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CHEMICAL RISK ASSESSMENT AND TRANSLATION TO SOCIO-ECONOMIC ASSESSMENTS - ENVIRONMENTAL WORKING PAPER No. 117

By Professor Weihsueh A. Chiu of Texas A&M University

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Authorised for publication by Simon Upton, Director, Environment Directorate.

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FOREWORD

This paper was prepared by Professor Weihsueh A. Chiu of Texas A&M University for the OECD Workshop on *Socioeconomic Impact Assessment of Chemicals Management* in Helsinki, 6-8 July 2016.

The workshop was organised in co-operation between the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology (Joint Meeting) and Working Party on Integrating Environmental and Economic Policies (WPIEEP), and was hosted by the European Chemicals Agency, with funding contributions from the European Commission, the European Chemicals Agency and the American Chemistry Council.

The paper underwent revision and takes into account feedback received from Delegates during and after the workshop and comments received from the Joint Meeting and WPIEEP by written procedure.

The opinions expressed and the arguments employed are those of the author.

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ABSTRACT

Across OECD member countries, socio-economic analysis is often used to inform public policy decisions regulating the production, use, and disposal of chemicals. Such analyses include characterizing the economic value of changes in human health and environmental outcomes that result from different policy alternatives. A key input, therefore, comes from risk assessments that estimate health and environmental impacts under various scenarios. The most comprehensive socio-economic analyses rely on risk assessments based on strong epidemiologic data, and thus involve well-studied chemicals with well-characterised human exposures. The purpose of this working paper is to review existing chemical risk assessment methods in the context of supporting socio-economic cost-benefit analysis, focusing on more "typical" risk assessments that may not have strong epidemiologic data and/or were not originally designed to support socio-economic analyses. A number of case studies of such "typical" chemical risk assessments were reviewed with respect to their suitability for supporting socio-economic analyses.

In order to be optimal for socio-economic analysis, chemical risk assessments need to include the following key features:

- Exposure assessment that estimates expected or central tendency values, variability in the population, as well as the impacts of risk management alternatives on exposure.
- Hazard identification that makes explicit conclusions as to whether a causal relationship between exposure and effect has been established, and where the endpoints identified are non-overlapping and can be assigned economic values (i.e., monetary benefits from avoidance).
- Dose-response assessment that estimates the functional relationship between exposure level and duration and the expected incidence or severity of effects.

The resulting risk characterisation therefore estimates the change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time, which can then be translated into the monetary benefits from avoided health effects under each alternative.

Most "typical" chemical risk assessments lack a number of the key features needed to support current approaches to socio-economic analysis, particularly in the areas of hazard identification and dose-response. However, a number of recent and ongoing improvements in risk assessment methods and practice provide opportunities to bridge this gap and better support socio-economic analysis, should information be available to apply them, including:

- Providing "central tendency" and population variability estimates in exposure assessments in addition to "reasonable worst case" estimates.
- Using more formal approaches for evaluating the evidence for causation between exposure and specific effects, particularly for non-cancer endpoints and for cases based on animal data.
- Applying probabilistic methodologies to make predictions of dose-response, and its uncertainty and variability, in the human population based on experimental animal data.

Additional progress can be made with further work towards better understanding the relationship between endpoints typically assessed in experimental studies and endpoints that have the potential to be assigned economic values.

Ideally, these approaches would be adopted as part of the standard practices in risk assessments, when information is available, but in the interim, the methods appear well-enough established that "bridging" analyses could be performed to fill the gap. Case studies applying such approaches may be a useful next step to demonstrate feasibility and also to identify opportunities for practical approaches to socio-economic analysis to be applied where only less 'ideal' risk assessments need to be utilised. It is anticipated that the resulting "bridges" from both domains will substantially increase the potential for translation of risk assessments to support socio-economic analysis and together support robust decision-making.

JEL Codes: I18, Q51, Q52, Q53, Q57, Q58.

Keywords: Cost-benefit analysis, risk assessment, environmental policy, causal inference, dose-response, population health, uncertainty and variability.

RÉSUMÉ

Dans les pays membres de l'OCDE, l'analyse socio-économique est souvent utilisée pour étayer les décisions de politique publique régissant la production, l'utilisation et l'élimination des produits chimiques. Ce type d'analyse consiste notamment à caractériser la valeur économique des changements provoqués par les différentes solutions publiques en matière de santé et d'environnement. L'évaluation des risques, qui permet d'estimer les impacts sanitaires et environnementaux selon divers scénarios, constitue donc un élément clé dans ce domaine. Les analyses socio-économiques les plus complètes font appel à des évaluations des risques fondées sur des données épidémiologiques solides et concernent donc des produits chimiques étudiés de manière approfondie et des expositions humaines caractérisées avec précision. Ce document de travail a pour objet d'examiner les méthodes existantes d'évaluation des risques chimiques dans le but d'étayer l'analyse socio-économique coûts-bénéfices, en se concentrant sur des évaluations plus « classiques » des risques, qui ne reposent pas nécessairement sur des données épidémiologiques solides et/ou qui ne sont pas destinées au départ à étayer des analyses socio-économiques. Plusieurs études de cas portant sur des évaluations « classiques » des risques chimiques ont été examinées du point de vue de leur capacité d'étayer des analyses socio-économiques.

Pour une analyse socio-économique optimale, les évaluations des risques chimiques doivent comporter les éléments clés suivants :

- une évaluation de l'exposition qui permet d'estimer la valeur probable ou la tendance centrale, la variabilité dans la population, ainsi que les impacts des diverses solutions possibles de gestion des risques sur l'exposition ;
- une identification des dangers qui permet de dégager des conclusions explicites concernant l'existence éventuelle d'une relation causale entre l'exposition et l'effet, et les situations où les critères d'effet identifiés ne font pas double emploi et peuvent se voir attribuer des valeurs économiques (à savoir les bénéfices monétaires de l'évitement) ;
- une estimation de la relation dose-effet qui permet de quantifier la relation fonctionnelle entre le niveau et la durée d'exposition, ainsi que l'incidence probable ou la gravité des effets.

La caractérisation des risques qui en découle permet donc d'estimer l'évolution de l'incidence et de la gravité de chaque critère d'effet pour chaque scénario (y compris le scénario de référence), en fonction du temps, ce qui peut ensuite être traduit en bénéfices monétaires induits par les effets sanitaires évités dans chacun des scénarios.

La plupart des évaluations « classiques » des risques chimiques sont dépourvues de plusieurs des caractéristiques nécessaires pour étayer les approches actuelles de l'analyse socio-économique, en particulier dans les domaines de l'identification des dangers et de l'estimation de la relation dose-effet. Toutefois, plusieurs améliorations récentes et en cours apportées aux méthodes et pratiques d'évaluation des risques offrent des possibilités de combler cette lacune et de mieux étayer l'analyse socio-économique si des informations sont disponibles pour les mettre en œuvre, notamment en :

- fournissant des estimations de la « tendance centrale » et de la variabilité de la population dans les évaluations de l'exposition, en plus des estimations de l'« exposition raisonnable la plus défavorable » ;
- utilisant des approches plus formelles pour évaluer les éléments de preuve établissant le lien de causalité entre l'exposition et des effets particuliers, notamment pour les critères d'effets non cancérigènes et pour les cas fondés sur des données relatives aux animaux ;
- appliquant des méthodologies probabilistes pour prédire, dans la population humaine, la relation dose-effet ainsi que son incertitude et sa variabilité, à partir de données issues d'animaux de laboratoire.

Des progrès supplémentaires peuvent être réalisés en approfondissant les travaux de façon à mieux cerner la relation entre les critères d'effet habituellement évalués dans les études expérimentales et les critères d'effet auxquels des valeurs économiques peuvent être attribuées.

Dans l'idéal, ces approches devraient être adoptées dans le cadre de pratiques standard d'évaluation des risques, lorsque les informations sont disponibles, mais en attendant que ce soit le cas, les méthodes semblent suffisamment bien éprouvées pour que des analyses établissant des « passerelles » puissent être réalisées pour pallier le manque. Des études de cas mettant en œuvre ce type d'approches pourraient constituer une prochaine étape utile pour démontrer la faisabilité ainsi que pour identifier les possibilités d'appliquer des approches pratiques de l'analyse socio-économique lorsqu'on peut se contenter d'utiliser des évaluations moins « idéales » des risques. Les « passerelles » ainsi jetées entre les deux domaines devraient permettre d'accroître notablement les possibilités de transposer les évaluations des risques pour étayer l'analyse socio-économique et en même temps renforcer la solidité du processus décisionnel.

Codes JEL : I18, Q51, Q52, Q53, Q57, Q58.

Mots-clés : Analyse coûts-bénéfices, évaluation des risques, politique de l'environnement, inférence causale, relation dose-effet, santé des populations, incertitude et variabilité.

CHEMICAL RISK ASSESSMENT AND TRANSLATION TO SOCIO-ECONOMIC ASSESSMENTS

1. Introduction

Public policy decisions regulating the production, use, and disposal of chemicals involves integration of data and information from a number of different sources using numerous different methods. A key component of this process involves risk assessment, defined as follows (WHO/IPCS, 2004):

- A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.
- The risk assessment process includes four steps: hazard identification, hazard characterisation (related term: Dose–response assessment), exposure assessment, and risk characterisation. It is the first component in a risk analysis process.

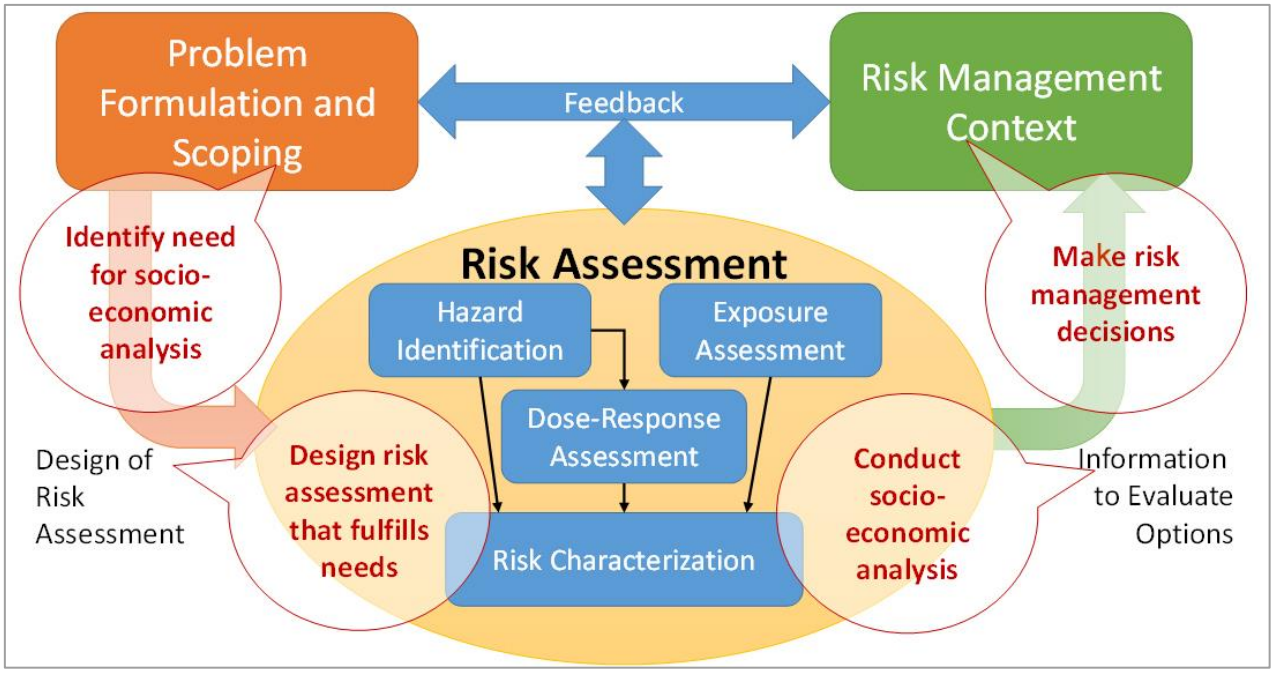
Risk assessments may take on a variety of forms, depending on the risk management problem at hand. As illustrated in Figure 1, risk assessment is informed by a problem formulation and scoping step, as well as the risk management context. Some of the most common risk management decision contexts are as follows:

- **Screening and/or Prioritisation Assessment:** The purpose of a "screening/prioritisation" risk assessment is to identify potential areas for further consideration or analysis. This type of assessment may also be used to prioritise among a set of choices, such as different products, agents, or exposure scenarios or pathways. In some cases, screening and prioritisation is the sole intent for the analysis. In other cases, screening and prioritisation may be conducted early in the risk assessment process, such as during problem formulation or planning and scoping, and may be used to identify areas of where additional data may be needed.
- **"Safety" Assessment**: The purpose of this kind of risk assessment is to determine whether existing or proposed exposure levels are "acceptable." These are typically conducted by deriving a level of exposure associated with a reasonable assurance of "safety" or "de minimis" level of risk for comparison against measured or predicted exposure levels in highly exposed individuals.
- **Population-Level Assessment:** The purpose of this kind of risk assessment is to evaluate the impact of one or more risk management options over an overall population. For instance, it could involve estimating number of cases of an effect in an exposed population, expressed as "X cases per million exposed" or "Y cases in the exposed population." Alternatively, it could involve estimating the change in the population distribution of a biological parameter related to health or environmental impacts, such as a shift in the overall distribution of IQ levels in a human population. In some cases, this type of assessment also represents a more sophisticated approach to "Safety Assessment," where the entire population is evaluated rather than just highly exposed or highly sensitive individuals.

- **Risk-Risk Comparison:** The purpose of this kind of risk assessment is to identify and compare the relative risks of different (alternative) agents that have a similar use function or can fulfil a needed purpose (e.g. use as a fuel additive or solvent) but differ in their toxic properties.

Figure 1. Risk assessment in the context of problem formulation and scoping and risk management

As applied to the need for socio-economic analysis.



Source: Adapted from (NAS, 2009).

Whereas risk assessments focus on calculating the frequency, severity, and likelihood of various health and environmental impacts resulting from particular exposures, risk management decisions take into account many more factors in addition to risk. Where adequate data are available, some of these additional factors can be addressed in socio-economic assessments, which weigh not only the benefits but also the costs of various regulatory actions on human health and the environmental. Specifically, benefit-cost analysis can be viewed as simulating a private market test for efficiency – i.e. for how much money could one "sell" a particular policy given its benefits in terms of improved human health and reduced environmental impacts, and how would the "price" associated with these improvements compare with the "costs" of implementing the policy (e.g. costs of compliance). Socio-economic analysis has been applied to regulatory policy for chemicals management across multiple OECD countries. Air pollution has been by far the most widely applied example of socio-economic analyses (e.g., U.S. EPA (2011c); Ontario Ministry of Energy (2005); OECD (2014); (AEA Technology Environment 2005)). Additional examples of socio-economic analyses are methylmercury and formaldehyde (U.S. EPA, 2005a, 2013).

The key feature of the vast majority of the socio-economic analyses related to chemicals is that they are based largely on epidemiologic data, which means that it is largely well-studied chemicals with wide-spread and well-characterised exposures have been the subject of socio-economic assessments. As such, the risk assessments upon which they are based have a number of common characteristics, including:

- Exposure assessment that estimates expected or central tendency values, as well as the impacts of risk management alternatives on exposure.

- Hazard identification that makes explicit conclusions as to whether a causal relationship between exposure and effect has been established, and where the endpoints identified can be assigned economic values (i.e., monetary benefits from avoidance).
- Dose-response assessment that estimates the functional relationship between exposure level and duration and the expected incidence or severity of effects.
- Risk characterisation that estimates the change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time, which can then be translated into the monetary benefits from avoided health effects under each alternative.

These will be discussed in more detail in Section 2.

In the US and some other OECD countries, socio-economic benefit-cost analysis is required for many regulatory actions, either by policy or by statute. For instance, in the EU, under REACH, socio-economic analyses play an important role in the restriction and authorisation process. In the US, statutes such as the Safe Drinking Water Act as well as executive orders require the consideration of benefits and costs of major regulatory actions. Recently, in a case involving regulation of power plants under the *Clean Air Act*, the US Supreme Court ruled in Michigan v. EPA that economic costs and benefits should be considered even when deciding *whether* to regulate chemicals, not just *how much* to regulate as was previously held. This ruling is part of a continuing trend of greater emphasis on economic analyses in many environmental decisions. Indeed, the US National Academy of Sciences has emphasised the need to "make economics…more central in the analysis" of human health risks from environmental exposures (NAS, 2009).

The purpose of this working paper is to review existing chemical risk assessment methods in the context of supporting socio-economic benefit-cost analysis. Section 2 reviews the general approach to socio-economic benefit-cost analysis, focusing specifically on the information requirements for estimating human health and environmental benefits of a particular regulatory action. Section 3 reviews the general approach to human health and environmental risk assessment for chemicals. Section 4 examines in more detail some typical risk assessments for their applicability to supporting socio-economic analyses. Section 5 summarises a number of key challenges and information gaps in the translation of traditional risk assessments to such analysis. Section 6 concludes with a summary and suggestions for further work.

2. Risk assessment data and information needs for socio-economic cost-benefits analysis

2.1. General approach to supporting socio-economic analyses with risk assessment

Socio-economic analyses are among the key inputs to many policy decisions. As outlined in guidance documents such as those from ECHA (2008); (ECHA, 2011) or the U.S. EPA (2014c), these analyses generally have a number of key components, including the following:

- **Statement of need for policy action** – A clear identification of the problem to be addressed and the justification as to why a policy action can correct the problem.
- **Policy options** – A delineation of the regulatory and/or non-regulatory approaches that will be considered in the analyses. An important component of delineating options is defining the "baseline" to which alternative options will be compared.
- **Benefits analysis** – Assessment of the benefits to society that will result from the various policy options (as compared to baseline), including monetary valuation of reducing risks to human health and the environment.

- **Cost analysis** – Assessment of the costs to society that will be incurred as a result of the various policy options.
- **Comparison of costs and benefits (net benefits)** – Assessment of the economic efficiency of various policy options, taking into account both costs and benefits.

Additional components of socio-economic analyses include cost-effectiveness analysis (e.g. relative cost for a given benefit), economic impact analysis (e.g. effects on employment), and environmental justice analysis (e.g. equity of distribution of benefits or costs).

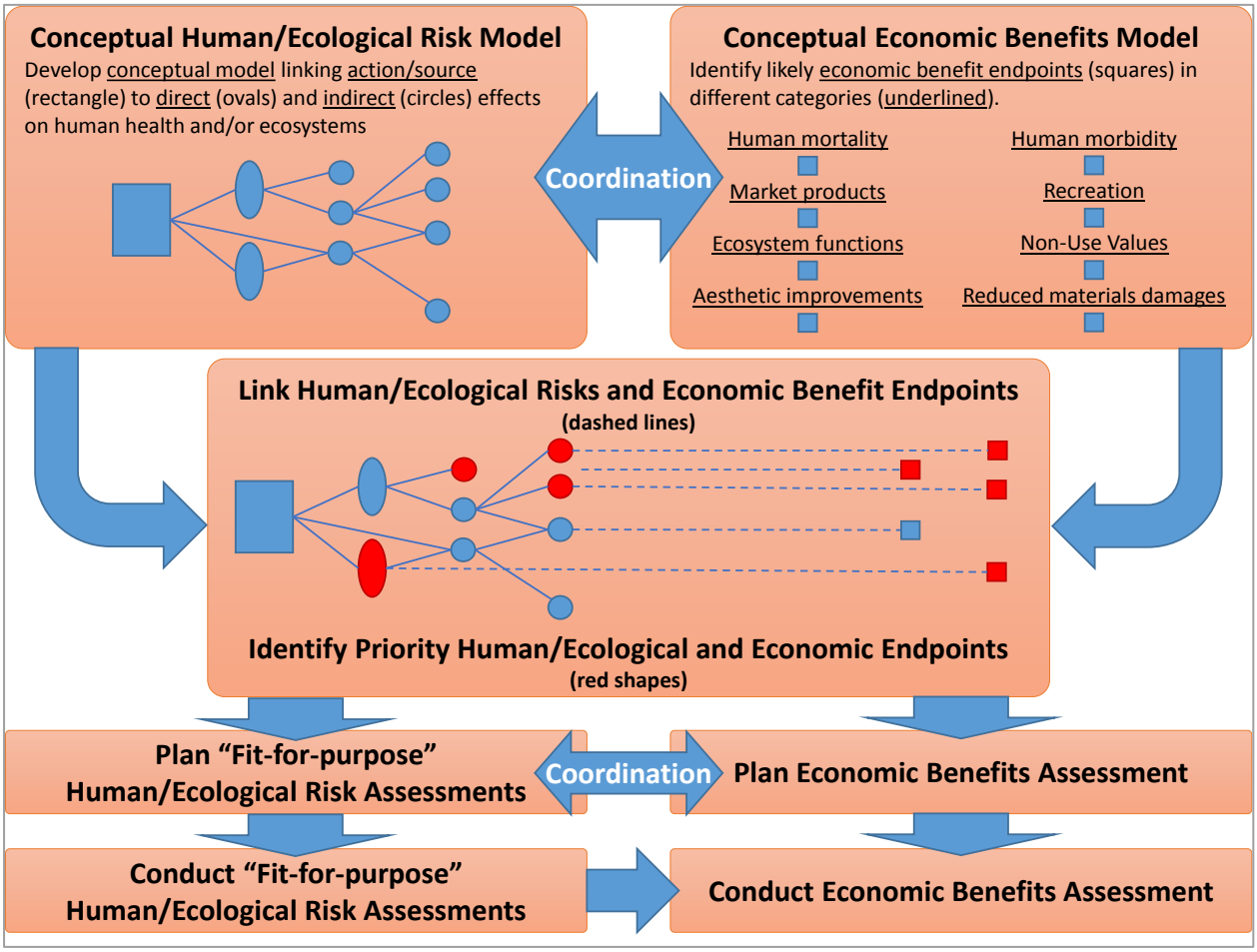
Risk assessment is the main source of data and information for the "benefits analysis" component, and will be the focus of this working paper. The general approach for developing a risk assessment to support economic benefits assessment is shown in Figure 2. A key feature of this approach is the *early* and *coordinated* linkage between the risk assessment endpoints and the economic benefit endpoints in the corresponding conceptual models. Ideally, all the benefits attributable to a particular policy option would be a single monetary value reflecting all effects of a policy, but this is generally not feasible for a variety of reasons. Instead, the general approach is to address each of the "effects" individually, and then aggregate the individual benefits into a sum total (which assumes, of course, that the economic valuation of the individual effects are independent). The general approach to "effect-by-effect" analysis is as follows:

1. Identify benefit categories and effects potentially affected by the policy options being considered. These include:
   a. Improvements in human health (mortality and morbidity).
   b. increasing delivery of ecosystem services[1] (e.g. increased fish harvests, reduced water treatment costs, increased recreation)
   c. Aesthetic improvements (e.g. improved taste or odour of tap water, enhanced visibility)
   d. Reduced material damage (e.g. slower corrosion of steel infrastructure)
2. Quantify changes in the extent, frequency, severity, and timing of effects under different policy options.
3. Estimate the economic value of the anticipated changes, i.e. the monetary value of the private goods and services individuals are willing to trade for anticipated benefits of different policy options.

[1] "Ecosystem services" are defined as the end products of ecological functions that are valued by people Millennium Ecosystem Assessment (2003). Ecosystems and human well-being: A framework for assessment. Washington, DC:Island Press, NAS (2004). Valuing ecosystem services: Toward better environmental decision-making. Washington, DC.

Figure 2. General approach to developing human health and ecological risk assessments

To support economic benefits analysis



Source: Adapted from U.S. EPA (2002, 2014c).

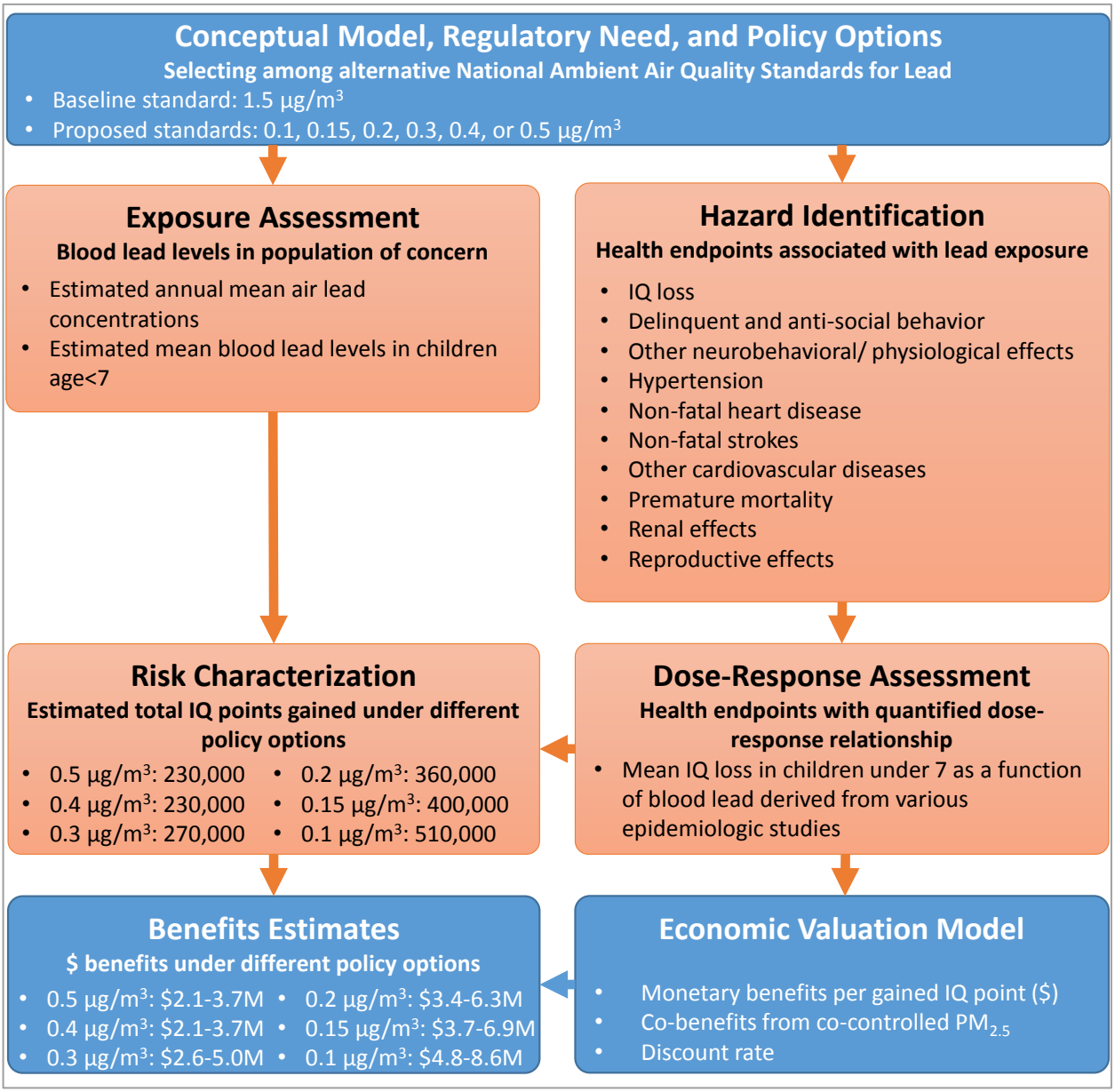
2.2. Examples of risk assessments supporting socio-economic benefits analyses

A prototypical example of how risk assessment supports socio-economic benefits analysis is shown in Figure 3, which summarises the benefits analysis performed by the U.S. Environmental Protection Agency (EPA) for revising the National Ambient Air Quality Standards (NAAQS) for lead. This corresponds to the bottom two boxes from A number of different options as to the revised standard were analysed. The risk assessment portion of the analysis was conducted as follows:

- The hazard identification (which here focused on human health effects) included all endpoints for which there was an association between human health effects and lead exposure.
- The dose-response assessment focused on a single health endpoint – the health impact of blood lead levels on cognitive function in young children as measured by IQ – that had a high confidence, quantified dose-response relationship across a range of exposure levels.
- The exposure assessment focused on young children -- the population for which the dose-response assessment was performed – and the specific regulatory options. Additionally, a conversion was needed between exposure estimates of air concentrations of lead and blood lead levels, which was the dose metric used in the dose-response assessment.

Figure 3. Benefits analysis performed as part of the Regulatory Impact Analysis

For the National Ambient Air Quality Standards for lead



Note: Steps involving Risk Assessment are in the orange boxes.
Source: (U.S. EPA 2008).

- The exposure assessment and dose-response assessments were combined to estimate the increase in IQ that would result from various revised standards for lead concentrations in air. This risk characterisation was based on mean or average estimates, so that the number of IQ points gained was an estimate of the total points across population.

The resulting IQ points gained under the different options were then converted to monetary values estimating the economic benefits that would result from each option.

Additional examples of benefits analyses are summarised in Table 1. These examples all represent risk assessments that were performed in direct support of socio-economic analyses. It should be noted that

because socio-economic effects ideally include all effects of a policy, changes in pollutants other than what is being targeted should also be assessed, such as the "co-benefits" of reducing other pollutants as a result of reducing PM (U.S. EPA 2011c).

Table 1. Examples of risk assessment support to economic benefits analysis

Pollutant and scenario	Risk assessment inputs to benefits analysis	Citation
$PM_{2.5}$ in air	• **Exposure** based on air concentrations for $PM_{2.5}$. • **Hazard and dose-response** based on avoided premature deaths for adults and one for infants as well as avoided morbidity effects for 10 non-fatal endpoints ranging in severity from lower respiratory symptoms to heart attacks, all based on epidemiologic studies. • **Risk characterisation and economic benefits** based on premature death, non-fatal heart attacks, hospital admissions, asthma, respiratory effects, lost work days, and restricted activity.	U.S. EPA (2012b)
Methylmercury in air in US	• **Exposure** based on estimated for maternal hair mercury concentration • **Hazard** based on human neurologic, cardiovascular, genotoxic, and immunotoxic effects, and wildlife neurologic effects. • **Dose-response** based on relationship between maternal hair mercury and childhood IQ in offspring in epidemiologic studies. • **Risk characterisation and economic benefits** based on IQ gains due to reduced mercury exposure.	U.S. EPA (2005a)
Methylmercury in EU	• **Exposure** based on estimated maternal hair mercury concentration • **Hazard and dose-response** based on relationship between maternal hair mercury and childhood IQ in offspring in epidemiologic studies. • **Risk characterisation and economic benefits** based on IQ gains due to eliminating mercury exposure.	Bellanger et al. (2015)
REACH restriction on lead in consumer articles	• **Exposure** based on estimated intake from mouthing behaviour in small children • **Hazard and dose-response** based on relationship between lead intake, blood lead, and IQ • **Risk characterisation and economic benefits** based on avoided losses of IQ due to restricting lead exposure.	(ECHA 2014)
Air pollution from coal-fired power plants in Ontario	• **Exposure** based on air concentrations of multiple air pollutants. • **Hazard and dose-response** based on human health effects of premature death, respiratory effects, cardiovascular effects, restricted activity, and asthma symptoms from epidemiologic data; and environmental effects of soiling of household materials, leaf damage of crops, and greenhouse gas damages. • **Risk characterisation and economic benefits** based on premature death, and from hospital admissions, emergency room visits, and minor illnesses due to identified hazards.	Ontario Ministry of Energy (2005)
Endocrine disruption in EU	• **Exposure** based on levels reported in epidemiologic studies. • **Hazard and dose-response** based on human health effects of IQ loss and associated intellectual disability, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility, and mortality associated with reduced testosterone. • **Risk characterisation and economic benefits** based on cost of illness for each of the health effects.	Trasande et al. (2015)
Formaldehyde standards for composite wood products in US	• **Exposure** based on levels calculated using exposure models and parameters for several thousand different exposure scenarios. • **Hazard and dose-response** based on human health effects of nasopharyngeal cancer (dose-response based on animal data) and eye irritation (dose-response based on human data). Non-monetised benefits include respiratory-related effects, and reduced fertility in women. • **Risk characterisation and economic benefits** based on mortality risk reduction for risk of fatal cancer, cost of illness for risk of non-fatal cancer, and avoiding eye irritation.	U.S. EPA (2013)[2] [proposed]

[2] https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0018-0495

2.3. Specific risk assessment needs of typical socio-economic benefits analyses

These examples illustrate some of the specific risk assessment needs of typical socio-economic analyses.

2.3.1. Exposure assessment

Socio-economic analyses require estimates of emissions, fate and transport, environmental concentrations, and ultimately individual intake or contact rate across the relevant population. These estimates need to be made under the specific policy options being considered, as well as the specified "baseline" condition, so that the *change* in exposure can be estimated. It may also be important to characterise the variability in exposure across the population, particularly if the dose-response relationship is not linear in the range of exposures. Specifically, whereas the mean exposure will correspond to a mean response for a linear dose-response relationship, this will not be the case for a non-linear dose-response and especially if there is a "threshold" below which no effects are assumed to occur (e.g. Bellanger et al., 2015). Additionally, benefits analysis generally involves estimation of mean or expected values, rather than "conservative" or "upper" confidence bounds. Especially for non-linear dose-response relationships, a probabilistic distribution for variability would be preferred so as to more accurately estimate the incidence and/or severity of effects in the population, which would be driven by high-end exposures. Distributions for uncertainty can also be accommodated, and are generally desirable.

2.3.2. Hazard identification

Ideally all the effects potentially related to exposure would be identified. In order for there to be a quantifiable benefit, these effects need to be causally related to exposure. Because causality is often not established with 100% confidence, an alternative would be to provide a probability for the likelihood of a causal relationship (e.g., Trasande et al., 2015). Additionally, it is important for the endpoints chosen to be economically meaningful, so that an individual would be willing to pay for reducing the effect. This criterion does not require that actual monetary valuation exists at the time of the assessment, since given interest in a particular endpoint, studies could be conducted to derive corresponding valuations. Many analyses include "unquantified" benefits due to lack of monetary valuations (e.g., U.S. EPA, 2005a, 2012b). However, if the endpoint is too far removed from an adverse apical effect (e.g. changes in gene expression) so that it may be difficult to conceive of its value, then it may be difficult to be included. Finally, the relationships among different effects and endpoints need to be characterised so that benefits are not "double counted." For instance, reduced blood pressure and reduced stroke are related, since reducing blood pressure also reduces stroke. Thus, stroke would be counted separately only to the extent that there are reductions in stroke that are unrelated to the reductions in blood pressure. This is the reason, for instance, that heart attacks in the analyses of air pollution only include non-fatal events, since fatal heart attacks are already addressed in premature mortality (U.S. EPA, 2012b).

2.3.3. Dose-response assessment

Socio-economic analyses invariably involve comparisons of predictions among different options. Moreover, in some cases, these options involve a continuum rather than just a few discrete options. Therefore, in order to support benefits analysis, the dose-response assessment generally needs to provide the functional relationship between different levels of exposure and effect. In most cases to date, this criterion has been satisfied by use of epidemiologic data at or near the levels of exposure of concern. If the "effect" is "discrete" (e.g. mortality, cancer), then the characterisation of response needs to address the frequency in the population of interest (including possibly sensitive subpopulations), as well as the timing of occurrence. For continuous endpoints (e.g. decreased birth weight), the magnitude or severity of the

effect should also be included. As with exposure assessment, benefits analysis generally requires estimation of mean or expected values for the dose-response relationship rather than "conservative" or "upper" confidence bounds, though probabilistic uncertainty and variability distributions can also be accommodated.

2.3.4. Risk characterisation

Risk characterisation involves the integration of exposure, hazard, and dose-response. In the context of benefits analysis, the purpose of this integration is to estimate the change (relative to baseline) in incidence and severity of each endpoint under each policy, all as a function of time. As with exposure and dose-response assessment, benefits analysis generally requires estimation of expected values for the risk characterisation rather than "conservative" or "upper" confidence bounds, though a probabilistic uncertainty distribution can also be accommodated.

3. General approach for typical chemical risk assessments

There is increasing interest in expanding the role of socio-economic analyses in regulatory decisions and chemical risk management. The next sections will provide a brief overview and examples of more "typical" chemical risk assessments that are not planned or designed specifically with socio-economic analyses in mind, as well as what "gaps" exist between such assessments and the needs for socio-economic analyses.

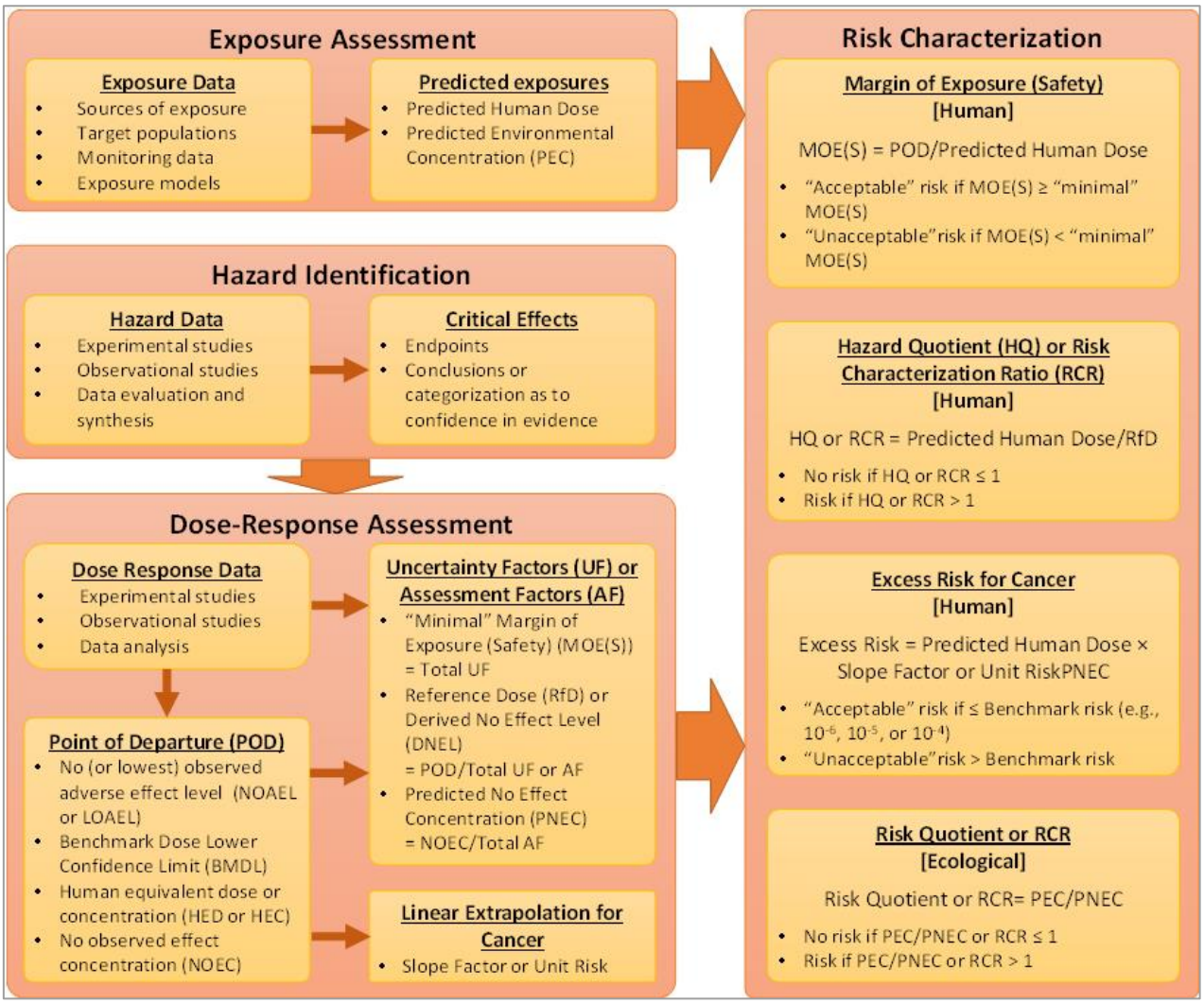
For the vast majority of chemical risk assessments, the decision context is one of screening / prioritisation or "safety assessment," with the general approach illustrated in Figure 4. Because there are many guidance documents across the OECD for chemical risk assessments of this type, each of the components are only briefly summarised below.

3.1. Exposure assessment

Exposure is contact made between a chemical, physical, or biological agent and the outer boundary of an organism (or "receptor"), and is a function of environmental concentration, time, and the receptor's behaviour. Exposure assessment is the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population of receptors exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment. Exposure may be assessed via direct measurement (i.e. at the point-of-contact), scenario evaluation (e.g. by combining fate and transport modelling in the environment and exposure models for contact between the environment and receptors), or exposure reconstruction (e.g. using pharmacokinetic models to estimate exposures from biomonitoring data). The most common approach to exposure assessment is scenario evaluation, in which the pathways of exposure are specified, and then equations are used to estimate the dose contributed by each pathway (see Figure 5). The specific parameters chosen depend on the context of the risk assessment, but may reflect varying levels of "conservatism":

- Central tendency estimate – Goal is to estimate an average or typical intake for a population, usually derived using input parameters that are arithmetic means or medians.
- High-end estimate – Goal is to estimate the intake for the higher-end percentiles (e.g. >90%) of the population, usually derived using a combination of high-end (e.g. 95%-ile) and central-tendency parameters.
- Bounding estimate – Goal is to estimate the highest possible or theoretical upper bound intake, usually derived using predominantly upper bound (e.g. maximum) parameters.

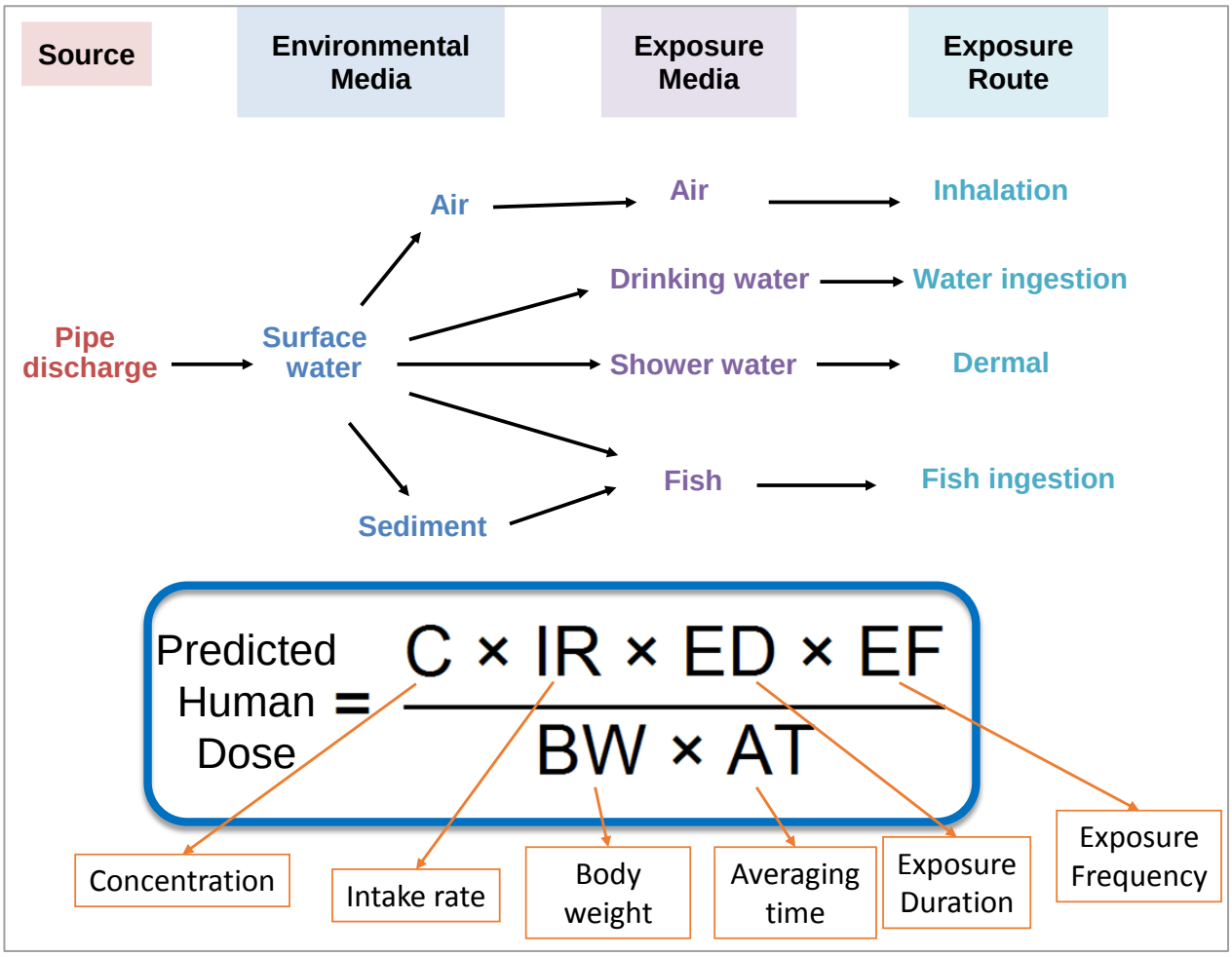
Figure 4. Process for a typical chemical risk assessment



Note: The result of the risk characterisation is a determination of whether the predicted exposures present a human health or ecological risk.

Additionally, it has become more common to conduct exposure assessments in which exposure parameters are each assigned probability distributions reflecting uncertainty, variability, or both, instead of single fixed (or "default") values. These "probabilistic" exposure assessments provide distributions as outputs, so can be used to derive central tendency, high-end exposure, as well as bounding estimates.

Figure 5. Exposure pathways and equations used in typical exposure assessments



Source: Adapted from U.S. EPA Expo-Box online tools: https://www.epa.gov/expobox.

3.2. Hazard identification

Hazard identification is the determination of whether exposure to a particular chemical causes particular effects in humans or ecological species, in terms of increased incidence and/or severity for an endpoint of concern. There are two related questions in this process:

- The first question is simply "what adverse effects have been observed or are anticipated, based on human, laboratory animal, in vitro, and/or chemical property data?" This step involves searching the appropriate scientific literature and identifying pertinent studies, evaluating the quality of those studies in the context of the risk assessment, and extracting the data and information on possible adverse health effects. In most chemical risk assessments, laboratory animal data are the most abundant type of data.
- For each adverse effect, the next question is concluding whether the agent can cause it in humans or organisms in the environment? There are many frameworks for this type of "causal determination" (Hill, 1965; U.S. EPA, 2005b, 2010, 2015; WHO/IARC, 2006). However, in many cases, this step is not "formalised" in that a separate causal determination is not made for each end point.

Recently, the application of systematic review methods has emerged as a recommended approach to hazard identification (NAS, 2011, 2014). Systematic review methods have been widely applied in the clinical medicine arena, where they are used to synthesise bodies of evidence for clinical decisions (Cook et al., 1997; Higgins and Green, 2011). There have been several approaches published that have aimed at adapting these approaches to the hazard identification step in risk assessment (Morgan et al., 2016; NAS, 2011, 2014; Rooney et al., 2016; Woodruff and Sutton, 2011).

Hazard identification usually also includes characterising the toxicokinetic (TK) and toxicodynamic (TD) properties of the agent. Toxicokinetics determines how a compound undergoes absorption, distribution, metabolism, and excretion after exposure, and can be used to identify the specific toxic moiety(ies) (e.g. parent compound or a metabolite). Toxicodynamics is related to the mechanistic events that are intermediate between the initial biological interactions of the toxic moiety(ies) at the target site and the ultimate adverse effect. Both of these can be used to support or dispute the biological plausibility of a causal relationship between exposure and adverse effect. They can also be used to identify specific quantitative issues to be considered in the dose-response assessment step (e.g. interspecies differences, intraspecies variability, dose-response shape). For typical chemical risk assessments, data are often available on TK, but there is usually much less data on TD.

3.3. Dose-response assessment

Dose-response assessment typically takes the results of hazard identification, and for each health effect identified, quantifies the relationship between the magnitude of exposure and magnitude of effect. In general, this is a two-part process:

a) *Dose-response analysis* of an experimental or observational dataset of health effects resulting from chemical exposure (the critical effects and studies would be identified in hazard identification). This usually involves statistical analysis of the dataset, either by pairwise comparisons or through statistical curve-fitting. This analysis is typically aimed at estimating a "point of departure" (POD), which is defined as an exposure level near the lower end of the observed range of effects. Examples of common PODs are in Table 2. Although scientifically, benchmark dose modelling approaches are preferable over the use of NOAELs or LOAELs, in practice many risk assessments still rely on NOAELs or LOAELs.

b) *Extrapolation* (or "inference") as to the potential effects in the target human population. This second part needs to account for differences in characteristics (e.g., species, exposure duration) between the dataset analysed and the human population of interest for risk assessment. In many cases, such as non-cancer endpoints, these extrapolations usually involve application of "uncertainty factors" (see Table 3). For many cancer endpoints, particularly if the mode of action is unknown or is due to mutation (e.g. genotoxic carcinogens), a common approach is to assume a linear dose-response relationship below the POD, which involves extrapolation to lower dose and lower levels of effect (e.g. 1 in a million cancer risks). The output of this part of the analysis is a numerical expression of the dose-response relationship that, when combined with exposure, gives information to characterise risk. Examples are shown in Table 2.

Alternatively, in a "Margin of Exposure" (MOE)-based approach, only the dose-response analysis is performed, and the POD is used to directly compare with exposure. In this case, the considerations related to "extrapolation" (e.g. magnitude of interspecies and intra-species differences) are often discussed as part of the risk characterisation, rather than as part of the dose-response assessment.

There are several more advanced quantitative approaches that can also be incorporated into dose-response assessment, when data is available. These are summarised below, but not described in detailed (representative citations are provided):

- Dosimetric adjustment involves using data or mathematical models to convert the POD in an experimental animal study to a "human equivalent" dose or concentration, such the following:
  - Allometric scaling of oral doses using an exponential power of body weight (U.S. EPA, 2011a).
  - Regional gas or particle deposition factors for inhalation concentration (U.S. EPA, 1994).
  - Physiologically-based pharmacokinetic (PBPK) modelling for deriving equivalent tissue concentrations (U.S. EPA, 2006; WHO/IPCS, 2010).
- Chemical-specific adjustment factors (also known as data-derived extrapolation factors) for Interspecies toxicokinetics (same as dosimetric adjustments, above), interspecies toxicodynamics, intraspecies toxicokinetics (e.g. physiological differences such as GFR, or use of population PBPK models), or intraspecies toxicodynamics (Abdo et al., 2015; U.S. EPA, 2014d; WHO/IPCS, 2005).
- Probabilistic approaches to characterise and propagate uncertainty and/or variability.
  - Probabilistic PBPK models to estimate human variability in internal dose, sometimes also including uncertainty estimation as well (Bois et al., 2010; Chiu et al., 2009).
  - Use of model ensembles or model averaging to characterise uncertainty in dose-response analysis (Shao and Gift, 2013; Wheeler and Bailer, 2013).
  - Replacement of uncertainty factors with probability distributions, thereby deriving a toxicity value with an uncertainty and/or variability distributions (Baird et al., 1996; Chiu and Slob, 2015; Evans et al., 2001; Hattis et al., 2002; Slob and Pieters, 1998; Swartout et al., 1998; WHO/IPCS, 2014).

A key advantage of the recently developed probabilistic dose-response approaches (Chiu and Slob, 2015; WHO/IPCS, 2014) is that the approach makes it possible to estimate the uncertainties in the human dose-response relationship, rather than only "worst-case" estimate of a "safe" human dose, without knowing how "conservative" that value might be (see Annex 1).

Table 2. Typical outputs of dose-response assessments

Outputs of dose-response assessment	Typical Definition	Modeling approach
Points of departure (PODs)		
NOAEL: No Observed Adverse Effect Level	The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control.	Pairwise statistical and/or biological significance
LOAEL: Lo Observed Adverse Effect Level	The lowest exposure level at which there are biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control.	Pairwise statistical and/or biological significance
NOEC: No Observed Effect Concentration	The highest concentration used in a (usually eco-)toxicity test that does not cause a toxic effect that is significantly different from the control.	Pairwise statistical significance
BMD(L) or BMC(L): Benchmark Dose or Concentration (Lower confidence limit)	A dose or concentration of a substance that when ingested produces a predetermined change ("benchmark response") in the response rate of an adverse effect relative to the background response rate of this effect.	Statistically-based curve-fitting
HED(C): Human Equivalent Dose or Concentration	A dose or concentration of a substance in humans is considered "equivalent" to the POD (usually LOAEL, NOAEL, or BMDL) in an experimental animal study. The basis of the equivalence may be empirical (e.g. allometric scaling) or based on toxicologically-relevant internal dose (e.g. PBPK modelling).	Multiple approaches
Toxicity values		
RfD or RfC: Reference Dose or Reference Concentration	An estimate of the dose or concentration of a substance (with uncertainty spanning perhaps an order of magnitude) to which a human population can be exposed (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.	POD (e.g., LOAEL, NOAEL or BMD/C[L]) divided by "default" uncertainty factors
DNEL: Derived No Effect Level	The level of exposure to the substance above which humans should not be exposed.	POD (e.g., LOAEL, NOAEL or BMD/C[L]) divided by "default" assessment factors
PNEC: Predicted No Effect Concentration	The concentration of a substance in any environment below which adverse effects will most likely not occur during long term or short term exposure. The PNEC needs to be determined for each environmental sphere (aquatic, terrestrial, atmospheric, sewage treatment, food chain).	POD (e.g., NOEC) divided by "default" assessment factors
MRL: Minimal Risk Level	An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.	POD (NOAEL, BMD[L], or BMC[L]) divided by "default" uncertainty factors
OSF: Oral Slope Factor	An upper-bound estimate of risk per increment of oral dose that can be used to estimate risk probabilities for different exposure levels.	Linear extrapolation from the BMD(L)
IUR: Inhalation Unit Risk	The upper-bound estimate of risk per increment of air concentration inhalation exposure that can be used to estimate risk probabilities for different exposure levels.	Linear extrapolation from the BMC(L)

Table 3. Typical uncertainty (or assessment) factors

Factor
UF_H– Human variability: Used to fill data gap in absence of chemical-specific data on human variability in susceptibility to toxicity. Also referred to as the "*intraspecies assessment factor*."
UF_A – Animal-to-human extrapolation: Used to fill data gap in absence of human toxicity data and chemical-specific data on interspecies toxicokinetic and/or toxicodynamic differences. Also referred to as the "*interspecies assessment factor*."
UF_S– Subchronic-to-chronic extrapolation: Used to fill data gap if a chronic study not available and the study does not fully cover the relevant window of susceptibility. Also referred to as the "*duration assessment factor*."
UF_L– LOAEL-to-NOAEL extrapolation: Used to fill a data gap if neither a BMD nor a NOAEL are available. Also referred to as the "*dose-response assessment factor*."
UF_D – Database deficiencies: Used to fill data gap in absence of toxicity data that may result in an under-protective RfD or RfC. For example, gaps in coverage of durations, lifestages, experimental species; or indications of the need for additional data (e.g., specific organ systems, life-stages). Also referred to as the "*quality of data set assessment factor*."

3.4. Risk characterisation

Risk characterisation is a description of the nature, and often the magnitude of human risk, including attendant uncertainty, obtained by combining the results of exposure assessment and dose-response assessment. This characterisation generally may include qualitative, semi-quantitative, and quantitative results:

- Qualitative risk characterisation may include identification of sensitive subpopulations, ecosystems or ecological entities, populations that are highly exposed, as well as limitations in the available data.
- Semi-quantitative risk characterisation is generally in the form of dimensionless "ratios" between exposure estimates and toxicity values, such as a margin of exposure (MOE), hazard quotient (HQ), or hazard index (HI) (see Table 4). The interpretation of these ratios is generally a matter of policy. For instance, if the MOE (HQ or HI) is below (above) an established benchmark, then there is increasing concern for risk the further exposure is above the benchmark. For the MOE, the "benchmark" is often set using the uncertainty factors previously discussed in terms of the RfD and RfC. For the HQ and HI, generally values below 1 are considered "safe," but sometimes values up to 3 or 10 may be "allowable" depending on the decision context.
- A fully quantitative risk characterisation provides a quantitative estimate of the incidence or severity of effects expected, as well as (ideally) the potential uncertainty or confidence bounds on those estimates. Most commonly, such a characterisation is presented only for cancer risks assuming a linear non-threshold model for the dose-relationship (see Table 4), and even then, it is often incomplete because it does not reflect quantitative uncertainties.

The degree to which uncertainty and variability are addressed in the risk characterisation usually depends on the degree to which they are addressed in the component exposure and dose-response assessments. As described above, it is most common for the outputs of exposure and dose-response assessments to be deterministic, "conservative" or "upper bound" estimates, which when combined are also considered "conservative" or "upper bound." Thus, all the typical risk characterisation outputs (Table 4) are considered "upper bound" values intended to avoid under-estimation of risk. Additionally, this approach usually does not distinguish between uncertainty and variability, which have very different policy implications. "Conservativeness" in the sense of variability means that a larger fraction of the population is protective, where as "conservativeness" in the sense of uncertainty relates to the accuracy of a specific estimate.

Table 4. Typical outputs of risk characterisation

Outputs of risk characterisation	Definition	Modeling Approach
MOE or MOS: Margin of Exposure or Margin of Safety	The POD divided by the actual or projected environmental exposure of interest.	Ratio
HQ: Hazard Quotient	The ratio of a single substance exposure level over a specified time period (e.g. subchronic) to an RfD or RfC for that substance derived from a similar exposure period.	Ratio
RCR or RQ: *Risk Characterisation Ratio* or *Risk Quotient*	Ratio of exposure to suitable no-effect levels, such as a DNEL (human health) or PNEC (ecotoxicology).	Ratio
HI: Hazard Index	The sum of more than one hazard quotients for multiple substances and/or multiple exposure pathways.	Sum of ratios
Upper bound cancer incidence	An upper bound on the number of new cancer cases at a given level of lifetime exposure, usually expressed on a per person exposed basis (i.e., lifetime risk of cancer).	Product of exposure and slope factor or unit risk

There have been some published risk characterisation approaches that attempt to disaggregate uncertainty and variability, usually using a probabilistic approach. The "integrated probabilistic risk assessment" (IPRA) approach estimates uncertainty and variability by introducing the concept of an "individual MOE" (Bosgra et al., 2009; van der Voet and Slob, 2007; van der Voet et al., 2009) (van der Voet and Slob, 2007; Bosgra et al., 2009; van der Voet et al., 2009). In this case, an MOE is calculated for each individual in a population, reflecting variability in both exposure and dose-response. Each individual MOE then has an uncertainty distribution, reflecting both the uncertainty in exposure, dose-response, as well as the degree of variability in the population. However, the output of this approach is an expression of risk (the MOE) that cannot be directly translated into an incidence. This approach has been recently been extended to cancer risk assessment (Slob et al., 2014). The result in this case is an estimate of population risk, with uncertainties, accounting for uncertainties in the individual dose-response relationships, variability across individuals, as well as uncertainty in the degree of variability.

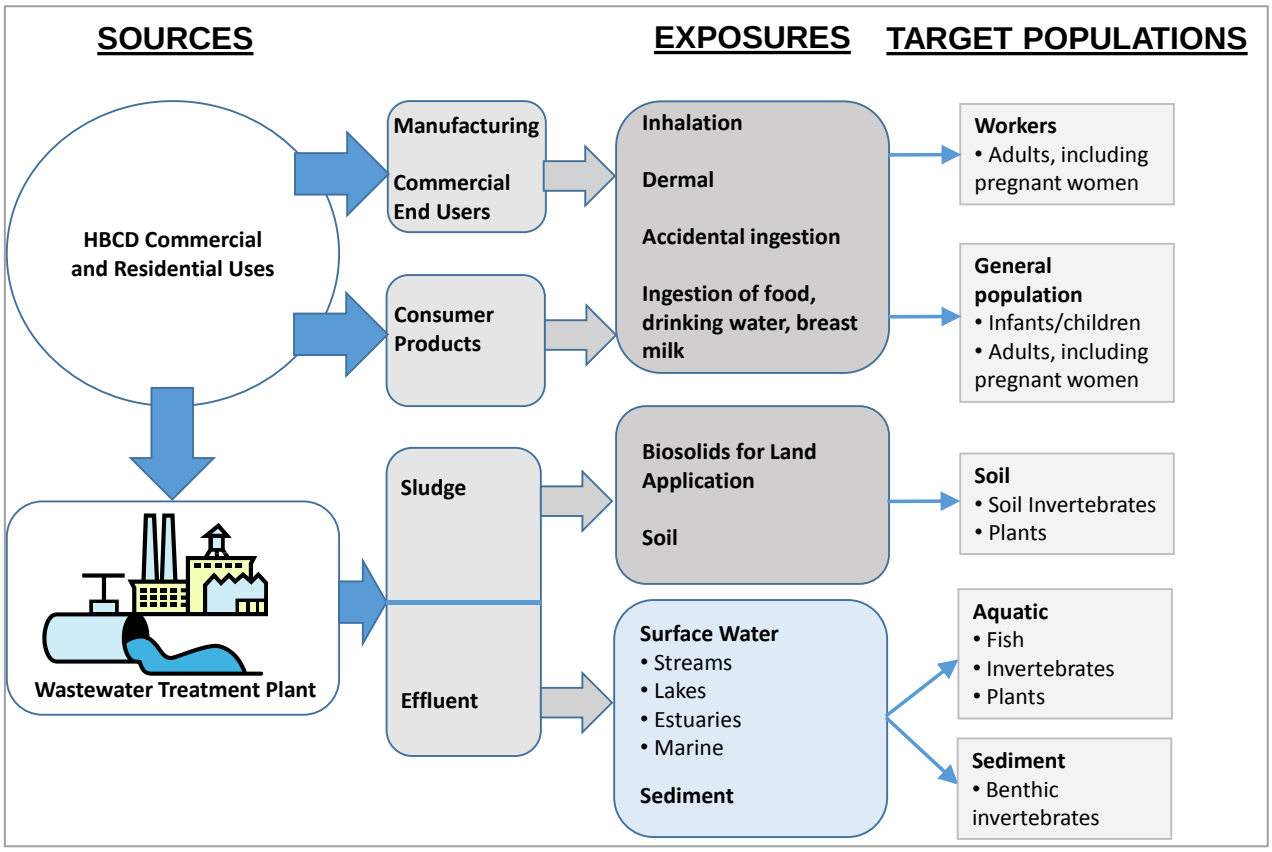
4. Issues in translating typical risk assessments for typical socio-economic benefits analysis

The issues in translating typical chemical risk assessment for use in typical socio-economic benefits analysis are illustrated in several examples summarised below. The first example discusses three risk assessments for the same chemical, hexabromocyclododecane. The next two examples – a DCM human health risk assessment by U.S. EPA and a PFOA human health risk assessment by ECHA – are a bit more sophisticated, as both of them include derivations based on internal dose, rather than just administered dose. All of these examples follow the general approach outlined previously in Figure 4. The description of each example is followed by a discussion potential for translating those risk assessments for use in socio-economic analysis.

4.1 Human and ecological risk assessments of Hexabromocyclododecane by EU, Canada, and Australia

Hexabromocyclododecane (HBCD) is a polybrominated flame retardant that has been in widespread use. Figure 6 presents a general conceptual model for HBCD exposure and the target populations for both humans and ecological species. HBCD is persistent, bioaccumulative, and toxic, and thus has been the subject of multiple risk assessments by OECD countries. These risk assessments are very similar in their overall methodology, even if some of the details differ, and thus HBCD is a good example of prototypical traditional risk assessments, both for human health effects as well as for ecological effects.

Figure 6. Conceptual model of human and ecological assessment of HBCD



Source: Adapted from U.S. EPA 2014a.

The three risk assessments summarised here for illustration are as follows:

- The European Commission Risk Assessment Report (EC 2008).[3]
- The Canadian Screening Assessment Report (Environment Canada/Health Canada 2011).
- The Australian Priority Existing Chemical Assessment Report (Australian Government 2012).

Note that the two different CASRNs denote either a non-specific mixture of the 16 possible isomers (25637-99-4) or a specific mixture of three main diasteromers (3194-55-6).

4.1.1. Human health risk assessments of HBCD

4.1.1.1. Target populations and exposure assessment

General population (consumer) exposure was assessed in all three assessments. Exposures were estimated using a pathway-based approach that summed contributions from multiple sources based on measured levels of HBCD in environmental media, food, and consumer products. In some cases, separate estimates for specific subpopulations (such as breastfed infants) were derived. Occupational exposure was assessed in the EU and Australian assessments, but not the Canadian assessment. These two assessments

3. This report is included for illustration only as to typical risk assessment approaches. HBCD has since been identified by the EU as persistent, bioaccumulative, and toxic, and hence a substance of very high concern (SVHC).

estimated inhalation and dermal exposures for different industries and/or occupational activities, based either on measured monitoring concentrations or modelled exposures.

4.1.1.2. Human health hazard identification

The EU assessment reviewed available data on acute toxicity, irritation, corrosivity, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive and developmental toxicity. The report concluded that significant effects were reported for repeated dose toxicity (effects in the liver, thyroid, and pituitary) and reproductive toxicity (reduced fertility and reduced primordial follicles). The Canadian assessment relied on previous reports, including the EU report, and only focused on "key" studies identified in the database, including some studies that were published after the EU report. In addition to the repeated dose toxicity and reproductive toxicity effects highlighted in the EU report, the Canadian assessment also considered developmental neurotoxicity effects of altered spontaneous behaviour as part of its risk assessment because it was an endpoint of potential concern for susceptible subpopulations (i.e. infants and children). The Australian assessment similarly relied on previous reports, and conducted additional literature searches for studies appearing after those reports. Similar to the EU assessment, the Australian report reviewed data on acute toxicity, skin and eye irritation, sensitisation, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity. The report concluded that HBCD poses "possible risk of harm to the unborn child" (multiple effects in pups and weanlings) and "may cause harm to breastfed babies" (pup mortality during lactation).

4.1.1.3. Dose-response assessment

All three assessments characterised the dose-response using a NOAEL approach for the "critical effects" selected in the Hazard identification. The EU and Australian reports defined a "minimally acceptable" value for the Margin of Exposure (MOE) or Margin of Safety (MOS) using uncertainty factors (UFs) for interspecies, intraspecies, and/or subchronic extrapolations. If the MOE or MOS is above the defined "minimal" level, then the exposure is considered acceptable/of little concern. The Canadian report did not explicitly specify a minimally acceptable value, bringing forward their critical effect value to the risk characterisation stage, where the adequacy of the MOE is evaluated.

4.1.1.4. Risk Characterisation

For the exposures to consumers/the general public, all three assessments concluded that the MOEs or MOSs were large enough so that there is little concern or risk. For occupational exposures, both the EU and Australian reports concluded that under some scenarios, the MOE or MOS was below the "minimal" level, and that therefore risk mitigation measures were needed.

4.1.1.5. Potential translation for economic benefits analysis

The potential for translation of these human health risk assessments for economic benefits analysis was considered in terms of the exposure assessment, hazard identification, dose-response assessment, and risk characterisations.

The exposure assessments in all three reports were relatively comprehensive in terms of the populations investigated (both public and occupational) as well as the exposure scenarios. Moreover, in most cases, although the ultimate risk characterisations were based on "reasonably worst case" exposure estimates, the exposure assessment included estimates for "typical" exposures, which would be needed for economic benefits analysis.

With respect to hazard identification, there was relatively wide coverage of endpoints investigated, but they were ultimately aggregated into general categories such as "repeat dose toxicity" and

"reproductive toxicity." Thus, although conclusions as to the hazard potential for these general categories were provided, conclusions as to specific endpoints were not. This would limit the ability of an economic benefits analysis to assign monetary values. However, the underlying data on the endpoints are in the reports, so the causal conclusions related to a "category" of endpoints could be applied to each endpoint individually. An additional issue with respect to hazard identification is interspecies concordance, since all the endpoints are based on extrapolation from experimental animal studies with the assumption of human "equivalence". Thus, endpoints based on extrapolation from other species may need to be specified more precisely (e.g. "reduced fertility" rather than "reproductive toxicity") in order to be used for economic benefit analysis.

For dose-response assessment, all three assessments utilised the NOAEL approach, along with the use of uncertainty factors to define a minimally acceptable MOE or MOS. This approach cannot be directly used for economic benefits analysis, since it lacks two key requirements for such analyses:

- A functional relationship between different levels of exposure and effects.
- Effects characterised either in terms of frequency in the population and/or magnitude/severity.

Moreover, the resulting dose-response assessments are intended to be inherently "conservative," without providing a sense as to a central tendency or expected value. In order to be used for economic benefits analysis, the underlying data would need to be re-analysed to provide a prediction of the human dose-response relationship in functional form, as opposed to providing only a point estimate toxicity value.

Finally, the risk characterisation is based on comparing the exposure estimates with the NOAELs, and comparing with a "minimally acceptable" MOE or MOS. The resulting dimensionless ratio does not give central value estimates of the incidence and severity of each endpoint for given exposure conditions. The re-analysis of the exposure and dose-response data described above would be necessary in order to provide the appropriate risk characterisation for use in economic benefits analysis.

In sum, if economic benefits analysis were to be conducted, a substantial re-analysis would be necessary in order to appropriately translate the results of these risk assessments. Key tasks would include specifying endpoints that would be more amenable to economic valuation, clarifying conclusions as to the evidence of a causal relationship, and conducting dose-response analyses that would characterise the functional relationship between exposure and effect.

4.1.2. Ecological/environmental risk assessments of HBCD

4.1.2.1. Target populations and exposure assessment

All three reports conducted environmental exposure assessment by estimating "predictive environmental concentrations" (PECs) in various environmental media relevant to ecological organisms, such as air, water, soil, and sediment, although there was some variation in the specific environmental compartments assessed. The EU and Canadian reports additionally assessed the risk due to secondary poisoning through the food chain. The EU report examine a wide variety of environmental release scenarios as well as different spatial scales (e.g. local, regional continental), estimating separate PECs for each of them using a combination of measured concentrations and modelled fate and transport. The Canadian report examined a much narrower range of exposure scenarios, using a generic facility release to surface water, application of sewage sludge for agricultural soil and pastureland, and food chain exposures. The Australian assessment considered a scenario where HBCD is released through a sewage treatment plant, either as effluent or as sewage sludge, but originating from a variety of different industrial sources.

4.1.2.2. Ecological hazard identification

All three reports reviewed literature on the ecotoxicity of HBCD, with data available for a wide range of species, including microorganisms, plants invertebrates, and vertebrates in various environmental media.

4.1.2.3. Dose-response assessment

All three reports estimated "Predicted No Effect Concentrations" (PNECs) based on the ecotoxicity data. The general approach to developing a PNEC is to first define a "No Observed Effect Concentration" (NOEC) based on the available experimental data, then divide by a number of "Assessment Factors" (AFs). Similar to the Uncertainty Factors used in human health risk assessment, these AFs account for various study limitations and extrapolations. The EU report calculated nine PNEC values for different environmental compartments (aquatic, marine, sediment, marine sediment, sewage treatment plant microorganisms, terrestrial, and secondary consumers) as well as for intermittent releases to aquatic and marine environments. The Canadian report calculated four PNEC values (pelagic organisms, benthic organisms, soil organisms, and wildlife consumers), and the Australian report calculated three PNEC values (aquatic, sediment, and soil).

4.1.2.4. Risk characterisation

The approach used by all three reports is to calculate a risk quotient, defined as the PEC/PNEC ratio. For risk quotients less than 1, the risk is considered acceptable without need for further refinement or risk mitigation. For risk quotients greater than one, the risk is considered unacceptable, and either additional information is needed to refine the PEC or PNEC values (e.g. less conservative values) or risk management measures are needed. All three reports concluded that for some scenarios, the risk quotient was greater than 1, indicating an unacceptable risk.

4.1.2.5. Potential translation for economic benefits analysis

The potential for translation of these ecological risk assessments for economic benefits analysis was considered in terms of the exposure assessment, hazard identification, dose-response assessment, and risk characterisations.

The exposure assessments in all three reports considered a wide range of ecosystems and target organisms. However, in all cases, considerable uncertainty was noted in the exposure predictions. Most of the assessments considered those predictions to be conservative, but neither the degree of conservatism nor alternative estimates as to "typical" exposures were characterised. Without more "central tendency" (or ideally variability distributions of) exposure estimates, conducting economic benefits analysis would be difficult.

With respect to hazard identification, most of the ecological effects considered were related to growth, survival, or reproduction. However, these effects were not translated to overall effects on ecological populations, which would be needed to related exposure to potential economic benefits, such as market products, recreation, or ecosystem functions or services. This would limit the ability of an economic benefits analysis to assign monetary values.

For dose-response assessment, all three assessments utilised the NOEC approach, along with the use of assessment factors to derive a PNEC. This approach cannot be directly used for typical economic benefits analysis, since it lacks two key requirements for such analyses:

- A functional relationship between different levels of exposure and effects.

- Effects characterised either in terms of frequency in the population and/or magnitude/severity.

Moreover, due to the use of assessment factors, the resulting dose-response assessment is inherently "conservative," without providing a sense as to a central tendency or expected value. In order to be used for economic benefits analysis, the underlying data would need to be re-analysed to provide a prediction of the ecological dose-response relationship in functional form, as opposed to providing only a point estimate toxicity value.

Finally, the risk characterisation is based on comparing the PECs with PNECs, resulting in a dimensionless "risk quotient" ratio. This ratio does not give central value estimates of the incidence and severity of each endpoint for given exposure conditions. However, as described above under hazard identification, even if re-analysis of the exposure and dose-response data were performed to derive exposure-response relationships, a key difficulty is the translation of ecological toxicity end points to economically meaningful ones.

4.2 Human health risk assessment of dichloromethane by U.S. EPA

Under their Existing Chemicals Program, U.S. EPA Office of Pollution Prevention and Toxics conducted a human health risk assessment of inhalation exposures to dichloromethane (DCM, CASRN 75-09-2) from uses as a paint stripper (U.S. EPA, 2014b). Major differences between this assessment and the assessments of HBCD include the use of a PBPK model to conduct interspecies extrapolation of doses and the derivation of an estimate of cancer risk using linear extrapolation, as opposed to an uncertainty factor-based approach. The approach and major conclusions of their final risk assessment, published in 2014, are summarised as follows.

4.2.1. Target populations and exposure assessment

Adult workers of both sexes in occupational settings, both as users of paint strippers and as bystander, were considered. Exposure estimates were based on occupational air monitoring data and use patterns in various industries. These exposure scenarios included both "low-end," "central tendency," as well as "high-end" estimates of DCM concentrations. Additionally, consumer exposures in a residential setting, both as users (assumed to be adults) and bystandards (any age), were also assessed. Exposures were modelled using a computational indoor air model under various use scenarios. These exposure scenarios included both "central tendency" as well as "upper-end" concentration estimates.

4.2.2. Human health hazard identification

For non-cancer endpoints, both for acute and chronic exposure, U.S. EPA concluded that DCM is primarily associated with neurological and hepatic effects. For acute exposures, the brain was considered the primary target, with evidence from multiple human studies. Neurological effects may result either from direct narcosis or from metabolic formation of carbon monoxide (CO), which reversibly binds to hemoglobin as carboxyhemoglobin (COHb) and can accumulate in the blood. Additionally, for chronic exposures, hepatic effects observed in animals include liver foci/areas of alteration, accumulation of lipid deposits in hepatocyte, fatty liver, and necrosis.

For cancer, the U.S. EPA classified DCM as "likely to be carcinogenic to humans," based primarily on evidence of carcinogenicity in mice exposed under chronic conditions. Additional support for the evidence of carcinogenicity consisted of epidemiologic data on the association between occupational exposures and brain, liver, and hematopoietic cancers in humans, as well as mechanistic data supporting a mutagenic mode of action related to create of mutagenic metabolites after biotransformation of DCM by the enzyme GSTT1.

4.2.3. Dose-response assessment

For neurological effects, multiple points of departure (PODs) were derived, all based on human studies. These included PODs associated with formation of 3% the toxic metabolite carboxyhemoglobin (COHb) in blood, considered a NOAEL; PODs associated with mild neurological effects, considered a LOAEL; and PODs for derived from Acute Exposure Guideline Levels (AEGLs), all considered NOAELs for CNS effects and COHb formation.

For hepatic effects, the POD was derived from a chronic toxicity study in rats which resulted in the formation of hepatic lesions. Specifically, using a rat PBPK model, administered doses in this study were first converted to *internal* doses. Then benchmark dose modelling was performed on the rat data to derive a POD in units of *internal* dose. Next, a human population PBPK model was used to derive a human equivalent concentration (HEC) in air, but accounting for human variability in toxicokinetics. In particular, the model was used to estimate the HEC99, which is the air concentration for which 99% of the population would have an internal dose less than the internal dose POD. The HEC99 was then used as the POD to be compared with exposure levels in the risk characterisation.

For cancer, an "inhalation unit risk" (IUR) was derived from chronic animal bioassay data on liver and lung tumour incidence in mice (Mennear et al. 1988; NTP 1986). The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m³ in air (U.S. EPA, 2005b, 2011b).

4.2.4. Risk Characterisation

For acute neurotoxicity, Uncertainty Factors (UFs) were established for each POD. The UFs ranged from 1 to 60, depending on study population and whether the POD was considered a NOAEL or LOAEL. The total UFs were considered to be a "benchmark" margin of exposure (MOE) to be used for comparison with MOEs derived for each exposure scenario. For some scenarios, the MOE derived from acute exposure estimates was less than the UF, indicating a concern about possible neurological health risks in those situations.

A similar approach was used for chronic hepatotoxicity, where there was a single POD with an UF (=benchmark MOE) of 10. As with neurotoxicity, some scenarios, the MOE derived from chronic exposure estimates was less than the UF, indicating a concern about possible hepatic health risks in those situations.

For cancer, the IUR was used to derive an excess cancer risk for each exposure scenario. Specifically, a lifetime average daily concentration was estimated for each scenario, and then multiplied by the IUR to derive an upper-bound excess lifetime cancer risk. The excess cancer risk that the U.S. EPA finds acceptable ranges from 1e-6 to 1e-4, so the excess cancer risk estimated for each scenario was compared to benchmarks of 1e-6, 1e-5, and 1e-4. For some scenarios, the estimated risk from DCM exceeded one or more of these benchmarks, indicating a concern about possible carcinogenic effects in those situations.

Overall, U.S. EPA (2014b) concluded in this assessment that there are both cancer and non-cancer hepatic and neurological risks from occupational exposures, as well as acute neurological risks from consumer exposures. These conclusions were based on the derived MOE or cancer risk estimates exceeding certain benchmark values for some occupational and consumer exposure scenarios.

4.2.5. Potential translation for economic benefits analysis

The potential for translation of these human health risk assessments for economic benefits analysis was considered in terms of the exposure assessment, hazard identification, dose-response assessment, and risk characterisations.

The exposure assessment considered a range of exposure scenarios and a range of estimates from "low-end" to "central tendency" to "high-end." The "central tendency" estimates would be directly applicable to economic benefits analysis, although variability distributions would be preferred.

With respect to hazard identification, the endpoints were focused primarily on central nervous system effects, the formation of carboxyhemoglobin, liver toxicity, and cancer. These all included relatively specific descriptions of the resulting health effects, and thus it would be conceivable that they are economically meaningful, even if they would ideally be further related to health states or limitations on function or activity. The risk assessment refers to previously published documents to support the identification of these hazards, but only made an explicit conclusion about the evidence supporting a causal relationship for cancer. However, CNS and carboxyhemoglobin effects were seen in multiple human studies, so it can be inferred that the causality is well established. However, it was not explicitly discussed the extent to which the CNS effects may be secondary to low oxygen delivery resulting from carboxyhemoglobinemia. Liver effects were observed in animal studies, and the causal conclusion with respect to humans is less clear.

For dose-response assessment and risk characterisation, non-cancer effects were treated separately from cancer effects.

For non-cancer, the assessment estimated PODs (LOAELs, NOAELs, or BMDLs), along with the use of uncertainty factors to define a minimally acceptable MOE. This approach cannot be directly used for typical economic benefits analysis, since it lacks two key requirements for such analyses:

- A functional relationship between different levels of exposure and effects.
- Effects characterised either in terms of frequency in the population and/or magnitude/severity.

Moreover, the resulting dose-response assessment is inherently "conservative," without providing a sense as to a central tendency or expected value. For liver effects, these can be partially addressed due to the use of a PBPK model for inter- and intra-species extrapolation. Although the assessment used "conservative" values from the PBPK model in its dose-response assessment, alternative "central tendency" values could be used instead. Overall, however, in order to be used for economic benefits analysis, the underlying data would need to be re-analysed to provide a prediction of the human dose-response relationship in functional form, as opposed to providing only a point estimate toxicity value. The risk characterisation for non-cancer was based on comparing the derived MOE with a "minimally acceptable" value. The resulting dimensionless ratio does not give central value estimates of the incidence and severity of each endpoint for given exposure conditions. The re-analysis of the dose-response data described above would be necessary in order to provide the appropriate non-cancer risk characterisation for use in economic benefits analysis.

For cancer, the assessment estimated the upper bound cancer inhalation unit risk based on experimental animal data. This approach does provide a (linear) functional relationship between exposure and effect, but it is intended to represent an upper bound rather than a central tendency. However, additionally dose-response modelling could be performed to estimate a central tendency instead, which would be more appropriate to use in economic benefits analysis.

In sum, substantial re-analysis, particularly of the non-cancer dose-response data, would be necessary in order to translate the results of this risk assessment for use in typical economic benefits analysis. However, such analyses appear feasible, particularly due to the well specified hazard endpoints and the confidence in the causal relationships between exposure and hazard.

4.3. ECHA restriction report risk assessment for PFOA, PFOA salts and PFOA-related substances

Under REACH, a restriction was proposed of perfluorooctanoic acid (PFOA) and related substances (ECHA, 2015b). The environmental risk characterisation is based on demonstration that PFOA and related substances are persistent, bioaccumulative and toxic (PBT). A quantitative risk assessment was not performed for ecological effects. The human health risk assessment and characterisation from this proposal are summarised as follows.[4]

4.3.1. Target populations and exposure assessment

Three target populations were considered. For fluoropolymer production workers in occupational settings, exposure estimates were based on two different approaches. First, occupational air monitoring data and generic assumptions as to activity patterns and inhalation rates were used to derive daily intake rates. Second, measured serum concentrations of PFOA in a variety of production workers were "back-calculated" to derive daily intake rates. These exposure scenarios included a range based on variability in either of the underlying measurements.

Similar to fluoropolymer workers, exposure estimates for professional skiwaxers in a seasonal occupational setting were calculated two ways, based on air monitoring or back-calculated from blood concentrations. These exposure scenarios included a range based on variability in either of the underlying measurements, as well as including both "intermediate" and "high exposure" assumptions for the inhalation rate.

In the general population setting as well, two approaches to estimating exposure were used. The first approach is a traditional aggregate exposure approach, in which intakes from food, indoor environment, drinking water, and breast-feeding (in the case of infants) are added together to estimate total intake from multiple exposure pathways. A second approach estimated intakes by back-calculating from general population blood concentrations. These exposure scenarios included a range based on variability in either of the underlying measurements, as well as including "low," "intermediate," and "high" assumptions for the various exposure factors.

4.3.2. Human health hazard identification

For repeated dose (non-cancer) toxicity, it was concluded that there is a "probable link" between PFOA and hypercholesterolemia and ulcerative colitis. The support for these conclusions was based on expert review by a panel of independent public health scientists, using formal criteria to evaluate the scientific literature. Separately, it was noted that various measures of microscopic liver damage as well as increased liver weights were found in studies of both mice and rats exposed to PFOA.

For developmental toxicity, in both humans and animals, it was concluded that the data suggest that PFOA may reduce fetal growth. The support for this conclusion includes systematic reviews of the available animal and human studies (Johnson et al., 2014; Koustas et al., 2014).

For cancer endpoints, it was concluded that there is a "probable link" between PFOA exposure and testicular and kidney cancer. The support for these conclusions was based on expert review by a panel of independent public health scientists, using formal criteria to evaluate the scientific literature.

4. This report is included for illustration only as to typical risk assessment approaches, particularly when internal dose measures are used. The key basis of the restriction is the persistent, bioaccumulative, and toxic properties of PFOA and related compounds, and not the human health hazard.

4.3.3. Dose-response assessment

The overall approach for dose-response assessment by ECHA is the derivation of DNEL(s) and DMEL(s) (ECHA, 2009). The DNEL is the level of exposure "above which humans should not be exposed," known as the "Derived No-Effect Level." The DMEL is a risk-based limit value for substances where no toxicological threshold is assumed, known as a "Derived Minimal Effect Level." In the case of PFOA, only DNELs were derived (ECHA, 2015b). Because the exposure assessment includes data on internal dose (blood concentrations), which are considered more reliable in terms of aggregating exposure from multiple pathways, most of the DNELs were derived on an internal dose basis. Although the same PODs were used for workers and the general population, different "Assessment factors" (AFs) were used for the two populations for extrapolation, resulting in different DNELs. Specifically, the intraspecies AF was assigned a value of three for workers and six for the general population (all other AFs were equal). Additionally, for two endpoints, the worker DNELs included an external dose DNEL in addition to the internal dose DNEL.

Overall, DNELs (NOAEL or LOAEL/AF) were derived from five endpoints: reduced pup weight in mice (NOAEL), for reduced neonatal survival in mice (NOAEL), delay in mammary gland development in mice (LOAEL), for increased total serum cholesterol and LDL in humans (LOAEL), and reduced birth weight in humans (LOAEL).

4.3.4. Risk characterisation

The general approach to risk characterisation used is to derive the "risk characterisation ratio" (RCR), which is the ratio between the exposure level and the DNEL. If the RCR > 1, it may be concluded that the risk is not controlled. As discussed above, exposures and DNELs were estimated based both on internal dose and external dose, with those based on internal dose considered more reliable.

For both fluoropolymer production workers as well as professional skiwaxers, the RCRs based on internal dose were in most cases greater than 1, sometimes by as much as several thousand-fold, with the most sensitive endpoint being reduced birth weight in humans. The RCRs based on external dose were even higher. Therefore it was concluded that the risk from PFOA to workers is not controlled.

For the general population, two different subpopulations were considered: adults and children. For at least half of the endpoints for each subpopulation, the RCR was greater than one, though not as high as for workers. Therefore, it was concluded that the risk from PFOA to the general population is not controlled.

Overall, ECHA concluded in this assessment that there are uncontrolled risks from both occupational and general population exposure to PFOA. Specifically, there is clearly a health concern for workers based on both experimental animal as well as human studies, and there is also a health concern for the general population when considering the human studies. Moreover, there is special concern for pregnant mothers (either workers or general population), since the endpoints used to characterising risk mainly involve developmental toxicity. Finally, it was noted that the specific effects reported in the human studies are supported by multiple studies in human and experimental animals.

4.3.5. Potential translation for economic benefits analysis

Although a socio-economic analysis was performed for the restriction of PFOA, it was based on its persistent, bioaccumulative and toxic properties, and did not quantify human health benefits. However, as an illustration of the approaches used in typical risk assessments, the potential for translation of the human health risk assessments of PFOA and related compounds for economic benefits analysis is considered below in terms of the exposure assessment, hazard identification, dose-response assessment, and risk characterisations.

The exposure assessment considered a range of exposure scenarios, as well as fairly detailed examination of the range of potential exposures. Because of its long half-life and the multiple exposure pathways involved, internal PFOA serum/plasma concentrations were used in the risk characterisation. The confidence in these exposure assessments was enhanced by the consistency across multiple studies as well as with estimates based on modelled intakes. Moreover, the results included both ranges and well as summary statistics, and thus provided a good characterisation of both the central tendency and the variability in internal concentrations across the populations of interest. These estimates would thus be directly applicable for use in economic benefits analysis.

With respect to hazard identification, many of the endpoints identified were based on human studies, such as hypercholesterolemia, ulcerative colitis, reduced fetal growth, and various cancers, and thus are likely to be considered economically meaningful (even if specific monetisation data are not available in the literature, e.g. for reduced fetal growth). Moreover, the risk assessment in many cases made explicit conclusions as to the evidence supporting a causal relationship: in several cases considering the hazard to be a "probable link" based on a scientific panel conclusion, and in the case of reduced fetal growth referring to a published systematic review concluding "sufficient" evidence in human studies. For some endpoints, such as effects on mammary gland development, it was only noted that effects were reported in animal studies, without an explicit conclusion as to causality in humans.

For dose-response assessment, the assessments derived DNELs for a variety of non-cancer endpoints, and did not derive any toxicity values for cancer endpoints. The DNELs were calculated both on an external dose basis, as well as on an internal dose basis if the data were sufficient to do so. The DNEL approach cannot be directly used for typical economic benefits analysis, since it lacks two key requirements for such analyses:

- A functional relationship between different levels of exposure and effects.
- Effects characterised either in terms of frequency in the population and/or magnitude/severity.

Moreover, by using fixed "default" assessment factors, the resulting DNELs are inherently "conservative", without providing a sense as to a central tendency or expected value. In order to be used for economic benefits analysis, the underlying data would need to be re-analysed to provide a prediction of the human dose-response relationship in functional form, as opposed to providing only a point estimate toxicity value.

Finally, the risk characterisation was based on comparing the internal exposure estimates with the internal dose-based DNELs, resulting in a RCR. The resulting dimensionless ratio does not give central value estimates of the incidence and severity of each endpoint for given exposure conditions. The re-analysis of the exposure and dose-response data described above would be necessary in order to provide the appropriate risk characterisation for use in economic benefits analysis.

In sum, if economic benefits analysis were to be conducted, substantial re-analysis, particularly of the non-cancer dose-response data, would be necessary in order to translate the results of this risk assessment. However, such analyses appear feasible, particularly due to the well specified hazard endpoints and the confidence in the causal relationships between exposure and hazard. Additionally, the availability of human data for many endpoints simplifies the potential re-analysis of dose-response, as it is more similar to the types of data that have been previously used in the context of socio-economic analysis.

5. Summary of key bridges needed to translate typical risk assessments to support typical socio-economic analyses

These case studies illustrate some of the common issues in translating typical risk assessments for use in typical socio-economic analyses, summarised in Table 5, and described in more detail in the following subsections. Because the suitability of the risk characterisation is completely dependent on the suitability of the exposure, hazard, and dose-response assessments, it is not separately summarised here.

Table 5. Summary of case studies of typical risk assessments regarding translation to support typical socio economic analyses

Key need for supporting typical socio-economic analyses	HBCD human	HBCD ecological	DCM human	PFOA human
Exposure assessment – *Expected or central tendency values*	+	–	+	+
Exposure assessment – *Variability across population*	+	–	+	+
Exposure assessment – *Impact of risk management alternatives*	–	–	–	–
Hazard identification – *Conclusion regarding causality*	+/–	+/–	+/–	+/–
Hazard identification – *Economically-meaning endpoints*	–	–	+	+
Hazard identification – *Non-overlapping endpoints*	–	–	–	–
Dose-response assessment – *Functional relationship with exposure*	–	–	+/–	–
Dose-response assessment – *Effects expressed as incidence or severity*	–	–	+/–	–
Dose-response assessment – *Expected or central tendency values*	–	–	–	–

5.1. Exposure assessment

A number of the exposure assessments reviewed include results that could translate to socio-economic analysis without much additional work. For instance, it has become common practice in human exposure assessments to estimate not only "high end" or "reasonable worst case" exposure levels, but also to characterise "typical" or "central tendency" exposures as well as, in some cases, "low-end" exposures. However, though these analyses sometimes do not clearly distinguish between uncertainty and variability, and ideally variability distributions for exposure would be provided rather than moments or individual percentiles. While for the purposes of economic analyses, uncertainty might be ignored through use of central tendency estimates, variability needs to be addressed as they can be drivers of population risk (e.g. use of population means rather than medians). Nonetheless, overall, existing exposure assessments represent characterisations that can adequately support socio-economic analysis. On the other hand, the ecological exposure assessment that was reviewed focused only on high-end or reasonable worst case exposures.

Because many of these risk assessments were not designed to evaluate "options," one key issue that is often not addressed is what the impact of different risk management options would be on *changing* exposure. Thus, any socio-economic analysis (unless it is simply a "burden of disease"-type calculation) would need to conduct additional exposure analyses under alternative risk management scenarios. Such exposure analyses may be complicated in terms of the timing of the intervention and its impacts on changing exposure, particularly for persistent substances with long environmental and biological half-lives such as PFOA.

Thus, given an existing exposure assessment, some of the additional steps that could be taken, when information is available, in order to translate the results for typical socio-economic analyses include:

1. Adding central tendency estimates while distinguishing between uncertainty and population variability.
2. Assessing the change in exposure under the different risk management options under consideration.

Methodologies exist and have been commonly applied for all of these steps, so while additional refinements are possible, current practices in exposure assessment appear able to provide adequate support for socio-economic analyses.

5.2. Hazard identification

With respect to hazard identification, typical risk assessments are uneven as to the extent to which they provide the information needed to support typical socio-economic analysis. Some assessments "lumped" endpoints together into general categories, such as "repeat dose toxicity" or "liver effects," which would make it more difficult to assign either causality conclusions or to relate to a measure of economic valuation. Additionally, it is sometimes the case that the biological relevance and/or clinical significance of endpoints, particularly from experimental animal studies, is ambiguous, though there is recent and ongoing work in this area (EFSA, 2016; ter Burg et al., 2015). For ecological endpoints, the endpoints tended to be at the individual level, and the additional step of relating those endpoints to the population level was not made.

Additionally, even if particular effects are identified, not all assessments make explicit conclusions as to the level of evidence for a causal relationship between exposure and particular effects. In some cases, such conclusions were made only for certain endpoints (such as cancer). Methodologies for making these causal determinations exist, as summarised previously in Section 3.2. The cases where causal conclusions were made more explicit tended to be where the data were derived from human epidemiology – i.e. more analogous to the data currently used for socio-economic analysis. However, the lack of human data does not preclude making explicit causal conclusions, as exemplified by the many causal frameworks for which conclusions can be based on experimental data alone (U.S. EPA, 2005b; WHO/IARC, 2006). The evaluation of causality in chemical toxicity based human, experimental, and other toxicological data is an active area of research that can potentially lead to improved translation of hazard identification to socio-economic analysis (see above, Section 3.2). Despite the different approaches, the summary hazard identification statements based on the overall evidence are remarkably similar, as shown in Table 6. All of these methodologies emphasise that the resulting categories as to the likelihood of a causal relationship are not ascribed a specific "probabilistic" interpretation. More recently, NAS (2014) recommended implementing a Bayesian approach to assign probabilities to hazard identification conclusions.

In the meantime, as described in Alberini (2016) [ENV/EPOC/WPIEEP(2016)10], it is clear from the economic literature that there is a non-zero economic value to avoiding even ambiguous hazards (i.e. those not known with certainty to exist). Therefore, economic analysts may be able to bridge this gap by simply down-weighting the economic value of an avoided *known* hazard. Moreover, then uncertainty in this down-weighting can be captured by using a *range* of likelihoods for the existence of a causal relationship. This approach was successfully applied by Trasande et al. (2015), who adapted an approach used by the Intergovernmental Panel on Climate Change (IPCC, 2005) for translating qualitative statements of confidence, such as those in Table 6, into quantitative expressions of likelihood.

Table 6. Selected hazard identification categories from various frameworks and approaches for synthesising evidence of hazard

Source	Hazard identification categories
U.S. Environmental Protection Agency [Cancer] (U.S. EPA 2005b)	• Carcinogenic to Humans • Likely to be Carcinogenic to Humans • Suggestive Evidence of Carcinogenic Potential • Inadequate Information to Assess Carcinogenic Potential • Not Likely to be Carcinogenic to Humans
World Health Organization / International Agency for Research on Cancer (WHO/IARC 2006)	• Carcinogenic to humans • Probably carcinogenic to humans • Possibly carcinogenic to humans • Not classifiable as to its carcinogenicity to humans • Probably not carcinogenic to humans
Navigation Guide (Woodruff and Sutton 2011)	• Known to be toxic • Probably toxic • Possibly toxic • Not classifiable • Probably not toxic
U.S. Environmental Protection Agency [National Ambient Air Quality Standards] (U.S. EPA 2015)	• Causal relationship • Likely to be a causal relationship • Suggestive of, but not sufficient to infer, a causal relationship • Inadequate to infer the presence or absence of a causal relationship • Not likely to be a causal relationship.
ECHA Guidance on the application of the CLP Criteria (ECHA 2015a)	• Category 1: Known or presumed human carcinogens 1A, known to have carcinogenic potential for humans, classification largely based on human evidence, or 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence • Category 2: Suspected human carcinogens
National Toxicology Program (Rooney et al. 2016)	• Known to be a hazard to humans • Presumed to be a hazard to humans • Suspected to be a hazard to humans • Not classifiable as a hazard to humans • Not identified to be a hazard to humans.

Another key issue is the specification of economically meaningful endpoints. Because of the emphasis on "screening/prioritisation" and "safety assessment" decision contexts, less attention has been paid to developing and applying methods to address this need. Economic valuation can present a particular challenge for hazards identified from studies that were not performed in the species of interest for the risk assessment. For instance, non-cancer endpoints analysed in experimental animal studies are often histological in nature, and thus do not directly have an analogous "disease" endpoint in humans. Even for cancers, site concordance is typically not assumed in the absence of specific mechanistic data. On the other hand, for some developmental effects such as malformations or reduced fetal weight, it is generally assumed that the effects observed in experimental animals correspond to an analogous human endpoint. Thus, for many endpoints, including experimental animal cancers, additional analyses or justification may be needed. As was the case for the nature of the causal relationship, it may be possible for economic analysts to elicit economic valuations for endpoints whose biological relevance or clinical significance is ambiguous. For instance, if endpoints could be placed into similar "bins" of severity based on objective criteria or expert judgment, then one may be able to transfer valuation measures among endpoints in the same bin. Given that these valuations would be based largely on analogy, the uncertainty in these valuation transfers could also be captured.

Specification of economic meaning may also be feasible if endpoints are available that could be used as predictive biomarkers (or risk factors) of "downstream" adverse effects (Chiu et al., 2013; Woodruff et

al., 2008). Specifically, an economic analyst could bridge the gap by utilising actuarial relationships between risk factors that are modulated by chemical exposure and future health outcomes with economic valuations. One example of such an endpoint is reduced fetal weight, which is associated, at least in humans, with a spectrum of downstream effects, both in the short term, such as neonatal mortality, as well as the long term, such as cardiovascular disease. Establishing quantitative relationships between fetal weight and these downstream outcomes could facilitate their being incorporated into socio-economic analyses. Because there may be additional independent data on some of those endpoints, care would need to be taken to not "double count" the overlapping portion of the risks. This will be the case with other "precursor" type endpoints which measure biomarkers that are predictive of multiple subsequent risks (e.g. for cardiovascular disease). This is necessarily a case-specific issue, and depends on the ability to define economically meaningful endpoints, discussed above.

Thus, given an existing hazard identification, some of the additional steps that could be taken in order to translate the results for socio-economic analyses include:

1. Inferring a probabilistic interpretation to the likelihood of a causal relationship between exposure and effect in the species of concern (human or ecological).
2. Identifying effects of exposure that may be economically meaningful. For endpoints without direct economic value, alternative techniques such as making analogies to more established endpoints or use of biomarkers/risk factors could be attempted.

Particularly for (1), and to a lesser extent for (2), it is uncommon for risk assessments to explicitly provide this information. Therefore, overall, economic analysts may need to take on some of these tasks in order to create a bridge from current practices in hazard identification to support of socio-economic analyses. Such analyses would benefit from closer communication and collaboration between the two communities.

5.3. Dose-response assessment

The greatest gaps with respect to typical risk assessments and typical socio-economic analyses are in the assessment of dose-response. As summarised in Table 5, all of the case studies examined lack, or partially lack, all three key pieces of dose-response information needed to support typical socio-economic analyses:

- First, with the exception of cancer endpoints in the DCM case study, none of the risk assessments provided a functional relationship between exposure and effect. Instead, these analyses derived "safe" exposure levels, through either an RfD-like or an MOE-like approach, which are essentially aimed at deriving a single point on the dose-response curve. The results provide no information as to the gradient of response as a function of dose, and are used to make dichotomous conclusions as to "acceptable" or "unacceptable" exposures. Only in the case of cancer endpoints in the DCM case study was a functional relationship (in this case linear) defined.
- Second, again with the exception of cancer endpoints, the dose-response assessment is based on the absence of observed effects (e.g., a NOAEL, or NOEC), meaning that the results do not explicitly define the frequency or magnitude of the effects at different doses.
- Finally, in all cases, the results are presented as "conservative" point estimates, without estimating a "central tendency" value that would be more applicable for socio-economic analyses. The "conservative" nature of the results goes beyond the specification of the POD, but also in the additional extrapolations that are applied.

In many cases, however, the data and methodologies exist for economic analysts to bridge this gap through re-analysis of the dose-response information:

- First, statistical curve-fitting/benchmark dose methodologies are well established for estimating dose-response functions rather than just a POD. It is well-established scientifically that this approach is superior to the NOAEL/NOEC approach typically used (ECHA, 2012; EFSA, 2009; FAO/WHO, 2005; NAS, 2001; U.S. EPA, 1995, 2012a; WHO/IARC, 2009), and established software packages exist for conducting such analyses (RIVM, 2012; U.S. EPA, 2016).
- Second, the use of statistical curve fitting/benchmark dose methodologies addresses the issue of estimating the actual frequency or magnitude of effect, as opposed to just the absence of effects. The resulting function specifies the incidence of an effect for a dichotomous endpoints, and the magnitude of an effect for a continuous endpoint (U.S. EPA, 2016).
- Third, a probabilistic approach for dose-response assessment, recently updated by WHO/IPCS (2014), provides a methodology for estimating the central tendency (along with confidence bounds) for the dose-response function derived from statistical curve fitting/benchmark dose analyses. The recently updated WHO/IPCS (2014) framework builds upon several decades of work on these approaches (see Section 3.3). Importantly, the WHO/IPCS (2014) framework also includes a compilation of the data needed to extrapolate from experimental studies to make predictions of dose-response (and its uncertainty) in the human population, as well as a spreadsheet tool to conduct these analyses (see Annex 1).

Because these approaches are still uncommon in many "typical" risk assessments, economic analysts may need to take on some of these tasks in order to create a bridge from current practices in dose-response assessment to support of socio-economic analyses.

6. Conclusions

Most risk assessments are not specifically designed in the context of socio-economic analysis. They are mostly meant for "screening" or "safety" assessments, and as illustrated in the case study examples, do not provide the results and conclusions needed to support typical approaches to socio-economic analyses. Risk assessment practices continue to evolve, both in terms of the sophistication of the methods used to analyse chemical toxicity data, as well as in the types of data that are available. Much of the toxicology community is focused on methods such as read-across (Berggren et al., 2015), quantitative structure-activity relationships (Steinbach et al., 2015), high-throughput screening data (Thomas et al., 2013), and adverse outcome pathways (Edwards et al., 2016) in order to fill data gaps for chemicals with very little or non-existent toxicity data. In these cases, even the "typical" risk assessments described in Section 4 would not be feasible, and little thought has been given to the potential to translate assessments based on such data for socio-economic analyses.

Given the current landscape of risk assessment, it would be unrealistic to conduct a wholly new risk assessment in every case where support is needed for socio-economic analyses. Ideally, new risk assessments would be conducted recognising the potential need to feed into socio-economic analyses. Whether in the context of re-purposing existing or developing new risk assessments, a critical need exists for approaches to socio-economic analysis that pragmatically take into consideration expected information gaps. A number of recent developments provide the tools necessary to greatly increase the potential for translation of typical risk assessment for use in typical socio-economic analyses, where information allows. These developments are summarized in Table 7.

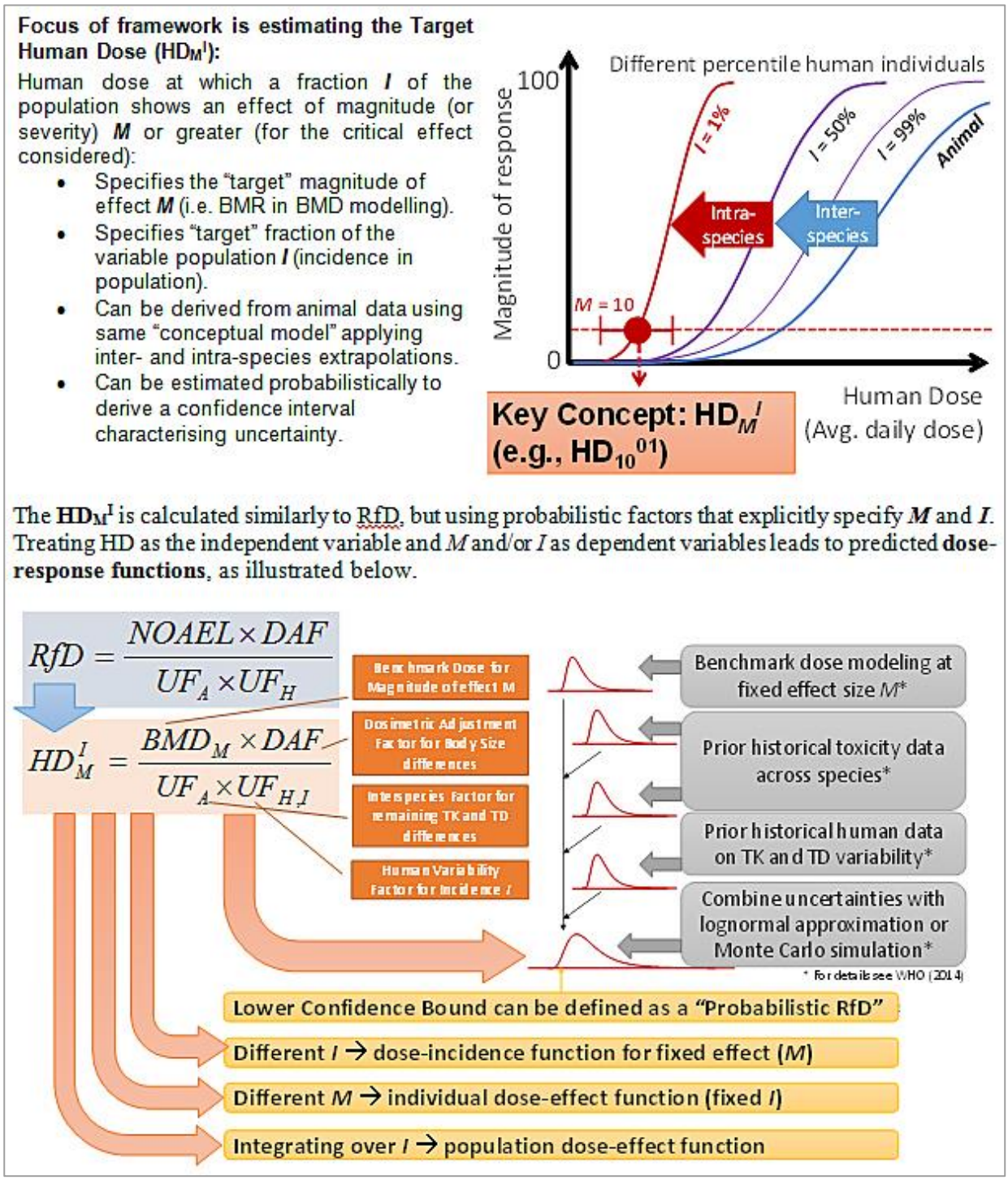
Table 7. Feasibility of adopting or adapting typical risk assessments to support socio-economic analyses

Risk Assessment Need	Feasibility and Approaches to Address Need
Exposure Assessment	
Central tendency values	**Feasible:** • Already exist for many risk assessments in addition to "reasonable worst case" estimates • Can derive using standard references for "central tendency" exposure parameters • Additional refinement: distinguishing between uncertainty and variability
Impact of risk management alternatives	**Feasible:** • Will always need to tailor the exposure assessment to the risk management alternatives being considered • Extensive experience already exists in the community
Hazard identification	
Conclusion regarding causality	**Feasible:** • Facilitated by trend towards adopting formal causal frameworks like those used at U.S. EPA, WHO/IARC, and U.S. NTP. • In short term, can assign probability (or range of probabilities) of causation, depending on the risk assessment conclusions. • Longer term, can develop willingness to pay for ambiguous hazards.
Economically-meaning endpoints	**Partially feasible:** • Facilitated by trend towards endpoint-by-endpoint causal determinations • Often challenged by uncertainty in animal-to-human extrapolation • In short term, likely limited to endpoints with unambiguous human counterparts (e.g., continuous/clinical measures or more severe effects)
Non-overlapping endpoints	**Partially feasible:** • Facilitated by trend towards using more mechanistic. • In short term, not likely to be an issue given limited number of economically meaningful endpoints
Dose-response assessment	
Interrelated needs: ***Functional relationship with exposure and time*** ***Effects expressed as incidence or severity*** ***Expected or central tendency values***	**Feasible** • Replacing LOAEL/NOAEL/BMDL with a function describing the dose-response data ○ Facilitated by trend towards using benchmark dose modelling (which requires a quantal or continuous endpoint) rather than LOAEL or NOAEL. ○ In short term, can either extract the underlying model fits or re-analyse the data to fit a model curve ○ In longer term, can incorporate additional sources of uncertainty, such as model uncertainty • Prediction of extrapolated human population dose-response function ○ Already feasible for cancer endpoints, assuming linearity ○ For non-cancer effects, enabled by probabilistic approach to replace fixed "default" uncertainty factors (recent Harmonized Guidance by WHO/IPCS includes probabilistic "default" distributions for immediate implementation) ○ In short term, will need to re-analyse data to derive predicted dose-response function, using default distributions.

Ideally, these approaches would be adopted as part of the standard practices in risk assessments, but this may not occur for some time. In the interim, however, the methods are well-enough established that economic analysts could apply them given adequate information, time, and resources. It is recognised that even with established methods and data, in many cases, the information needed may not be presented in the risk assessments themselves, and these "bridging" analyses may need to examine the original data sources. Thus, it is important that the original data, particularly for dose-response, are accessible. Therefore, there also needs to be discussion between risk assessors and economists of how to ensure information availability given the information needs from both domains. A useful next step may be the development of

some case studies in which supplementary analyses are performed – perhaps in collaboration between risk assessors and economic analysts – in order to demonstrate the feasibility of applying these approaches post-hoc. It is anticipated that the resulting "bridges" will substantially increase the potential for translation of risk assessments to support socio-economic analysis.

ANNEX 1: OVERVIEW OF WHO/IPCS PROBABILISTIC DOSE-RESPONSE FRAMEWORK



Sources: WHO (2014): Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment. Harmonization Project Document 11. Chiu, W.A . and W. Slob (2015): A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. EHP, DOI: 10.1289/ehp.1409385.

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