gomez:** Risk assessment for carcinogens: a comparison of approaches of the ACGIH® and the EPA. *Appl. Occup. Environ. Hyg. 5(8)*:510–17 (1990).
37. **ECETOC:** Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances. Technical Report No. 101 (2006).
38. **Waters, M., et al.:** Exposure estimation and interpretation of occupational risk: Enhanced information for the occupational risk manager. *J. Occup. Environ. Hyg. 12(Suppl. 1)*:S99–S111 (2015).
39. **Adkins, C., et al.:** Occupational exposure limits: do they have a future? (2009).
40. **National Institute for Occupational Safety and Health (NIOSH):** A Strategy for Assigning New NIOSH Skin Notations. Current Intelligence Bulletin 61 (2009).
41. **deCock, J., D. Heederik, H. Kromhout, and J.S. Boleij:** Strategy for assigning a 'skin notation': a comment. *Ann. Occup. Hyg. 40(5)*:611–14 (1996).
42. **Czerczak, S. and M. Kupczewska:** Assignment of skin notation for maximum allowable concentration (MAC) list in Poland. *Appl. Occup. Environ. Hyg. 17(3)*:187–99 (2002).
43. **Drexler, H.:** Assignment of skin notation for MAK values and its legal consequences in Germany. *Int. Arch. Occup. Environ. Health 71(7)*:503–05 (1998).
44. **Deutsche Forschungsgemeinschaft (DFG):** Percutaneous Absorption. In *List of MAK and BAT Values*. Anonymous.. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co., 2014. pp. 208–209.
45. **Boeniger, M.F.:** The significance of skin exposure. *Ann. Occup. Hyg. 47(8)*:591–93 (2003).
46. **Nielsen, J.B. and P. Grandjean:** Criteria for skin notation in different countries. *Am. J. Ind. Med. 45(3)*:275–80 (2004).
47. **Kupczewska-Dobecka, M. and S. Czerczak:** The skin notation in the MAC list and classification of dangerous chemicals. *Int. J. Occup. Med. Environ. Health 19(2)*:84–91 (2006).
48. **Lavoué, J., A. Milon, and P.O. Droz:** Comparison of indices proposed as criteria for assigning skin notation. *Ann. Occup. Hyg. 52*: 747–56 (2008).
49. **Chen, C.P., et al.:** Efficacy of predictive modeling as a scientific criterion in dermal hazard identification for assignment of skin notations. *Regul. Toxicol. Pharmacol. 61*: 63–72 (2011).
50. **Scansetti, G., G. Piolatto, and G.F. Rubino:** Skin notation in the context of workplace exposure standards. *Am. J. Ind. Med.14(6)*:725–32 (1988).
51. **ECETOC:** Strategy for Assigning a "Skin Notation". ECETOC Document No. 31 (Revised) (1993).
52. "Exploratory Survey of OELs for CMR Substances." [Online] Available at: https://osha.europa.eu/en/tools-and-publications/publications/reports/548OELs (2015).
53. **Dotson, G.S., et al.:** Setting occupational exposure limits for chemical allergens—Understanding the challenges. *J. Occup. Environ. Hyg. 12(sup1)*:S82–98 (2015).

54. **Deutsche Forschungsgemeinschaft (DFG):** Sensitizing substances. In *List of MAK and BAT Values.* Anonymous. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co., 2014. pp. 181–197.
55. **Haber, L.T. and A. Maier:** Scientific criteria used for the development of occupational exposure limits for metals and other mining-related chemicals. *Regul. Toxicol. Pharmacol. 36(3)*:262–79 (2002).
56. **Crump, K.S.:** A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol. 4(5)*:854–71 (1984).
57. **Edler, L., et al.:** Mathematical modelling and quantitative methods. *Food Chem. Toxicol. 40(2-3)*:283–326 (2002).
58. **Filipsson, A.F., S. Sand, J. Nilsson, and K. Victorin:** The Benchmark Dose Method - Review of Available Models, and Recommendations for Application in Health Risk Assessment. *Crit. Rev. Toxicol. 33(5)*:505–42 (2003).
59. **U.S. Environmental Protection Agency (EPA):** Benchmark Dose Technical Guidance. EPA/100/R-12/001. Washington, D.C.: EPA, 2012.
60. **Andersen, M.E., M.G. MacNaughton, and D.J.Paustenbach:** Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model. *Am. Ind. Hyg. Assoc. J. 48(4)*:335–43 (1987).
61. **Laparé, S., J. Brodeur, and R. Tardif:** Contribution of toxicokinetic modeling to the adjustment of exposure limits to unusual work schedules. *Am. Ind. Hyg. Assoc. J. 64(1)*:17–23 (2003).
62. **International Programme on Chemical Safety (IPCS):** Part 1: IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans and Case-Studies; Part 2: IPCS Framework for Analysing the Relevance of a Non-Cancer Mode of Action for Humans. Harmonization Project Document No. 4 (2007).
63. **Boobis, A.R., et al.:** IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit. Rev. Toxicol. 38(2)*:87–96 (2008).
64. **Sonich-Mullin, C., et al.:** IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regul. Toxicol. Pharmacol. 34(2)*:146–52 (2001).
65. **Meek, M., et al.:** New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. *J. Appl. Toxicol. 34(1)*:1–18 (2014).
66. **Meek, M., C.M. Palermo, A.N. Bachman, C.M. North, and R.J. Lewis:** Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. *J. Appl. Toxicol. 34(6)*:595–606 (2014).
67. **International Programme on Chemical Safety (IPCS):** Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration–Reponse Assessment. Harmonization Project Document No. 2 (2005).
68. **Deveau, M., et al.:** The global landscape of Occupational Exposure Limits – Implementation of harmonization principles to guide limit selection. *J. Occup. Environ. Hyg. 12(Sup1)*:S127–44 (2015).
69. "GESTIS International Limit Values." [Online] Available at: http://limitvalue.ifa.dguv.de/WebForm_gw2.aspx (Accessed April 2017).

70. **American Conference of Governmental Industrial Hygienists (ACGIH®):** *Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition: Vinyl Chloride.* Cincinnati, OH: ACGIH®, 2001.
71. **Scientific Committee on Occupational Exposure Limits (SCOEL):** Recommendation from the Scientific Committee on Occupational Exposure Limits: Risk Assessment for Vinyl Chloride. SCOEL/SUM/109 (2004).
72. **WHO:** Air quality guidelines for Europe. (1987).
73. **WHO:** Guidelines for air quality. (1999).
74. **WHO:** Air quality guidelines for Europe. (2000).
75. **Clewell, H., P. Gentry, J. Gearhart, B. Allen, and M. Andersen:** Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: examples with vinyl chloride and trichloroethylene. *Chemosphere 31(1)*:2561–78 (1995).
76. "Safe Work Australia: Hazardous Chemical Information System (HCIS) - Exposure Standard Documentation: Vinyl chloride, monomer." [Online] Available at: http://hcis.safeworkaustralia.gov.au/ExposureStandards/Document?exposureStandardID=656 (Accessed April 3, 2017).
77. **American Conference of Governmental Industrial Hygienists (ACGIH®):** *Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition: Formaldehyde.* Cincinnati, OH: ACGIH®, 2017
78. **Scientific Committee on Occupational Exposure Limits (SCOEL):** Formaldehyde – Recommendation from the Scientific Committee on Occupational Exposure Limits. SCOEL/REC/125. Brussels: SCOEL, 2016. .
79. **Lang I., T. Bruckner, and G. Triebig:** Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. *Regul. Toxicol. Pharmacol. 50(1)*:23–36 (2008).
80. **Mueller J.U., T. Bruckner, an G. Triebig:** Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. *Int. Arch. Occup. Environ. Health 86*: 107–17 (2013).
81. **National Institute for Occupational Health and Safety (NIOSH):** Letter dated February 9, 1987 from Richard A. Lemen (Director, Division of Standards Development and Technology Transfer, NIOSH) to Tom Hall (Docket Office, U.S. Department of Labor). (1987).
82. **National Institute for Occupational Safety and Health (NIOSH):** NIOSH Skin Notation Profiles: Formaldehyde/Formalin. DHHS (NIOSH) Publication No. 2011–145.
83. **Occupational Alliance for Risk Science (OARS):** Workplace Environmental Exposure Level: 2,4-Dinitroanisole (DNAN). (2014).
84. **Lent, E.M., L.C. Crouse, T. Hanna, and S.M. Wallace:** The subchronic oral toxicity of 2,4-dinitroanisole (DNAN) in rats. Toxicology Study No. 87-XE-0DBP-10 (2012).
85. **Scientific Committee on Occupational Exposure Limits (SCOEL):** Recommendation from the scientific committee on occupational exposure limits for carbon tetrachloride. SCOEL/SUM/31 (2009).
86. **American Conference of Governmental Industrial Hygienists (ACGIH®):** *Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition: Carbon Tetrachloride.* Cincinnati, OH: ACGIH®, 2001.

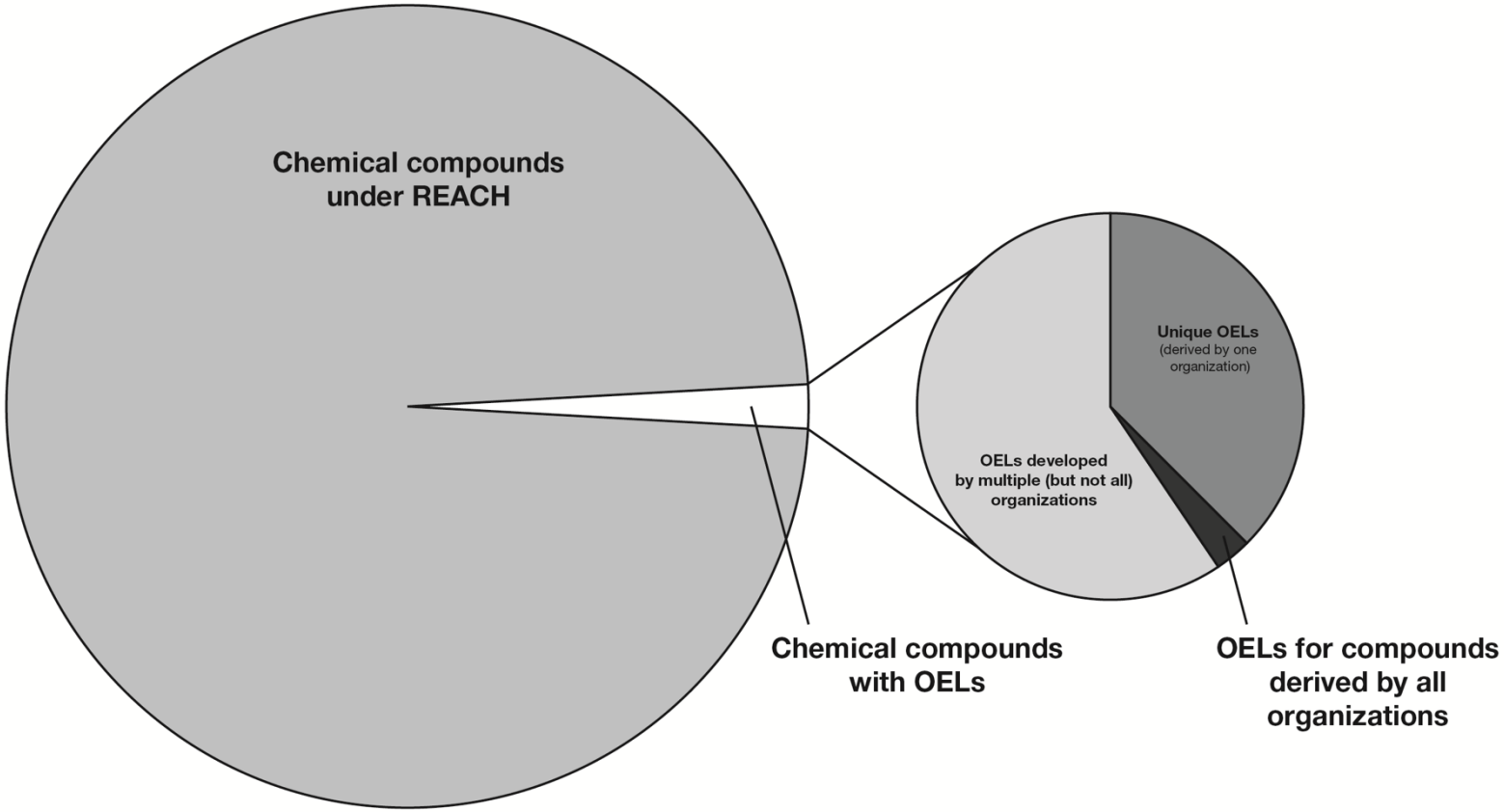
87. **Paustenbach, D.J., H.J. Clewell, M.L. Gargas, and M.E. Andersen:** A physiologically based pharmacokinetic model for inhaled carbon tetrachloride. *Toxicol. Appl. Pharmacol.96(2)*:191–211 (1988).
88. **Occupational Alliance for Risk Sciences (OARS):** Workplace Environmental Exposure Level: Decamethylcyclopentasiloxane (D5). (2015).
89. **Klaunig, J.E., W. Dekant, K. Plotzke, and A.R. Scialli:** Biological relevance of decamethylcyclopentasiloxane (D5) induced rat uterine endometrial adenocarcinoma tumorigenesis: Mode of action and relevance to humans. *Regulatory Toxicology and Pharmacology*74:S44–56 (2016).
90. "REACH registration dossier: Decamethylcyclopentasiloxane." [Online] Available at: http://echa.europa.eu/registration-dossier/-/registered-dossier/14807/7/1 (Accessed July 4, 2016).
91. **National Institute for Occupational Safety and Health (NIOSH):** Current intelligence bulletin 66: derivation of immediately dangerous to life or health (IDLH) values. DHHS (NIOSH) Publication No. 2014–100 (2013).
92. "Acute Exposure Guideline Levels for Airborne Chemicals." [Online] Available at: https://www.epa.gov/aegl (Accessed July 4, 2016).
93. "Emergency Response Planning Guidelines™." [Online] Available at: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Pages/default.aspx (Accessed July 4, 2016).
94. "Integrated Risk Information System." [Online] Available at: https://www.epa.gov/iris (Accessed July 4, 2016).
95. "Reviewing National Ambient Air Quality Standards – Scientific and Technical Information." [Online] Available at: https://www.epa.gov/naaqs/ (Accessed April 19, 2017).
96. "First Priority Substances List (PSL1) Assessments." [Online] Available at: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php (Accessed July 4, 2016).
97. "Second Priority Substances List (PSL2) Assessments." [Online] Available at: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php (Accessed July 4, 2016).
98. "Residential Indoor Air Quality Guidelines." [Online] Available at: https://www.canada.ca/en/health-canada/services/air-quality/residential-indoor-air-quality-guidelines.html (Accessed April 19, 2017).
99. "Minimal Risk Levels (MRLs) List." [Online] Available at: http://www.atsdr.cdc.gov/mrls/mrllist.asp (Accessed July 4, 2016).
100. "Alphabetical list of EHCs." [Online] Available at: http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/ (Accessed July 4, 2016).
101. **World Health Organization (WHO):** WHO Guidelines for Indoor Air Quality: Selected Pollutants. (2010).
102. "TOXNET International Toxicity Estimates for Risk (ITER)." [Online] Available at: https://toxnet.nlm.nih.gov/newtoxnet/iter.htm (Accessed July 4, 2016).
103. "International Toxicity Estimates for Risk Assessment." [Online] Available at: https://iter.ctc.com/publicURL/pub_search_list.cfm (Accessed April 19, 2017).

104. **Deveau, M., D. Krewski, and A. Maier:** Development and application of a framework for the selection of an appropriate occupational exposure limit. *Presented at the Society for Risk Analysis, Denver, CO, December 2014* (2014).
105. **Ritter, L., C. Totman, K. Krishnan, R. Carrier, A. Vezina, and V. Morisset:** Deriving uncertainty factors for threshold chemical contaminants in drinking water. *J. Toxicol. Environ. Health B Crit. Rev.10(7)*:527–57 (2007).
101. **Jarabek, A.M.:** The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. *Toxicol. Lett.*79(1):171-184 (1995).

Additional Reading

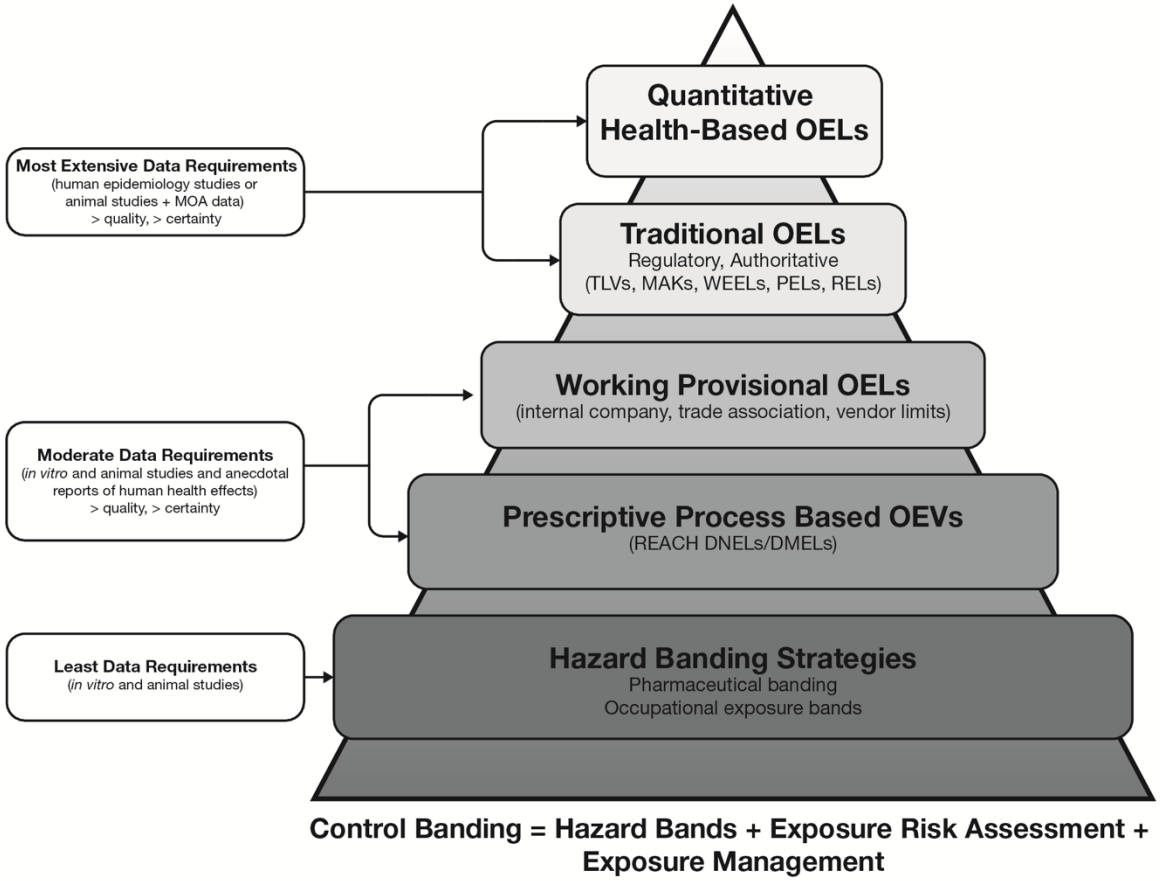
Galer, D.M., H.W. Leung, R.G. Sussman, and R.J. Trzos: Scientific and practical considerations for the development of occupational exposure limits (OELs) for chemical substances. *Reg. Toxicol. Pharmacol. 15*:291–306 (1992).
Haber, L.T., J.E. Strawson, A. Maier, I.M. Baskerville-Abraham, A. Parker, and M.L. Dourson: Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings. In *Patty's Toxicology*, 6th edition. Bingham, E., B. Cohrssen (eds.). Hoboken, NJ: John Wiley & Sons Inc., 2012.
Haber, L.T. and A. Maier: Scientific criteria used for the development of occupational exposure limits for metals and other mining-related chemicals. *Regul. Toxicol. Pharmacol. 36(3)*:262–79 (2002).
Nielsen, G.D., and S. Ovrebo: Background, approaches and recent trends for setting health-based occupational exposure limits: A mini review. *Regul. Toxicol. Pharmacol. 51(3)*:253–69 (2008).
Paustenbach, D.J., D.M. Cowan, and J. Sahmel: The history and biological basis of occupational exposure limits for chemical agents. In *Patty's Industrial Hygiene*. Cohrssen, R.V. and B. Cohrssen (eds.). Hoboken, NJ: John Wiley & Sons Inc., 2011.
Schenk, L., S.O. Hansson, C. Rudén, and M. Gilek: Occupational exposure limits: a comparative study. *Regul. Toxicol. Pharmacol. 50(2)*:261–70 (2008).
Schenk, L.: Comparison of data used for setting occupational exposure limits. *Int. J. Occup. Environ. Health 16(3)*:249–62 (2010).
Schenk, L. and G. Johanson: Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit. Rev. Toxicol. 40(9)*:791–98 (2010).
Special Issue: State of the Science of Occupational Exposure Limit Methods and Guidance. Journal of Occupational and Environmental Hygiene, 12(S1), S1–S144, 2015

Figure 38.1 – Graphical representation of the availability of OELs



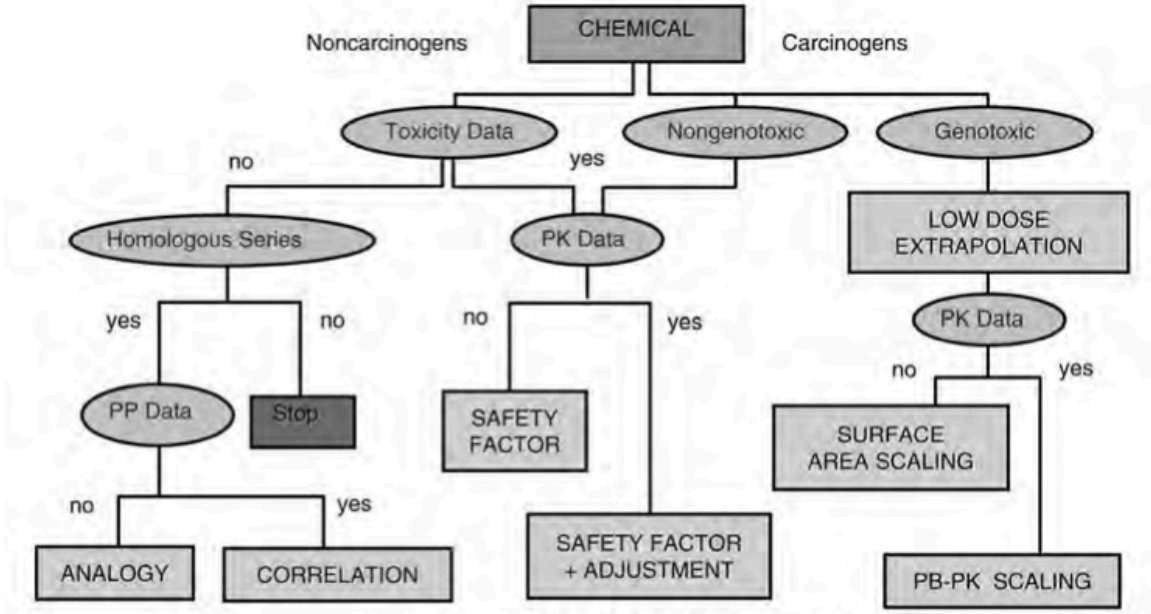
Previously published in Deveau et al.; [68] based on data from ECHA[4] and a study of 18 OEL-deriving organizations by Schenk et al.[6]

Figure 38.2 – A hierarchy of occupational exposure limits



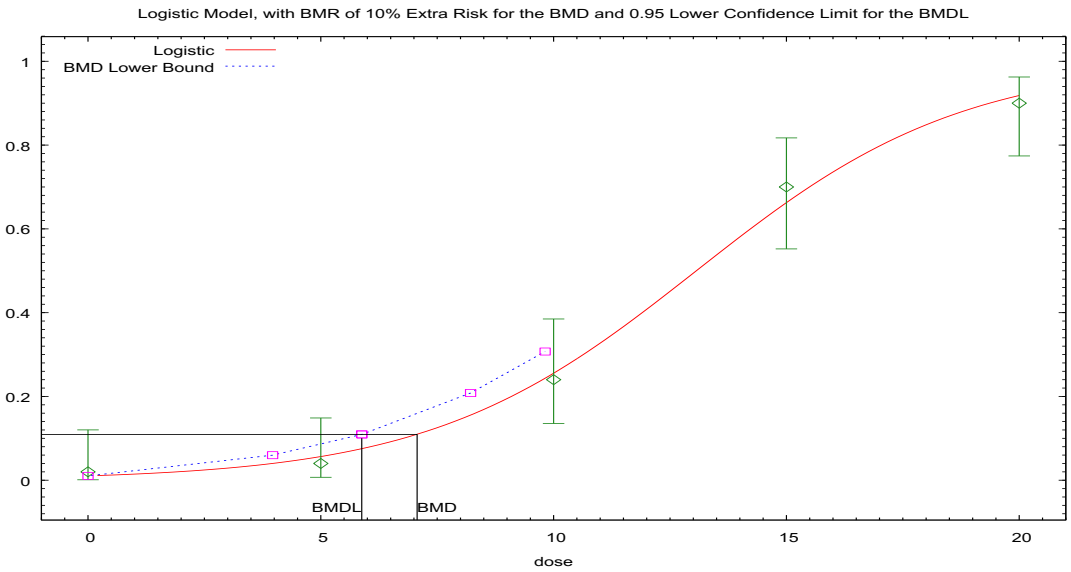
Previously published in Deveau et al. [68]; based on Laszcz-Davis et al., 2014[8]

Figure 38.3 – Decision logic for OEL derivation



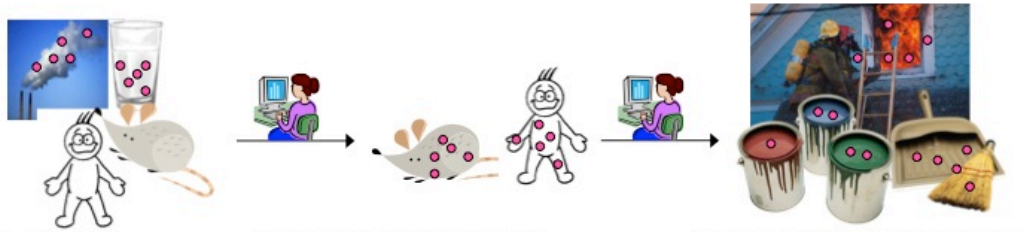
Adapted from Galer et al., 1992[12] and Andrew Soiefer presentation, AIHce 1998 PDC entitled: "Establishing, Interpreting and Applying Occupational Exposure Limits: Current Practices and Future Directions" PP: physicochemical properties; PK: pharmacokinetic; PB-PK: physiologically-based pharmacokinetic.

Figure 38.4 – Calculation of BMD and BMDL



Produced using U.S. EPA Benchmark Dose Software, version 2.6. The y-axis represents fraction affected (i.e. the proportion of the exposed population demonstrating the adverse effect; a fraction affected of 0.1 is equivalent to an incidence of 10%). The x-axis is the concentration in air (in ppm). The BMD_{10} is 7.1 ppm and the $BMDL_{10}$ is 5.9 ppm.

Figure 38.5 – Application of PBPK modeling in OEL derivation

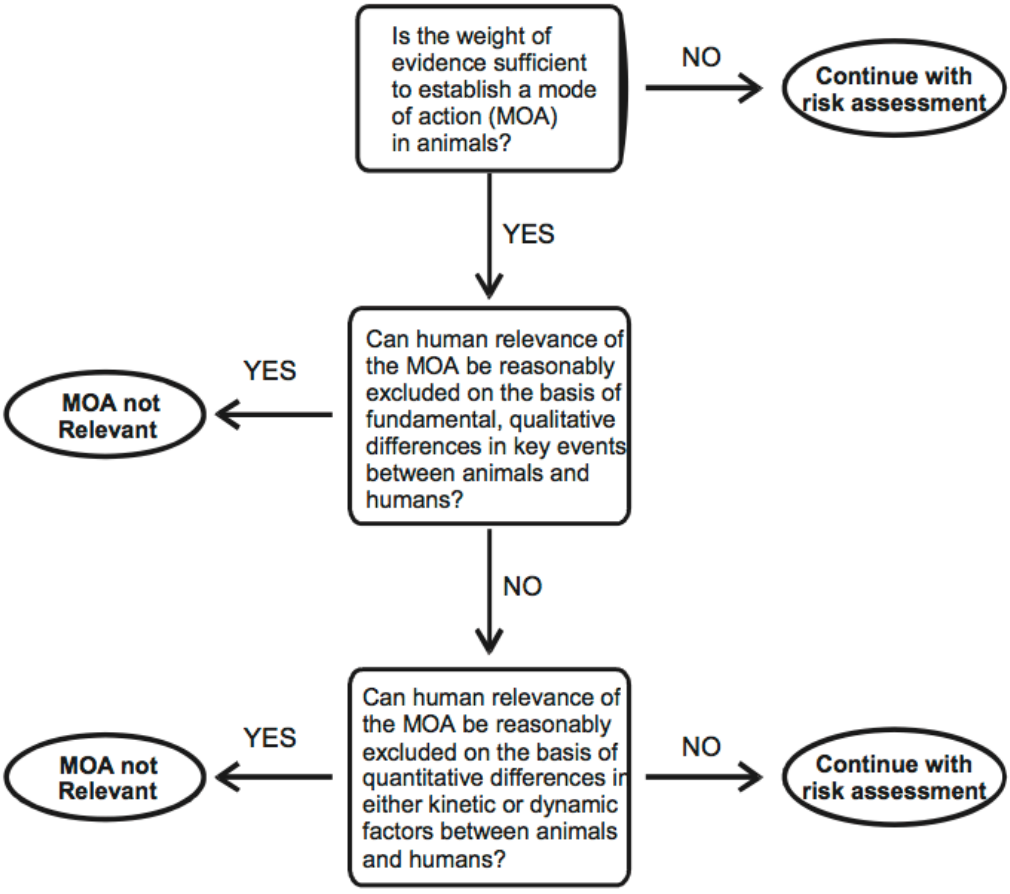


1. Identify external exposure levels in critical study in animals or humans (e.g. in air, water, food)

2. Run PBPK model (for species in critical study) to estimate the point of departure (LOAEL, NOAEL, BMD, cancer slope factor, etc.) for the internal dose

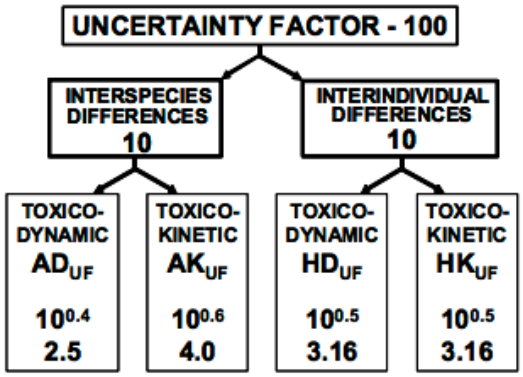
3. Run human PBPK model for OEL-relevant exposures (e.g. 8 hours/day, 5 days/ week) to estimate the air concentration that would result in the internal point of departure

Figure 38.6 – IPCS mode of action analysis framework



From IPCS[62]

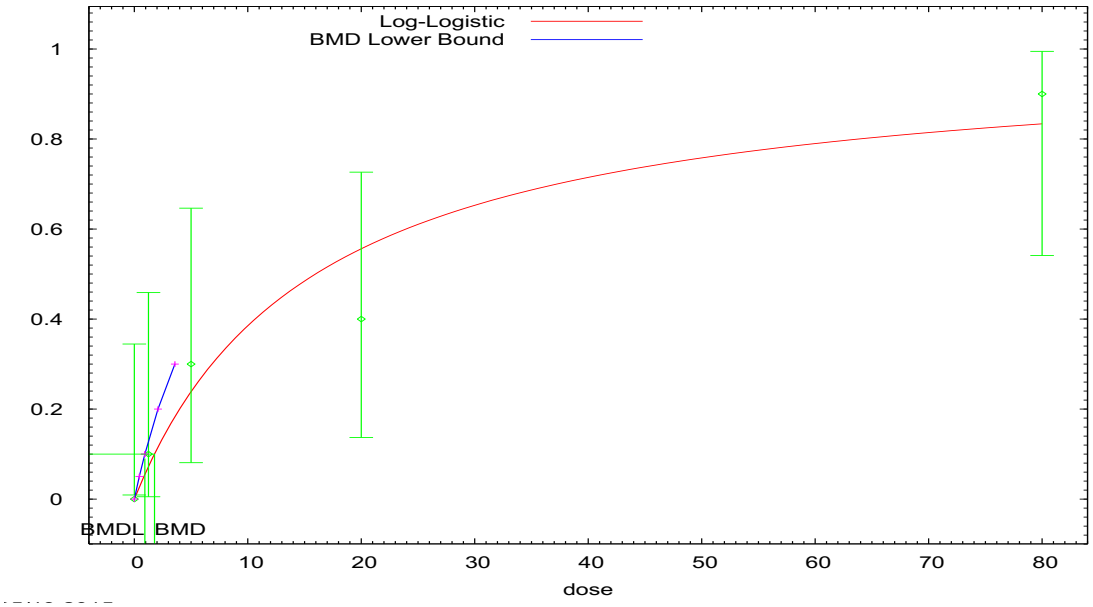
Figure 38.7 – Basis of inter- and intra-species uncertainty factors used to derive chemical-specific adjustment factors



AD_{UF} = Uncertainty factor for animal to human differences in toxicodynamics
AK_{UF} = Uncertainty factor for animal to human differences in toxicokinetics
HD_{UF} = Uncertainty factor for human variability in toxicodynamics
HK_{UF} = Uncertainty factor for human variability in toxicokinetics

From IPCS[67]

Figure 38.8 – BMD model output for DNAN-induced extramedullary hematopoiesis



Produced using U.S. EPA Benchmark Dose Software, version 2.6. The y-axis represents fraction of rats with measured (incidence in dose groups) or estimated (calculated BMD values) extramedullary hematopoiesis. BMD values represent estimates for 10% affected (i.e. fraction affected of 0.1). The x-axis is the ingestion dose in the study (in mg/kg/d). The $BMDL_{10}$ is 0.93 mg/kg/d.

Table 38.1 – Brief descriptions of tiers in the hierarchy of OELs

Data requirements	Tier	Description
Most extensive	Quantitative health-based OELs	Risk-based OELs that quantify the probability of developing an adverse health outcome at a specific exposure level (e.g. the OEL is based on a probability of 1 in 10,000 [or 10^{-4}] of developing cancer). Typically based on chemicals with robust epidemiological and/or toxicological data. Used as the basis of some OSHA PELs and NIOSH RELs. Peer reviewed.
	Health-based OELs	Traditional OELs that are most commonly used by industrial hygienists. Based on a point of departure (POD) identified from a dose–response assessment performed after synthesis of a broad database of toxicological and epidemiological data. Developed by expert committees (e.g. ACGIH TLVs, OARS WEELs, SCOEL IOELVs) or governmental organizations (e.g. OSHA PELs, NIOSH RELs, German MAKs); peer reviewed. Might be adjusted for economic or technical feasibility by some organizations (*e.g.*, OSHA).
Moderate	Working or provisional health-based OELs	Internal values derived by companies, vendors, or trade associations. Typically based on the same processes as health-based OELs, but might also incorporate proprietary data. Independent peer review not always performed.
	Prescriptive or process-based OELs	Derived using a prescribed method, with reduced flexibility for the incorporation of complex data or risk assessment approaches. The major examples are Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs) required under the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation. Independent peer review is not required.
Least extensive	Hazard- or category-based strategies	Semi-quantitative approach used in the absence of sufficient data for the derivation of more robust OELs, or in screening methodologies e.g. occupational exposure banding. Banding places chemicals into potency bands (often associated with provisional OEL ranges) based on qualitative descriptors of health effects or other health effects data (e.g.: read-across methods, the Threshold of Toxicological Concern [TTC] approach). "Read-across" estimates the potency of compounds based on similarities in chemical structure to chemicals with known toxicity, while the TTC approach can be used to establish potency defaults based on distributions of the potency of related chemicals or endpoints. Independent peer review is not typically performed.

Based on Laszcz-Davis et al., 2014[8]

Table 38.2 – Descriptions of uncertainty factors that can potentially be applied for OEL derivation

Type of UF	Purpose of UF
Interspecies UF	Reflects the potential pharmacokinetic and pharmacodynamic differences between animals and humans. Assumes that humans could be more sensitive than animals unless otherwise demonstrated by data.
Intraspecies UF	Reflects potential variability in reaction to chemicals within the human population (e.g. due to metabolic differences, existing illnesses, or other factors that might increase an individual's susceptibility to a chemical)
LOAEL-to-NOAEL UF	Applied if the selected POD is a LOAEL, rather than a NOAEL. Reflects the fact that the starting point for the OEL is a level at which adverse effects were observed, and that the key study was not able to identify any dose with no health effects.
Subchronic-to-chronic UF	Applied if the selected POD is from a study of shorter duration (e.g. subacute studies, or other studies of a duration less than the study subject's lifetime) to account for the possibility that longer-duration exposures might have caused adverse effects at a lower dose than used as the basis for the POD.
Database deficiency UF	Applied if the database for a chemical is incomplete. A complete database is typically considered to have a minimum of chronic toxicity studies in two different mammalian species, developmental toxicity studies in two different mammalian species, and one multigenerational reproductive study in a mammalian species. Addresses the possibility that additional data would identify a more sensitive adverse effect and thus a lower POD.

Based on Fairhurst, 1995; [24] Ritter et al., 2007; [105] Paustenbach et al., 2011; [18] Cohen et al., 2006; [9] ECETOC, 2010; [27] Dankovic et al., 2015[28]

Table 38.3 - Classification of NIOSH Skin Notations

Skin notation	Description
SK: SYS – systemic	Chemical is considered to be a systemic toxicant (i.e. has potential to cause substantial toxicity of organs and systems away from the site of dermal exposure, including cardiotoxicity, carcinogenesis [except skin cancers], hematotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, or reproductive and developmental effects)
SK: SYS (FATAL)	Subnotation of systemic; chemicals might be lethal or life-threatening following dermal exposure
SK: DIR – direct	Chemical is considered to cause toxic effects at or near the site of dermal exposure after acute or chronic exposure, through non-immune processes (e.g. skin carcinogenesis, pigmentation changes, chloracne, compromised skin barrier integrity, defatting or drying, or phototoxicity)
SK: DIR (IRR) – irritant	Subnotation of direct-acting toxicity; can result in skin irritation at points of contact (e.g. inflammation, dryness, or redness associated with pain or discomfort)
SK: DIR (COR) – corrosive	Subnotation of direct-acting toxicity; can result in skin corrosion at points of contact (irreversible effects, including tissue lesions, blisters, or burns)
SK: SEN – sensitizing	Chemical causes or contributes to immune-mediated responses (e.g., allergic contact dermatitis; airway hyperreactivity)
~~SK~~	Existing data are sufficient to conclude that dermal exposure to the chemical is not associated with systemic, direct, or sensitizing effects
$ID^{(SK)}$	Existing data are insufficient to evaluate health hazards of skin exposure
ND	Dermal toxicity of chemical has not been evaluated using the current NIOSH strategy

Based on NIOSH, 2009[40]

Table 38.4 – ACGIH Cancer Notations

Notation	Description
A1	**Confirmed Human Carcinogen** – Sufficient weight of evidence based on epidemiological studies demonstrating cancer in humans
A2	**Suspected Human Carcinogen** – Evidence of human carcinogenicity, but conflicting or insufficient data; OR evidence of carcinogenicity in animals considered relevant to workers' exposure
A3	**Confirmed Animal Carcinogen with Unknown Relevance to Humans** – Evidence of carcinogenicity in animals that might not be relevant to occupational exposures, without supportive epidemiological evidence. Agent unlikely to cause cancer except under uncommon or unlikely routes or levels of exposure
A4	**Not Classifiable as a Human Carcinogen** – Absence of data to assess the potential for carcinogenicity in humans
A5	**Not Suspected as a Human Carcinogen** – Sufficient weight of evidence based on epidemiological studies demonstrating absence of cancer in humans OR mode of action data confirming the lack of relevance to humans of cancer found in animals

Based on ACGIH, 2015[11]

Table 38.5 – Examples of countries with OEL notations related to developmental or reproductive toxicity

Country	Notation(s) are used to reflect
Germany	Damage to the embryo or fetus Germ cell mutagens
Poland	Fetotoxicity
Slovenia	Embryotoxicity Reprotoxicity
Spain	Chemicals that are harmful to the fertility of humans or toxic to their development

Based on European Agency for Safety and Health at Work, 2009; [52] DFG, 2014[31]

Table 38.6 – Types of PBPK model extrapolations relevant for OELs

Extrapolation type	Purpose of extrapolation
High- to low-dose extrapolation	Absorption, metabolism, or excretion processes might become saturated at high levels of exposure for some chemicals, which results in different chemical behaviors at high vs. low doses. Because doses in animal studies can exceed occupationally relevant exposure levels, PBPK modeling ensures that any dose-related non-linearities in pharmacokinetics are addressed.
Animal-to-human extrapolation	Various differences between animals and humans—such as physiological characteristics (e.g., organ size, blood flow rates, inhalation rates) and pharmacokinetic characteristics (e.g., absorption, metabolism, and excretion rates)—can be addressed in modeling. Species differences in saturation points for absorption, metabolism, and excretion are taken into account.
Intraspecies (human variability) extrapolation	Physiological or pharmacokinetic characteristics can be used to represent sensitive members of the worker population, or particular subpopulations (e.g. subpopulations with lower levels of relevant enzymes). If probabilistic methods (e.g. Monte Carlo simulation) are used, modeling can also capture the distribution of various parameters in the population.
Duration extrapolation	Modeling can be used to quantitatively address durations of key studies that might differ from occupational exposure scenarios (e.g. if exposures in the key study are continuous or are of shorter duration than a typical work shift), in a way that can incorporate any potential non-linearities in pharmacokinetics.
Route-to-route extrapolation	Modeling can be used to quantitatively reflect differences in chemical behavior dependent on the route of exposure (e.g. a chemical might enter systemic distribution immediately after inhalation, but might instead undergo hepatic metabolism prior to distribution when ingested). A special type of modeling (called dosimetry modeling) can also be used to reflect the influence of the locations of particle deposition in the respiratory tract on systemic absorption.[101]

Table 38.7 – Modified Bradford-Hill criteria considered relevant for MOA analysis

Bradford-Hill consideration	Application in MOA analysis
Consistency	Evaluate whether the observed patterns (across species, organs, etc.) is as expected for the MOA.
Specificity / Essentiality of Key Events	Evaluate whether the critical effect occurs if an earlier key event in the MOA is prevented.
Temporality & biological gradient / Temporal & dose–response concordance	Evaluate whether key events occur earlier, with higher incidence rates, and at lower doses than the critical effect.
Plausibility / biological concordance	Evaluate whether the understanding of the MOA in general (i.e. the broad database of the MOA, not restricted to chemical-specific data) and the MOA is consistent with general biological knowledge.
Analogy	Evaluate whether related chemicals produce adverse effects by a similar MOA

Based on Meek et al., 2014[66]

Table 38.8 – Questions to guide the identification of concerns during the evaluation of an OEL

- When was the OEL last derived, evaluated, or affirmed?
  - Do newer studies suggest health effects at lower levels than the POD?
  - Was the OEL derived using outdated OEL-derivation approaches?
- What is the severity of the adverse effect(s) upon which the OEL is based?
  - Is the health effect irreversible?
  - Is the chemical considered to be a mutagen?
  - Do dose–response data indicate that the severity of the effect increases rapidly at doses slightly above the POD?
- What is the level of uncertainty in the OEL?
  - Is the OEL based on a LOAEL?
  - Did human studies used as the basis of the PODs have only a small number of participants and/or exposure measurements, incomplete health evaluations, or short durations?
  - Did animal studies not meet relevant research protocol guidelines?
  - Did studies only investigate overt health effects (e.g. those that can be reported by workers), and not consider subtle effects (e.g. those that require special tests to be identified)?
  - Did any critical data gaps exist for the major study types?
  - Was the OEL based on read-across due to absence of chemical-specific data?
  - Do UFs sufficiently address the sources of uncertainty in the OEL?
  - Do UFs reflect the diversity in the human population, including any potentially sensitive workers?
- What is the relevance of the POD to the exposure scenario?
  - Were key studies based on routes of exposure other than inhalation?
  - Did exposure patterns differ from typical workshifts?
  - Were linear assumptions (without consideration of PBPK approaches) used to extrapolate from other routes of exposure or exposure patterns?
  - Is a chronic OEL based on acute data?
- Was the OEL adjusted for technological or economic feasibility?
  - Would a health-based OEL be lower than the final OEL?
- Have any hazard notations been applied to the OEL?
  - Is there evidence of dermal absorption, sensitization, carcinogenesis, or developmental and/or reproductive toxicity that could not be quantitatively reflected in the OEL?

Table 38.9 – Overview of OELs presented in case studies

Chemical	OELs	OEL and date established
Vinyl chloride	1–5 ppm (2.5–13 mg/m^3) (TWA) 2–5 ppm (6–30 mg/m^3) (STEL)	Obtained from GESTIS[69] database; TWA range includes 25 organizations and STEL range includes 6 organizations
	1 ppm (TWA)	ACGIH TLV[70]; 1999
	Risk of 3×10^{-4} for 1 ppm, 6×10^{-4} for 2 ppm, and 9×10^{-4} for 3 ppm	SCOEL IOELV[71]; 2004
	5 ppm (TWA)	Safe Work Australia[76]; based on 1991 ACGIH
Formaldehyde	0.016–2 ppm (TWA); 0.1–2 ppm (STEL)	Obtained from GESTIS[69] database; TWA range includes 20 organizations and STEL range includes 24 organizations
	0.1 ppm (TWA); 0.3 ppm (C)	ACGIH TLV[77]; 2017
	0.2 ppm (TWA); 0.4 ppm (STEL)	SCOEL IOELV[78]; 2008
	0.016 ppm (TWA); 0.1 ppm (STEL)	NIOSH REL[81]; 1986
2,4-dinitroanisole	0.1 mg/m^3	OARS WEEL[83]; 2014
Carbon tetrachloride	0.1–10 ppm (TWA); 1–40 ppm (STEL)	Obtained from GESTIS[69] database; TWA range includes 26 organizations and STEL range includes 18 organizations
	1 ppm (TWA); 5 ppm (STEL)	SCOEL IOELV[85]; 2009
	5 ppm (TWA)	ACGIH TLV[86]; 1996
Decamethylcyclopenta-siloxane	10 ppm (TWA)	OARS WEEL[88]; 2015
	24.2 mg/m^3 (local); 97.3 mg/m^3 (systemic)	REACH DNELs for workers[90]; assessment first published in 2011

Chapter 7 – The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection

Deveau, M[1,2]; Chen, C-P[3]; Johanson, G[4]; Krewski, D[1]; Maier, A[5]; Niven, KJ[6]; Ripple, S[7]; Schulte, PA[8]; Silk, J[9]; Urbanus, JH[6]; Zalk, DM[10]; Niemeier, RW[11]

Authors' affiliations
[1]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada K1N 6N5
[2]Faculty of Graduate and Postdoctoral Studies, University of Ottawa, Ottawa, Canada K1N 6N5
[3]Department of Occupational Safety and Health, College of Public Health, China Medical University, Taichung 40402, Taiwan
[4]Work Environment Toxicology, Institute of Environmental Medicine, Karolinska Institutet, S17177, Stockholm, Sweden
[5]Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH, 45267-0056
[6]Shell Health, Shell International B.V., 2501 AN, The Hague, The Netherlands
[7]Global Industrial Hygiene Expertise Center, The Dow Chemical Company, Midland, MI, 48674
[8]Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, 45226
[9]Directorate of Standards and Guidance, Occupational Safety and Health Administration, Washington, DC, 20210 (Retired)
[10]ES&H Directorate, Lawrence Livermore National Laboratory, Livermore, CA, 94551
[11]Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, 45226 (Retired)

Citation

Deveau, M., Chen, C.-P., Joahnson, G., Krewski, D., Maier, A., Niven, K.J., Ripple, S., Schulte, P.A., Silk, J., Urbanus, J.H., Zalk, D.M., Niemeier, R.W. (2015) The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection. J Occup Environ Hyg., 12 Suppl 1(sup1):S127-44. doi: 10.1080/15459624.2015.1060327.

ABSTRACT

Occupational exposure limits (OELs) serve as health-based benchmarks against which measured or estimated workplace exposures can be compared. In the years since the introduction of OELs to public health practice, both developed and developing countries have established processes for deriving, setting, and using OELs to protect workers exposed to hazardous chemicals. These processes vary widely, however, and have thus resulted in a confusing international landscape for identifying and applying such limits in workplaces. The occupational hygienist will encounter significant overlap in coverage among organizations for many chemicals, while other important chemicals have OELs developed by few, if any, organizations. Where multiple organizations have published an OEL, the derived value often varies considerably—reflecting differences in both risk policy and risk assessment methodology as well as access to available pertinent data. This paper explores the underlying reasons for variability in OELs, and recommends the harmonization of risk-based methods used by OEL-deriving organizations. A framework is also proposed for the identification and systematic evaluation of OEL resources, which occupational hygienists can use to support risk characterization and risk management decisions in situations where multiple potentially relevant OELs exist.

INTRODUCTION

Occupational exposure limits (OELs) are important tools for the interpretation of workplace exposures within a health risk context.[(1)] Although the term "Occupational Exposure Limit" was adopted by the International Labour Organisation (ILO) in 1977 to encompass all chemical exposure guidelines for workplace air,[(2)] the need for quantitative benchmarks for occupational exposures was identified much earlier. Early work on OELs for airborne workplace

chemicals occurred in Germany in the 1880s, when the pioneering animal experiments of Gruber and Lehmann were used to identify safe exposure levels for carbon monoxide, ammonia, and hydrogen chloride.[3] Since the publication of the first table of acute exposure limits by Kobert in 1912,[3] many organizations around the world have been added to the global capacity for establishing OELs (Table I).[4] The first list of maximum allowable concentrations (MACs)—eventually known as Threshold Limit Values (TLVs)—was published by the American Conference of Governmental Industrial Hygienists (ACGIH) in the 1940s.[3] By the 1970s, many countries were developing or adopting their own values, such as the U.S. Occupational Safety and Health Administration Permissible Exposure Limits (OSHA-PELs) and the German Maximale Arbeitsplatz-Konzentration (MAKs).[5] The lack of OELs for many commercially important chemicals spurred the creation of non-governmental OEL-setting organizations, such as the Workplace Environmental Exposure Level (WEEL) Committee initially established under the auspices of the American Industrial Hygiene Association (AIHA), to help meet this need. International initiatives aimed at resource sharing and harmonization have also emerged, including collaboration among Nordic countries, and joint publication of criteria documents between these countries and NIOSH.[6] The European Scientific Experts Group (now the Scientific Committee on Occupational Exposure Limits [SCOEL]) was created in 1990, and has been proposing OELs for adoption by European Commission (EC) Member States since 1991.[7]

Since the first introduction of OELs over a century ago, the processes for developing, setting, and using the occupational exposure guidelines have enjoyed widespread global uptake.[3,8,9] However, the proliferation of international OEL-setting bodies, faced with the challenges of evaluating and interpreting complex scientific data on potential health impact of occupational exposures, has yielded a confusing landscape of OELs. As a result, occupational hygienists can

be confronted with multiple relevant—but often conflicting—OELs for a particular situation, leading to difficulties in selecting the most appropriate value for health protection purposes. In addition, duplication of effort can result in missed opportunities to develop OELs for new agents.

The aim of this paper is to highlight the aspects of the OEL-setting process contributing to differences in guideline values, with the goal of assisting occupational hygienists in making more informed decisions when selecting between several potentially relevant OELs. Although this manuscript discusses various issues that might be of relevance during the OEL-derivation process, the aim of this paper is not to instruct occupational hygienists to calculate OELs; therefore, readers seeking detailed discussions of the science behind OEL derivation should consult two additional papers published in this issue.[10,11] The key points of emphasis in this paper include:

- Exposure limit guidance is absent for most chemicals, and existing OELs often vary quantitatively among organizations from around the world.
- The basis for differences in OELs for the same chemical reflects a mix of differences in risk policy and risk science methodology, which are discussed in detail.
- Harmonization of the approaches used to develop OELs can contribute to increased consistency in OEL derivation by organizations around the world.
- A systematic framework can aid the occupational hygienist in documenting and selecting OELs when multiple relevant values are encountered, encouraging the most effective use of current OEL resources.

These points are elaborated upon in the sections that follow.

AVAILABILITY OF TRADITIONAL INTERNATIONAL OEL RESOURCES

OELs are derived by various organizations around the world, including those listed in Table I. Because these global OEL efforts are in general not directly coordinated among organizations, a confusing landscape of traditional OELs has emerged. Existing values span only a small percentage of all chemical compounds, with different organizations often deriving different values for the same substance. Evaluation of the current status of OEL availability can be framed in the context of several considerations, including: 1) the relationship between traditional OELs and other alternative exposure guidance benchmarks, using a hierarchy of OEL concept; 2) the extent to which existing OELs cover the universe of chemicals of interest in occupational exposure settings; and 3) an evaluation of the reasons for variability in OELs provided by different organizations.

Hierarchy of OELs

Traditional OELs are developed by many international bodies; these values vary as to whether they are legally binding and with respect to the consideration given to feasibility of implementation. A brief summary of several well recognized OELs from different organizations and their attributes—including analytical, economic, and engineering feasibility, and whether or not they are health based—has been highlighted by Waters et al. [1] Those that are adopted as legally binding under an appropriate rulemaking authority include various state or provincial level OELs, OSHA PELs, and OELs promulgated by various countries around the world. [12,13] If the European Commission, based on scientific advice received from SCOEL, develops a Binding Occupational Exposure Limit Value (BOELV), member states must establish their own binding OEL at or below the BOELV. [14] Many examples of non-binding or recommended OELs exist,

such as the NIOSH Recommended Exposure Limits (RELs), ACGIH TLVs, Occupational Alliance for Risk Science (OARS) Workplace Environmental Exposure Levels (WEELs; formerly developed under the purview of AIHA), and SCOEL Indicative Occupational Exposure Limit Values (IOELVs). This distinction between binding and non-binding limits can become blurred, however, as some regulatory authorities adopt non-binding OELs under existing rulemaking authority. For example, the ACGIH TLVs are adopted as *de facto* legally binding standards in many Canadian provinces, [3,15] various European countries, [2] and many other countries around the world. [16-18] Moreover, distinctions can be made between "health-based" OELs and those that are "regulatory-adjusted," [8] with the latter involving consideration of technical and economic feasibility. Feasibility considerations might not be limited to binding values, as some OELs—such as the NIOSH RELs—may be a hybrid of both health-based and technical considerations. In some cases, organizations have clearly delineated between the two, such as with the German MAKs based on health effects and Technische Richtkonzentrationen (TRKs), the latter of which are based primarily on technological feasibility[19]. However, other organizations might not clearly identify when OELs are hybrids of health-based and regulatory adjusted values; the opacity in these hybrids could create difficulties in the implementation of risk management decisions.

These traditional OELs can be viewed as a component of a larger body of occupational risk-based exposure benchmarks. Alternative methods exist that can provide a useful approach for occupational hygienists to consider when an OEL is not available or cannot be derived for a chemical of concern. These alternatives comprise a hierarchy of OELs (Figure 1). The hierarchy concept provides a means to develop occupational risk benchmarks similar to OELs where traditional OELs are not available. Consistent with the concept of problem formulation (ensuring

that the risk assessment approach meets the needs of the scenario being evaluated), [20,21] the alternative techniques in the hierarchy may be adequate for preliminary assessments, screening processes, or specific risk assessment protocols. In general, as one moves down the hierarchy, the available methods can accommodate less data, although the reduced resource needs may be achieved at the expense of increased uncertainty in the assessment. In some cases, there may be adequate data to set a formal traditional OEL. The lower rungs of the hierarchy are designed to allow development of benchmarks for making risk decisions and are often precautionary in nature. The hierarchy and more in-depth descriptions of the alternative occupational exposure benchmarks are presented elsewhere. [22] Examples of these OEL alternatives include working provisional OELs, values derived for internal use within a company or by trade associations or vendors, which serve to fill an information gap in the absence of an OEL from a recognized body. [23] Prescriptive process-based levels are those that are developed using a prescribed derivation approach: the Derived No Effect Levels (DNELs) required under the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation fit in this category, as DNELs are required for all compounds manufactured, used, or imported in the EU in volumes exceeding 10 tonnes, independent of the data availability. [24] DNELs should be considered with some caution, because there is no peer review or public consultation involved in their establishment. Furthermore, although they should be derived according to extensive regulatory guidance, there are no established competency requirements for those who carry out the derivation. Where inadequate data exist to derive OELs or the alternative benchmarks, qualitative strategies—such as Hazard Banding[25-30]—can be applied. A similar concept is the Threshold of Toxicological Concern (TTC), a semi-quantitative approach that can be used to identify levels where exposure to a compound would be expected to have little toxicological

concern derived based on observed distributions of potency for large numbers of chemicals. [23,31] Refinements to the TTC approach have included assigning different potency cut points based on a chemical's structural features, such as those embodied in the Cramer Class. [31,32] Such tools have been proposed for use in occupational risk assessments within the pharmaceutical industry. [33] Despite the availability of these alternative methods for deriving quantitative benchmarks for assessing occupational risk, there remains a strong emphasis on new OEL derivation, which requires substantial data and resources, as the preferred approach.

Other exposure limits might not be considered as part of the hierarchy of OELs, but could still be useful tools for occupational hygienists. These tools might have levels of data requirements and scientific validity that are consistent with the traditional OELs, but differ from OELs in the exposure scenarios to which they apply. Exposure limits intended for shorter duration, such as Immediately Dangerous to Life or Health (IDLH) values and Acute Exposure Guidelines (AEGLs) are not OELs in the sense described earlier in this paper, but are sometimes erroneously treated as such. A recent publication on NIOSH IDLH values has stated that "it is important to note that IDLH values are concentrations that may cause adverse effects, and thus, they are not intended to be used as surrogates for [OELs]. OELs…are intended to protect workers from adverse health effects associated with repeated chemical exposure…for a working lifetime. The IDLH values should not be used as comparative indices of toxicity or to infer a 'safe' level for exposures to chemicals under routine occupational exposure conditions." [34] These tools, however, might be useful for application in non-routine occupational exposure scenarios. Another tool that might be helpful for occupational hygienists faced with an absence of OELs is an environmental health exposure guideline. Environmental exposure guidelines have parallel derivation processes to OELs, but tend to be more conservative as they are typically

derived for continuous exposures for a 70-year duration, and are also applied to subpopulations that might be more sensitive than healthy workers (e.g. children, pregnant women, and elderly). The potential application of tools such as IDLH values, AEGLs and general population exposure guidelines in absence of OELs will be further discussed in the section entitled "Framework for the Selection of Appropriate OELs."

The Patchwork Landscape of OELs

The extent to which commercial chemicals have traditional OELs is graphically represented in Figure 2, which demonstrates that OELs only exist for a small fraction of the universe of chemicals. Brandys and Brandys[35] have published a list of OELs from around the world, which includes over 5,000 different chemicals, and a separate study of 18 organizations identified OELs for 1341 compounds.[36] Although these OELs encompass a wide variety of chemicals—particularly those that are most common in the occupational environment—a vast number of chemicals still do not have OELs. The Chemical Abstracts Service Registry recently registered its 75 millionth substance, with 5 million substances added during the past year. The rate of innovation in the area of chemicals is rapid and broad, including aspects such as the development of nanomaterials. While all of these chemicals are not commercially produced, it is clear that the potential for numerous and varied chemical exposures in workplaces is substantial.[37] Given that chemicals considered "in commerce" in the U.S. are numbered at approximately 84,000,[38] that Canada's Domestic Substances List includes 23,000 chemicals,[39] and notifications for over 107,000 different substances have been received under REACH,[40] the majority of chemicals in use currently have no OEL. In addition, many of the existing lists of

OELs include substances that were added many years ago, and are no longer commercially important; thus, the number of relevant OELs is even smaller than the total number included.

Even when traditional OELs exist for a particular compound, it is possible that not all OEL-setting bodies have that chemical in its lists of OELs. In a comparative study of values from 18 organizations, most of the OEL-setting bodies addressed less than half of the 1,341 substances that comprised the total list of compounds covered by the organizations in the study.[36] More than one-third (460) of the substances in the study were mentioned by only one organization (Finland was exceptional in that it had 189 unique OELs). Less than 2% of the substances (25) were mentioned by all 18 organizations. The reason that the selection of substances is not more harmonized might be explained in part by differences in industry base among countries. This patchwork nature of the OEL landscape might result in occupational hygienists' need to consult OELs from diverse organizations, which can become especially complicated when various organizations have derived different values for the same chemical. In addition, the need for a comprehensive search for OELs results from the lack of an easily accessible compendium of OELs for all agencies and organizations.

When multiple organizations have established a traditional OEL, these values often vary, as demonstrated for n-hexane in Table II. Based on a review of eight different organizations, the values of 14 different OELs (benzo[a]pyrene, carbon tetrachloride, p-dichlorobenzene, dichlorofluoromethane [FC-21], enflurane, 2-ethoxyethanol, ethylene dibromide, halothane, 2-hexanone, hydrazine, nickel subsulfide [as Ni], phenyl glycidyl ether, tetranitromethane, and vinyl cyclohexene dioxide) varied at least 100-fold, with some differences as high as 200-fold (for ethylene dibromide and tetranitromethane).[41] The variation in occupational risk assessment practice is not limited to the evaluation of inhalation exposures. In an exploratory investigation

of seven different organizations, a total of 480 chemicals were carrying at least one skin notation (SN). Only approximately 3% of these chemicals were considered by all of the evaluated organizations as a skin exposure hazard, whereas 47% were only assigned a SN from a single organization.[42] Studied organizations varied significantly in the assignment of SNs; these variances occurred even though the SN assignment was in essence a process of hazard identification, and required a lesser amount of quantitative decision making compared to the traditional OEL derivation process. These analyses indicate that OELs and related notations can vary significantly among occupational health organizations. Thus, informed use of OELs requires an understanding of the basis for the underlying differences in the approaches used by OEL-deriving organizations.

The Basis for Differences in OELs

The variability in traditional OELs can present a confusing landscape within which the occupational hygienist must navigate. To properly assess the appropriateness of an OEL for a specific occupational exposure scenario, an understanding of the different decisions that can be made in the risk assessment process is helpful. Because OELs are derived from a series of complex decisions, many of which are based on limited data and require scientific assumptions, they are inherently imprecise.[1] Although the OEL-setting process rests on a scientific foundation, many of the decisions can be influenced by an organization's science judgment practices. Although different decisions might be made among organizations, this does not invalidate the results when considered in the context of the risk assessment and risk management policies and practices of individual organizations. The sources of variation in OELs derived among organizations, as identified in Figure 3, can help an OEL user understand the differences

among values and the implications for their own occupational exposure and risk assessment scenarios. According to this scheme, contributions to the differences in OELs can be divided into two broad categories—risk science and risk policy. The assumptions that are made and decisions that are taken when confronted with each of these sources of uncertainty vary among organizations, leading to differences in derived OELs. [43]

Problem formulation

The problem formulation stage of risk assessment can influence differences in OELs among organizations. The goal of problem formulation is to design risk assessments to be able to answer specific risk management questions, [20] which might be different for each type of OEL. It follows that even though values can differ, they can be equally appropriate—fitting the purpose of the organization that developed them. Although traditional OELs are generally derived based on continuous inhalation exposure for 8 hours per day, 5 days per week, over a working lifetime, slight aspects of the exposure scenarios can differ, including the definition of the duration of a working life. The breadth of the population considered in the values can also vary among organizations. Whereas the U.S. Occupational Safety and Health Act of 1970 prescribes that "…medical criteria will assure insofar as practicable that no employee will suffer diminished health, functional capacity, or life expectancy as a result of his work experience," [44] the ACGIH TLVs "represent conditions under which it is believed that *nearly all* workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects," [45] [emphasis in the original] and will not necessarily prevent discomfort or injury for a small percentage of workers that are especially sensitive to an agent.

Risk science decisions

Different decisions can be made in the area of risk science, which can create variability in OELs derived by different organizations for the same chemical. Diversity in decision making can occur for many reasons, including differences in problem formulation among organizations (resulting from differing goals and needs), the evolution of risk science over time, and the capabilities of different organizations. In selecting an OEL, it should be borne in mind that one decision (or resulting OEL) is not necessarily "better" than another; the decisions could be equally defensible, but one might be more appropriate than another for a specific occupational exposure scenario, linking back to the problem formulation stage. Several key risk science decisions are often at the root of the differences in OELs, including selection of the point of departure, application of uncertainty factors, and integration of weight of evidence.

Selection of the point of departure

A point of departure (POD) is the no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), benchmark dose (BMD), or some other similar value derived from critical health effects in key studies, which is used as the basis of an OEL calculation. Both the selection of the critical study and of the POD on which the OEL is based can vary among organizations. If organizations develop OELs at different times, the critical study for a newer value might not have been available at the time that older OELs were derived. Practices in some organizations might limit the selection of the critical studies to those that are available in the open literature, whereas others might allow for the use of data sourced outside the international public domain (e.g., industrial research, internal reports), which can stimulate controversy due to limited transparency and selectivity being suspected or inferred.[17,46] Moreover, some organizations might use the highest quality studies available, resulting in a large

percentage of OELs based on animal studies (e.g., in 2009, approximately 50% of the ACGIH TLVs were based on animal data), [3] whereas others might favor key study selection based on human data. Once a critical toxicity endpoint (e.g., the most sensitive effect) has been selected, organizational practices can also affect the selection of the POD, a specific exposure level that is derived from the critical studies and upon which the OEL is grounded. For example, organizations could identify adversity at different points along the continuum of severity (i.e., no effect < no observable effect < compensatory effects that are not adverse < borderline effects with an unknown significance to health < early adverse effect < overt disabling effect < death), [47] leading to the selection of different PODs for deriving an OEL. Other factors that could impact the selection of the POD include the use of a threshold approach vs. linear extrapolation; basing the POD on exposure levels used in the study (i.e. selecting a LOAEL or NOAEL) vs. performing dose–response modeling (e.g., BMD modeling); and various quantitative choices, such as the use of a specific response level when performing dose–response modeling.

It should also be noted that the types of health effects upon which OELs are based sometimes do not include the full range of health effects that are possible. This issue has been addressed in part by the development and implementation of the United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS). The GHS includes criteria internationally negotiated and agreed upon for identifying the hazards of a broad range of health effects that may be encountered in the workplace, which is most useful for data-poor compounds. These criteria also address the degree or severity of the hazard in the classification scheme. Thus the GHS can now be employed as a tool for countries when considering the development of an OEL. Prior to addressing risk assessment issues, the GHS classification criteria can be used to fully characterize the health, physical, and environmental hazards of a

chemical. This complete hazard assessment can facilitate the process of further considering exposure and risk when deriving an OEL from available data, as well as ensure that all health effects, and relevant physical and environmental hazards, are addressed when establishing risk management. [48] The GHS also provides an approach to classify mixtures of chemicals. Mixed exposures are prevalent in workplaces, and proper protection includes consideration of how to deal with combined exposures.

Application of uncertainty factors

Many OELs account for variability, uncertainty or weakness in a substance-specific literature database using a combination of uncertainty and adjustment factors that are typically selected from a standard set of values. [3,11,49-54] Data-derived adjustment factors can also sometimes be used instead of default uncertainty factors. [55,56] Although most organizations start with a standard group of values, the methods of selecting and applying the uncertainty factors are not fully harmonized. [7] First, most OEL-setting organizations provide little quantitative guidance on uncertainty factors. Second, if advice is given (as is the case for REACH guidance on DNELs), [57] this advice is limited to default conditions and provides little quantitative guidance on when and how to depart from the defaults. The lack of quantitative guidance might result in arbitrary choices in the range of applicable uncertainty factors, leading to inconsistent OELs.[58]

Integration of weight of evidence

Even if an OEL is derived mainly from a single study, the entire body of available scientific literature is usually considered during the hazard assessment process. To integrate the totality of evidence in OEL development, some organizations might use a formal hierarchical

approach, whereas others might be less regimented. Frameworks for systematically evaluating weight of evidence exist and are receiving emphasis in risk assessment; as noted previously, the GHS provides criteria for hazard assessment, which includes consideration of weight of evidence. Some approaches focus on overall holistic methods for integrating complex data. Data fusion is a formal method using specialized techniques to gather and integrate data from a variety of sources to decrease uncertainty in the risk assessment process.[59,60] In addition, there has been an increased emphasis on providing decision tools or frameworks that assist development of risk decisions in a systematic way. For example, the International Programme on Chemical Safety (IPCS) mode of action framework can be used to systematically evaluate the degree of human relevance of adverse effects that are observed in animal studies.[61] The IPCS methods incorporate principles of the Bradford Hill criteria to assess the body of literature (e.g., strength of association, consistency, specificity, temporality, presence of dose–response relationship, and plausibility).[62] A hypothesis-based weight of evidence process has also been proposed as a way of assessing and communicating a body of data, and the uncertainties therein, for the evaluation of chemical toxicity.[63] Further areas where organizations might vary in their weight of evidence analyses include in their evaluations of quality, reliability, and relevance of each study—tools to harmonize such systems used in the context of chemical registration include the Klimisch et al.[64] criteria for toxicology studies and the Money et al.[65] criteria for epidemiology studies. Severity scoring and categorical regression affords an objective means of integrating data from diverse toxicity endpoints into a single analysis, as has been previously performed.[66,67] Expert elicitation may also be used in integrating scientific evidence that is subject to uncertainty.[68] The organizations might also have different ways of dealing with conflicting data, or in using supporting studies to help resolve uncertainty. The degree to which documented and systemic

processes for decision-making use formal decision tools is not consistent; at present, most organizations develop OELs using peer input and review methods, rather than formal decision tools.

Risk policy decisions

The essential elements of risk policy decisions are also an important factor in generating a landscape of varying OELs. Risk policy decisions differ from risk science decisions in that they are largely extra-scientific and hence more value-laden. As with the risk science decisions, one risk policy decision is not inherently better than another. Two important types of risk policy decisions that affect OEL values are risk acceptance and feasibility.

Risk acceptance

Various organizations and jurisdictions tolerate different levels of risk, which contributes to inter-organization variability in OELs. Risk acceptance is inherently a trans-scientific issue, [69] with differences dependent on subjective responses to adverse effects. [17] To set a numerical value by using uncertainty factors or performing dose–response modeling implies an agreement upon what frequency of injury, disease, or discomfort is deemed acceptable. Past regulatory decisions indicate that risk levels in the range of 1/1,000 to 1/10,000 (10^{-3} to 10^{-4}) are considered acceptable for occupational risk scenarios. [70] For example, the 1980 Benzene decision by the Supreme Court noted that risks of 1 in 1,000 (10^{-3}) and 1 in 1,000,000,000 (10^{-9}) might be considered by a reasonable person to be significant and insignificant, respectively; based on this decision, a lifetime mortality risk of 1 in 1,000 is considered by OSHA to present a clearly significant risk to workers. [71] However, organizations with different views on acceptable levels of risk might derive different OELs, even if using the same data sources. Risk acceptance

considerations are typically considered in the context of non-threshold compounds (e.g. genotoxic carcinogens), but might also influence decisions made in the evaluation of threshold effects (e.g. in the application of uncertainty factors). [1,11]

Feasibility

One major factor contributing to differences between OELs is the consideration of feasibility. A distinction can be made between health based and regulatory adjusted OELs, with the former being generally more precautionary than the latter because they are based on health considerations only. For the "regulatory adjusted" OELs, health-based OEL values might be modified to include non-health based considerations. Because non-health considerations—primarily economics and technical feasibility, including engineering controls and analytical measurement capability—might vary by geographic region, a regulatory adjusted OEL developed in one country is not necessarily universally applicable. These factors lead to differences not only between health based and regulatory adjusted OELs, but also between jurisdictions with different socioeconomic contexts and technological capabilities. [8]

Other sources of differences in decisions

Other differences between OELs might not be easily explained by scientific or policy differences between organizations. In the comparative study of OELs by Schenk and coworkers, [36] the authors found no evidence of variability of OELs among organizations that could be associated with risk assessment or management principles, health vs. feasibility approaches, level of health protection, or whether a value was legally mandated. The authors also postulated that "…there might be scientific controversy regarding some substances that lead to different conclusions being drawn from the risk assessments." [36] This implies a need to examine

processes used when deriving the OELs available for each chemical before selecting it for application to a risk assessment to ensure the validity of the risk assessment methods used, and to identify whether the OEL is truly health based or modified by other technical, social and economic considerations.

The time at which the assessment was performed can also drive differences in OELs. Although the age of an assessment does not directly fit into the categories of risk science or risk policy decisions, it can influence both. Dose–response assessment approaches evolve over time, and the introduction of new epidemiology and toxicology studies broadens the database available for the derivation of OELs. Moreover, as a society's willingness to accept risk can change, risk acceptance might also vary correspondingly. Finally, for OELs that account for economic and technological feasibility, economic growth and technological advancements can decrease the burden of lower guideline values. In general, the progression of time has resulted in lower OELs. As demonstrated by Hansson, [18] in the years since the original publication of the ACGIH TLVs, the levels gradually decreased over time; by 1996, the geometric mean of the ratios of the most recent TLVs to those on the 1946 list was only 0.23. OEL-setting organizations also differ in the degree to which they have ongoing work programs to maintain the values current based on availability of new health studies.

INTERNATIONAL HARMONIZATION OF OELS

Selecting an OEL for occupational hygiene applications presents a challenge when the processes used by OEL-setting organizations differ significantly around the world. Not only do the risk science and risk policy decision-making processes differ, but the ways of presenting and communicating these decisions can also vary between organizations, adding another barrier for

occupational hygienists who are charged with gathering, interpreting and applying such information. Harmonization of the OEL derivation processes applied around the world has been suggested as a means of minimizing variability in approaches. Harmonization, as defined in the IPCS Harmonization Project Strategic Plan, is the establishment of "common principles, understanding and approaches and enhanced transparency in risk assessment, facilitating use for regulatory purposes." [72] A goal of international harmonization of OELs is to have compatible—and not necessarily exact or standardized—values in different countries as a result of the application of convergent methods and practices by different organizations. Thus, the application of harmonization principles to the OEL development processes from organizations around the world could help in making the selection of appropriate exposure guideline values less complicated for occupational hygienists. Both risk policy and risk science drivers for varying OELs could be the subject of harmonization efforts. Although there are examples of existing harmonization initiatives to build upon, the advantages and challenges of harmonization merit a more detailed discussion.

Harmonization of decision-making processes

Various elements of the OEL derivation process can be harmonized so that similar approaches are applied by different organizations. As previously framed by the International Council on Mining & Metals (ICCM), [73,74] aspects for which standardized criteria can be provided include:

- review and evaluation of relevant scientific literature;
- selection of critical health endpoint(s);
- determination of whether critical effects are threshold or non-threshold;

- selection of key studies and PODs for dose–response assessments;
- selection of uncertainty factors that most appropriately represent the uncertainty and variability associated with a literature database; and
- calculation of the OEL.

Standardized criteria for the consideration of policy decisions in the OEL-derivation process, including risk acceptance and technological and economic feasibility, could also be developed.

Harmonization of OEL derivation documentation

ICCM also recommended standardized criteria for the documentation and publication of all key steps in the derivation process. [73,74] Common templates could also be developed for the documentation of the processes involved in the derivation of an OEL (e.g. criteria documents), improving consistency in the documentation of the OEL derivation processes among different organizations. [2,69] An ideal format for a standardized scientific supporting document might easily be agreed upon, because there are often only minor differences between existing scientific documentation for OELs. Proposed characteristics of an ideal "standardized" supporting document that might increase the likelihood of acceptance as the scientific basis for an OEL by organizations around the world are presented in Table III. Commonly accepted definitions for the terms used in the OEL documentation could also help lead to the harmonization of scientific supporting documents.[75]

Existing harmonization initiatives

There has been a long history of attempts to harmonize the OEL derivation process among countries around the world. A successful international harmonization initiative was a 1989 workshop held in The Hague, Netherlands, organized by the Directorate General of Labour

in the Netherlands and the Commission of the European Communities. The workshop had the objective of initiating the examination of harmonization and cooperation in the preparation of scientific supporting documents for OELs, both within the Europe and elsewhere. [2] This international discussion ultimately paved the way for establishment of the Concise International Chemical Assessment Documents (CICADs), which were first published in 1998. [76] CICADs are technical documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals on human health and the environment, including the characterization of hazard and dose-response from exposure to a chemical, which countries can then use to develop an OEL. The documents are based on selected national or regional evaluation documents or on existing Environmental Health Criteria assessments published by WHO. Similarly, at the level of the European region, the European Commission created the Scientific Experts Group (now the SCOEL) in 1990. This committee has been proposing Indicative Limit Values (ILVs; now IOELVs) and Binding Limit Values (BLVs; now BOELVs) for adoption by EC Member States since 1991. [7] Other agreements have been developed between a few organizations or countries; one example of this is the Nordic Expert Group (NEG)—a collaboration between Sweden, Norway, Denmark, Finland and Iceland that develops criteria documents for the establishment of OELs. [6] Activities of the NEG include describing the scientific database for a chemical; using these data, the Scandinavian countries derive their own OEL values. The NEG has also furthered its collaborations in the establishment of agreements with NIOSH and the Dutch Expert Committee on Occupational Safety. [6,69]

Steps toward harmonization of OELs have also been taken by many organizations to promote mutual awareness of other organizations' activities, priorities, and thought processes, as well as the exchanging of information. To date, the extent of harmonization efforts regarding

OELs has been based largely on information sharing. The ILO is a key organization encouraging international collaboration, as it promotes information and data sharing among countries. Perhaps as a result of data sharing, many of the OELs adopted around the world are based on those from other organizations, such as ACGIH, NIOSH, OSHA, and the EU. [77] Cross-membership among OEL groups, for example with SCOEL members acting as representatives for other OEL-deriving organizations, also provides a significant opportunity for shared information. In addition, significant efforts have been initiated to improve the transportability of toxicity and health effects data that serve as the input to the OEL derivation process. For example, the concept of a toxicity data portal with exposure response arrays has been described. [78] To date, no single effort has seen global acceptance, but the trend is to increase data sharing and transparency.

Benefits and drawbacks of harmonization initiatives

Harmonization of OELs can have many advantages. The process of developing OELs is complex, lengthy, and resource intensive. [69] The time-consuming process of OEL development can restrict the number of values that are derived, with few updates to existing OELs for many organizations, [36] leading to aging of OELs. Strong international collaboration efforts could reduce the need for multiple OEL-setting entities, [12] or could encourage work sharing between organizations, thereby preventing duplication of personnel and financial resources that results when multiple organizations derive OELs for the same chemicals. [2] Harmonization principles can also reduce confusion and economic inefficiencies that can occur, which can particularly affect multi-national companies that are required to comply with many different mandatory OELs. [12] Inconsistent OEL derivation practices can also result in discrepancies in worker

protection amongst countries. [12] Harmonization could be particularly beneficial to workers in smaller countries. If performed properly, harmonization can also lead to greater transparency and use of best practices.

A unified scientific approach to the setting of OELs is one part of the path toward increased harmonization, but many impediments can stall progress. Many differences among organizations and countries can hinder the development of consistent OELs, such as legal, regulatory, economic, political, and cultural distinctions. [8] Even if harmonized guidance on deriving OELs were available, inconsistencies between organizations might still occur—because of the nature of the data used in their derivation, exposure limits would be difficult to derive using one standardized approach. [3] Caution must also be taken to ensure that harmonization does not magnify existing problems with the OEL development process. Centralization of the decision process, if done improperly, could lead to decreased transparency and increased distance between regulators and the public, including business owners and workers. [36] Consistency in OEL development could also be a concern if less desirable approaches are promoted, or if it leads to a lower margin of safety. [79] An important value of harmonization is the sharing of information on methods, while recognizing the value of flexibility available through the application of alternative approaches.

FRAMEWORK FOR THE SELECTION OF APPROPRIATE OELs

As previously noted, greater harmonization in the development of OELs has many advantages, including increased congruity in the approaches used by different organizations to derive the values. However, even with harmonization, some of the policy differences outlined in the section entitled “The Patchwork Landscape of OELs” will likely always exist among the

OEL-setting organizations, resulting in a number of defensible OELs that can be used. This can lead to complexities when occupational hygienists need to select the most appropriate value from several potentially relevant OELs. Because little guidance exists in such cases, a framework is proposed to aid in the systematic selection of the most appropriate OEL for a particular situation. A schematic representation of this process is presented in Figure 4, which is elaborated upon in the remainder of this section. The framework was designed to provide occupational hygienists with a guide of the decision logic process of assessing reliability and relevance of existing OELs.

Although much of this document has focused on traditional OELs, additional exposure limits might be useful for consideration in the framework. As discussed in the section entitled "Hierarchy of OELs," tools such as IDLHs, AEGLs, and environmental health exposure guidelines can have data requirements and scientific validity that are similar to traditional OELs, but are derived for different exposure scenarios. Moreover, in data-poor situations, occupational exposure benchmarks that are lower on the OEL hierarchy—such as company- or vendor-derived values for internal use, or DNELs calculated under REACH legislation—might also be useful for consideration in the framework. However, as these values are not traditional OELs, occupational hygienists should apply the entire framework to carefully assess whether the benchmarks are appropriate for the relevant exposure scenario.

Although detailed knowledge of the science behind OEL derivation is not necessary for the application of the framework, familiarity with the processes might be helpful. Other papers from this journal issue will be helpful to occupational hygienists, [10,11] and comprehensive analyses of the processes for setting OELs have been developed elsewhere. [3,17,23,51,52,73,81,83] As the derivation of environmental exposure guidelines parallels that for OELs, occupational hygienists might also find guidelines for the derivation of these values to be useful. [80,82]

In many situations, the framework does not need to be followed in its entirety. After a cursory review of each of the eligible OELs, the occupational hygienist might immediately identify that most do not address the predefined scenario of use. Moreover, rather than evaluating each of the risk science and risk policy decisions, the occupational hygienist might decide to select the regulatory OEL, the most conservative guideline, or the newest value (if the assumption is that the most recent assessment will contain the most current risk assessment approaches and key studies). If the occupational hygienist has adequate time and sufficiently understands the processes behind the derivation of OELs, the entire framework should be followed, wherever possible. However, the most important aspects of the decision-making process, independent of how the framework is applied, are consistency and proper documentation of the approach.

For occupational hygienists who are able to apply the framework in its entirety, a series of key elements should be considered throughout the decision-making process. As described below, the steps begin with defining the scenario and gathering relevant OELs, and culminate in evaluation of the risk science and risk policy bases of the selected OELs.

Define use or scenario

Prior to identifying relevant OELs for a compound, the nature of exposure should be defined. This involves identifying *how* the exposure primarily occurs and *who* is exposed. Although traditional OELs are generally derived based on continuous inhalation exposure of healthy adult workers for 8 hours per day, 5 days per week, over a working lifetime, occupational risk assessments increasingly require variable exposure scenarios to be addressed. For example, occupational hygienists might have to consider exposures of an intermittent or

infrequent nature, or exposures via dermal absorption. Moreover, in addition to a healthy workforce, occupational hygienists might also need to consider more susceptible populations in the workforce (e.g. workers who are potentially pregnant) or in the general population (in cases of community stewardship, or assessments of para-occupational or "take-home" exposures). Consideration of co-exposures to other agents might also be important. The goal is to identify traditional OELs or other exposure benchmarks that match the usage patterns and target population for the scenario being evaluated, because the type of exposure for which the benchmark is designed can influence the key studies that are used or the scientific assumptions and adjustments that are made.

Gather potentially relevant OELs and related exposure benchmarks

Attempts should be made to identify as many potentially relevant OELs for the compound(s) of interest as possible. This process would include gathering applicable mandatory standards from state/provincial, national, or regional levels, as well as non-mandatory recommended OELs from organizations, such as the ACGIH TLVs, NIOSH RELs, and AIHA or OARS WEELs. OELs that are used in other jurisdictions could also be obtained. More extensive lists can be found in the online GESTIS database[84]—a collection of occupational OELs gathered from various EU member states, Canada (Québec, Ontario), Japan, Switzerland, the United States, and other countries—and in books with collections of OELs.[35,45] Internet links to many countries' OEL programs can also be found on the ILO (http://www.ilo.org/safework/info/publications/WCMS_151534[85] and TERA OARS (http://www.tera.org/OARS) websites. Labels and safety data sheets provided by suppliers in accordance with the GHS will also provide the occupational hygienist with information

identifying some existing OELs for a workplace. Depending on the nature of exposure, AEGLs and IDLH values might also be useful for inclusion. For compounds with a paucity of OELs, obtaining documentation for non-traditional benchmarks lower in the hierarchy of OELs might provide useful information for the exercise. In these cases, working provisional OELs can be sought from product manufacturers or relevant trade associations, and DNELs can be obtained from the ECHA database; [86] however, these benchmarks should be considered with caution, and should undergo a thorough review (following the steps in the framework) prior to their application, because peer review or public consultation might not have been involved in their establishment. The occupational hygienist might also consider obtaining environmental health exposure guidelines from organizations such as the Environmental Protection Agency and Agency for Toxic Substances and Disease Registry in the United States, Health Canada, and IPCS. In addition to simply gathering the OELs and related exposure benchmarks, any documentation behind the derivation or establishment of these values should be obtained, when available.

For simplification of the presentation of the framework, the collective title of the gathered exposure benchmarks—including traditional OELs, acute values, environmental health exposure guidelines, and tools further down the hierarchy of OELs—will be referred to hereafter as OELs.

Assess the relevance of OELs

As previously discussed in this manuscript, the problem formulation stage of risk assessment—which ensures that risk assessments answer specific risk management questions—can influence the decisions made in the OEL derivation process. The exposure scenario defined

in the first stage should be compared to the existing OELs to ensure that the assumptions used to derive the value align with the target population and exposure pattern assumed in the scenario of interest. If the problem formulation for certain OELs is sufficiently different from that of the defined scenario, the OEL might not be relevant. Key considerations in determining relevancy include:

- target populations – potentially sensitive worker subpopulations (such as women who are pregnant or of a childbearing age, or workers with pre-existing conditions that might increase their susceptibility to a chemical) vs. healthy workers;
- route of exposure – inhalation vs. dermal vs. oral routes; and
- use patterns – intermittent vs. continuous use, and short-term vs. chronic exposures.

Even if all of these elements do not align, it might still be possible to adapt the OEL for the particular circumstances of interest. For example, if the target population of the OEL is broader—and encompassing more sensitive subpopulations—than those that will actually be exposed, the occupational hygienist could review the details behind the derivation of the value to identify if the uncertainty factor for human variability in susceptibility had been applied and could be modified for the current application of the OEL. If the key study used as the basis for the OEL has a different exposure pattern to the defined scenario, further adjustments for exposure duration could be made. A variety of techniques for the adjustment of OELs for differing exposure durations and temporal patterns are available. [3] Moreover, an overly conservative approach could be applied, if feasible; for example, if the scenario of interest is limited to acute or short-term exposures, but maintaining exposures below a chronic OEL is achievable, this lower value could be retained in the assessment process. Any OELs that are not

applicable to the defined scenario, or that cannot be adjusted to better match the defined scenario, should be eliminated from further consideration. If no values remain, and no other OELs can be found from a more extensive search of the literature, it might be necessary to derive a new value or adopt a value modified from an alternative scenario (including those derived for environmental exposures for the general population).

Compare mandatory standards to non-mandatory OELs

For legal reasons, it is important to ensure exposure is maintained below all mandatory OELs as a minimum practice. However, further consideration of non-mandatory OELs is highly recommended if they are lower than mandatory values. Phase 2 of the assessment should be completed with these non-mandatory OELs to determine if they represent more appropriate guides for worker health protection.

Assess the reliability of OELs

Scenario-relevant OELs must then be evaluated with respect to their scientific bases and the science policy assumptions applied in their derivation. The reliability assessment steps are to be completed for each OEL that has not been excluded based on misalignment with the problem formulation statement. To increase validity and transparency in the selection process, a list of acceptable and unacceptable scientific approaches and science policy decisions should be developed prior to performing the assessment, wherever possible. Detailed information on the bases of each of the OELs is needed for this assessment; consequently, it might be necessary to gather various technical documents that provide this information, or to contact the OEL-setting organization for more information if these details are not published. Gathering the documentation for each of the OELs or obtaining as many details as possible about the derivation

is critical to identifying whether the appropriate risk science and policy methods and approaches were applied.

Evaluate the risk science basis for the OEL

Prior to evaluating the validity of the scientific approaches applied by each of the OEL-developing organizations, an important step is to obtain an update on the body of literature that exists for the chemical. Many easily accessible databases are within reach of the practicing occupational hygienists for this purpose (e.g., U.S. National Library of Medicine Toxnet.) [87] In particular, knowledge of the toxicological and epidemiological publications that could be used as key studies for the assessment—as well as the strengths and limitations of each study—is important, since these resources will inform the judgment as to whether currently listed OELs are adequately up to date. For users with more experience with OELs, such information can also be used to verify that the most relevant adverse endpoint(s) for the OEL and the key studies that form acceptable bases for the OEL are documented. Such data serve a number of purposes: 1) to ensure the key effects based on newer data are addressed; 2) to verify that the effects the OEL is based on are relevant to the scenario of interest; 3) to guide decisions on the margin between exposure and OEL that might be suitable for initiating risk management (i.e., for severe toxicity a bigger margin between exposure and the OEL is typically desired); and 4) to inform additional preventive risk management strategies such as medical surveillance needs. OELs that are developed based on adverse effects that are not currently the most relevant (e.g., if more conservative or acceptable endpoints have been identified, or if an endpoint in animals is no longer considered relevant to humans) or inappropriate studies (e.g., studies that are no longer based on current scientific principles, or that are no longer the most conservative or relevant in

the body of literature for the compound) can be eliminated from further review. The occupational hygienist should then review the remaining OELs to ensure that the choice of the point of departure (NOAEL, LOAEL, BMD, or cancer slope factor) and any applied uncertainty factors are acceptable.

As part of the risk science evaluation of the OEL, the occupational hygienist should also identify whether the OEL was peer reviewed. Peer review is important when developing an OEL, as it increases the validity and reliability of the guideline value. When experts not directly involved in the OEL derivation process review the value, they can help to identify any missing considerations and potential biases that could negatively impact its calculation. Public consultation or other similar external review processes might also be considered to be a sufficient peer review activity. The occupational hygienist should identify whether each remaining OEL has undergone peer review, and, wherever possible, obtain comments from the peer review process that could help to identify limitations with the value. If an OEL under consideration has not been peer reviewed, the occupational hygienist could consider obtaining such a review to ensure its validity.

Evaluate the risk policy assumptions for the OEL

The occupational hygienist will evaluate all OELs that were deemed to have an adequate scientific basis to ensure the policy assumptions for the OEL are relevant. If the OEL is based on direct estimates of risk (including, but not limited to, linear extrapolations of cancer risk), ensure that the assumed acceptable risk level (e.g., 1 in 1000) is in line with organizational policies. Moreover, feasibility of the OEL should also be considered. If the OELs under review have been

evaluated for economic, engineering, and analytical feasibility, ensure that the assumptions made in these assessments are consistent with the target organization's capabilities.

Select the appropriate OEL

If more than one OEL was retained from the assessment, the most appropriate OEL should be selected. The occupational hygienist should rank the OELs to identify which value was derived using assumptions that are most similar to those used within the target organization. Using pre-identified criteria, the OELs based on risk science and risk policy decisions that are most closely aligned with the occupational hygienist's organizational policies should be selected. If some risk science or risk policy decisions are of particular importance for the organization, the criteria can be arranged so that greater weight is placed on these higher priority options. The occupational hygienist must ensure that the selected value is equivalent to or more conservative than any legally mandated standards. Although many organizations select the lowest among the pool of "relevant and reliable" OELs, others actually review the literature and points of departure of the existing OELs and select the most robust OELs for their purposes. Such strategies are appropriate—the primary recommendation is that the process is documented to ensure consistency.

If no OELs are deemed appropriate during the assessment, the occupational hygienist can consider deriving a working provisional OEL for the organization. Using existing OELs, a new value could be derived by selecting a combination of appropriate risk science and risk policy assumptions from the various OELs. Another potential approach would involve selecting a single OEL or other exposure benchmark as a starting point and changing the risk science and risk policy decisions to ones that are aligned with the organization's practices. Typical adjustments

might address assumptions related to the duration and route of exposure and areas of uncertainty included in current exposure guidelines. An overview of the steps involved in deriving an OEL can be found in Table IV and more detailed guidance has been provided elsewhere in the literature. [3,10,11,17,23,51,52,73,81,83] Any provisional OELs should be peer reviewed to strengthen the confidence in the value.

If no OELs can be found for a particular chemical, or if it is not possible to derive a new value based on existing OELs, the OEL hierarchy concept can be applied. In the absence of quantitative limits, risk management strategies can be applied that address prior handling experiences with similar compounds using techniques such as control banding. Control banding strategies have a proven utility when there is uncertainty, whether with a lack of firm toxicological and exposure information or in the absence of OELs. [88] Both the pharmaceutical and nanotechnology industries highlight control banding's utility under these circumstances and there is a strong research basis internationally for its role in implementing controls commensurate to risk in the absence of OELs for nanomaterials. [89-91] As more materials become available in bulk and nanosized dimensions, multiple OELs might need to be developed for the same material, as NIOSH has done for titanium dioxide. [92] The hazard classifications provided under the GHS can be used to accomplish this approach. The vast number of potential nanomaterials will likely necessitate the development of categorical approaches based on mode of action or physical and chemical characteristics.[93,94]

Although a decision framework for selecting an appropriate (relevant and reliable) OEL is proposed in this paper, the concepts presented in the framework are not novel. Many organizations already have similar decision processes in place; one example of this is the process used by The Dow Chemical Company, displayed in Figure 5.

The selection process should be guided by a knowledgeable occupational hygienist; however, participatory occupational hygiene approaches can be used to involve workers in the selection of the most appropriate OEL. Participatory approaches have previously been recommended for application in other areas of occupational hygiene, including the use of control banding in a Risk Level Based Management System, [95] and could also be extended for the use of more traditional OELs. Workers can help in the gathering and presentation of information for each of the OELs. Decision-making activities can provide an opportunity to empower workers to participate in the process of preventing diseases that might result from exposures to chemical substances. [96]

CONCLUSION

OELs are developed by many organizations around the world and provide an essential tool for occupational health risk assessment. Because of the uncertain nature of risk assessment and differing levels of data availability, a patchwork of OELs has evolved over time. OELs have been developed for only a small fraction of the universe of chemicals; where OELs have been derived, multiple values exist for most substances. With many OEL-setting organizations currently in existence around the world, each with their own approaches, these values can differ appreciably. The need to identify the most appropriate OEL for a compound when a range of values exists presents a challenge for occupational hygienists; to address this challenge, a systematic framework to guide the process of evaluating and selecting the most appropriate OEL for use in specific circumstances has been proposed. To further simplify this process, it is recommended that international harmonization activities be expanded to promote commonalities

and transparency in the approaches used by organizations around the world in their development of OELs.

ACKNOWLEDGMENTS

The authors would like to thank the peer reviewers (including H. Griem, C. Laszcz-Davis, T.J. Lentz, K. MacMahon, and J. Perkins) for their valuable expertise and many helpful comments that served to improve the initial draft of this manuscript. The work of staff at the National Institute for Occupational Safety and Health (NIOSH) who assisted with technical aspects of this paper, including graphic design (G. Fazio) and reference database maintenance (D. Baker), is also gratefully acknowledged.

This work, in part, was performed under the auspices of the US Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344, LLNL-JRNL-651212. D. Krewski is the Natural Sciences and Engineering Research Chair in Risk Science at the University of Ottawa.

Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

REFERENCES

1. **Waters M., L. McKernan, A. Maier, M. Jayjock, V. Schaeffer, and L. Brosseau:** Occupational risk probability and interpretation of occupational exposure limits: Enhanced information for the occupational risk manager. *J. Occup. Environ. Hyg.* Submitted for publication (2014).

2. **Zielhuis R. L., P. C. Noordam, C. L. Maas, J. J. Kolk, and H. P. Illing:** Harmonization of criteria documents for standard setting in occupational health: a report of a workshop. *Regul. Toxicol. Pharmacol.* 13(3): 241–262 (1991).

3. **Paustenbach D. J., D. M. Cowan, and J. Sahmel:** The history and biological basis of occupational exposure limits for chemical agents. In *Patty's Industrial Hygiene,* R. V and B. Cohrssen (eds.). Hoboken, NJ: John Wiley & Sons Inc, 2011.

4. "Derivation of MAK values." [Online] Available at: http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/structure/working_groups/derivation_mak/index.html (Accessed November 9, 2013).

5. **Ripple S.:** History of occupational exposure limits. *Exposure Setting Processes—An International Challenge, Workshop at the International Occupational Hygiene Assocation (IOHA) Conference, Rome, Italy* (October 1, 2010).

6. "The Nordic Expert Group." [Online] Available at: http://www.av.se/arkiv/neg/the_neg/ (Accessed November 11, 2013).

7. **European Commission:** Methodology for the Derivation of Occupational Exposure Limits: Key Documentation (Version 7). (2013).

8. **Adkins C., L. Booher, D. Culver, T. Grumbles, M. Guillemin, F. Hearl, et al:** Occupational exposure limits: do they have a future? (2009).

9. **Paustenbach D. J.:** Occupational Exposure Limits. In *ILO Encyclopaedia of Occupational Health and Safety,* pp. 30.27–30.34. Geneva: International Labour Organisation, 1997.

10. **Wheeler M. W., R. Park, A. J. Bailer, and C. W. Sofge:** Historical context and recent advances in exposure-response estimation for deriving occupational exposure limits. *J. Occup. Environ. Hyg.* Submitted for publication (2014).

11. **Dankovic D. A., B. D. Naumann, M. L. Dourson, A. Maier, and L. Levy:** The scientific basis for uncertainty, safety and modifying factors in OEL setting. *J. Occup. Environ. Hyg.* Submitted for publication (2014).

12. **Howard J.:** Setting occupational exposure limits: are we living in a post-OEL world? *U. Pa. J. Lab. Empl. L.* 7(3): 513–528 (2005).

13. **United States Department of Labor:** Occupational Health and Safety Standards 1910.1000 Z Toxic and Hazardous Substances.

14. **European Commission:** Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work. (1998).

15. **Salter L. and E. Levy:** In the Eye of the Storm: Case Study One: The American Conference of Governmental Industrial Hygienists. In *Mandated Science: Science and Scientists in the Making of Standards,* L. Salter (ed.), pp. 36–66. Dordrecht, Netherlands: Kluwer Academic Publishers, 1988.

16. **Piney M.:** Exposure limits, practicability and health risks: Arguments for a paradigm shift. In *The Politics of Chemical Risk: Scenarios for a Regulatory Future,* R. Bal and W. Halffman (eds.), pp. 27–73. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1998.

17. **Vincent J. H.:** International occupational exposure standards: a review and commentary. *Am. Ind. Hyg. Assoc. J.* 59: 729–742 (1998).

18. **Hansson S. O.:** *Setting the Limit: Occupational Health Standards and the Limits of Science.* New York, NY: Oxford University Press, 1998.

19. **American Conference of Governmental Industrial Hygienists (ACGIH):** Sources, Abbreviations, Definitions and Terms Used Within the Database and Its Reports. In *Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values: 2006 CD-ROM,* ACGIH (ed.), pp. 1–15. Cincinnati, OH: ACGIH, 2006.

20. **National Academy of Sciences (NAS):** *Science and Decisions: Advancing Risk Assessment.* Washington, D.C.: National Academy Press, 2009.

21. **Krewski D., M. Westphal, M. E. Andersen, G. Paoli, W. Chiu, M. Al-Zoughool, et al:** A framework for the next generation of risk science. *Environ. Health Perspect.* 122(8): 796–805 (2014).

22. **Laszcz-Davis C., A. Maier, and J. Perkins:** The hierarchy of OELs: A new organizing principle for occupational risk assessment. *The Synergist*: 26–30 (March 2014).

23. **Nielsen G. D. and S. Ovrebo:** Background, approaches and recent trends for setting health-based occupational exposure limits: a minireview. *Regul. Toxicol. Pharmacol.* 51(3): 253–269 (2008).

24. **Kreider M. L. and E. S. Williams:** Interpreting REACH guidance in the determination of the derived no effect level (DNEL). *Regul. Toxicol. Pharmacol.* 58(2): 323–329 (2010).

25. **Ader A. W., J. P. Farris, and R. H. Ku:** Occupational health categorization and compound handling practice systems: roots, application and future. *Chem. Health Saf.* 12(4): 20–26 (2005).

26. **American Industrial Hygiene Association (AIHA) Control Banding Working Group:** *Guidance for Conducting Control Banding Analyses.* Fairfax, VA: AIHA, 2007.

27. **Naumann B. D.:** *Control banding in the pharmaceutical industry. Occupational Hygienists Conference Proceedings 2005.* Tullamarine, Australia: Australian Institute of Occupational Hygienists, 2005. Available at: http://www.aioh.org.au/downloads/documents/ControlBandingBNaumann.pdf (Accessed November 15, 2014).

28. **National Institute for Occupational Safety and Health (NIOSH):** Qualitative Risk Characterization and Management of Occupational Hazards: Control Banding (CB). DHHS (NIOSH) Publication No. 2009-152 (2009).

29. **Ripple S.:** Hyped about hazard banding. *The Synergist*: 43–45, 60 (October 2009).

30. **Zalk D. M. and D. I. Nelson:** History and evolution of control banding: a review. *J. Occup. Environ. Hyg.* 5(5): 330–346 (2008).

31. **Barlow S.:** Threshold of Toxicological Concern (TTC): A Tool for Assessing Substances of Unknown Toxicity Present at Low Levels in the Diet. (2005).

32. **Kroes R., J. Kleiner, and A. Renwick:** The threshold of toxicological concern concept in risk assessment. *Toxicol. Sci.* 86(2): 226–230 (2005).

33. **Dolan D. G., B. D. Naumann, E. V. Sargent, A. Maier, and M. Dourson:** Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. *Regul. Toxicol. Pharmacol.* 43(1): 1–9 (2005).

34. **National Institute for Occupational Safety and Health (NIOSH):** Current intelligence bulletin 66: derivation of immediately dangerous to life or health (IDLH) values. DHHS (NIOSH) Publication No. 2014–100 (2013).

35. **Brandys R. C. and G. M. Brandys:** *Global Occupational Exposure Limits for Over 6,000 Specific Chemicals.* Occupational and Environmental Health Consulting Services Inc., 2008.

36. **Schenk L., S. O. Hansson, C. Rudén, and M. Gilek:** Occupational exposure limits: a comparative study. *Regul. Toxicol. Pharmacol.* 50(2): 261–270 (2008).

37. **Chemical Abstracts Service:** "CAS REGISTRY(SM) surpasses 75 million small molecules." (November 11, 2013).

38. "TSCA Chemical Substance Inventory: Basic Information." [Online] Available at: http://www.epa.gov/oppt/existingchemicals/pubs/tscainventory/basic.html (Accessed November 9, 2013).

39. **Health Canada:** Proposal for Priority Setting for Existing Substances on the Domestic Substances List Under the Canadian Environmental Protection Act, 1999: Greatest Potential for Human Exposure. (2003).

40. **European Chemicals Agency (ECHA):** Classification and Labelling Notification Report on 4 January 2011. (2011).

41. **Schenk L.:** Comparison of data used for setting occupational exposure limits. *Int. J. Occup. Environ. Health* 16(3): 249–262 (2010).

42. **Chen C. P., H. W. Ahlers, G. S. Dotson, Y. C. Lin, W. C. Chang, A. Maier, et al:** Efficacy of predictive modeling as a scientific criterion in dermal hazard identification for assignment of skin notations. *Regul. Toxicol. Pharmacol.* 61(1): 63–72 (2011).

43. **Haber L. T. and A. Maier:** Scientific criteria used for the development of occupational exposure limits for metals and other mining-related chemicals. *Regul. Toxicol. Pharmacol.* 36(3): 262–79 (2002).

44. **United States Department of Labor:** OSH Act of 1970. (1970).

45. **American Conference of Governmental Industrial Hygienists (ACGIH):** *2014 TLVs and BEIs.* Cincinnati, OH: ACGIH, 2014.

46. **Castleman B. I. and G. E. Ziem:** Corporate influence on threshold limit values. *Am. J. Ind. Med.*13(5): 531–559 (1988).

47. **Henschler D.:** Evaluation of adverse effects in the standard-setting process. *Toxicol. Lett.* 64–65: 53–57 (1992).

48. **United Nations Economic Commission for Europe:** Globally Harmonized System of Classification and Labelling of Chemicals. Fifth revised edition (2013).

49. **ACUTEX:** Methodology to develop AETLs. (2006).

50. **European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC):** Guidance on Assessment Factors to Derive a DNEL. Technical Report No. 110 (2010).

51. **Illing H. P.:** Extrapolating from toxicity data to occupational exposure limits: some considerations. *Ann. Occup. Hyg.* 35(6): 569–580 (1991).

52. **Ku R. H.:** An overview of setting occupational exposure limits (OELs) for pharmaceuticals. *Chem. Health Saf.* 7(1): 34–37 (2000).

53. **Ritter L., C. Totman, K. Krishnan, R. Carrier, A. Vezina, and V. Morisset:** Deriving uncertainty factors for threshold chemical contaminants in drinking water. *J. Toxicol. Environ. Health B Crit. Rev.* 10(7): 527–557 (2007).

54. **Schenk L. and G. Johanson:** Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit. Rev. Toxicol.* 40(9): 791–798 (2010).

55. **Renwick A. G., J. C. M. Dorne, and K. Walton:** Pathway-related factors: The potential for human data to improve the scientific basis of risk assessment. *Hum. Ecol. Risk Assess.* 7(1): 165–180 (2001).

56. **International Programme on Chemical Safety (IPCS):** Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration–Reponse Assessment. Harmonization Project Document No. 2 (2005).

57. **European Chemicals Agency:** Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. ECHA-2010-G-19-EN (2012).

58. **Schenk L. and G. Johanson:** A quantitative comparison of the safety margins in the european indicative occupational exposure limits and the derived no-effect levels for workers under REACH. *Toxicol. Sci.* 121(2): 408–416 (2011).

59. **Dyck R., M. S. Islam, A. Zargar, A. Mohapatra, and R. Sadiq:** Application of data fusion in human health risk assessment for hydrocarbon mixtures on contaminated sites. *Toxicology* 313(2–3): 160–173 (2013).

60. **Islam M. S., A. Zargar, R. Dyck, A. Mohapatra, and R. Sadiq:** Data fusion-based risk assessment framework: An example of benzene. *Int. J. Syst. Assur. Eng. Manag.* 3(4): 267–283 (2012).

61. **International Programme on Chemical Safety (IPCS):** Part 1: IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans and Case-Studies; Part 2:

IPCS Framework for Analysing the Relevance of a Non-Cancer Mode of Action for Humans. Harmonization Project Document No. 4 (2007).

62. **Tao T., Y. Bhuller, Y. Bonvalot, M. Hill, A. Klein, G. Kozak, et al:** Weight of Evidence: General Principles and Current Applications at Health Canada. (2011).

63. **Rhomberg L. R., L. A. Bailey, and J. E. Goodman:** Hypothesis-based weight of evidence: a tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action--naphthalene as an example. *Crit. Rev. Toxicol.* 40(8): 671–696 (2010).

64. **Klimisch H. J., M. Andreae, and U. Tillmann:** A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol.* 25(1): 1–5 (1997).

65. **Money C. D., J. A. Tomenson, M. G. Penman, P. J. Boogaard, and R. J. Lewis:** A systematic approach for evaluating and scoring human data. *Regul. Toxicol. Pharmacol.* 66(2): 241–247 (2013).

66. **Chambers A., D. Krewski, N. Birkett, L. Plunkett, R. Hertzberg, R. Danzeisen, et al:** An exposure-response curve for copper excess and deficiency. *J. Toxicol. Environ. Health B Crit. Rev.* 13(7–8): 546–578 (2010).

67. **Dourson M. L., L. K. Teuschler, P. R. Durkin, and W. M. Stiteler:** Categorical regression of toxicity data: a case study using aldicarb. *Regul. Toxicol. Pharmacol.* 25(2): 121–129 (1997).

68. **Tyshenko M. G., S. El Saadany, T. Oraby, S. Darshan, W. Aspinall, R. Cooke, et al:** Expert elicitation for the judgment of prion disease risk uncertainties. *J. Toxicol. Environ. Health A* 74(2-4): 261–285 (2011).

69. **Lundberg P.:** National and international approaches to occupational standard setting within Europe. *Appl. Occup. Environ. Hyg.* 9(1): 25–27 (1994).

70. **Travis C. C. and H. A. Hattemer-Frey:** Determining an acceptable level of risk. *Environ. Sci. Technol.* 22(8): 873–876 (1988).

71. **United States Government Accountability Office (USGAO):** Chemical risk assessment: Selected federal agencies' procedures, assumptions, and policies. No. GAO-01-810 (2001).

72. "International Programme on Chemical Safety Harmonization Project Strategic Plan: Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals." [Online] Available at: http://www.who.int/entity/ipcs/methods/harmonization/strategic_plan.pdf (Accessed November 11, 2013).

73. **International Council on Mining and Metals:** *The Setting and Use of Occupational Exposure Limits: Current Practice.* , 2007.

74. **International Council on Mining and Metals:** *Towards a Harmonized Approach to Setting Occupational Exposure Limits: Report of an ICMM-Sponsored Workshop, London, 9–11th November 2005.* 2006.

75. **Mikheev M. I.:** Toward WHO-recommended occupational exposure limits. *Toxicol. Lett.* 77(1–3): 183–187 (1995).

76. **International Programme on Chemical Safety (IPCS):** 1,2-Dichloroethane. Concise International Chemical Assessment Document No. 1 (1998).

77. **Ding Q., L. Schenk, K. Malkiewicz, and S. O. Hansson:** Occupational exposure limits in Europe and Asia--continued divergence or global harmonization? *Regul. Toxicol. Pharmacol.* 61(3): 296–309 (2011).

78. **Woodall G. M. and R. B. Goldberg:** Summary of the workshop on the power of aggregated toxicity data. *Toxicol. Appl. Pharmacol.* 233(1): 71–75 (2008).

79. **Schenk L., S. O. Hansson, C. Rudén, and M. Gilek:** Are occupational exposure limits becoming more alike within the European Union? *J. Appl. Toxicol.* 28(7): 858–866 (2008).

80. **Dourson M. L. and J. F. Stara:** Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.* 3(3): 224–238 (1983).

81. **Seeley M. R., L. E. Tonner-Navarro, B. D. Beck, R. Deskin, V. J. Feron, G. Johanson, et al:** Procedures for health risk assessment in Europe. *Regul. Toxicol. Pharmacol.* 34(2): 153–169 (2001).

82. **WHO:** Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits. Environmental Health Criteria 170 (1994).

83. **Haber L. T., J. E. Strawson, A. Maier, I. M. Baskerville-Abraham, A. Parker, and M. L. Dourson:** Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings. In *Patty's Toxicology,* E. Bingham and B. Cohrssen (eds.), pp. 89–132. Hoboken, NJ: John Wiley & Sons, 2012.

84. "GESTIS International Limit Values." [Online] Available at: http://limitvalue.ifa.dguv.de/Webform_gw.aspx (Accessed December 16, 2013).

85. "Chemical exposure limits." [Online] Available at: http://www.ilo.org/safework/info/publications/WCMS_151534 (Accessed December 6, 2013).

86. "Information on Chemicals." [Online] Available at: http://echa.europa.eu/information-on-chemicals (Accessed December 7, 2013).

87. "TOXNET: Toxicology Data Network." [Online] Available at: http://toxnet.nlm.nih.gov (Accessed December 16, 2013).

88. **Zalk D. M.:** *Control Banding: A Simplified, Qualitative Strategy for the Assessment of Risks and Selection of Solutions.* Delft, Netherlands: TU Delft, 2010.

89. **Brouwer D. H.:** Control banding approaches for nanomaterials. *Ann. Occup. Hyg.* 56(5): 506–514 (2012).

90. **Van Duuren-Stuurman B., S. R. Vink, K. J. Verbist, H. G. Heussen, D. H. Brouwer, D. E. Kroese, et al:** Stoffenmanager Nano Version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. *Ann. Occup. Hyg.* 56(5): 525–541 (2012).

91. **Zalk D. M., S. Y. Paik, and P. Swuste:** Evaluating the Control Banding Nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. *J. Nanopart. Res.* 11(7): 1685–1704 (2009).

92. **National Institute for Occupational Safety and Health (NIOSH):** Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide. DHHS (NIOSH) Publication No. 2011-160 (2011).

93. **Kuempel E., V. Castranova, C. Geraci, and P. Schulte:** Development of risk-based nanomaterial groups for occupational exposure control. *J. Nanopart. Res.* 14(9): 1–15 (2012).

94. **Schulte P., V. Murashov, R. Zumwalde, E. Kuempel, and C. Geraci:** Occupational exposure limits for nanomaterials: state of the art. *J. Nanopart. Res.* 12(6): 1971–1987 (2010).

95. **Zalk D. M., R. Kamerzell, S. Paik, J. Kapp, D. Harrington, and P. Swuste:** Risk level based management system: a control banding model for occupational health and safety risk management in a highly regulated environment. *Ind. Health* 48(1): 18–28 (2010).

96. **Zalk D. M.:** Participatory occupational hygiene: a path to practical solutions. *Asia. Pac. Newsl. Occup. Health Saf.* 9(3): 51 (2002).

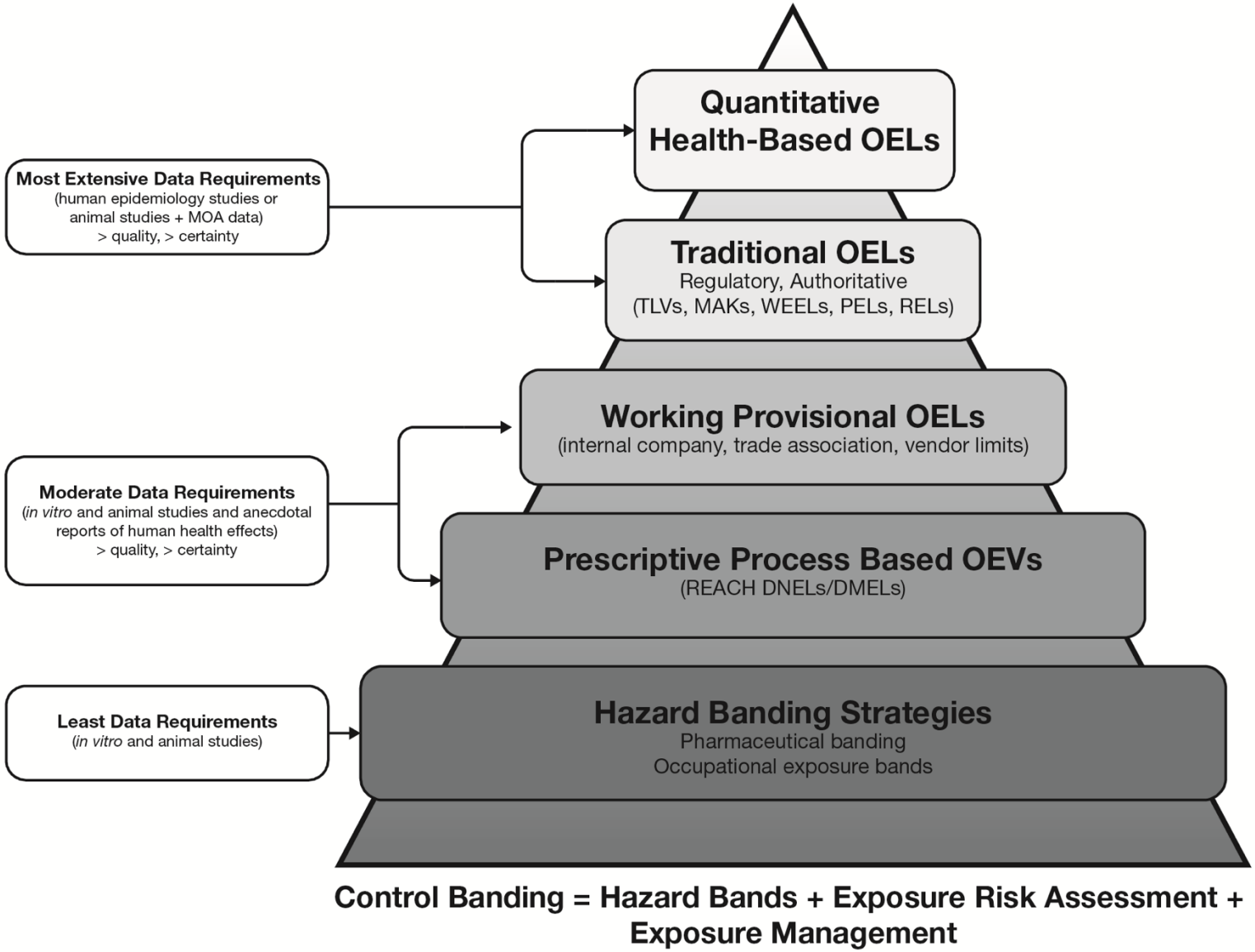


Figure 1. A hierarchy of risk-based occupational exposure benchmarks
As more toxicological and epidemiological data become available, one moves up the hierarchy. Adapted from a version of the hierarchy developed by Laszcz-Davis et al.[22]

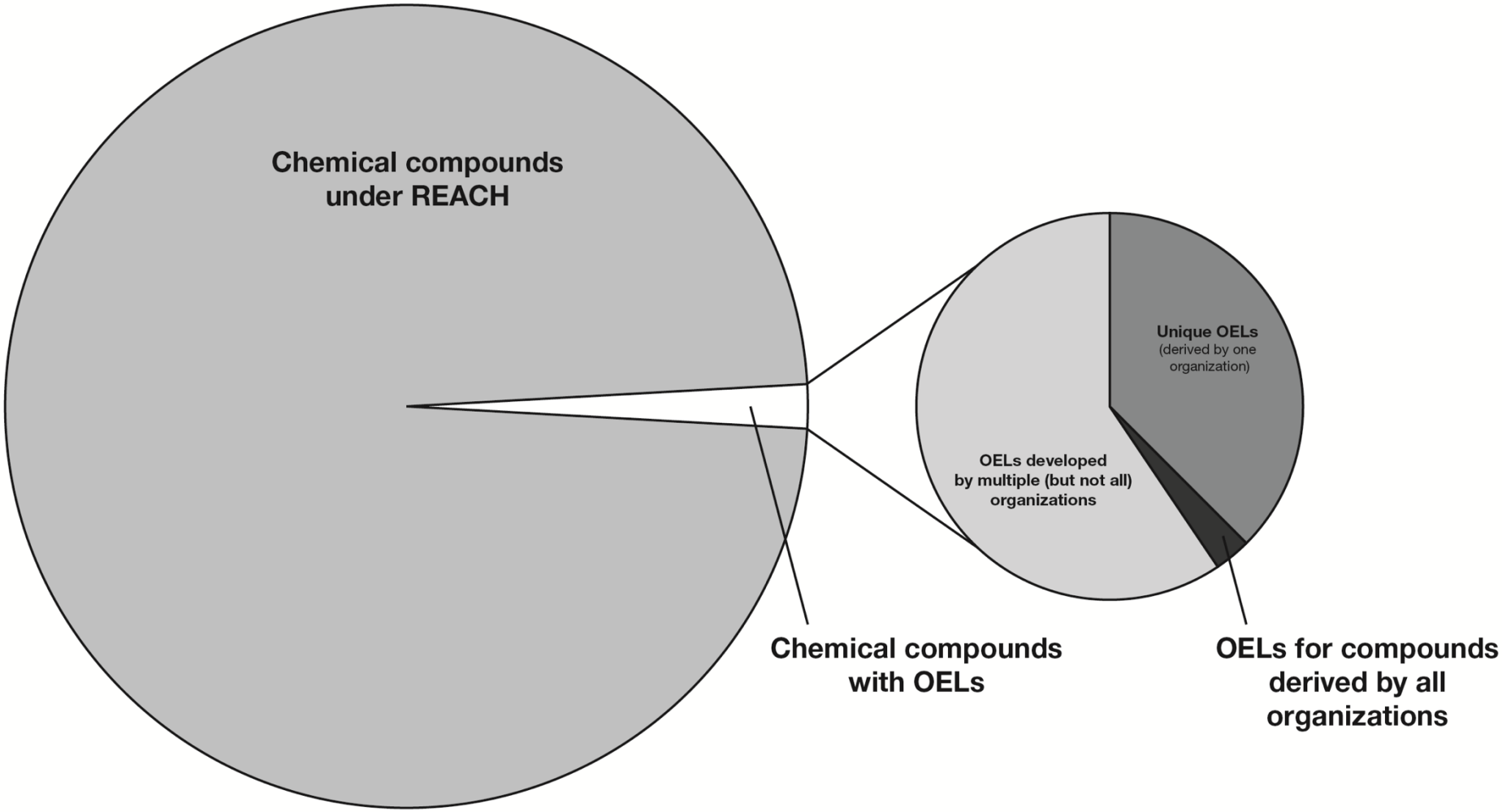


Figure 2. Graphical representation of the fraction of chemicals in commerce with occupational exposure limits (OELs) (REACH data from ECHA, 2011[40]; data from 18 international organizations from Schenk et al., 2008a[36]).

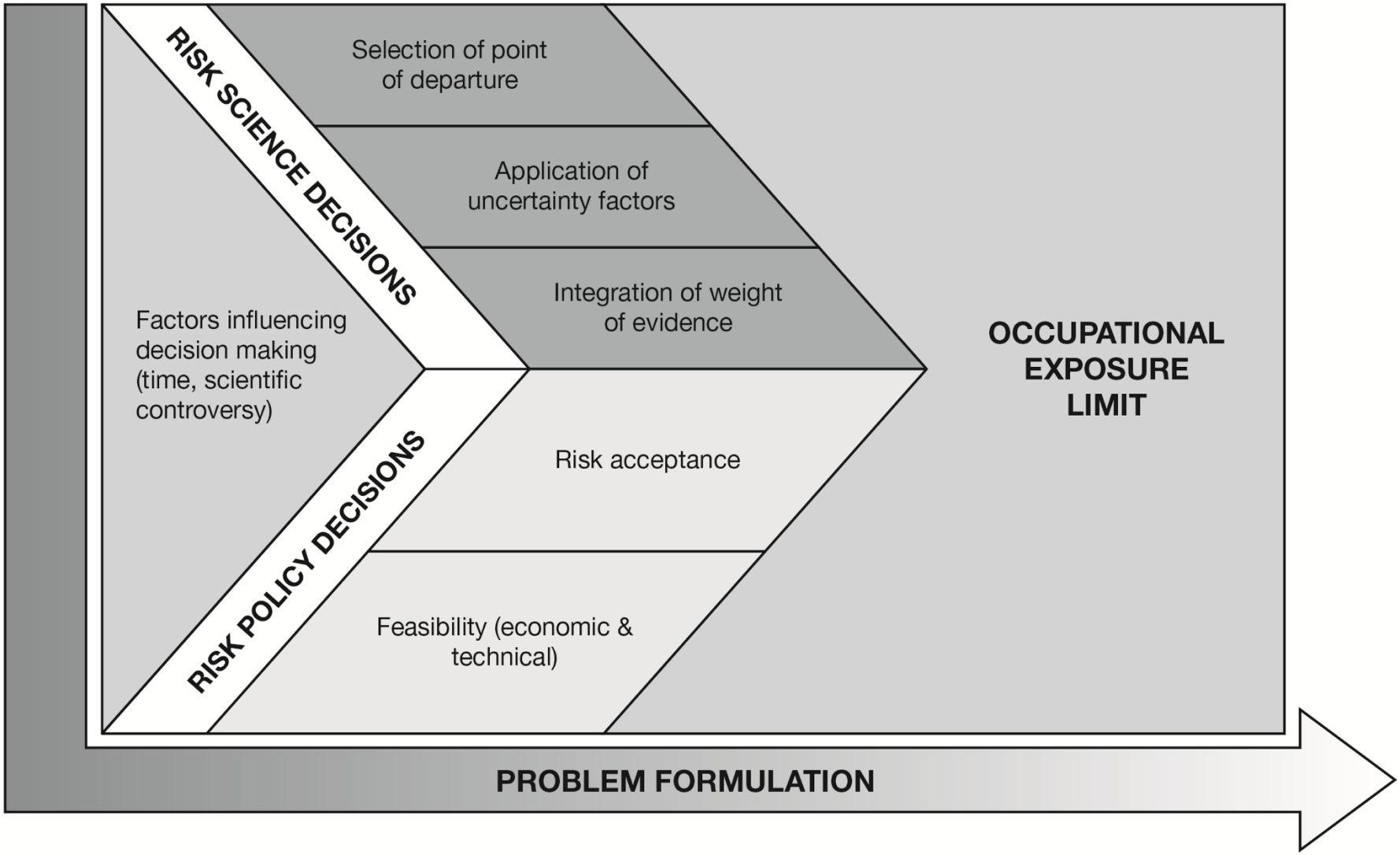


Figure 3. Potential sources of variability in science and policy decisions taken during the establishment of occupational exposure limits (OELs).

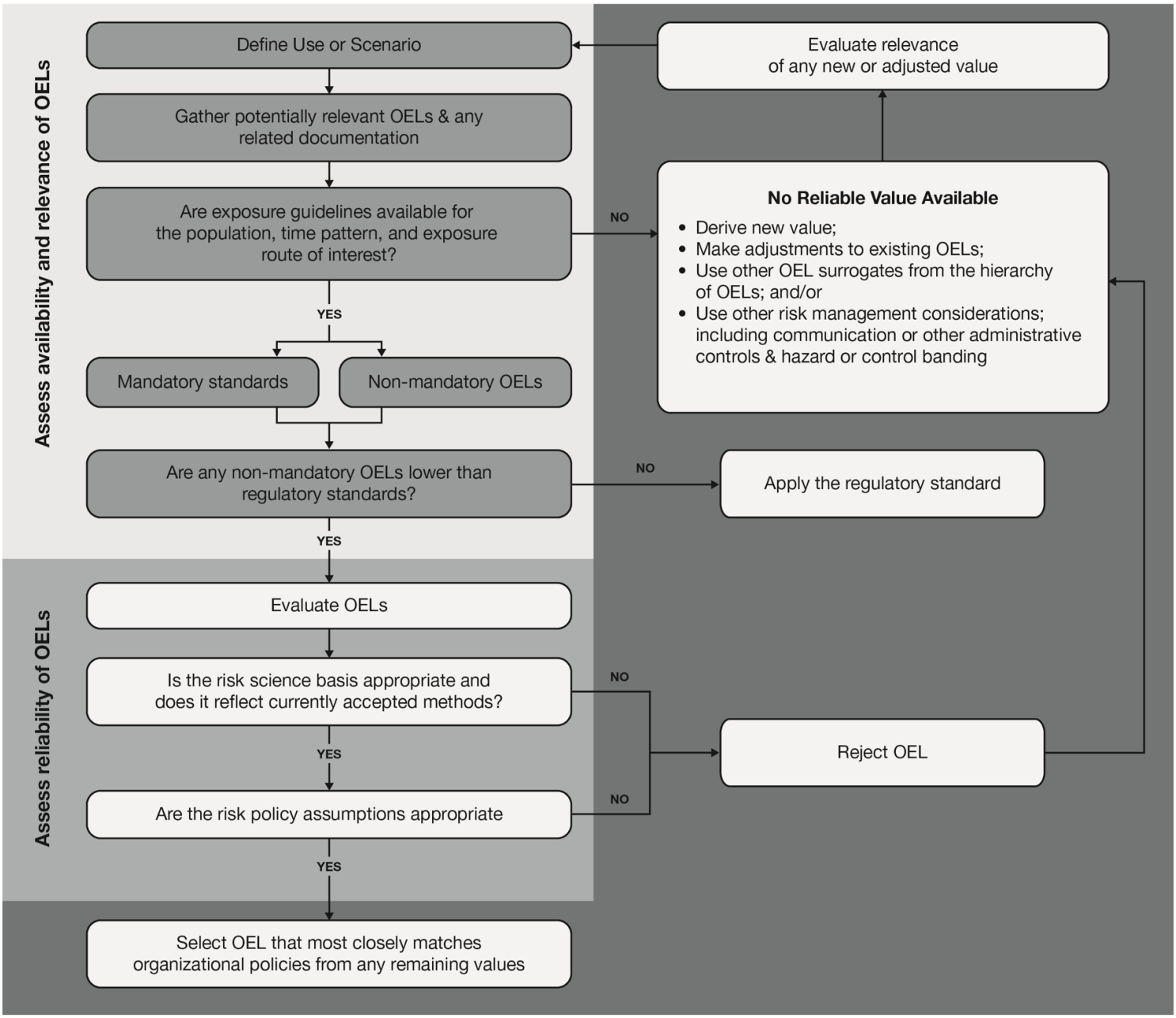


Figure 4. Framework for the selection of an appropriate occupational exposure limit (OEL)

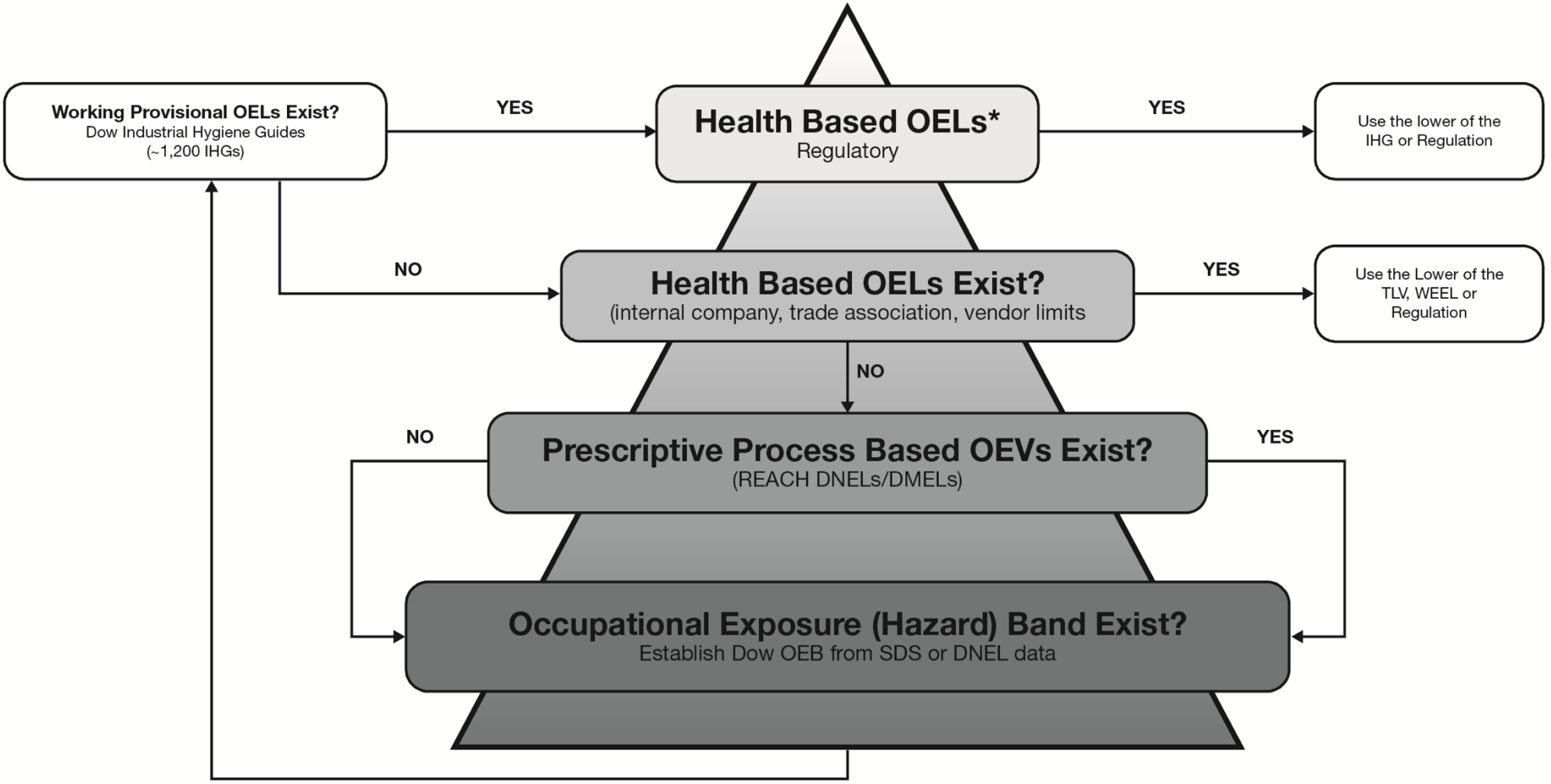


Figure 5. The Dow Chemical Company decision logic for selecting occupational exposure limits (OELs)

Table 1. The early history of institutional occupational exposure limit (OEL) development

Decade first published	Type of OEL
1910s	U.S. and South African limits (for crystalline silica/quartz only)
1920s	U.S. Bureau of Mines exposure limits International Critical Tables
1930s	German exposure limits USSR Ministry of Labor MACs
1940s	American Conference of Governmental Industrial Hygienists (ACGIH) maximum allowable concentrations of atmospheric contaminants (preceding Threshold Limit Values) American National Standards Institute standards
1950s	People's Republic of China's Provisional Hygienic Standards for the Design of Industrial Premises
1970s	U.S. Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs) National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs) Nordic Expert Group (NEG) for Criteria Documentation of Health Risks from Chemicals Deutsche Forschungsgemeinschaft (DFG) Maximale Arbeitsplatz-Konzentration (MAKs)
1980s	American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Limits (WEELs)
1990s	European Scientific Experts Group (now Scientific Committee on Occupational Exposure Limits [SCOEL]) Binding Occupational Exposure Limit Values (BOELVs) and Indicative Occupational Exposure Limit Values (IOELVs)

Based on Paustenbach et al., 2011;[3] DFG, 2013;[4] Ripple, 2010;[5] EC, 2013[7]

Table 2. Variability in exposure limits derived for n-hexane

Type of exposure guideline	Value (ppm)
Traditional occupational exposure limits	
Indicative Occupational Exposure Limit Value (Scientific Committee on Occupational Exposure Limits)	20
Threshold Limit Value (American Conference of Governmental Industrial Hygienists)	50
Recommended Exposure Limit (U.S. National Institute for Occupational Safety and Health [NIOSH])	50
Maximale Arbeitsplatz-Konzentration (German Ausschuss für Gefahrstoff)	50
Permissible Exposure Limit (Occupational Safety and Health Administration)	500
Alternative inhalation values	
Reference Concentration (U.S. Environmental Protection Agency [EPA])	0.2
Derived No-Effect Level for general population (derived under European REACH regulations)	4.5
Derived No-Effect Level for workers	21
Immediately Dangerous to Life and Health (NIOSH)	1100
Acute Exposure Guideline Level (AEGL-2, for 30-minute to 8-hour exposures; EPA)	3300

Table 3. Ideal characteristics of standardized scientific supporting documents for Occupational Exposure Limits (OELs)

- Reflects current knowledge as presented in the scientific literature
- Includes research publications that are preferably peer-reviewed scientific papers, or are at least available publicly, and limits personal communications as references
- Communicates approaches and resulting OELs openly, particularly toward the general public
- Is developed either by a scientific committee consisting of independent scientists from academia and government, or by experts within an agency with an additional peer, stakeholder, and public review process.
- Presents and scrutinizes all relevant epidemiological and experimental studies, especially "key studies" that present data on the critical effect, and describes all observed effects
- Presents and scrutinizes environmental and biological monitoring possibilities, including toxicokinetic data
- States and describes the establishment of dose–response and dose–effect relationships and points of departure for each observed effect
- Identifies the critical effect (i.e., the effect that occurs at the lowest exposure level) in the conclusions, along with reasons as to why a certain effect is the critical one
- Highlights mutagenic, carcinogenic, teratogenic, and allergic/immunological properties
- Provides a reference list for all studies described, including a list of reviewed but unused references, and also lists databases that have been used in the literature search

Based on Zielhuis, 1991;[2] Lundberg, 1994 [69]

Table 4. Overview of steps involved in the derivation of an occupational exposure limit

1. Define the scenario and develop the problem formulation
2. Gather and summarize the scientific literature most relevant to the problem formulation (e.g. primary literature and existing reviews on toxicology, epidemiology, pharmacokinetics, physicochemical properties), using the problem formulation to guide the literature selection process
3. Select a point of departure (e.g. NOAEL, LOAEL, BMD, or risk-based level) based on factors outlined in the problem formulation, such as protectiveness, strength of evidence, and human relevance
4. If necessary, perform extrapolations to increase the relevance of the point of departure
    a. Adjust for route of exposure and exposure duration/patterns (using default assumptions on rates of ingestion/inhalation or physiologically based pharmacokinetic [PBPK] models)
    b. Perform animal-to-human extrapolations and human variability extrapolations (using uncertainty factors, chemical-specific adjustment factors, or PBPK modeling)
    c. Apply any additionally required uncertainty factors (e.g. database deficiency, severity of effect)
5. Submit value for review by external parties

Chapter 8 – Application of a Framework to Guide the Selection of Relevant and Reliable Occupational Exposure Limits

Deveau, M[1,2]; Niven, KJ[3]; Urbanus, JH[3]; Krewski, D[1]; Maier, A[4]

Authors' affiliations
[1]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada K1N 6N5
[2]Faculty of Graduate and Postdoctoral Studies, University of Ottawa, Ottawa, Canada K1N 6N5
[3]Shell Health, Shell International B.V., 2501 AN, The Hague, The Netherlands
[4]Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH, 45267-0056

This chapter is a detailed manuscript produced from a poster presented at the Society for Risk Analysis Annual Meeting and American Industrial Hygiene Conference and Exhibition. Manuscript content was last updated in 2018; therefore, OEL availability and descriptions may not be current as of 2021.

ABSTRACT

Occupational exposure limits (OELs) serve as health-based benchmarks for interpreting workplace exposures. Many organizations have established processes for developing OELs to protect workers exposed to chemicals in the workplace. These processes vary widely, often resulting in multiple OEL values for a chemical; such differences present challenges for occupational hygienists in selecting an appropriate guidance value from among several potentially relevant OELs. A framework was developed to guide occupational hygienists in the selection of the most appropriate OEL for a particular occupational exposure scenario. Application of the framework involves the assessment of OELs for availability, relevance to specific exposure scenarios (e.g., for exposure duration patterns and routes, exposed populations, and organizational policies), and reliability. In situations where published OELs are not available, occupational hygienists are guided to consider and adjust non-traditional occupational and environmental benchmarks. To demonstrate the versatility of the tool, the framework was applied to case studies for a chemical with multiple OELs (n-hexane) and a substance that is well studied (methamphetamine) but lacks published OELs. Application of a systematic framework is seen to be helpful in identifying the most appropriate OEL for use in pre-identified occupational exposure scenarios when a variety of alternative values are available. The framework is sufficiently flexible to support risk management decisions by an occupational hygienist in situations where many OELs are available (OEL-rich) as well as when they are lacking (OEL-poor).

1.0 INTRODUCTION

Occupational exposure limits (OELs) are benchmarks for the interpretation of workplace exposures within a health risk context. Since the introduction of OELs over a century ago, they have enjoyed global uptake. Due to the proliferation of OEL-setting bodies, occupational hygienists can be confronted with multiple relevant—but often conflicting—OELs for a particular occupational exposure scenario (1-3), leading to difficulties in selecting the most appropriate value for health protection purposes. Moreover, OELs only exist for a small fraction of chemicals with which occupational exposures might be associated (1,2).

The purpose of this article is to provide guidance to occupational hygienists in the selection of an appropriate OEL for specific occupational risk scenarios, using a framework to promote a systematic decision process (1).To demonstrate the versatility of the framework in different occupational exposure scenarios, two case studies are presented. An additional application of the framework to manganese OEL selection has been published elsewhere (4), and will be presented in Chapter 9.

2.0 FRAMEWORK FOR THE SELECTION OF APPROPRIATE OELs

Differences in OELs can arise for a variety of reasons, which have been outlined in greater detail in other publications (1,2,5). Although OELs are based on a scientific foundation, various assumptions must be made during the OEL derivation process, usually due to data limitations. Decisions made by differing OEL-setting organizations might vary, but corresponding OELs might be equally acceptable and robust, depending on their intended purpose. The basis for differences in OELs should be explored by

occupational hygienists prior to deciding which value is most appropriate for a particular situation. The framework shown in Figure 1 was developed to support a systematic approach to making decisions about OEL selection (1).

Guidance for occupational hygienists on the assessment of OELs for availability, relevance, and reliability was incorporated into the framework, which builds upon concepts of a hierarchy of OELs (6) and a framework for OEL evaluation and interpretation (7). The framework guides occupational hygienists through the process of defining the exposure scenario, gathering OELs, assessing relevance of values to the defined exposure scenario, comparing mandatory standards to non-regulatory values, and evaluating the risk science and risk policy bases of each value.

The OEL evaluation and selection framework is described briefly below. Readers seeking more in-depth discussions of the selection process are encouraged to consult the publication in which the framework was initially proposed (1).

2.1 Assess availability and relevance of OELs

2.1.1 Define use or scenario

The initial step is the identification of exposure patterns. Traditional time-weighted average (TWA) full shift OELs are derived based on continuous inhalation exposures of healthy adult workers for eight hours per day, five days per week, over a working lifetime; however, different types of exposure guidelines might need to be considered if exposures are intermittent, infrequent, or also occur via the dermal route. Furthermore, exposure guidelines derived for the general population might need to be included when considering susceptible populations—including workers with pre-existing

health conditions, pregnant workers, workers in non-industrial settings where expectations about exposure might be more strict, or the general population (for assessments of community stewardship or para-occupational/"take-home" exposures). The goal of this stage is to identify the types of OELs or other exposure benchmarks that most closely correspond with the exposure scenario or intended application of the OEL.

2.1.2 Gather OELs and Other Relevant Limit Values

OELs and other exposure benchmarks should be obtained from as many sources as possible. Documentation supporting the derivation of the values is also important to gather, whenever available. In addition to legally mandated values, other sources of OELs should be sought, including the American Conference of Governmental Industrial Hygienists® (ACGIH) Threshold Limit Values® (TLVs); U.S. National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs); and Workplace Environmental Exposure Levels® (WEELs) derived formerly under the American Industrial Hygiene Association (AIHA), and currently under the Occupational Alliance for Risk Science (OARS). Values from other jurisdictions should also be considered—collections of these OELs can be found in the online GESTIS database (8), in books summarizing published OELs (9), and via links to other countries' OEL programs (10).

In the absence of traditional OELs, or if warranted by the exposure scenario, occupational hygienists are encouraged to consider exposure benchmarks other than traditional 8-hour TWAs. Alternative benchmarks include those lower in the hierarchy of OELs, including values derived for internal use within a company, or using prescribed

regulatory approaches, such as Derived No Effect Levels (DNELs) under the European Union legislation for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), or semi-quantitative approaches such as Occupational Exposure Banding or Threshold of Toxicological Concern (6,11). Additional values that may merit consideration are those of equivalent rigor to traditional OELs, but with different exposure scenarios. These include environmental health exposure guidelines (e.g., those derived by the U.S. Environmental Protection Agency, U.S. Agency for Toxic Substances and Disease Registry, Health Canada, and the International Programme on Chemical Safety), and exposure limits intended for shorter duration (e.g., Acute Exposure Guideline Levels, Acute Reference Concentrations, etc.).

2.1.3 Assess relevance of gathered OELs

The gathered OELs are then compared to the defined exposure scenario to identify values relevant from the perspective of target populations, exposure routes, and use patterns. OELs not applicable to the defined scenario—or that cannot be adjusted to the defined scenario—should be eliminated from further evaluation.

2.1.4 Compare mandatory standards to non-mandatory OELs

For legal purposes, exposure must be maintained below mandatory or regulatory OELs; however, consideration should be given to non-mandatory OELs that may be more protective of worker health. OELs lower than regulatory OELs should therefore be evaluated with the framework.

2.1.5 Assess the reliability of OELs

Occupational hygienists are guided to assess the reliability of remaining OELs, both from risk science and risk policy perspectives. As details behind the derivation of each of the OELs are required for these assessments, OELs should be eliminated from the evaluation if supporting documentation cannot be obtained.

2.1.6 Evaluate the risk science basis for the OEL

The following factors related to the determination of an OEL should be evaluated:

- Selection of the Point of Departure (POD), the basis of the OEL calculation (e.g. no or lowest observed adverse effect levels [NOAELs or LOAELs] or benchmark dose). Reject OELs based on studies or adverse effects that are no longer sufficiently protective, are not relevant to humans, or not based on current scientific principles. This consideration is often the basis for rejecting older OELs. Wheeler et al. (12) provide more information on the POD concept.
- Application of uncertainty factors (UFs), which account for variability and uncertainties in data used as the basis for the OEL. Reject OELs without a sufficient margin of safety between the POD and OEL. The margin of safety should be large enough to reflect each of the factors outlined in Table I that are applicable to a particular chemical. The appropriate margin of safety might vary among chemicals, and depends on the variability and uncertainty in the compound's database. Many OEL-setting bodies have outlined their standard approach to selection of UFs; several UFs for different aspects are often combined into a composite UF, but appropriateness of composite values can still be judged.

UFs reflecting each source of uncertainty or variability typically range from 1 to 10; higher composite UFs (or greater margins between the POD and OEL) will reflect a greater amount of uncertainty or variability in the available data. Dankovic et al. (13) provide more guidance on this topic.

- Integration of weight of evidence. Reject OELs that do not adequately consider all relevant data on health aspects of OEL determination discussed in the literature, accounting in particular for key studies used to establish the OEL and available information on mode of action.

2.1.7 Evaluate the risk policy basis for the OEL

Based on the occupational hygienist's organizational policies and practices, the following factors should be considered.

- Risk acceptance, to verify whether acceptable levels of risk (typically in the range of 1/1,000 to 1/10,000, or 10^{-3} to 10^{-4} for occupational carcinogens) are in line with organizational policies.
- Feasibility, to assess the organization's capability of achieving the OEL with reasonable engineering and other controls, and ensure analytical approaches are sufficiently sensitive to measure below the OEL.

2.1.8 Select an appropriate OEL

After the reliability assessment is performed for OELs obtained for a chemical, occupational hygienists are guided to select the most relevant and appropriate of retained values. This selection ideally identifies the most scientifically robust OEL. However, even if divergent OELs remain after the relevance assessment, individuals who do not

feel comfortable assessing the reliability of remaining OELs on a toxicological basis could use a simpler approach in selecting the most appropriate OEL. This could include selecting the lowest value (with the assumption that it is the most protective), the most recent value (if the assumption is that the most recent assessment will contain the most current risk assessment approaches and key studies), or the value from an organization with which the hygienist has established a basis for a general preference. No matter which approach is selected, consistency and documentation of the decision-making process are important.

If all OELs are rejected, occupational hygienists could develop a provisional OEL (either *de novo* or by adjustment of rejected values)—an overview of the steps involved in this process is included in Table II. If the occupational hygienist does not have sufficient expertise, or if there are insufficient data to derive an evidence-based OEL, control banding, hazard banding, or other risk management approaches should be considered.

3.0 CASE STUDIES

Two case studies are presented to illustrate decision processes that might be used when applying the framework. The case studies represent hypothetical occupational exposure scenarios for compounds with varying availability of OELs. The first case study focuses on n-hexane, which has many different OELs; conversely, only an environmental exposure benchmark—and no OELs—could be identified for methamphetamine, the agent of interest in the second case study.

3.1 Case study #1—OEL-rich scenario (n-hexane)

In the OEL-rich scenario, auto mechanics exposed to n-hexane in aerosol degreasers on a daily basis (for most of the workshift) was considered. An overview of this case study is presented in Figure 2. The GESTIS International Limit Values database (8) identified over 25 8-hour time weighted average OELs. Many of the gathered OELs were eliminated from further review due to absence of documentation describing the derivation of the value. Additional OELs were eliminated because values were based on other OELs included in the process. Retained values were from ACGIH (14), NIOSH (15), Occupational Safety and Health Administration (OSHA) (16), the European Commission's Scientific Committee on Occupational Exposure Limits (SCOEL) (17), Germany (18), and Poland (19) (see Table III for the retained OELs and basis for each value, as provided by their respective organizations).

The OSHA Permissible Exposure Limit (PEL) was eliminated from further consideration because the value was established prior to the release of studies demonstrating effects at concentrations lower than the PEL; however, applying more stringent OELs will ensure regulatory compliance in the US. PODs for remaining OELs were similar both qualitatively (based on neurotoxicity, with electrophysiological changes) and quantitatively. UFs were applied by all organizations, and appeared to be sufficient. The OELs were also considered to be measurable using current analytical methods and achievable with existing engineering and administrative controls at the place of employment. Therefore, five OELs were considered relevant and reliable.

Of the values that were retained, the European Union (IOELV) of 20 ppm was selected because IOELV documentation identified mild effects as low as 50 ppm, and

therefore allowed for the greatest margin of exposure between the OEL and exposures at which adverse health effects were observed. However, if some occupational hygienists do not find the margin of exposure of 2.5 to be sufficient for observed neurological outcomes, they could adjust the IOELV consistent with the framework approach to add additional (or larger) UFs for further protection of those workers viewed as susceptible under the specific scenario being evaluated. A related practical approach available to the occupational hygienist would be to use this OEL, but make risk mitigation decisions using a lower action level.

3.2 Case study #2—OEL-poor scenario (methamphetamine)

In the OEL-poor scenario, the target population consisted of workers who clean clandestine methamphetamine laboratories. An overview of this case study is presented in Figure 3. Cleaners—who are non-pregnant, healthy adults for this scenario—were exposed regularly to resuspended methamphetamine particulates in air, throughout most of their 8-hour shifts.

No traditional OELs could be identified for methamphetamine. The only identified exposure benchmark was an environmental health guideline—the California EPA Reference Dose (RfD) of 0.3 μg/kg-d (20). The RfD was based on a Lowest Observed Adverse Effect Level (LOAEL) of 0.08 mg/kg-d for decreased bodyweight gain (considered as a proxy for neurological effects) in a controlled dosing study of pregnant women; to be appropriate for the target toddler population, the LOAEL was divided by a UF of 300 (×10 for interindividual variability, ×10 to extrapolate from a LOAEL to a No Observed Adverse Effect Level (NOAEL), and ×3 for the absence of

health effects data in toddlers). The target population (toddlers), duration of exposure (24 hours/day), and route of exposure (ingestion/total exposure measured in mg/kg-d) of the RfD all differed from the exposure scenario. The guideline was therefore rejected based on the relevance assessment step of the framework. However, because no other reliable values were available, the RfD was adjusted to develop a scenario-specific interim OEL.

This RfD was adjusted for the occupational scenario of interest in three ways, namely: 1) an exposure duration adjustment (to extrapolate from the continuous exposure value to 5 weekly 8-hour shifts); 2) a UF adjustment (to decrease or eliminate UFs related to uncertainty and variability in the sensitive subpopulation); and 3) an exposure route adjustment (using default assumptions for inhalation rates and bodyweight to derive a μg/m^3 value from the μg/kg-d value). An example of a generic version of this calculation is presented in Equation 1 below.

$$\frac{point\ of\ departure}{uncertainty\ factor} \times\ duration\ adjustment\ \times \frac{body\ weight}{inhalation\ rate} = interim\ OEL \qquad (1)$$

The CalEPA UF of 300 was reduced to a value of 10 in this scenario. This was done by removing the 3-fold UF that had been added to protect toddlers (as this population is not relevant to the scenario), reducing the 10-fold UF for interindividual variability (as this value is more consistent with the lower UFs typically applied for OELs, to reflect healthy worker populations), and reducing the 10-fold UF for LOAEL-to-NOAEL (as the full UF was not warranted because greater weight loss occurred at the POD than in next highest dose group).

After dividing the California EPA LOAEL of 0.08 mg/kg-d by a UF of 10 (selected to be a sufficient reflection of variability in a population of healthy adult

workers), and adjusting for shift length and default body weights and inhalation rates (using the body weight and inhalation assumptions used by the OARS WEEL Committee), an interim value of 0.23 mg/m^3 (230 µg/m^3) was calculated (Equation 2).

$$\frac{0.08\ mg/kg\text{–}d}{10} \times \frac{24\ h}{8\ h} \times \frac{7d}{5d} \times \frac{55\ kg}{8\ m^3} = 0.23\ mg/m^3 \quad (2)$$

Several limitations exist in the derivation of this interim OEL. The key study and POD were based on a population that is different than this worker group; in particular, the POD might not be the most appropriate for non-pregnant adults. Moreover, the adjustment for duration of exposure was performed using the linear assumptions of Haber's law (which states that hazard is a product of concentration and time), which is not necessarily applicable to all chemicals. Finally, the POD was based on ingestion of methamphetamine as a pharmaceutical in a sustained-release form, whereas the occupational exposure scenario pertains to inhalation spread out over a longer duration. Because of the potential differences in systemic absorption from the two routes—including the absence of the first-pass effect with inhalation exposures, which would have allowed for some pre-systemic hepatic metabolism via the ingestion route—linear adjustment might also not be appropriate. Despite these limitations, the interim value might be cautiously applied until a more robust OEL is derived. A more detailed examination of the pharmacokinetics of methamphetamine could be completed to further modify the proposed OEL, if exposures were found to approach the interim OEL.

4.0 CONCLUSION

The need to identify the most appropriate OEL from a range of values presents a challenge for the occupational hygiene practitioner; however, application of a systematic

framework can be helpful in guiding the process. The framework presented in this paper can be tailored to the needs of various organizations, and is sufficiently flexible to support risk management decisions in both OEL-rich and OEL-poor situations. However, evaluating existing OELs is often difficult because most OEL-deriving organizations do not publish details on the decisions underlying the determination of these values. To help occupational hygienists in the application of OELs, increased transparency by OEL-deriving organizations is highly recommended.

Although in-depth understanding of the toxicological and epidemiological basis for OEL derivation is not necessary to apply the framework, it will be of greatest benefit to occupational hygienists with at least a basic familiarity with OEL derivation processes. Occupational hygienists without this background might benefit from collaboration with other hygienists or toxicologists to gain the experience required to evaluate the risk science basis of OELs. However, a less in-depth application of the framework can still be useful even if time is lacking or if a hygienist is less proficient with the epidemiological and toxicological basis of OELs. For example, the framework might be used to evaluate the relevance of eligible OELs, including the steps involving the identification of existing values, comparison of these values with the predefined use scenarios, and comparisons of regulatory OELs to non-mandatory values. In many cases, the OELs remaining after the assessment of relevance and comparison of mandatory and non-mandatory values might be similar, which could eliminate the need to select one OEL among the final candidates after this initial evaluation; this scenario will be presented in the next chapter.

REFERENCES

1. **Deveau M., C.-P. Chen, G. Johanson, D. Krewski, A. Maier, K. J. Niven, et al.:** The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection. *J Occup Environ Hyg*. 12(Suppl. 1):S127–144 (2015).

2. **Schenk L., S. O. Hansson, C. Rudén, and M. Gilek:** Occupational exposure limits: a comparative study. *Regul. Toxicol. Pharmacol.* 50(2):261-270 (2008).

3. **Schenk L.:** Comparison of data used for setting occupational exposure limits. *Int. J. Occup. Environ. Health* 16(3):249-262 (2010).

4. **Deveau M., A. Maier, and D. Krewski:** Application of a framework for the selection of an appropriate occupational exposure limit for manganese. *Neurotoxicology* 58:249–256 (2017).

5. **Schenk L. and G. Johanson:** Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit. Rev. Toxicol.* 40(9):791–798 (2010).

6. **Laszcz-Davis C., A. Maier, and J. Perkins:** The hierarchy of OELs: A new organizing principle for occupational risk assessment. *The Synergist*: 26–30 (March 2014).

7. **Maier A., R. Sussman, B. Naumann, and R. Roy:** "Characterizing the Impacts of Uncertainty and Scientific Judgment in Exposure Limit Development." Poster presented at the American Industrial Hygiene Conference and Exhibition, Indianapolis, June 16–21, 2012. http://www.tera.org/OARS/posters/OEL%20Uncertainty%20Poster%20-%2011%20x17%20Final.pdf

8. "GESTIS International Limit Values." [Online] Available at: http://limitvalue.ifa.dguv.de/Webform_gw.aspx (Accessed December 16, 2013).

9. **Brandys R. C. and G. M. Brandys:** *Global Occupational Exposure Limits for Over 6,000 Specific Chemicals.*: Occupational and Environmental Health Consulting Services Inc., 2008.

10. "Chemical exposure limits." [Online] Available at: http://www.ilo.org/safework/areasofwork/WCMS_118291/lang--en/index.htm (Accessed May 29, 2017).

11. **Chebekoue S.F. and K. Krishnan:** Derivation of occupational thresholds of toxicological concern for airborne systemically-acting non-carcinogenic organic chemicals. *Toxicol. Sci.* 160(1):47–56 (2015). https://doi.org/10.1093/toxsci/kfx155

12. **Wheeler M.W., R.M. Park, A.J. Bailer, and C. Whittaker:** Historical Context and Recent Advances in Exposure-Response Estimation for Deriving Occupational Exposure Limits. *J Occup Environ Hyg*. 12(Suppl. 1):S7–17 (2015).

13. **Dankovic D.A., B.D. Naumann, A. Maier, M.L. Dourson, and L.S. Levy:** The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. *J Occup Environ Hyg*. 12(Suppl. 1):S55–68 (2015).

14. **American Conference of Governmental Industrial Hygienists (ACGIH):** *Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition: Hexane (N-Hexane).* Cincinnati: American Conference of Governmental Industrial Hygienists, 2001.

15. **National Institute for Occupational Safety and Health (NIOSH):** CDC–NIOSH 1988 OSHA PEL Project Documentation: List by Chemical Name: n-HEXANE. http://www.cdc.gov/niosh/pel88/110-54.html (2011).

16. **Occupational Safety and Health Administration (OSHA):** Chemical Sampling Information: Hexane (n-Hexane). https://www.osha.gov/dts/chemicalsampling/data/CH_245400.html (2017).

17. **European Commission (EC).:** Recommendation from the Scientific Expert Group on Occupational Exposure Limits for n-Hexane. http://ec.europa.eu/social/BlobServlet?docId=6795&langId=en (1995).

18. **DFG:** MAK Value Documentation for Hexane (n-Hexane). In *The MAK Collection for Occupational Health and Safety.* http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics?filter=MAKSmbe11054#MAKSmbe11054 (2000).

19. **Jakubowski M.:** Heksan: Dokumentacjadopuszczalnychwielkościnarażeniazawodowego [Polish; Translated by Google Translate]. *Podstawy i Metody Oceny Środowiska Pracy. http://archiwum.ciop.pl/zasoby/Heksan.pdf* 21(1(47)):December 14, 2014-109–129 (2006).

20. **California Environmental Protection Agency:** Development of a Reference Dose (RfD) for Methamphetamine. http://oehha.ca.gov/media/downloads/crnr/methrfdfinal022609.pdf (2009).

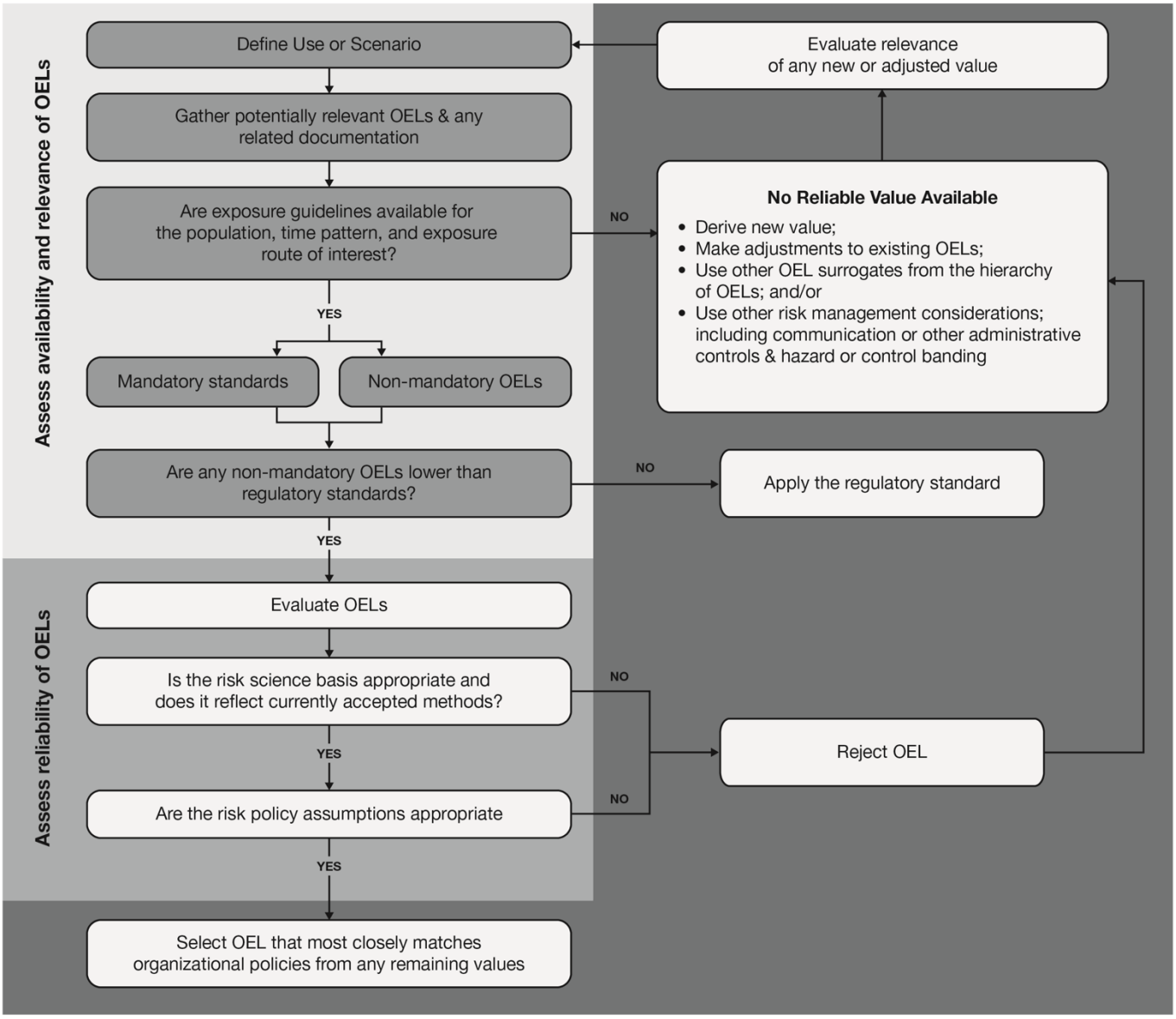


Figure 1. Framework for the selection of an appropriate occupational exposure limit

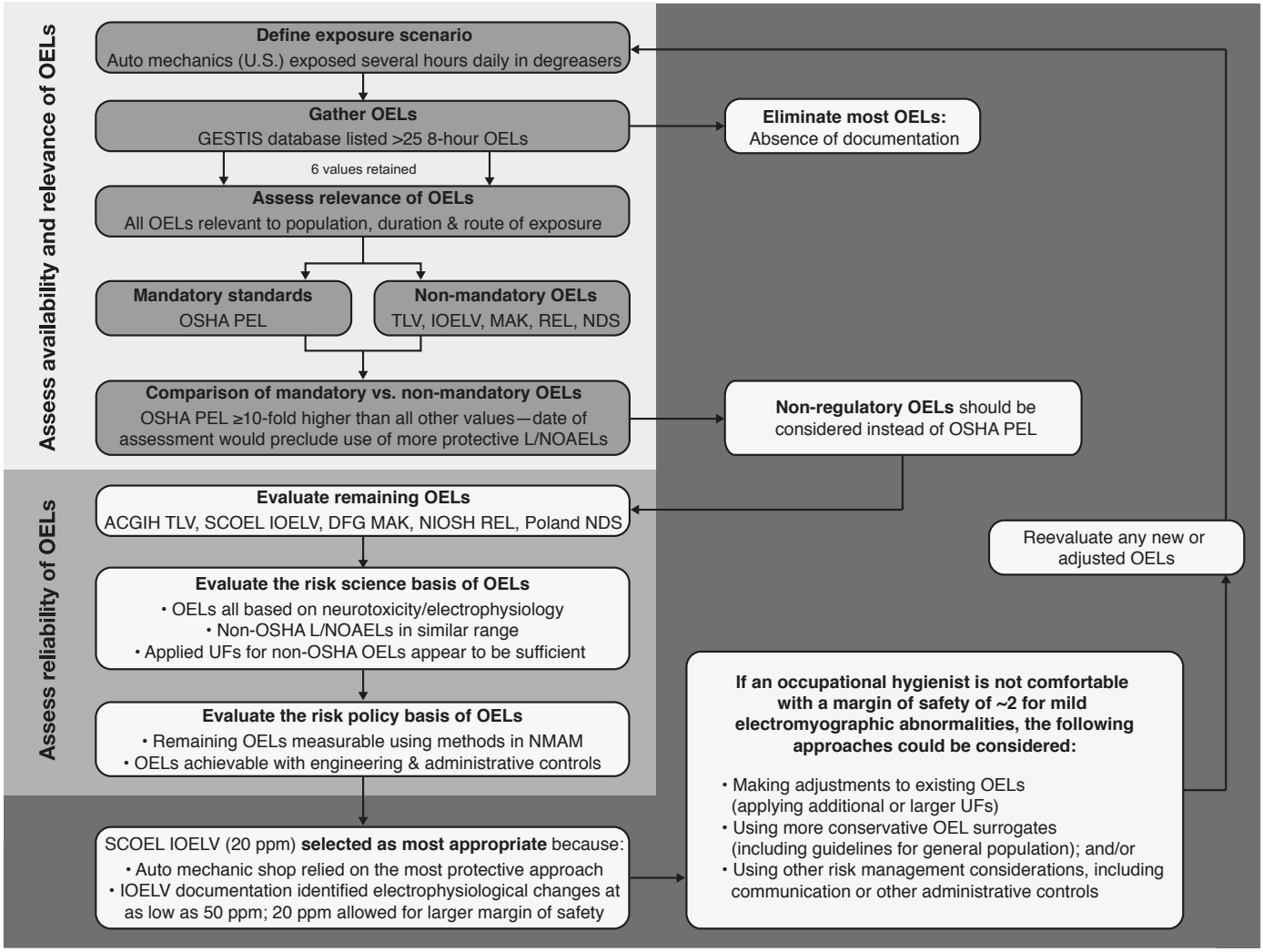


Figure 2. Application of the framework for the selection of an appropriate occupational exposure limit (OEL) to an OEL-rich chemical (n-hexane)

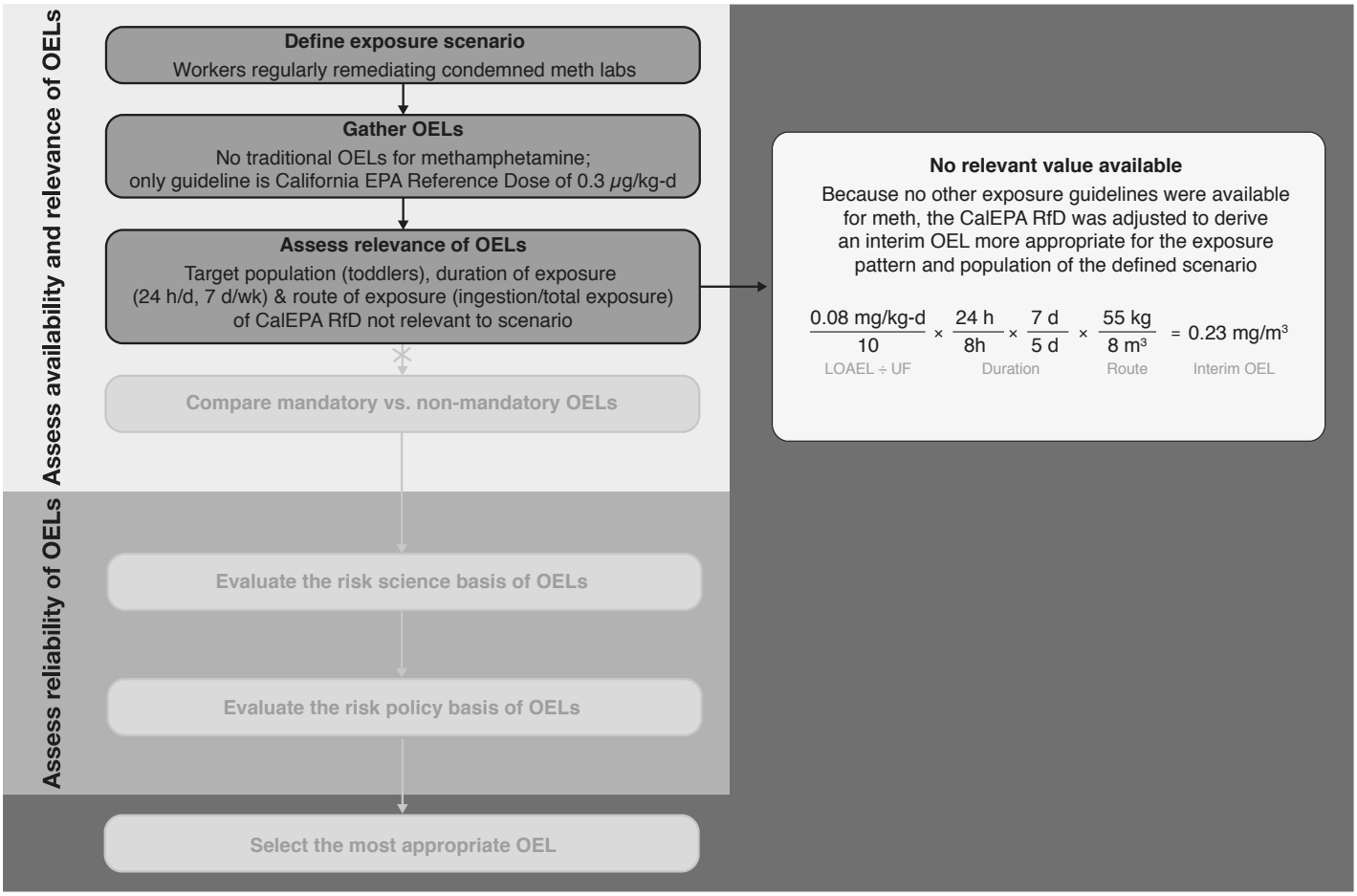


Figure 3. Application of the framework for the selection of an appropriate occupational exposure limit (OEL) to an OEL-poor chemical (methamphetamine)

Table 1. Sources of uncertainty and variability that should be considered when evaluating an OEL

Source of uncertainty or variability	Aspects that should be reflected in uncertainty factors (UFs) for an OEL
Interspecies differences in sensitivity (including uncertainty about relative sensitivity)	Should be considered for any OELs that are based on animal points of departure. Reflects biological differences between humans and other species, and typically assumes that humans could be more sensitive than animals. Lower UFs might be warranted if data strongly support that humans are less sensitive than animals, and is not applied for OELs based on a human point of departure.
Intraspecies uncertainty and variability (including potentially sensitive subpopulations)	Should be considered for OELs based on either animal or human points of departure. Reflects biological variability in chemical sensitivity that can occur among the human population. A higher UF might be applied if a point of departure is based on a small sample size or relatively homogeneous population; larger populations with heterogeneous populations would warrant lower UFs.
Use of a LOAEL instead of a NOAEL	Should be considered for OELs when the point of departure is a LOAEL, because adverse effects were observed at the point of departure, and no dose was without health effects in the key study.
Use of a study of shorter duration	Should be considered for OELs when the point of departure is based on a study duration that is shorter than the study subject's lifetime (or working lifetime). This is to account for the possibility that longer exposures might cause adverse effects at a lower dose.
Gaps in the chemical's literature database	Should be considered if the database for a chemical is incomplete. A complete database is typically considered to have a minimum of long-term toxicity studies in mammalian species, developmental toxicity studies in two different mammalian species, and one multigenerational reproductive study in a mammalian species. In addition, indicators of specific systemic or functional toxicity might require additional specialized studies for a complete database. This aspect is considered because additional data might identify a more sensitive adverse effect and thus a lower point of departure.

Table 2. Overview of steps involved in the derivation of an occupational exposure limit

Step 1: Define the exposure scenario and develop the problem formulation (decide upon the relevant scientific and policy aspects that should be considered and that can guide decision-making processes when deriving the OEL)
Step 2: Use the problem formulation to identify the scientific aspects that need to be addressed when deriving an OEL, gather and summarize relevant scientific literature (e.g. primary literature and existing reviews on toxicology, epidemiology, pharmacokinetics, physicochemical properties)
Step 3: Select a point of departure (e.g. NOAEL, LOAEL, BMD, or risk-based level) based on scientific and policy factors outlined in the problem formulation, such as protectiveness, strength of evidence, and human relevance
Step 4: If necessary, perform extrapolations to increase the relevance of the point of departure
a) Adjust for route of exposure and exposure duration/patterns (using default assumptions on rates of ingestion/inhalation or physiologically based pharmacokinetic [PBPK] or dosimetric models)
b) Perform animal-to-human extrapolations and human variability extrapolations (using uncertainty factors, chemical-specific adjustment factors, or PBPK modeling)
c) Apply any additionally required uncertainty factors (including database deficiency and severity of effect)
Step 5: Submit value for review by external parties

Table 3. Occupational exposure limits (OELs) examined for risk science and risk policy evaluation for n-hexane

OEL	TWA (ppm)	Basis
ACGIH TLV	50	Neurotoxic effects and narcosis, as well eye & mucous membrane irritation. LOAELs of 500 ppm in humans and 250 ppm in animals. UFs were not explicitly stated, but value of 50 if based on human data.
Germany MAK	50	Neurotoxic effects in workers (NOAEL of 58 ppm) and electrophysiological effects in animals (NOAEL of 100 ppm). UF not specified, but 1 for humans and 2 for animal studies.
NIOSH REL	50	Peripheral neuropathy at 210 ppm (LOAEL) & delay in onset of neurological symptoms. UF was not stated, but ~4-fold.
OSHA PEL	500	Based on CNS depression, nausea, headache, narcosis, and eye and throat irritation. Details of OEL derivation could not be obtained (based on 1968 ACGIH TLV documentation).
Poland NDS	20	Value of 100 mg/m^3 (28 ppm) was proposed based on a NOAEL of 204 mg/m^3 (58 ppm) for neurotoxic effect in workers and UF of 2 for individual sensitivity; therefore, the SCOEL of 20 ppm was deemed appropriate.
SCOEL IOELV	20	Electromyographic abnormalities in workers at 70 ppm (LOAEL), supported by various workplace observations of these changes at 50–100 ppm. UF of 2, which was sufficient for mild effects.

Chapter 9 – Application of a Framework for the Selection of an Appropriate Occupational Exposure Limit for Manganese

Michelle Deveau[a], Andrew Maier[b], Daniel Krewski[a]

[a]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada K1N 6N5
[b]Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH, 45267-0056

Reproduced Material

Citation

Deveau, M., Maier, A., Krewski, D. (2017) Application of a framework for the selection of an appropriate occupational exposure limit for manganese. Neurotoxicology. 58:249-256. doi: 10.1016/j.neuro.2016.09.014.

ABSTRACT

Occupational exposure limits (OELs) serve as benchmarks for the interpretation of workplace exposures within a health risk context. Different organizations derive OELs for many chemicals, including manganese. OELs recommended by different organizations can vary quantitatively, which can present a challenge to occupational hygienists or other risk managers that need to select a value for decision-making purposes. In this article, we illustrate the application of a previously-developed OEL selection framework to demonstrate the decisions that would be required to select the most appropriate OEL for various manganese exposure scenarios. The framework helped to identify the need to focus an evaluation on three quantitatively similar values—the ACGIH TLV, SCOEL IOELV, and DFG MAK. These values were compared with regulatory standards and considered for their relevance and reliability. The OEL selection framework was a useful tool in guiding the selection process for manganese OELs.

1. Introduction

Occupational exposure limits (OELs) serve as benchmarks for the interpretation of workplace exposures within a health risk context. These values are derived by many different organizations, including those at the state or provincial and federal levels in the United States and Canada, and at national and regional levels elsewhere around the world. For various reasons, including limited harmonization efforts among organizations, large differences in these OELs can arise (Deveau et al., 2015; Schenk et al., 2008; Schenk, 2010). Many of these differences are related to risk science and risk policy decisions that are made throughout the OEL-derivation process. Although these decisions can vary among OEL-setting organizations, they may be equally acceptable and robust, and selected due to differences in problem formulation or organizational policies on risk assessment (Deveau et al., 2015). Occupational hygienists should explore the basis for differences in OELs prior to deciding which value is most appropriate for a particular workplace scenario.

Deveau et al. (2015) previously developed a framework designed to provide guidance to occupational hygienists who might need to select the most appropriate OEL for their workplaces. This framework guides occupational hygienists through the systematic evaluation of availability, relevance, and reliability of OELs. Steps in the selection process include defining the exposure scenario, gathering existing OELs, assessing the relevance of values to the defined exposure scenario, comparing mandatory standards to non-regulatory values, and analyzing the risk science and risk policy basis of each value. The framework has previously been applied for both OEL-rich scenarios (as for n-hexane, which has many different OELs) and OEL-poor scenarios (as for methamphetamine, which has exposure guidelines for the general population but not for occupational scenarios) (Deveau et al., 2014).

Occupational exposure to manganese can occur in individuals involved in mining and smelting, welding and fabrication, production and use of agricultural products, and production of manganese-containing metals, alloys, steel, chemicals, fireworks, matches, porcelain, pigments, paints, glass, and dry-cell batteries (ACGIH, 2013; SCOEL, 2011). Many different organizations have derived OELs for manganese, which can present difficulties for occupational hygienists or other risk managers who interpret the results of workplace exposure sampling. The objective of this manuscript is to illustrate the use of the framework developed by Deveau et al.

(2015) as a tool for systematically examining the various factors that should be considered when identifying the most appropriate manganese OEL to be applied in a particular occupational exposure scenario.

2. Materials and Methods

A flowchart for the framework used to guide the OEL selection process is given in Figure 1. This framework will be used to demonstrate the types of questions and decisions that will need to be addressed by risk managers in specific exposure circumstances. As no specific exposure scenario is contemplated in this article, no specific recommendation on the most appropriate OEL for manganese is made. The approach outlined for this purpose will nonetheless be useful to other individuals or organizations seeking to identify the most appropriate OEL for manganese under specific exposure circumstances.

The GESTIS International Limit Values database (http://limitvalue.ifa.dguv.de/) and the SER OEL database (https://www.ser.nl/en/oel_database.aspx)—databases developed in Germany and the Netherlands, respectively—were used to facilitate the gathering of OELs from many different organizations. As a follow-up, websites of the health and safety programs for each of the countries identified in the databases were visited, in an attempt to validate the values. The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values® (TLVs®)—OELs that are widely used and are derived by an expert committee of volunteers—were also obtained directly from the organization's publications (ACGIH, 2013; ACGIH, 2016), as these values are not typically found in either of the aforementioned databases. Attempts were made to gather details underlying the derivation of values in the database, wherever this documentation was made readily available by each of these organizations. Although many other countries around the world are likely to have OELs for manganese beyond those listed in the GESTIS and SER databases, the goal was not to identify an exhaustive list of manganese OELs; therefore, no further attempt was made to identify values from other countries.

3. Results

Factors that should be considered in an OEL selection process for manganese are presented in the following subsections that align with the steps of the OEL selection framework. A flowchart providing highlights of the OEL selection process can be found in Figure 2.

3.1 Define exposure scenario

To properly define the exposure scenario, occupational hygienists should consider two key factors—*how* exposures are occurring, and *who* is being exposed. Aspects such as duration and patterns of exposure, particulate size, and target population characteristics should be identified.

To define the nature of manganese exposure in a workplace, information on task schedules should be gathered. As many different work tasks might exist in a workplace, with variability in the nature of the exposure, exposure scenarios should be defined for as many groups of workers as necessary. Information on a task schedule is important because the exposures typically considered in the derivation of traditional OELs (8 hours per day, 5 days per week, over a working lifetime) might not be relevant for all manganese-exposed workers.

Data on expected particulate size in the workplace is also relevant for the definition of the exposure scenario. OELs might vary by particulate fraction, because of differences in particle deposition in the respiratory tract. When particulate fractions have been specified for manganese OELs, the two fractions considered are respirable and inhalable particles. Respirable particulates are small enough to pass through all segments of the respiratory tract (including nose, trachea, and ciliated bronchioles), facilitating their deposition in the alveolar region (Ratney, 2011; Witschi et al., 2008), where manganese can be absorbed into blood and lymph fluids (ATSDR, 2012). According to particle deposition distributions used by ACGIH, the International Standards Organization (ISO), and the European Committee for Standardization (CEN), 50% of particles with an aerodynamic diameter of 4 μm would be expected to be deposited in the alveolar region (with higher deposition for particles with a smaller aerodynamic diameter) (ACGIH, 2016; Ratney, 2011). In contrast, the inhalable fraction may be deposited anywhere in the respiratory tract; 50% of particle deposition is expected to occur at 100 μm (ACGIH, 2016;

Ratney, 2011). The inhalable fraction includes not only the small particulates reaching the alveolar region, but also large particulates that are deposited primarily in the upper airways. Because particulates deposited in the nasopharyngeal and tracheobronchial regions are primarily removed via mucociliary clearance and pass through the gastrointestinal tract (Witschi et al., 2008)—where homeostatic mechanisms result in a low gastrointestinal absorption of manganese (ACGIH, 2016; SCOEL, 2011)—only a smaller fraction of inhaled manganese is systemically absorbed. Industrial processes in the workplace can therefore affect the systemic uptake of manganese—for example, processes in ferroalloy industries can result in larger, inhalable manganese particulates, whereas manganese fumes produced during welding are primarily respirable (ACGIH, 2013). Consideration might be given to co-exposures with other agents that are associated with neurobehavioural effects to assess cumulative risks, as OELs for individual compounds might not be sufficiently protective if workers are exposed to multiple neurotoxic agents. As a default approach, occupational hygienists often address co-exposures to neurotoxicants (or other compounds affecting similar organs through potentially similar modes of action) using additive assumptions. Using this approach, a hazard index can be calculated by dividing the exposure concentration of each similar chemical by its OEL, and then summing each of these ratios (ACGIH, 2016). A hazard index approaching or greater than one will therefore indicate a greater concern for overexposure to neurotoxicants, even if exposure to each individual chemical is below its OEL.

Characteristics of the exposed population should also be noted. OELs might be derived for healthy workers, which might not necessarily reflect all those who are exposed. Some organizations might also consider exposures of non-workers, for purposes of community stewardship or addressing paraoccupational exposures (such as manganese dusts transported home, on clothing or hair). Information about workers with health conditions that might result in greater sensitivity to manganese exposure—including conditions such as iron-deficiency anemia and liver disease, which can increase manganese absorption or decrease manganese excretion, respectively (ATSDR, 2012)—might also be useful; such information on susceptibility factors might not be readily available out of respect for privacy of workers, but the underlying issues could be shared with occupational medicine providers and be considered when assessing the adequacy of an exposure margin for a given population. Strategies for the consideration of

scenario-specific and individual susceptibility factors in occupational risk assessments are described by Lentz et al. (2015).

3.2 Gather OELs

The GESTIS and SER databases identified OELs derived by over 20 different organizations. The ACGIH TLV was not listed in the two databases, but was obtained directly from the TLV booklet (ACGIH, 2016). All OELs that could be verified on the websites for each of the health and safety programs are listed in Table 1. Documentation for each of the identified values was sought wherever this information was readily available; however, because the present exercise is intended to be illustrative rather than definitive, OEL-deriving organizations were not contacted to obtain further information on the basis of their OEL values where documentation was not publicly available.

Although the OEL selection framework (Deveau et al., 2015) also recommends consideration of the need to gather exposure benchmarks other than traditional OELs, these values were not included in the present assessment. Non-traditional OELs that might be included are those that are lower in the hierarchy of OELs—including internal OELs derived by individual companies or industry organizations, which might be based on less robust data, or Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs), which are based on processes that are prescribed under REACH (Laszcz-Davis et al., 2014). The framework also suggests considering gathering exposure limits that are equally robust to OELs, but that have been derived for other purposes, such as for acute exposure scenarios or environmental health exposure guidelines derived for the general population. These additional values might be useful benchmarks in OEL-poor situations, where occupational hygienists are presented with few recent OELs. However, many OELs were obtained for manganese, including several recently derived values; therefore, it was not deemed necessary to consider gathering additional exposure benchmarks.

As demonstrated in Table 1, variability in several different aspects of the OELs can be identified. Some organizations provided different OELs based on particulate size. Many organizations provided OELs for respirable particulates, while others provided values only for inhalable or total particulates, and a few provided guidelines for multiple particle sizes. Values

for respirable particulates were lower than those for inhalable or total particulates, as greater alveolar absorption occurs upon exposure to the smaller-sized particles, resulting in increased systemic absorption. Furthermore, short-term exposure limits (STELs)—typically derived for 15-minute durations—were provided by several organizations, whereas other organizations provided values only for a full-shift duration (8-hour time weighted averages [TWA]).

Derived OELs also varied quantitatively. The lowest values were around 0.02 mg/m^3 for respirable particulates, with other values being one to two orders of magnitude higher.

Although many different OELs existed, most of the values were eliminated from further consideration in the framework, as technical supporting documentation describing the scientific basis for the derivation of the values could not be readily identified. For more detailed application of the framework, organizations can be contacted to request documentation that might be available internally; however, this practice was outside the scope of this exercise. Details on the derivation of retained OELs are presented in Table 2. Despite the absence of documentation for regulatory OELs, these values were also maintained in the evaluation because they are mandatory criteria that must be met (although this does not preclude the application of more stringent criteria). For the present exercise, regulatory values were considered for two different jurisdictions—the United States Occupational Safety and Health Administration Permissible Exposure Limits (OSHA PELs) and the Canadian province of Ontario.

3.3 Assess relevance of OELs

At this stage, the relevance of all retained OELs listed in Table 2 can be assessed by comparing the values against the exposure scenario defined in Section 3.1.

Duration and pattern of exposure described in Section 3.1 should be compared to the OELs listed in Table 2. All OELs considered at this stage were derived based on chronic exposure; therefore, all of the organizations provide values against which an 8-hour time-weighted average (TWA)—or a typical workday—should be compared. However, many workers might only be exposed to manganese for a period of shorter duration on each workday. One concern about the application of an OEL based on an 8-hour TWA to an exposure of a shorter duration is that exposures to high levels of manganese during that period could still result in TWAs that are mathematically below the 8-hour OELs. However, the absence of a short-term

exposure limit for manganese is not in and of itself sufficient reason to eliminate OELs, because occupational hygienists often use excursion limits as a basis for preventing these short-term, high-level exposures. In discussion of excursion limits in the TLV guidelines, ACGIH recommends that exposures occur at levels 3 times higher than the 8-hour TWA should be exceeded for no more than 4 intervals of 15 minutes, which should occur at least an hour apart; furthermore, exposure levels should never exceed 5 times the TLV-TWA (ACGIH, 2016). These recommendations were selected based on statistical analysis of the likelihood of overexposure, and should therefore be modified in workplaces that are highly variable or when warranted on a toxicological basis. For compounds with the potential for adverse effects of an acute nature (such as sensory irritation or acute central nervous system depression) to occur at levels lower than the excursion levels derived for chronic adverse effects, an absence of a STEL that accompanies an 8-hour TWA might be reason to eliminate an OEL. However, for manganese, acute effects are only expected at higher levels. To address acute effects of manganese, the DFG specifically explored irritation—they prescribed an excursion factor of 8 (the maximum value that can be prescribed according to DFG policy (DFG, 2014), with the exception of permanganates, which have an excursion factor of 1) because irritation was not the main effect for the 95th percentile of the population studies by in Roels et al. (1992) at 3.3 mg/m^3 (DFG, 2011). Workers might also be exposed to manganese for durations of longer than 8 hours—for example, if their shifts are 10 or 12 hours, or if they are working overtime. OELs should be adjusted for workers with longer daily durations of exposure. One approach to this is to use linear adjustment methods, such as Brief and Scala (ACGIH, 2016). Risk managers should ensure this approach is appropriate for manganese, from both a pharmacokinetic and pharmacodynamic perspective. (After the non-work recovery period, the body burden of manganese or retained cellular damage from its exposure should be expected to be the same, whether exposure is for 8 hours or longer.) However, the application of the Brief and Scala approach appears to be a conservative approach for adjustment of OELs, compared with other duration adjustment approaches (Verma, 2000). Therefore, this approach can be used to derive a conservative duration-adjusted OEL even if a more complex pharmacokinetic approach is not applied.

The size of particulates to which workers are exposed should also be considered when assessing the relevance of retained OELs. If respirable particles are generated in the workplace,

all OELs that were developed only for inhalable or total particulates should be eliminated, as the values might not be sufficiently protective. If workplace exposure to manganese particulates has been confirmed to only occur via larger, inhalable particles, an organization might consider eliminating values that only provide recommendations for respirable particulates, as these OELs might be lower than needed for the scenario. However, all OELs remaining in Table 2 provide values for both respirable and inhalable fractions; therefore, the values are likely relevant to workplaces with all sizes of manganese-containing particulates. The OELs designed for respirable particulates should also be used as a protective benchmark in situations where particle size fractionation is not performed. In addition, for any special scenarios where nanoscale exposures predominate, the review of the adequacy of OELs would warrant special attention. This is because such particles might have greater bioavailability or enhanced biological reactivity when assessed on an exposure mass basis. In some cases, OELs for nanoscale particles are lower than traditional OELs on a mass basis for the same substance (NIOSH, 2011; Schulte et al., 2010).

The target population defined in Section 3.1 should also be compared against the OELs included in Table 2. OELs are typically derived for healthy workers, and will be relevant for many occupational scenarios. However, organizations with workers who might be more vulnerable to manganese overexposure—including those with iron-deficient anemia and liver disease—might want to further explore whether the OELs are sufficiently protective for these workers, or consider eliminating manganese exposure insofar as possible for these workers. Organizations that are also managing risks to the general population—through paraoccupational exposure, or if developing community stewardship programs—should consider exposure guidelines derived for the broader population (such as those developed by Health Canada, U.S. EPA, IPCS, and others), in addition to OELs.

3.4 Comparison of mandatory vs. non-mandatory OELs

The remaining values should be compared with the appropriate legislative value for the workplace's jurisdiction to ensure regulatory compliance. If the regulatory OEL is not the lowest benchmark, the basis of the value should be compared with those non-regulatory OELs that have not yet been eliminated from the evaluation process.

In the United States, OSHA typically establishes regulatory OELs at the federal level. Many of the PELs were established in the late 1960s and early 1970s, and are recognized by OSHA as being potentially outdated (OSHA, 2015), leading to the release of an annotated PEL list published on the OSHA website that provides alternative OEL resources for chemicals that have an existing PEL. The OSHA PEL for manganese is a ceiling value of 5 mg/m^3 (OSHA, 2015), which is higher than the other identified OELs. Although a detailed description of the basis of the PEL is not available, documentation for the values listed in Table 2 indicated that manganism—an overtly adverse clinical effect—could be observed at concentrations around 5 mg/m^3 (ACGIH, 2013); therefore, consideration of non-mandatory OELs would be recommended for workplaces in the US.

OELs typically fall under provincial jurisdiction in Canada, leading to potentially different regulatory values in each province. A TWA of 0.2 mg/m^3 is included in Ontario legislation (Ontario Ministry of Labour, 2015); however, as no particle size appears to be specified, it is assumed that this is for the concentration of manganese from the total particulate sample. Documentation could not be found to confirm the basis of the OEL; however, ACGIH TLVs are often adopted as regulatory values in Ontario (Ontario Ministry of Labour, 2015). The historical timeline of ACGIH TLVs, as listed in the current TLV documentation for manganese (ACGIH, 2013), indicates that the Ontario value is equivalent to a TLV adopted in 1995. Because this value was updated based on newer science during more recent ACGIH reevaluations, the use of non-regulatory OELs should be considered by workplaces in this jurisdiction.

If a regulatory OEL is lower than or equivalent to the lowest remaining OELs, further application of the framework might not be required. For example, if the current ACGIH TLV—as the lowest identified OEL—is adopted *de facto* within a jurisdiction's legislation, this value must be applied as a minimum, and higher OELs must be eliminated from further consideration. However, as a good practice, the occupational hygienist should still review the basis of the value to ensure that its provided level of protection is judged to be adequate. The later stages of this framework can be used to help guide this evaluation process.

3.5 Evaluate the risk science basis of OELs

To evaluate the risk science basis of the remaining OELs (ACGIH TLV, SCOEL IOELV, and German MAK), the details of how each of the values was derived must be explored. The results of this examination are summarized in Table 2, and described in greater detail below.

3.5.1 Basis of OELs for the respirable particulate fraction

Selection of points of departure (PODs): The selected PODs for all three organizations were based on several studies, which were largely consistent among the organizations included in this assessment. The effects measured at the lowest levels in these studies were primarily subtle neuromotor decrements, including subclinical tremors and slight decrements in psychomotor tests. The POD selected by SCOEL was 0.05 mg/m^3, which was within the range of LOAEC, NOAEC, and BMD values that they had indicated for the grouping of studies used as the basis for the IOELV (see Table 2). ACGIH stated that the LOAECs from their selected key studies fell in the range of 0.03–0.04 mg/m^3. The NOAEC for the German MAK was stated as being 0.04 mg/m^3 (for the geometric mean) to 0.07 mg/m^3 (for the arithmetic mean), with LOAECs falling within this range as well.

Application of uncertainty factors (UFs): SCOEL stated that they did not apply an uncertainty factor in the derivation of the IOELV, as assumptions providing a higher degree of precaution were made throughout the dose–response process; therefore, the value incorporated inherently protective decisions into the point of departure. The applied UFs were not specified by ACGIH or DFG, but can be inferred because both organizations explicitly stated their PODs. The ACGIH indicated that their TLV was 1.5–2 times lower than the specified range of LOAECs, and DFG selected a MAK that was 2–3.5 times lower than the NOAEC (varying depending on whether geometric [GM] or arithmetic mean [AM] is used as the POD).

Integration of weight of evidence: Although none of the organizations appeared to use a formal weight of evidence analysis approach to integrate data, the discussions in the documentation indicate a strong weight of evidence for the effects used as the basis for the POD. The selected PODs for the SCOEL IOELV and ACGIH TLV were obtained from several epidemiology studies indicating effects at similar exposure levels; a single study was used as the basis of the German MAK, but quantitative support was provided by several other studies. The

key studies that were selected included both cross-sectional and longitudinal data, with detailed exposure measurements, for a sufficiently large number of workers.

3.5.2 Basis of OELs for the inhalable particulate fraction

The OELs for inhalable particulates were derived based on empirical evidence for the SCOEL IOELV and German MAK, which are described below. In contrast, the ACGIH did not derive a value based specifically on data for the inhalable fraction; their value is instead adjusted based on its value on estimated ratios of the inhalable:respirable mass in dusts of various workplaces. The ACGIH stated that they considered the ratio of inhalable to respirable fraction to vary from 1:1 (for particulates generated by welding) to 10:1 or higher (for particulates generated in the ferroalloy industry). Using the mid-point of this range of ratios (5:1), the respirable TLV of 0.02 mg/m^3 was considered to be equivalent to an inhalable TLV of 0.1 mg/m^3.

Selection of PODs: The PODs used for the inhalable fraction by SCOEL and DFG were higher than those used for the respirable fraction. The PODs for the inhalable SCOEL IOELV were obtained primarily from the same studies as those used to identify the POD for the respirable fraction, but instead using the dose–response data for the specified inhalable fraction. The adverse effects (subclinical neuromotor changes) used as the basis of the guidelines were the same as for the respirable fraction. For the SCOEL IOELV, the LOAECs ranged from 0.07–1.3 mg/m^3, and the NOAECs ranged from 0.11–0.21 mg/m^3; the selected POD from this range was 0.2 mg/m^3. The German MAK was based on a LOAEC of 0.3 (GM) or 0.75 (AM) mg/m^3 for motor function and cognition from Bast-Petterson et al. (2004).

Application of UFs: As discussed in Section 3.5.1, SCOEL deemed that sufficient protection was already incorporated into decisions made throughout the dose–response analysis process, and therefore did not add an additional composite UF. The margin between the LOAEC and German MAK ranged from 1.5 to 3.75, depending on whether the LOAEC is based on the GM or AM, respectively.

Integration of weight of evidence: The SCOEL IOELV was based on a POD that was selected because it was in line with results from many different studies. Although the LOAEC for the German MAK was obtained from one study, support was provided by other PODs that

were quantitatively similar, including the value from a meta-analysis that included five studies that investigated motor function from manganese in total dust. Further support for the SCOEL and DFG inhalable exposure values is also provided by their quantitative similarity to ACGIH's inhalable value, despite being derived using a different approach.

3.5.3 Conclusion on risk science basis of values

The three remaining OELs were quantitatively similar. The values were each based on several epidemiology studies, which had large sample sizes, observed effects at similar exposure concentrations, and were conducted relatively recently. No particular reasons to reject any of the values were identified in the risk science evaluation of their derivation. However, as risk science—including the availability of data on the health effects of manganese—is constantly evolving, occupational hygienists and other risk managers performing this exercise in the future could also evaluate whether the OELs would be altered by new studies or approaches.

3.6 Evaluate the risk policy basis of OELs

A final step in evaluating OELs is to assess the risk policy basis of the remaining OELs. All of the OELs that remain were health-based values; therefore, economic or technological feasibility considerations were not incorporated into the final values. Even if an OEL-deriving organization has not considered feasibility in the derivation of an OEL, occupational hygienists must identify whether the values can be feasibly applied for conditions relevant to their workplaces.

A major factor to consider at this stage includes analytical capabilities. The quantitation of air concentrations of manganese should be achievable under typical conditions, as the different analytical techniques outlined in the NIOSH Manual of Analytical Methods (NIOSH, 2016) appear to be appropriate for the measurement of much lower manganese levels than those at the OELs. However, if air concentrations cannot be measured well below the OEL using a workplace's current analytical techniques, action may need to be taken to implement more sensitive analytic methods.

Each organization must also identify whether reasonable controls can be implemented to ensure that workers do not become exposed to manganese concentrations that exceed the OEL.

Each work setting differs and has its own challenges; therefore, the evaluation is best performed by individuals that are familiar with specific workplaces. The occupational hygienist can identify whether existing or other available control measures—including elimination or substitution of manganese in workplace processes, isolation of equipment, improved ventilation, dust control measures, training, schedule adjustments, and personal protective equipment—are sufficient to be able to eliminate exposures. To this point, the lowering of OELs for manganese in recent years has generated significant activity in development of new exposure control and protective equipment for various scenarios, including welding and other operations where fine particulates are expected.

If manganese exposures cannot be feasibly measured or controlled in the workplace, occupational hygienists might decide that exposures be kept as low as reasonably achievable, rather than applying a quantitative OEL.

3.7 Select the most appropriate OEL

The values remaining in the database all appear to be equally justifiable, with only slight differences in their derivation. If one particular value needed to be selected over another, some factors that could be used to select the OEL include:

- whether an organization deems the application of an uncertainty factor to be appropriate; whether they believe there is already inherent conservatism in the value; or whether scenario-specific needs might warrant greater uncertain factors;
- whether the occupational hygienist prefers to apply an inhalable particulate value that was derived from empirical data (i.e. SCOEL and DFG inhalable values), or an inhalable value that was derived from extrapolations based on the respirable value (i.e. ACGIH inhalable value);
- the occupational hygienist's level of familiarity with each of the OEL-deriving organizations;
- the date of OEL derivation (with a focus on selecting the most recently derived value); or
- the comparative level of protective assumptions of the OELs (with a focus on selecting the lowest value).

The selection of OELs is preferably based on factors such as reliability and relevance (the earlier bullets in the aforementioned list). However, the latter approaches for selecting an OEL are also justifiable, and might represent a more practical option for occupational hygienists who have little expertise in toxicology or OEL-development processes. The selection process and justification for the specific OEL selected should be documented, and consistent approaches should be used for the selection of OELs for other chemicals.

In some cases, all existing OELs might be rejected. This could occur, for example, if new science indicates that the OELs are outdated, if occupational hygienists are not comfortable with the level of protection offered by the applied uncertainty factors, or if the work schedules are drastically different from those for which the values were derived. If warranted, an occupational hygienist could derive a new interim OEL that incorporates new science or larger uncertainty factors, or that provides a value that is more relevant to a facility's work schedules.

4. Discussion and Conclusion

Using the OEL-selection framework, values derived by three organizations (ACGIH, SCOEL, and DFG) were considered to be relevant for a variety of occupational exposure scenarios, and reliable based on recent scientific approaches. The difference between manganese and other previous case studies (Deveau et al., 2014) is that all manganese OELs that were considered in the process were qualitatively and quantitatively similar; a previous case study (n-hexane) involved the comparison of OELs that had more diverging bases and values. The fact that the OEL values converge, despite being based on slightly different derivation approaches, increases the confidence in these relatively recently derived OEL values for manganese.

The exploration of available OELs can be useful for occupational hygienists, as the process can identify values that are the most relevant and reliable, rather than depending on a value from a single organization. However, the level of existing training for occupational hygienists is variable, and they might have differing levels of experience in toxicology, epidemiology, and OEL derivation. If an occupational hygienist does not have strong expertise in these areas, collaboration with experts in these fields might be warranted.

A key area for improvement that was identified in the application of this framework is the need for increased availability of OEL documentation. The basis of derived values could not be

ascertained for the majority of OELs, as documentation were not readily available. The absence of such data limits occupational hygienists' application of inadequately documented values.

An important factor to be considered by researchers in epidemiology and toxicology is the communication of study results to risk practitioners such as occupational hygienists. The dissemination of new research results that could have potential quantitative impacts on existing OELs can be helpful to ensure that occupational hygienists are aware of the most up-to-date science when evaluating and applying OELs. This is especially important, considering that the update of OELs can be a long process that might be performed infrequently.

Acknowledgements

The authors would like to thank the peer reviewers for their valuable expertise and many helpful comments that served to improve the initial draft of this manuscript. The authors are also grateful for contributions of co-authors on the initial publication of the OEL framework (C. Chen, G. Johanson, K.J. Niven, S. Ripple, P. Schulte, J. Silk, J.H. Urbanus, D.M. Zalk, and R.W. Niemeier). The graphic design work performed by G. Fazio (NIOSH) on Figure 1 is also gratefully acknowledged. D. Krewski is the Natural Sciences and Engineering Research Chair in Risk Science at the University of Ottawa.

References

ACGIH, 2016. 2016 TLVs and BEIs, ACGIH, Cincinnati, OH.

ACGIH, 2013. Manganese, elemental and inorganic compounds, in: 2015 TLVs® and BEIs® – Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices with 7th Edition Documentation. ACGIH, Cincinnati, pp. 1–18.

ATSDR, 2012. Toxicological profile for manganese. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Bast-Pettersen, R., Ellingsen, D.G., Hetland, S.M., Thomassen, Y., 2004. Neuropsychological function in manganese alloy plant workers. Int Arch Occup Environ Health 77, 277–87.

Deveau, M., Krewski D., Maier A., 2014. Development and application of a framework for the selection of an appropriate occupational exposure limit. Presented at the Society for Risk Analysis, Denver, CO, December 2014.

Deveau, M., Chen, C.P., Johanson, G., Krewski, D., Maier, A., Niven, K.J., Ripple, S., Schulte, P., Silk, J., Urbanus, J.H., Zalk, D.M., Niemeier, R.W., 2015. The global landscape of occupational exposure limits—Implementation of harmonization principles to guide limit selection. Journal of Occupational and Environmental Hygiene Suppl. 1, S127–44.

DFG, 2014. Limitation of exposure peaks, in: List of MAK and BAT Values. Wiley-VCH Verlag GmbH & Co., Weinheim, Germany, pp. 207–8. http://dx.doi.org/ 10.1002/9783527682027.ch6.

DFG, 2011. Manganese and its inorganic compounds [MAK value documentation], in: The MAK-Collection for Occupational Health and Safety. Wiley-VCH Verlag GmbH & Co. KGaA. http://dx.doi.org/10.1002/3527600418.mb743996e5014.

Ellingsen, D.G., Konstantinov, R., Bast-Pettersen, R., Merkurjeva, L., Chashchin, M., Thomassen, Y., Chashchin, V., 2008. A neurobehavioral study of current and former welders exposed to manganese. Neurotoxicology 29, 48–59.

Gibbs, J.P., Crump, K.S., Houck, D.P., Warren, P.A., Mosley, W.S., 1999. Focused medical surveillance: A search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust. Neurotoxicology 20, 299–313.

Health Canada, 2010. Human health risk assessment for inhaled manganese. Report No. H128-1/10-600E. Water, Air and Climate Change Bureau, Ottawa, ON.

IFA, 2015. GESTIS international limit values. http://limitvalue.ifa.dguv.de/WebForm_gw2.aspx (accessed September 2015).

Laszcz-Davis, C., Maier A., Perkins J., 2014. The hierarchy of OELs: A new organizing principle for occupational risk assessment. The Synergist March, 26–30.

Lentz, T.J., Dotson, G.S., Williams, P.R.D., Maier, A., Gadagbui, B., Pandalai, S.P., Lamba, A., Hearl, F., Mumtaz, M., 2015. Aggregate exposure and cumulative risk Assessment—Integrating occupational and non-occupational risk factors. Journal of Occupational and Environmental Hygiene Suppl. 1, S112–26.

Lucchini, R., Apostoli, P., Perrone, C., Placidi, D., Albini, E., Migliorati, P., Mergler, D., Sassine, M., Palmi, S., Alessio, L., 1999. Long term exposure to "low levels" of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology 20, 287–98.

Mergler, D., Huel, G., Bowler, R., Iregren, A., Belanger, S., Baldwin, M., Tardif, R., Smargiassi, A., Martin, L., 1994. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res 64, 151–80.

Myers, J.E., Fourie, M., Zogoe, H.A., Naik, I., Theodorou, P., Tassel, H., Daya, A., Thompson, M.L., 2003a. Nervous system effects of occupational manganese exposure on South African manganese mineworkers. Neurotoxicology 24, 649–56.

Myers, J.E., Thompson, M.L., Ramushu, S., Young, T., Jeebhay, M.F., London, L., Esswein, E., Renton, K., Spies, A., Boulle, A., 2003b. The nervous system effects of occupational exposure on workers in a South African manganese smelter. Neurotoxicology 24, 885–94.

NIOSH, 2016. NIOSH manual of analytical methods, 5th edition. Department of Health and Human Services, Cincinnati, OH. http://www.cdc.gov/niosh/nmam/default.html.

NIOSH, 2011. Current intelligence bulletin 63: Occupational exposure to titanium dioxide. Report No. DHHS (NIOSH) Publication No. 2011-160. Centers for Disease Control and Prevention, Department of Health and Human Services, Cincinnati.

Ontario Ministry of Labour, 2015. Current occupational exposure limits for Ontario workplaces required under Regulation 833. http://www.labour.gov.on.ca/english/hs/pubs/oel_table.php (accessed May 2016).

OSHA, 2015. Permissible exposure Limits—Annotated tables. https://www.osha.gov/dsg/annotated-pels/ (accessed May 2016).

Ratney, R.S., 2011. Assessment of exposure to respirable dusts, in: Rose, V.E., Cohrssen, B., Patty, F.A. (Eds.), Patty's Industrial Hygiene. Wiley, Hoboken, N.J., pp. 287–331.

Roels, H.A., Ghyselen, P., Buchet, J.P., Ceulemans, E., Lauwerys, R.R., 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49, 25–34.

Schenk, L., 2010. Comparison of data used for setting occupational exposure limits. Int J Occup Environ Health 16, 249–62.

Schenk, L., Hansson, S.O., Rudén, C., Gilek, M., 2008. Occupational exposure limits: A comparative study. Regul Toxicol Pharmacol 50, 261–70.

Schulte, P.A., Murashov, V., Zumwalde, R., Kuempel, E.D., Geraci, C.L., 2010. Occupational exposure limits for nanomaterials: State of the art. Journal of Nanoparticle Research 12, 1971–87.

SCOEL, 2011. Recommendation from the Scientific Committee on Occupational Exposure Limits for manganese and inorganic manganese compounds. Report No. SCOEL/SUM/127. http://ec.europa.eu/social/BlobServlet?docId=6934&langId=en.

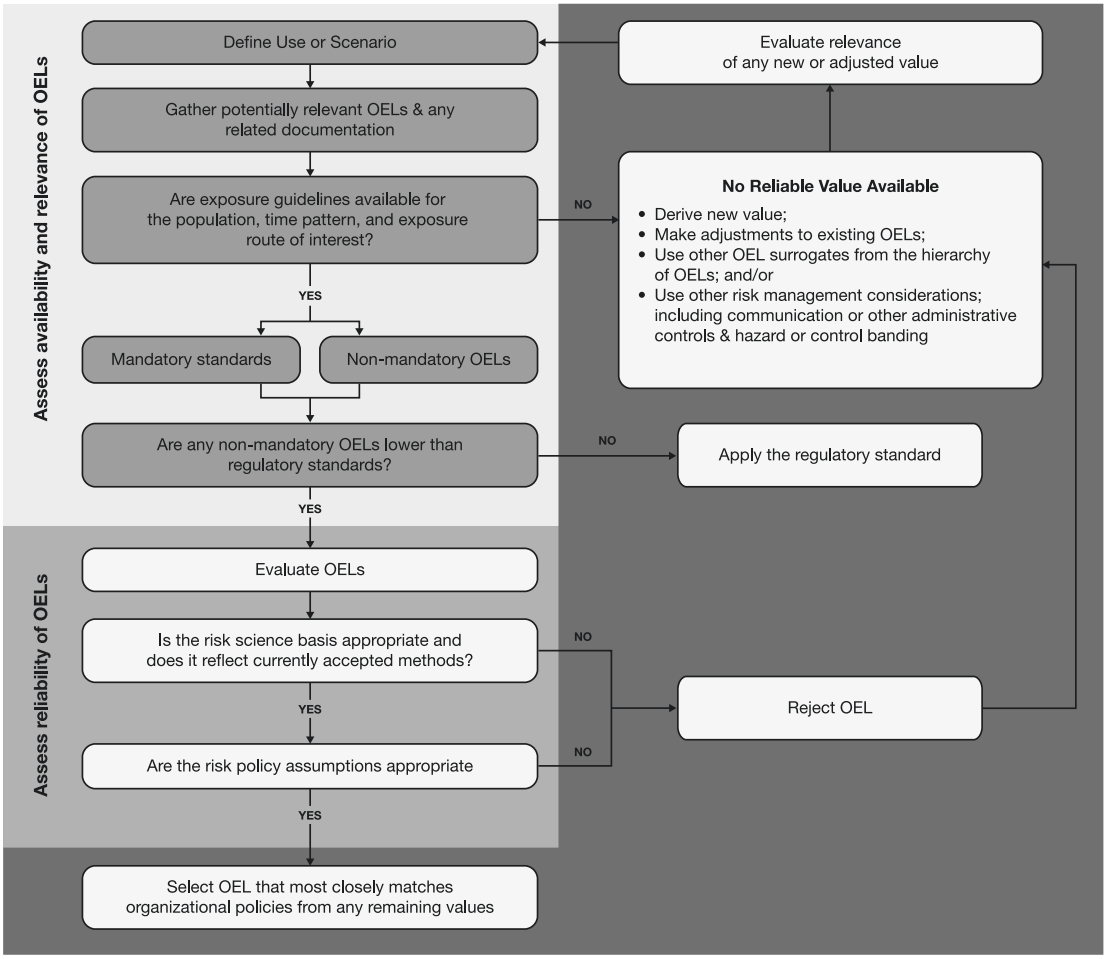
SER, 2015. OEL database. https://www.ser.nl/en/oel_database.aspx (accessed September 2015).

Verma, D.K., 2000. Adjustment of occupational exposure limits for unusual work schedules. AIHAJ-American Industrial Hygiene Association 61, 367–74.

Witschi, H.R., Pinkerton, K.E., Van Winkle, L.S., Last, J.A., 2008. Toxic responses of the respiratory system, in: Klaassen, C.D. (Ed.), Casarett & Doull's Toxicology: The Basic Science of Poisons (7th Edition). McGraw-Hill, New York, pp. 609–50.

Young, T., Myers, J., Thompson, M.L., 2005. The nervous system effects of occupational exposure to manganese–measured as respirable dust–in a South African manganese smelter. Neurotoxicology 26, 993–1000.

Figure 1 – OEL selection framework



Originally published in Deveau et al. (2015)

Figure 2 – Application of the OEL selection framework for manganese

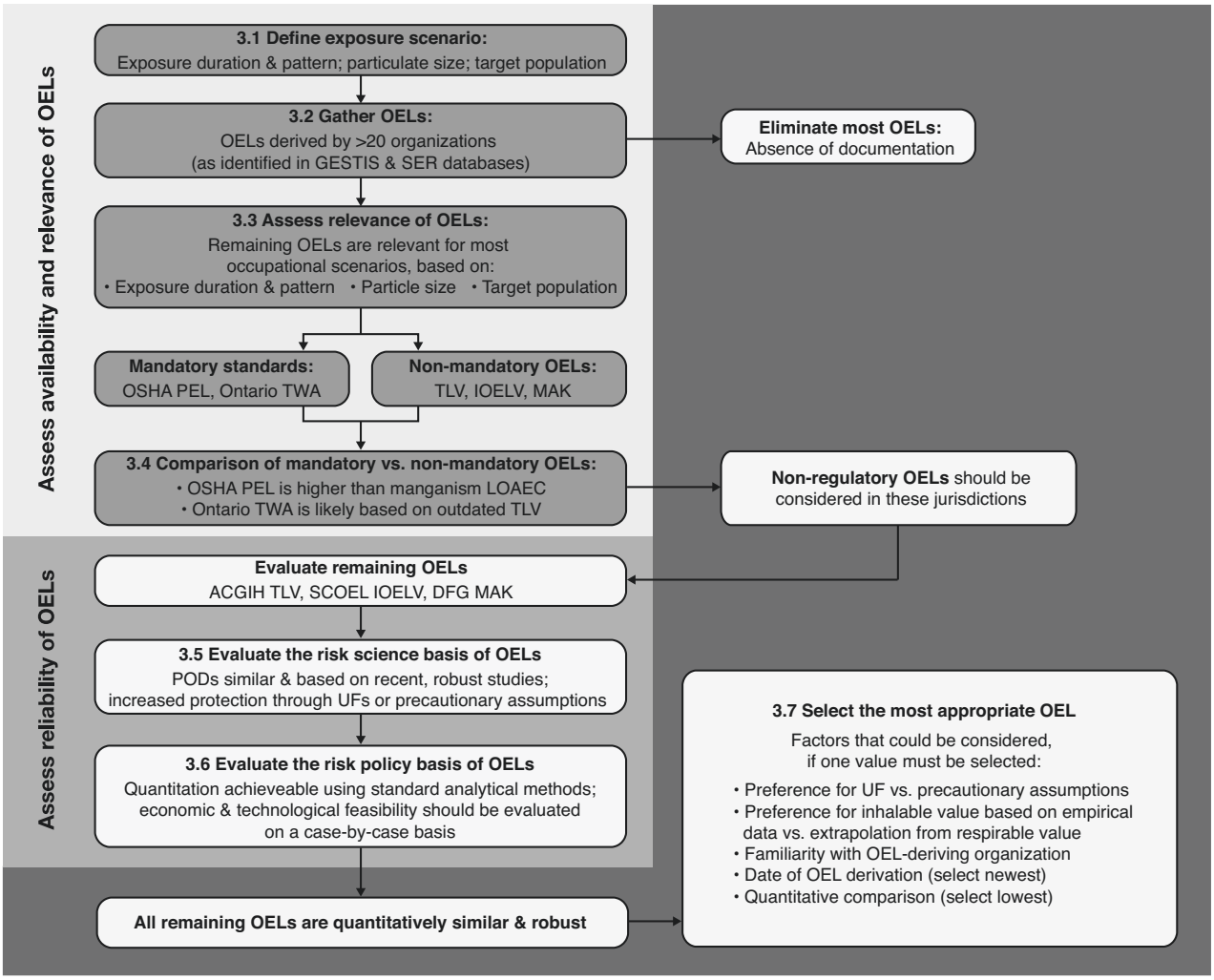


Table 1. Occupational exposure limits identified for manganese

Organization	OEL (mg/m^3)	Organization	OEL (mg/m^3)	Organization	OEL (mg/m^3)
ACGIH (2013)[a]	0.02 (R) 0.1 (I)	France (1983)	1	Spain	0.2
Austria	0.5 (R; TWA) 2 (R; STEL)	Germany (2010)	0.02 (R) 0.2 (I)	Sweden (2005)	0.1 (R) 0.2 (T)
Belgium	0.2 (I)	New Zealand	1 (I; TWA) 3 (I; STEL)	Switzerland	0.5 (I)
Canada – Ontario	0.2	Norway (2007)	0.1 (R) 1 (I)	US – NIOSH	1 (TWA) 3 (STEL)
Canada – Quebec	0.2 (T)	SCOEL (2011)	0.05 (R) 0.2 (I)	US – OSHA	5 (C)
Denmark (2005, 2000)	0.1 (R) 0.2 (T)	Singapore	1 (TWA) 3 (STEL)		

Values obtained from GESTIS (2015); SER (2015); ACGIH (2015a) and modified, where required, based on verification with OEL lists from each of the countries' websites

[a]Date of the derivation of the OEL is presented whenever readily obtainable from the organization

Duration: 8-hour time-weighted average (TWA) unless otherwise specified; STEL = short-term exposure limit (15 minutes); C = ceiling

Particulate size, if indicated: R = respirable; I = inhalable; T = total

Table 2. Basis of occupational exposure limits with readily available documentation

Organization	OEL (mg/m^3)	POD (mg/m^3)	UF	Basis[a]
SCOEL IOELV (2011)	0.05 (R)	0.05	1	LOAECs: 0.01–0.34, NOAECs: 0.04–0.11 & BMD: 0.02 mg/m^3 (Bast-Pettersen et al., 2004; Ellingsen et al., 2008; Gibbs et al., 1999; Health Canada, 2010; Lucchini et al., 1999; Roels et al., 1992; Young et al., 2005)
	0.2 (I)	0.2	1	LOAECs: 0.07–1.3, NOAECs: 0.11–0.21 (Bast-Pettersen et al., 2004; Ellingsen et al., 2008; Gibbs et al., 1999; Myers et al., 2003a; Myers et al., 2003b; Roels et al., 1992)
ACGIH TLV (2013)	0.02 (R)	0.03–0.04	1.5–2	LOAECs from Bast-Petterson et al. (2004), Lucchini et al. (1999), Mergler et al. (1994) and Roels et al. (1992)
	0.1 (I)	See above		Ratio of inhalable:respirable varies from 1:1 (welding) to 10:1 or higher (ferroalloy industry); 5:1 was selected because it represents the midpoint
German (DFG) MAK (2011)	0.02 (R)	0.04 (GM)–0.07 (AM)	2–3.5	NOAEC (Gibbs et al., 1999), with LOAECs for moderate motor & cognition within this range (Bast-Pettersen et al., 2004; Lucchini et al., 1999; Young et al., 2005)
	0.2 (I)	0.3 (GM)–0.75 (AM)	1.5–3.75	LOAEC of 0.3 (GM) or 0.75 (AM) (Bast-Pettersen et al., 2004)

[a]All points of departure are for neurological effects, notably motor function (including tremor) and cognition
Particulate size: R = respirable; I = inhalable
GM = geometric mean; AM = arithmetic mean
LOAEC = lowest observed adverse effect level; NOAEC = no observed adverse effect level; BMD = benchmark dose

Chapter 10 – Synthesis and Reflections

1.0 Introduction

The goal of this conclusion chapter is to discuss the thesis as a whole. Detailed findings, discussions, and weaknesses of individual studies have already been discussed in previous chapters and will not be reiterated. The chapter begins with a summary of the overall thesis, along with a discussion of the major and the contributions of the research towards furthering scientific knowledge in the area of risk science and weaknesses of the research. Subsequently, I describe my reflections on how the thesis fits within the context of population health risk assessment and management. Finally, I use these reflections to provide recommendations for the improvement of regulatory dose–response analyses.

2.0 Summary of thesis

Two distinct but inter-related sections of the thesis were developed to explore and address differences in science–policy or risk–policy decisions taken in the dose–response assessment process. Part one of the thesis explores the outputs of these dose–response decisions in different environments and the factors that can influence decision-making, whereas part two focuses on providing guidance to risk managers who use risk assessment outputs that are affected by these varying decisions.

In part one, variability in the incorporation of chemical- and scenario-specific data in dose–response assessments was investigated. The focus of inquiry was on dose–response applications of physiological modelling, which was explored in peer-reviewed scientific publications (Chapter 2) and regulatory reports (Chapter 3). Overall, many similarities between scientific peer-reviewed literature and regulatory reports were observed with respect to the evolution of physiological models in dose–response analysis. Some of the similarities included the timing, quantity, and annual frequency of publications, and the predominance of use of models for assessment of chemicals in the general environment and by US scientists or organizations. These observations contradict the commonly held view that uptake of physiological modelling was delayed in regulatory organizations when compared with the broader scientific community, and suggest that a key factor in the low dose–response use of physiological modelling—compared with the overall production of physiological models—may

be an absence of data. However, although a lack of data may impact the use of physiological models in regulatory dose–response analyses, additional factors likely affect their incorporation, as differences among—and even within—regulatory organizations were noted in the timing, frequency, and manner of physiological model application. As a culmination of Part I of the thesis, Chapter 4 demonstrates that although regulatory risk assessors most commonly identified the availability of data as a major factor that impacted their ability to incorporate chemical- and scenario-specific data into dose–response assessments, various other internal and external contextual factors were either barriers or facilitators to their adoption of increasingly data-informed approaches. Interconnected internal contextual factors—namely management support, time and financial resources, and training—often required risk assessors to do more with less time. As a result, organizations with less flexibility in deadlines, fewer resources, and less experience with physiological modelling could rely on dose–response analyses published in scientific literature or by other regulatory organizations rather than performing an entirely new analysis. However, using such approaches is reliant on availability of appropriate data. As noted in Chapter 2, only a small subset of available physiological models was used for dose–response modelling in the scientific literature. Therefore, a recommendation common to Chapters 2, 3, and 4 was to nurture relationships between modellers and risk assessors, to ensure that data is not only available, but is also presented in manner that meets the needs of regulatory risk assessments.

Part II focused on the interplay between dose–response assessment and risk management, specifically on how different dose–response analysis decisions can present risk managers with diverse risk values, one of which they must select for decision-making. The latter section of the thesis concentrated on occupational exposure limits (OELs), as presented in Chapter 5, partially because a large proportion of regularly-used OELs (American Conference of Governmental Industrial Hygienists [ACGIH] Threshold Limit Values® [TLVs®]) are older evaluations, and may be based on approaches that might not be considered as protective as if they had been derived using current scientific standards. The different levels of protectiveness incorporated in the values may warrant risk management actions at varying exposure levels relative to the OEL. As a result, we developed a tool for risk managers, such as occupational hygienists, which guides the analysis of available OELs, to allow for evaluation of robustness

and protectiveness of values, as well as the selection of the most appropriate value for a given situation. The foundation for the framework, the tool itself, and demonstrations of its application were presented in the thesis in Chapters 6 to 9. After reviewing the approaches that can be used in the derivation of OELs in Chapter 6, Chapter 7 began with an analysis of reasons for variability in OELs, along with a discussion on harmonization of OELs among organizations. In the absence of harmonization, and with many organizations deriving OELs using different approaches or in different risk contexts, variability in the derived values is often observed. Chapter 7 also described the framework developed to provide guidance to occupational hygienists on the evaluation of the reliability and relevance of OELs, and subsequent selection of the most appropriate OEL. The application of the OEL selection framework was demonstrated in Chapters 8 and 9, for a data-rich compound (n-hexane), a data-poor compound (methamphetamine), and one additional compound (manganese).

The thesis contributes to knowledge in the areas of environmental and occupational health risk assessment. It is the first in-depth exploration of when, how, and by whom physiological modelling has been used specifically for dose–response analyses. Results of the explorations identified many similarities in the overall evolution of physiological modelling in the scientific literature and in regulatory reports, which has never previously been reported. Moreover, it presents the first quantitative comparisons of differences in use of physiological models among regulatory risk assessment programs. Although previous discussions of the factors hindering physiological model uptake tended to focus on scientific or technical limitations, this thesis presents the first attempt to conceptualize the barriers and facilitators and concentrate primarily on the regulatory context. Finally, the thesis presents original guidance for risk managers in the form of a tool that can be used to evaluate differences in decisions in various OELs, particularly with respect to relevance and reliability.

The major weakness in the overall thesis is that, due to resource limitations, the exploration of incorporation of chemical- and scenario-specific data in dose–response assessments was limited to physiological modelling. Evolution of other increasingly data-informed approaches potentially followed different trajectories. As seen in Chapter 5, physiological modelling had the earliest applications and was the most commonly-used of the approaches in a subset of regulatory organizations. However, because physiological modelling

was more commonly used than other approaches, it allowed for a more in-depth analysis of differences in applications among regulatory organizations. Moreover, the survey described in Chapter 4 asked participants about their experience with all of the initially considered approaches, and although data availability might vary among the approaches, contextual barriers and facilitators are likely more universal.

One additional weakness when considering Part I collectively is that the research and regulatory initiatives are presented as being distinct, whereas in reality there is more overlap. This distinction occurred in the development of databases in Chapters 2 and 3, due primarily to the need to use different methods to gather the databases. However, although the literature applications of physiological models are presented separately from regulatory applications, many of the publications in the literature database were developed by regulatory organizations. One reason for this is that regulatory organizations often include research programs, which can explore the development and application of physiological models to evaluate their utility for regulatory applications. Furthermore, government funding is also provided for many of these applications even when performed by academic researchers. As such, future work will involve combining the two developed databases and analyzing them collectively. The major differences in search strategies required for the two databases, and limitations presented by handsearching of regulatory documents, point to the potential need for regulatory risk assessments to be indexed in literature databases.

3.0 Reflections on collective thesis findings in the context of population health

The examinations and discussions in this thesis primarily centred around dose–response assessment, which is only one small component of population health risk assessment. To appreciate the implications of sum of the parts of this thesis, it is imperative to consider the findings within the bigger picture of population health risk assessment and management. This discussion is guided conceptually by the NexGen framework (1) presented in Chapter 1, and is informed not only by my thesis results, but also incorporates broader learning from classes, seminars and conferences I've attended, and conversations I've had with other risk assessors throughout my tenure as a PhD student.

3.1 Problem formulation as a driver for protectiveness versus predictiveness

Problem formulation establishes the basis of the risk assessment process, and sets out the general philosophy that influences science–policy and risk–policy decisions that are taken throughout the risk assessment process. As presented throughout the thesis, these science–policy and risk–policy decisions can vary among risk assessment programs, even when presented with the same data, which can result in different exposure guidelines or other dose–response outputs. This section will discuss how both the risk context and suite of decision-making options can influence the need to incorporation of chemical- and scenario-specific data, particularly in the context of the continuum from presumed protective to biologically-based predictive presented in Chapters 1 and 2.

The nature of the risk assessment and decision-making options can have a large impact on the value of applying physiological models. The need for precise risk estimates might not be as important for screening assessments or margin of exposure approaches, if large margins of safety are calculated between exposure estimates and dose–response assessments based on presumably conservative default assumptions. More narrow margins of safety could prompt the need to investigate the use of chemical-specific approaches rather than default assumptions. This approach would be consistent with the use of a tiered process, with more refined approaches being reserved as required at higher tiers (2-4) and the Risk21 principle of "enough precision to make a decision" (5, 6). Likewise, the need for a more refined risk assessment can be an important consideration in the development of an exposure guideline or limit, such as a drinking water guideline or occupational exposure limit. In some cases, slight differences in exposure limits might warrant different control measures (or degrees thereof), with different costs associated with large-scale application of these measures. The degree to which incrementally lower exposure guidelines impact the relative costs of control measures might therefore also need to be considered in the problem formulation process.

Risk context can influence the location along the continuum of presumed protectiveness to biologically-based predictiveness where a dose–response assessment will fall, which can affect the approaches that are used and other decisions that may be taken. Lipscomb (7) presents examples at either end of the spectrum. The example of a risk assessment at the protective end of the spectrum is Reference Dose (RfD) values used to derive drinking water guidelines, which are

biased towards conservatism, to control exposures to drinking water concentrations in which there is a high confidence that they will protect against potential harm. One trade-off with developing values based on conservative assumptions is that they cannot be reliably used to quantify the predicted adverse impacts of particular exposures on human health. In situations where risk managers may require more refined estimates of risk, such as to quantify the magnitude of adverse health effects from an uncontrolled emergency spill situation[3], dose–response assessments will be more useful if they fall closer to the predictive end of the spectrum. Additional examples of regulatory context where protective dose–response assessments are insufficient are for the development of regulatory impact analyses and cost–benefit analyses, as predictive data are required to make appropriate conclusions.

It should be noted that the assumption that default approaches are more conservative than the chemical-specific extrapolations is not always true. A preliminary analysis of the dose–response applications of physiological models in the scientific literature, which used the database presented in Chapter 3, found that at least 15% of publications produced risk assessment outputs that were more conservative than default approaches[4]. Certain characteristics of a chemical can indicate whether humans exposed at low doses might be more sensitive than the animal models in potential key studies; for example, direct-acting chemicals for which the parent compound is the toxic moiety (8), or chemicals for which the toxic moiety is a reactive intermediate from a saturable process (8, 9). For these chemicals, there is an increasing need for the incorporation of chemical-specific data, as default approaches might not be sufficiently protective of human populations; therefore, using increasingly data-informed approaches is presumably more readily embraced by public health organizations and their stakeholders. Indeed, Bhat et al. (10) identified that dose–response assessments frequently continued to use default uncertainty factors if chemical-specific adjustment factors would result in higher risk outputs. The remainder of the

[3] Interestingly, Lipscomb (7) specifically gave the example of acute exposure guideline level (AEGL) values and their three-tiered effect severity system; however, analysis of the development of AEGLs identified that physiological models were primarily incorporated non-quantitatively, by supporting the removal of components of uncertainty factors.

[4] Results were not presented in this thesis; future work will compile all dose–response uses of physiological models from the two databases generated in Chapters 3 and 4, and perform further explorations of the approaches used when applying the models and their impact on risk assessment outcomes.

discussion therefore focuses on scenarios where incorporation of increasingly data-informed approaches results in less conservative dose–response analyses.

Although it is often assumed that lower risk values are more protective of human health than higher risk values, this is not necessarily always true. For example, minimal additional health benefits might be conferred from increasingly lower risk values beyond a certain point. Applying additional resources to reduce exposures in cases when it would result in only marginal improvements in health could be considered to be a suboptimal use of resources. However, this law of diminishing returns might not be applicable to all chemicals (11), notably for chemicals presumed to act by a non-threshold mode of action (for example, mutagens, respiratory effects of certain air pollutants, or the neurotoxic effects of lead in children). For these chemicals, incrementally lower exposure guidelines might be expected to result in corresponding increases in health benefits; therefore, the use of conservative default approaches might be preferred.

The goal, then, for the use of increasingly data-informed approaches in dose–response assessments designed to protect the health of the public is to find an appropriate balance between protectiveness and predictiveness, where we are unlikely to underestimate risk, while still reducing overestimation of risk. US EPA's RfD can be used as an example of this. As discussed above, Lipscomb (7) presented the RfD as an example of a value on the protective end of the protective–predictive continuum. However, as noted in Chapter 3, many RfD values incorporate increasingly data-informed approaches such as physiological modelling, after careful evaluation of available models, or development of new models. The incorporation of chemical- and scenario-specific data is therefore not necessarily antithetical to a protective approach, depending on the decisions made in the use of such data. As posited by Finkel (12), plausible conservatism is an approach that can be used by regulatory agencies to refine risk assessments when chemical-specific data are available and reliable, wherein incorporation of the data and models still uses decisions in the process that tend towards protective or conservative. For example, data used in the risk assessment should represent 95th percentile estimates of variability or uncertainty, rather than central tendencies. However, as distributional data and probabilistic approaches are only minimally incorporated into regulatory dose–response assessments, these decisions around whether an option is protective enough are often value-laden, resulting in diverse decisions by different organizations.

3.2 Dose–response assessment within the NexGen framework

As discussed above, regulatory risk assessments would ideally incorporate more chemical- and scenario-specific data in dose–response analyses, but in a manner that incorporates conservative decisions. One approach to producing dose–response analyses that are both protective and predictive is to ensure that uncertainty and variability are accounted for when incorporating chemical- and scenario-specific data. Another aspect of this is to ensure transparency in the dose–response assessment process, particularly regarding uncertainty, so that risk managers can more clearly identify the balance between protectiveness and predictiveness of risk values. These topics will be discussed in this section.

One preliminary observation that was noted when compiling databases of dose–response applications of physiological models in regulatory publications and the broader scientific literature is that the models were not used to their full potential to reflect human variability. This observation was not discussed in the earlier chapters, as more detailed analyses of the dose–response methods and results will be performed on the full database in future work. However, fewer than half of included publications from peer reviewed journals explored human variability to some degree. Although similar quantitative estimates were not performed on regulatory assessments, it was noted that regulatory use of physiological models was heavily focused on interspecies extrapolations, and inclusion of human variability was not common. As a result, it is recommended that regulatory organizations, and the scientific community as a whole, further explore use of the models in quantifying intraspecies differences.

The NexGen framework presents health determinants and interactions—specifically, the interaction between biological and genetic, environmental and occupational, and social and behavioural determinants—as a foundation of risk assessment; however, efforts to address human variability in dose–response analyses have largely ignored the social and behavioural determinants. Greater consideration should be given to ensuring that all aspects of uncertainty and variability are incorporated in dose–response assessments, so that analyses of variability represent the true distribution of risk factors in the population. In both the scientific literature and regulatory risk assessments, discussions of human variability tend to be limited to biological and genetic factors such as age, pharmacokinetic capacity, and physiological parameters. Social determinants of health potentially present a large impact on human variability, but have rarely

been explored in dose–response analysis. Although various manuscripts have encouraged the incorporation of social determinants of health as non-chemical stressors into cumulative risk assessments (4, 13-20), little progress has been made specifically related to the dose–response component of cumulative risk assessments. Research, primarily in the form of epidemiological studies, has begun to demonstrate the impact of the combination of environmental chemicals and social determinants on adverse health outcomes (15, 21-31). However, in screening the broader scientific literature for inclusion (as presented in the methods of Chapter 3), only one example was identified of an attempt to incorporate social determinants of health into the dose–response component of a cumulative risk assessment. In the publication, a physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos incorporated various adverse outcomes associated with socioeconomic status, focusing on nutritional status impacts on chlorpyrifos dosimetry and acetylcholinesterase inhibition (32). To further the incorporation of social determinants of health in dose–response assessments, a first step could be to compile the different elements of social determinants that could impact dose–response factors and human variability, and identify what data currently exist to allow for quantification of these factors. The identified data gaps could subsequently be used to guide future research. Increased interdisciplinarity is likely required to perform these initial steps, as researchers in social determinants can guide identification of factors that might impact dose–response, and clinicians can help to identify quantitative extremes of physiological processes.

The availability of data on the impact of social determinants on human variability and their cumulative effects with chemical exposures could improve with the advancement of toxicity testing. Chiu et al. (33) proposed a framework for using toxicogenomics and systems biology to evaluate the impact of susceptibility and sensitivity factors—including social determinants of health—on chemically-induced perturbations associated with human disease, evolving to disease-driven, rather than the current stressor-drive, assessment processes. However, as more data become available, we will need to be mindful that the social context is much larger than what can be represented in the laboratory. Although the adverse impacts of social determinants of health can be expressed as biological outcomes, which may impact recovery from toxic insult, social determinants must be thought of more broadly than their biological manifestations, as their negative social consequences can be much farther reaching

than biological impact alone. Moreover, population health considers not only the health of individuals added together; instead, the health of a population is also dependent on the connections between individuals and the health of the community as a whole, which is greater than the sum of its parts (34).

Another important central aspect of the NexGen framework is ensuring that risk assessments are sufficiently informative for risk managers and other stakeholders. To ensure informativeness, there is a need to be more transparent about what the outputs of dose–response assessment represent, particularly in the context of protectiveness vs. predictivity. This involves more clearly representing default assumptions as science–policy decisions—such decisions may be warranted and justified, but problems can arise if they are instead presented as limitations in science-based approaches rather than a preference for a more conservative value.

An additional approach to transparency and informativeness is presenting more details on how alternative decisions would impact dose–response outputs. As uncertainties in physiological models (e.g., in model structure, parameters, and their impact on model outputs) can be evaluated quantitatively (35), evaluations of the resulting implications on the dose–response assessment should be documented in risk assessments incorporating physiological modeling. This could be addressed by increasing the consideration of decision and uncertainty analysis in dose–response assessments, which as noted in Chapter 5 is very limited at present. Although quantitative uncertainty analyses cannot be performed as easily when default approaches are used, risk assessors could still qualitatively discuss whether alternative decisions would have increased or decreased risk estimates.

3.3 Risk management implications of dose–response assessment output

Dose–response analyses do not improve the health of populations until their outputs are used to identify risk management actions. The outputs of dose–response assessment are used to identify the need for—along with the immediacy, magnitude, and complexity of—measures to reduce risks of chemical exposures. The higher a population's exposure is above a risk value, the greater the resource requirements are to mitigate the risks of exposures. Consequently, it could be argued that using an approach that is overly conservative could present excessive resource requirements to implement risk management measures. This section discusses two concepts

resulting from the interplay of dose–response and risk management: the relative importance of any risk value versus a more refined risk value, and the costs borne by different groups from the use of more protective versus more predictive approaches.

Without any risk values for particular compounds, it becomes difficult to make evidence-based decisions on the need for risk management action. As discussed in Chapter 7, exposure guidelines exist for only a small fraction of chemicals in commerce. Greater incorporation of chemical- and scenario-specific data is more resource-intensive than the use of conservative approaches; therefore, using protective default assumptions can result in protection from a broader array of chemicals than overreliance on dose–response refinement. As a result, *any* protective value can be more important than the one that incorporates the "best science." These values can help to guide the setting of relative priorities for risk management among different chemicals and populations. Further, populations with the highest exposures to chemicals will potentially have exposures well above any risk values, even those that are more refined; therefore, incorporation of chemical- and scenario-specific data will not benefit the most highly exposed populations if it results in delays in risk management actions due to longer risk assessment timelines. As higher exposures often occur in communities of lower socioeconomic status (17), which could result in biological vulnerabilities as described in the previous section, refinements that reflect the majority of the population but potentially not the most highly exposed further amplify problems in delaying risk management action for the purpose of achieving more predictive dose–response assessments.

When considering who bears the broader costs of the decisions to use—or not use—increasingly data-informed approaches, we must consider three sources of costs: inaction, insufficient action, and excessive action. As discussed above, if the incorporation of chemical- and scenario-specific data in dose–response assessments causes a delay in derivation—or reduced availability—of risk values, the costs of inaction are primarily borne by the public or workers, particularly in communities with higher exposures. Insufficient action can result if risk managers are using dose–response outputs that are underprotective. This can occur either if increasingly data-informed approaches are based on data that inadequately represents the broader population, or if the incorporation of chemical- and scenario-specific data is not performed when

it would result in more conservative risk values than the default approach. In both of these cases, the public and workers bear the burden of insufficiently protective risk values.

Identifying who bears the costs of excessive action is a more complex task. As discussed above, there may be a law of diminishing returns for some—but not all—chemicals, in which the cost of incremental reduction of exposures below a certain point may not result in correspondingly equivalent gains in health benefits. In cases where these extra costs are incurred by industry, with more stringent requirements for protection of the public and workers, it could be argued that this should be considered the cost of doing business. However, these costs could be passed on to workers and consumers, if offset by laying off workers, relocating workplaces to areas with less stringent requirements, or increasing the price of goods and services. In other situations, risk management actions are performed by governments; examples of this can include the treatment of drinking water or cleanup of contaminated sites that fall under governmental purview. In such cases, resource allocation is required due to finite financial and time resources. It has been argued that one potential benefit to using less conservative but more predictive dose–response approaches is that resources that would otherwise be spent on reducing exposure to a chemical to a lower level without corresponding increased benefit could be reallocated to areas of greater health concern (36). This could include protection from a greater number of chemicals, implementation of risk management measures in more communities, or distribution of funds to social programs that could broadly impact health through the improvement of social determinants of health. However, it is also possible that the additional resources are distributed to areas that provide no benefit to health.

Another factor complicating the discussion on the costs of excessive action is the consideration of whether the costs are worthwhile. Judgement of whether actions taken are "sufficiently" or "excessively" protective is value-laden, and will depend on the audience. As posited by Finkel (12), the public would generally prefer to err on the side of caution, even if risk management action is associated with increased economic costs. As the role of governments is to serve the public, there may be value in incorporating more conservative assumptions, even if associated with greater costs.

4.0 Changing perspectives

In the decade since I began my PhD, some of the focus of toxicology and risk assessment has evolved. Two larger initiatives in North America, Tox21 and Risk21, have involved collaborations from scientists from different sectors and organizations, with a goal of advancing toxicity testing and risk science to meet 21st century needs. As such, toxicity testing has focused more on high throughput *in vitro* approaches and pathway analysis. In response, risk assessment is increasingly exploring more high throughput approaches, such as the use of high throughput toxicokinetic (HTTK) modelling to interpret *in vitro* points of departure, and the use of tiering to reduce efforts to the extent that there is "enough precision to make a decision." These factors may present mindful justifications for the tendency towards a decline in the use of physiological modelling in dose–response assessments, as presented in Chapters 2 and 3.

My own thoughts on the usefulness of incorporation of chemical- and scenario-specific data in dose–response analysis have also evolved over the decade that it took me to complete my research. The change in my outlook has been informed not only by the evolving science, but also through what I have learned over time—from the culmination of PhD coursework that focused heavily on the social determinants of health, my own research results, insightful seminars and conferences, and experiences in performing regulatory risk assessments. My former view was that if the data were available to use increasingly data-informed approaches, then it was our responsibility as risk assessors to incorporate it into our evaluations, in the name of using "better science" and obtaining more precise reflections of risk. Using that focus, the internal and external contextual barriers would be the largest contributors to not incorporating available chemical- and scenario-specific data.

However, my evolved perspective on increasingly data-informed approaches is that just because we *can* incorporate more data doesn't mean that we always *should* do so. From the problem formulation aspect of this, our risk assessments should be fit-for-purpose; therefore, there is not always a need for a more refined analysis. From the population health perspective, we must ensure that the use of such approaches will benefit the populations we seek to protect. Consequently, the incorporation of chemical- and scenario-specific data in dose–response assessments should occur in a thoughtful and judicious manner. In my opinion, this would involve using the following principles.

- Identify who would bear the costs of using the approaches, and focus on using the approaches when the benefits are expected to outweigh the costs for the general public.
- Ensure that the approaches are always used when the incorporation of chemical- or scenario-specific data would be expected to result in more protective risk values. However, even if resulting values are less conservative, they can still balance incorporation of data with protectiveness using the approaches described in subsequent bullets.
- Use the ethos of "plausible conservatism," erring on the side of reasonably supportable conservatism in all decisions and inputs in the analyses.
- Be more transparent in the presentation of dose–response analyses. Clearly explain each decision that was made, alternative decisions that could have been made, along with the impact of each decision on the final risk values. Identify the proportion of the population expected to be represented by each decision; if statistical data cannot be used to present the percentiles, provide a narrative description. Consider presenting the range of risk values that could have been derived if alternative decisions had been made. Be transparent about which decisions are policy-based and which are based in science.
- Focus on improving expressions of uncertainty and variability. If we can more clearly represent uncertainty and variability from a mathematical perspective, differences of opinion about dose–response outputs that are based on value judgements might become more transparent.
- Place more focus on the outliers of distributional curves. This does not mean ignoring the rest of the population, but when risk assessments are designed to be protective of the 95th percentile—and it is not clear if that is even the case in all dose–response analyses—we need to better consider who falls in the unprotected 5th percentile. This is particularly important if vulnerabilities coincide and those less protected people are also more highly exposed to environmental stressors, which is plausible given that factors providing lower resilience to these

individuals on a biological basis might also be associated with them living or working in locations that make them more highly exposed.

- Maximize efficiency and minimize delays that are caused by using the approaches, by incorporating existing published assessments, categorical approaches, or generic models that require only minor inputs of readily-available chemical property data, and increasing harmonization and collaboration among programs.

In conclusion, risk assessment and the development of risk values is only one small component of population health risk management. When performing dose–response analyses, we need to ensure that what we produce is sufficiently protective of and useful for the public and workers. As a potentially larger problem is that certain at-risk communities are exposed well above safe levels of chemicals, refining a risk value so that it is more precise is not likely going to help improve the health of these communities. Rather, risk values that are sufficiently protective, transparent, and available for a broader range of chemicals can provide a stronger basis for risk management interventions in at-risk communities.

REFERENCES

1. Krewski D, Westphal M, Andersen ME, Paoli GM, Chiu WA, Al-Zoughool M, et al. A framework for the next generation of risk science. Environmental Health Perspectives. 2014;122(8):796-805.

2. IPCS. Assessment of Combined Exposure to Multiple Chemicals: Report of a WHO/IPCS International Workshop. 2009. Report No.: IPCS Harmonization Project Document No. 7.

3. Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Van Raaij M, Vickers C. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regulatory Toxicology and Pharmacology. 2011;60(2):S1-S14.

4. Zeise L, Bois FY, Chiu WA, Hattis D, Rusyn I, Guyton KZ. Addressing human variability in next-generation human health risk assessments of environmental chemicals. Environmental Health Perspectives. 2013;121(1):23-31.

5. Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, et al. A 21st century roadmap for human health risk assessment. Critical Reviews in Toxicology. 2014;44(sup3):1-5.

6. Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M, et al. Risk assessment in the 21st century: Roadmap and matrix. Critical Reviews in Toxicology. 2014;44(sup3):6-16.

7. Lipscomb JC. Purpose-driven risk assessment. Toxicol Pathol. 2019;47(8):1027-34.

8. Andersen ME, Krishnan K. Physiologically based pharmacokinetics and cancer risk assessment. Environmental Health Perspectives. 1994;102 Suppl 1:103-8.

9. Travis CC, Hattemer-Frey HA. Pharmacokinetics and its application to risk assessment. Saxena, J (Ed) Hazard Assessment of Chemicals, Vol 7 Xiii+340p Hemisphere Publishing Corp: New York, New York, USA; London, England, Uk Illus Isbn 1-56032-024-9; 0 (0) 1990 39-82. 1990.

10. Bhat VS, Meek ME, Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47(9):729-49.

11. Pappin AJ, Mesbah SM, Hakami A, Schott S. Diminishing returns or compounding benefits of air pollution control? The case of NOx and ozone. Environmental science & technology. 2015;49(16):9548-56.

12. NRC. Science and Judgment in Risk Assessment. Washington, DC: National Academies Press; 1994.

13. NRC. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press; 2009.

14. Rider CV, Dourson ML, Hertzberg RC, Mumtaz MM, Price PS, Simmons JE. Incorporating nonchemical stressors into cumulative risk assessments. Toxicological Sciences. 2012;127(1):10-7.

15. Schwartz J, Bellinger D, Glass T. Exploring potential sources of differential vulnerability and susceptibility in risk from environmental hazards to expand the scope of risk assessment. American Journal of Public Health. 2011;101(S1):S94-S101.

16. Linder SH, Sexton K. Conceptual models for cumulative risk assessment. American Journal of Public Health. 2011;101(S1):S74-S81.

17. Sexton K, Linder SH. Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. American Journal of Public Health. 2011;101(S1):S81-S8.

18. Gee GC, Payne-Sturges DC. Environmental health disparities: A framework integrating psychosocial and environmental concepts. Environmental Health Perspectives. 2004;112(17):1645-53.

19. deFur Peter L, Evans Gary W, Hubal Elaine AC, Kyle Amy D, Morello-Frosch Rachel A, Williams David R. Vulnerability as a function of individual and group resources in cumulative risk assessment. Environmental Health Perspectives. 2007;115(5):817-24.

20. Burwell-Naney K, Wilson SM, Whitlock ST, Puett R. Hybrid resiliency-stressor conceptual framework for informing decision support tools and addressing environmental injustice and health inequities. International Journal of Environmental Research and Public Health. 2019;16(8).

21. Mair CA, Cutchin MP, Kristen Peek M. Allostatic load in an environmental riskscape: The role of stressors and gender. Health & Place. 2011;17(4):978-87.

22. Zota AR, Shenassa ED, Morello-Frosch R. Allostatic load amplifies the effect of blood lead levels on elevated blood pressure among middle-aged U.S. adults: a cross-sectional study. Environmental Health. 2013;12(1):64.

23. Evans AM, Rice GE, Teuschler LK, Wright JM. Joint exposure to chemical and nonchemical neurodevelopmental stressors in U.S. women of reproductive age in NHANES International Journal of Environmental Research and Public Health. 2014;11(4).

24. Souza-Talarico JN, Suchecki D, Juster R-P, Plusquellec P, Barbosa Junior F, Bunscheit V, et al. Lead exposure is related to hypercortisolemic profiles and allostatic load in Brazilian older adults. Environmental research. 2017;154:261-8.

25. Thomson EM. Air pollution, stress, and allostatic load: Linking systemic and central nervous system impacts. Journal of Alzheimer's Disease. 2019;69:597-614.

26. Clougherty JE, Shmool JLC, Kubzansky LD. The role of non-chemical stressors in mediating socioeconomic susceptibility to environmental chemicals Current Environmental Health Reports. 2014;1(4):302-13.

27. Morello-Frosch R, Shenassa Edmond D. The environmental “riskscape” and social inequality: Implications for explaining maternal and child health disparities. Environmental Health Perspectives. 2006;114(8):1150-3.

28. Solomon GM, Morello-Frosch R, Zeise L, Faust JB. Cumulative environmental impacts: Science and policy to protect communities. Annu Rev Public Health. 2016;37(1):83-96.

29. Payne-Sturges DC, Scammell MK, Levy JI, Cory-Slechta DA, Symanski E, Carr Shmool JL, et al. Methods for evaluating the combined effects of chemical and nonchemical exposures for cumulative environmental health risk assessment. International Journal of Environmental Research and Public Health. 2018;15(12).

30. Clougherty Jane E, Kubzansky Laura D. A framework for examining social stress and susceptibility to air pollution in respiratory health Environmental Health Perspectives. 2009;117(9):1351-8.

31. Huang H, Wang A, Morello-Frosch R, Lam J, Sirota M, Padula A, et al. Cumulative risk and impact modeling on environmental chemical and social stressors. Current Environmental Health Reports. 2018;5(1):88-99.

32. Wason SC, Smith TJ, Perry MJ, Levy JI. Using physiologically-based pharmacokinetic models to incorporate chemical and non-chemical stressors into cumulative risk assessment: a case study of pesticide exposures. Int J Environ Res Public Health. 2012;9(5):1971-83.

33. Chiu WA, Euling SY, Scott CS, Subramaniam RP. Approaches to advancing quantitative human health risk assessment of environmental chemicals in the post-genomic era. Toxicol Appl Pharmacol. 2013;271(3):309-23.

34. Reidpath DD. Population health. More than the sum of the parts? Journal of Epidemiology and Community Health. 2005;59(10):877.

35. Andersen ME. Toxicokinetic modeling and its applications in chemical risk assessment. Toxicology Letters. 2003;138(1-2):9-27.

36. McClellan RO. A commentary on the NRC report "Science and judgment in risk assessment". Regul Toxicol Pharmacol. 1994;20(3 Pt 2):S142-68.