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Commentary

Improving risk assessment approaches for chemicals with both endogenous and exogenous exposures

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ABSTRACT

To conduct risk assessments of exogenous chemicals for which there are also endogenous exposures, knowledge of the chemistry and biology of both types of exposures needs to be integrated into problem formulation and carried through to risk characterization. This issue is framed in a risk assessment context, highlighting the importance of quantifying increments of dose from all sources of the same or similar chemicals interacting with biological targets; understanding the influence of endogenous chemical concentrations on disease risk; and assessing total dose to targets in evaluating risk from incremental environmental exposures. Examples of recent assessments illustrate the importance of addressing this issue. Evaluations of data on blood or organ concentrations of ammonia, methanol, formaldehyde, acetaldehyde, and three gaseous signaling molecules (hydrogen sulfide, carbon monoxide, and nitric oxide) provide examples where current data are already informing perspectives on relative exposures at the portal of entry and systemically. To facilitate quality risk assessments of exogenous chemicals with endogenous exposures, a series of specific questions are presented that need to be addressed in systematic review to enhance problem formulation, improve the development of holistic conceptual models, and to facilitate the identification of priority data needs for improving risk assessments.

1. Introduction

Over the last two decades, risk assessments have tried addressed the "black box" between exposure and health effects through improved toxicokinetics, understanding of mode-of-action (MOA), and applying systems approaches. While the importance of addressing background and endogenously produced chemicals has become more apparent, risk assessments for exogenous chemicals with endogenous exposures continue to be a challenge for risk assessors as well as risk management decision-makers.

There is, therefore, a need for the development of useful, consensus approaches for addressing total dose consistently in the risk assessment process, to encourage the development of data and models to put exogenous exposures to endogenous or background chemicals in context as an integral part of risk assessment, and to review endogenous or background chemicals with exogenous exposures in a systematic manner. The challenge for 21st century toxicology and risk assessment is to identify these chemicals and processes, understand their physiological role, regulation and range, and any toxicological effects related to that regulation and range, and then to assess individual exogenous exposures in this context. This issue is also important to address the value of potential risk reduction strategies for specific exogenous exposures in the face of natural occurrences, including endogenous production.

This commentary provides a systematic approach for risk assessors to consider and address exogenous exposures to endogenous or background chemicals "up front" in the problem formulation step in order to make it an integral part of risk assessment, and to effectively engage risk managers and peers early in the process to allow regulatory options to inform the focus and scope of such risk assessments. This commentary is informed by technical discussions of examples that illustrate the issue, by robust roundtable discussions at the Society for Risk Analysis (SRA) Annual Meeting (2015), and a workshop session at the Society of Toxicology (SOT) Annual Meeting (2016).

Chris Wild in his seminal publication coined the term "exposome" (Wild, 2005) to characterize the complex set of external and internal

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stressors that occur over a person's lifespan. However, risk assessors have grappled with how to address this concept when evaluating specific chemical exposures. “Natural” chemical exposures through food, life-style choices, and/or actions of the microbiome, or even just “normal biology” (intermediary metabolism), often confound estimation of risk from exposures to those same chemicals from environmental and anthropogenic sources. Endogenously produced chemicals, often products of intermediary metabolism or biological synthesis whose levels are maintained through active metabolism and/or excretion pathways, present challenges for the assessment of the same or similar chemicals from exogenous sources. Background concentrations of chemicals derived primarily from routine intake in foods or through the action of the gut microbiome in human populations result in variations in endogenous exposures that are not mimicked well by experimental animal models on defined, prepared diets. Acetaldehyde provides such an example where animal models may underestimate background human levels, particularly in cases of ALDH2-deficiency. (Lachenmeier and Salaspuro, 2017).

Although there may be exceptions where individual exposures have unique MOAs, the norm is more likely that chemical exposures will feed into ongoing physiological processes, involving the same or similarly-acting chemicals that are typically managed internally through normal homeostatic processes. These processes include chemical synthesis, maintenance of steady-state concentrations, active elimination, and molecular repair, any of which may or may not support an underlying risk of disease. This complex milieu, the “endogenous exposome,” while often ignored for simplicity's sake, provides a real-world challenge for risk assessors.

An early example of the recognition of addressing endogenous exposures is illustrated by the treatment of dietary-derived background concentrations of nitrosamines in the context of occupational exposures and risk assessments (Bartsch and Montesano, 1984). The US Environmental Protection Agency (USEPA) has also acknowledged the importance of consideration of background concentrations and endogenous chemicals in its: *Review of the Reference Dose and Reference Concentration Processes* (USEPA, 2002), and in the USEPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). The issue of endogenous exposures has been acknowledged in several hazard assessments including ammonia (USEPA 2016a), methanol (USEPA 2013), ethylene oxide (EtO) (USEPA 2016b), and formaldehyde (USEPA 2010; NRC, 2011), all developed as part of the USEPA's Integrated Risk Information System (IRIS) evaluations, although with varying degrees of scientific rigor, prompting comments regarding the need for additional explanation from peer reviewers.

The USEPA’s 2002 guidance recognized the presence of “background” and addressed the issue of the significance of “additions to the background.” According to this USEPA Review, decisions about the amount of change to consider adverse must always be made using professional judgment and should be viewed in light of all the data available on the endpoint of concern. Further, it stated that all (emphasis added) toxicological data on a chemical must be reviewed before deciding whether an effect is biologically significant and adverse. In addition, the USEPA 2002 guidance states that using a default cutoff value to define adversity for continuous measures is discouraged. The USEPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005) also addressed this issue. Discussing cancer epidemiology, the Guidelines mention the goals of identifying the distribution of cancer risk and determining the extent to which the risk can be attributed causally to specific exposures to exogenous or endogenous (emphasis added) factors. In discussing comparison groups in epidemiology, the Guidelines recognize that comparison groups may not be free from exposure to the agent and that this fact can bias the risk estimates for specific exposures toward a lower value, particularly if the agent is already involved in the disease process. The “true” implications of the exposure of interest, therefore, may be masked. The Guidelines state that an analysis can be improved by considering background exposures in the exposed and comparison groups. The Guidelines also specifically discuss the fact that some carcinogens do not interact directly with DNA, but they can produce increases in endogenous levels of DNA adducts by indirect mechanisms (e.g., 8-hydroxyguanine). They take the approach that dose-response models should be corrected for this “background” using a linear approach from the point of departure (POD) to the origin, where the origin has been corrected for background. However, no details are provided in the Guidelines on the best ways to approach such a correction or to estimate endogenous exposures or their potential sequelae, e.g., DNA adducts and/or mutations. Also, in its 2009 report, entitled *Science and Decisions: Advancing Risk Assessment*, the National Research Council (NRC) included the issues of endogenous chemicals and background exposures, and discussed a unified approach to dose-response assessment (NRC, 2009). The report presents the conclusion that evaluation of background exposures and predisposing disease processes are needed to improve risk assessments. A 2014 publication in Toxicological Sciences (Schroeter et al., 2014) provides an example of this by demonstrating that the modeling of endogenous formaldehyde in nasal tissues affected inhaled formaldehyde dosimetry predictions in the rat, monkey, and human nasal passages. According to the authors, endogenous formaldehyde in nasal tissue affected nasal uptake at lower exposure concentrations, most notably at air concentrations < 10 ppb. At a concentration of 1 ppb, predicted formaldehyde uptake was greatly reduced, to the point that formaldehyde desorption from nasal tissues was predicted in humans. Exposure concentrations < 1 ppb also yielded net desorption of inhaled formaldehyde from nasal tissues in the rat and monkey models. This led the authors to conclude that both endogenous and exogenous formaldehyde need to be considered in risk assessment.

This contribution offers ideas on a path forward to address the controversy and challenges.

2. Improving problem formulation for better decisions

Over the last decade, the scientific community has come to realize the importance of scoping and problem formulation in the risk assessment process (USEPA 2014; Fenner-Crisp and Dellarco, 2016). As the NRC (2009) stated in *Science and Decisions*, “By focusing on early and careful problem formulation and on the options for managing the problem, implementation of the framework can do much to improve the utility of risk assessment. Indeed, without such a framework, risk assessments may be addressing the wrong questions and yielding results that fail to address the needs of risk managers.” This statement is particularly true for endogenous chemicals with exogenous exposures. Population variability in the estimates of these concentrations is no less important, and enhanced availability and review of such data are critical for problem formulation in risk assessments. Understanding relative contributions of all sources of dose to biological targets, and putting risk in context for decision makers through early and continuous attention to endogenous and exogenous sources of total dose during the risk assessment process, will help better characterize risk. Table 1 presents questions whose answers will be critical in a robust problem formulation for compounds which fall into the category of endogenous chemicals with exogenous exposure, and these questions should become a routine part of systematic review. Some questions may need to be addressed with existing data from studies that fall outside of the range of typical toxicology literature accessed in current risk assessments; others may need data to be collected as a priority for experimental work and information gathering if a risk assessment is contemplated. The information needs and knowledge gained from integrating these questions into problem formulation will ensure that these critical considerations are carried all the way through the evaluation and comprehensively presented in the risk characterization.

Table 1
Key questions for consideration in problem formulation.

"Background" Concentrations
1) Is the chemical of interest produced endogenously or is it encountered systemically because of ubiquitous exposures or the action of the human microbiome(s)?
2) What general exogenous sources (nutrition, pharmaceutical, microbiome-derived, others?) need to be considered to put specific exogenous sources of endogenous chemicals in context?
3) Have endogenous levels, and their controls and functions in cells and tissues, been characterized to inform risk assessment? If not, what data/information are needed to adequately assess the impact of total dose on portal of entry effects? Systemic effects?
4) What do we know of genetic determinants or pre-existing diseases that might alter these endogenous levels?
Potential for Effects at "Background" Concentrations
1) Based on hypothesized MOAs, is it likely that "normal" levels of endogenous chemicals contribute qualitatively to degenerative or disease processes? Why or why not?
2) If so, can we quantify the background incidence or population distribution of these impacts? What data or information are, or would be, needed to answer this question?
3) Can alterations of "normal" endogenous levels by failure of homeostatic controls because of genetics or disease lead to adverse effects?
Response-Additivity
1) If endogenous concentrations and exogenous exposures result in dose-additivity at a target, what information would support the assumption of response-additivity at that target?
2) What toxicodynamic model best fits the assessment of total dose? At expected exogenous levels of exposure, is the exogenous exposure (additive to background) increasing the probability of an effect, or can it be controlled like normal fluctuations in internal concentrations with no increased probability of adverse consequences until homeostatic mechanisms are overcome? For individuals? For populations?

3. Understanding sources of chemicals and endogenous concentrations

Considering specific exogenous exposures in the context of total endogenous concentrations is complex. Typically, chemical exposure assessment has invoked toxicokinetics to deal with processes such as absorption, distribution, metabolism, and excretion (ADME) to assist in estimating dose to target tissues. USEPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005) state that "toxicokinetic modeling is the preferred approach for estimating dose metrics from exposure." The function of toxicokinetic models is to describe the relationship between exposure concentrations and measures of internal dose in target tissue over time. Complex models often reflect sources of individual or population differences in processes affecting the fate of the exogenous exposure, such as polymorphisms affecting metabolism and differing clearance rates. What has been lacking, in most instances, is the consideration of dose of the same or similar chemicals from other internal or external sources at targets of interest. These sources include, for instance, intermediary metabolism, dietary intake, disease states, and microbiome activity. Intermediary metabolism produces reactive moieties which are known to play a role in disease processes (DeBerardinis and Thompson, 2012). Homeostatic mechanisms on the other hand are thought to preserve a balance between formation and elimination of these moieties, and repair processes have evolved to modulate their impact. Thus, a key to understanding risk from exogenous exposures is to assess the contribution of such exposures from and to these ongoing processes.

More recently, the concept of aggregate exposure pathways (AEPs) has been introduced (Teeguarden et al., 2016) as an "intuitive framework to organize exposure data within individual units of prediction common to the field, setting the stage for exposure forecasting." Recognizing the existence of endogenous chemicals, background levels, and exogenous sources, the authors "envision direct linkages between aggregate exposure pathways and adverse outcome pathways [AOPs], completing the source to outcome continuum for more meaningful integration of exposure assessment and hazard identification." The complementary concepts of AEPs and AOPs highlight the importance of understanding intra-individual- and population-related variability in endogenous processes, and of integration of total exposure, to understand response in the context of chemicals which affect the broader biological system for improved risk assessment.

As part of the AEP concept, Teeguarden et al. (2016) have recognized the importance of characterizing "internal exposure," including absorbed dose from a variety of potential exogenous sources and endogenous processes which lead to blood, tissue, and eventually target concentrations. The recent focus on metabolomics has demonstrated that endogenous chemicals and those arising from ingested drugs or foods are present in the "metabolome" at concentrations that are orders of magnitude higher than those chemicals classed as pollutants from environmental sources (Rappaport et al., 2014). The "metabolome," or blood exposome, represents a composite snapshot of the physiologic state, including endogenous and exogenous chemicals. However, given the differences in concentrations of these chemicals in the blood mentioned above, it is unlikely that detection in the metabolome will be particularly useful for identifying and comparing relative contributions of endogenous and exogenous chemicals except in the rare case of exceptionally high exogenous exposures. Nonetheless, the relative difference between concentrations of specific environmental exposures and endogenous chemicals supports the importance of attempting to understand background or endogenous chemical concentration ranges when assessing risk from exogenous exposures to the same or similar chemicals.

Several examples can help to illustrate the importance of this understanding to the assessment of risk. In their 2014 publication, entitled *The Endogenous Exposome*, Nakamura et al. (2014) focused on the production of endogenous electrophilic molecules in our cells that can damage DNA. They provide quantitative data on endogenous DNA damage and its relationship to spontaneous or background mutagenesis. This body of work has begun to address the question of when (e.g., under what exposure levels/conditions) exogenous chemical exposures that produce identical DNA adducts to those arising from normal metabolism might cause biologically significant increases in total identical DNA adducts. Their work provides important perspective on the differences in tissue-specific dose- and response-additivity, and how homeostatic processes may modulate risk. Starr and Swenberg (2016), in an update to work published in 2013, illustrate an alternative, "bottom-up" approach for including endogenous exposures to formaldehyde and putting the consequent DNA-adduct burden in perspective when calculating risk for exogenous exposures.

Route of exposure and portal of entry effects in specific tissues deserve consideration; impact on normal, homeostatically-controlled levels of chemicals and derived adducts or other biomarkers of exposure must be assessed; dose to certain organs or molecular targets may be influenced by metabolic capacities, e.g., reductive elimination or compartmentalization. Several examples help to illustrate these points. For example, ammonia and H_2S inhaled concentrations must exceed typical exhaled breath concentrations to produce local irritation (USEPA 2016; Guidotti, 2010). H_2S as an endogenous systemic signaling molecule introduces additional considerations and complications when assessing systemic effects (Li et al., 2011). In the case of formaldehyde, in tissues distant from the portal of entry, local endogenous reactive moiety production tied to histone demethylation in the nucleus may have greater impact on DNA adduct or crosslink formation and eventual mutagenesis than transport of exogenous reactive molecules systemically through the cytoplasm to the nucleus (Shi et al., 2004). Exposure to EtO at higher doses (i.p.) has been shown to induce a physiologic response resulting in an increased ethylene production *in vivo* which indirectly increases endogenous levels of the major EtO-related adduct (Marsden et al., 2009). The biological effects of EtO-

specific adducts, which vary from not mutagenic (N7-hydroxyethylguanine, HEG) to pro-mutagenic (O^6-HEG) (Philippin et al., 2014), and the adduct distribution profile (where N7-HEG is predominant, e.g., Tompkins et al., 2008) must also be considered (Pottenger et al., 2018). These results call into question any extrapolation of estimates of the relative efficiency of DNA damage production at typically high dose levels in experimental systems when applied to relatively low-dose levels dominated by endogenous concentrations. For acetaldehyde, variability in background exposures through diet, characteristics of the microbiome, or genetic polymorphisms, may all affect levels of background and, therefore, risk from exposure to exogenous sources (NTP, 2014).

Further, the discussion of the exposome concept and a focus on endogenous compounds supports the emphasis in this commentary on understanding the sources of endogenous compounds and their concentrations when assessing exogenous exposures to the same or similar compounds. Both qualitative and, in some cases, quantitative information exist that allow for characterization of sources and levels of these endogenous toxins (O'Brien and Bruce, 2009). O'Brien and Bruce's extensive treatment of the subject illustrates the growing understanding of the delicate balance necessary for endogenous chemicals, given their roles as positive and negative modulators of biology. From DNA damaging agents, to sources of irreversible protein modification, to lipid peroxidation and other means of molecular perturbation, and as critical signaling molecules, endogenous chemicals play a major role in normal biology and the disease state. Advances in analytic technologies will continue to improve the availability and accuracy of these estimates. Data on blood or organ concentrations of ammonia, methanol, formaldehyde, acetaldehyde, and the three gaseous signaling molecules (H_2S, carbon monoxide (CO), and nitric oxide (NO)) provide examples where current data inform our perspectives on relative exposures at the portal of entry and systemically. Such data also provide a potential "floor" for management of exogenous exposures when they are likely to be a small contributor to and, perhaps, indistinguishable from the range of exposures that might be caused by endogenous concentrations from nutrition or normal metabolism. Such information is valuable for both problem formulation and for prioritizing risk management options based on likelihood to affect adverse outcomes.

One area of active research that will affect our understanding of endogenous compounds in the future is related to functions of the microbiome(s). While the gut microbiome plays a major role in metabolism of exogenous chemicals and production and/or metabolism of "endogenous" chemicals (Claus et al., 2016), other microbiomes may also contribute to endogenous concentrations of chemicals. Since the n-nitroso compounds, which require microbial biotransformation for activity, represented one of risk assessments earliest successes in attempting to understand and manage cancer risk for both endogenous and exogenous compounds (Bartsch and Montesano, 1984), it is likely that new data and insights on functions of the microbiome will continue to affect our thinking on this topic.

4. Contributions of endogenous chemicals to disease risk

Another area where recent research has contributed to our understanding of the implications of endogenous compounds and risk relates to their role in underlying disease. Given our improved understanding of the diversity and magnitude of DNA damage events in "normal" cells and tissues, it is likely that DNA damage provides a baseline for cancer and, perhaps, some non-cancer disease incidence(s) such as atherosclerosis. This inference is supported by population studies that suggest higher incidence of disease with certain genetic polymorphisms affecting metabolism and increasing concentrations of endogenous chemicals, like aldehydes, and/or when repair of induced lesions is reduced due to genetics (Yukawa et al., 2014; Hira et al., 2013). Hira et al. (2013) found that aldehyde dehydrogenase 2 (ALDH2) deficiency dramatically accelerates bone marrow failure (BMF) in Japanese Fanconi's anemia patients. A recent animal study highlighted that exposure to both endogenous and exogenous formaldehyde has been established to be carcinogenic, likely by virtue of forming nucleic acid and proteins adducts such as N6-formyllysine (Edrissi et al., 2017). The study found that differences in the formation and clearance of exogenous and endogenous formaldehyde adducts provide insight into the molecular basis of formaldehyde toxicity and carcinogenicity. The consistent observation of formaldehyde-induced protein and nucleic acid adducts only in the most immediately exposed tissues, and not at sites distant to the portal of entry also raises questions about the proposed link between inhaled formaldehyde and some cancers. Pre-existing disease, such as liver and kidney disease, can also disrupt normal homeostatic processes which ordinarily would limit or eliminate risk of disease, and result in higher concentrations of endogenous compounds leading to adverse consequences as is seen with hyperammonemia (USEPA 2016a). In the last 20 years, the important roles of H_2S have been documented for virtually every organ system, with its effects on the nervous and vascular systems being highlighted and even exploited for therapeutic discoveries. This has led to the acceptance of H_2S as the third identified gaseous signaling molecule, along with CO and NO (Li et al., 2011). The question of whether endogenous concentrations of these chemicals provide a background of disease in the general population or in specific subpopulations, to which exogenous compounds can contribute through some undefined (non-linear or linear) dose- and response-additivity, is critical for the choice of conceptual models for risk assessment. The role of homeostatic mechanisms regulating endogenous concentrations, and their ability to handle exogenous exposures which do not result in total concentrations outside of normal physiologic limits, are key to understanding risk. Tolerance distribution models will always suggest that some individuals in the population will be on the "edge" of expressing disease. Identification of susceptible individuals, life stages, or populations, quantitative estimates of severity of response, and overall incidence of disease will all be required to better inform risk management for the general population as well as to develop an understanding of susceptibility.

As mentioned above, discussion of genetic or physiologic susceptibility affecting either toxicokinetics (ADME) or toxicodynamics of endogenous compounds will be critical for understanding risk of specific exogenous exposures. Examples of both have been illustrated with the cases discussed above. A range of response based on variability in background concentrations and potential severity of outcomes can inform priorities and risk management options. Hazard identification is basically a "yes or no" determination which has become outmoded; hazard characterization as currently practiced seeks quantitative information regarding potential hazard. Such information may be more readily available for endogenous chemicals, as opposed to novel synthetic chemicals, because of studies of normal physiology and metabolism, genetic polymorphisms, and pharmaceutical targets. Such data should be a routine part of information collection and consideration in problem formulation for endogenous chemicals with exogenous exposures.

5. The importance of understanding total dose to targets

Improved risk assessment for exogenous exposures to chemicals with endogenous or background levels will require better estimates of total dose to targets to put exposures in context. Estimates of background concentrations of the same or similar chemicals at molecular targets in humans will be required. Animal models will need to be assessed to determine relevance to such assessments based on total, not incremental, dose to targets. Key data may be found in the physiology literature and in newer studies of metabolomics, and should be discoverable, if available, through well-constructed systematic reviews. Absence of quantitative information on endogenous levels of compounds under assessment, both for animals and humans, should be included in the discussion of uncertainties in such assessments, and

should represent targets for future data collection.

Toxicokinetic models and the adoption of the AEP concept (Teeguarden et al., 2016), which incorporate these background levels will assist in these estimates. Further understanding of homeostatic control mechanisms and passive processes that regulate intracellular concentrations will be needed. More detailed descriptions of molecular compartments and accessibility of dose from different sources will improve these models.

A recent publication (Kirman and Hays, 2017) has introduced the concept of endogenous equivalent (EE) values for EtO, which allows one to put endogenous and exogenous levels of EtO in perspective. According to the USEPA EtO assessment (USEPA 2016b), standard risk assessment practices result in the calculation of risk-based concentrations for EtO in air that are approximately two orders of magnitude lower than levels predicted in exhaled breath of humans with no exogenous EtO exposure. Such findings, at the very least, highlight a signal-to-noise issue for risk assessment when exogenous exposures fall well below those consistent with ubiquitous endogenous exposures. As theses authors conclude, in such cases, small exogenous exposures may not contribute to total exposure or to potential effects in a biologically meaningful way.

While the concept of response-additivity from multiple sources is attractive on first principles, recognition that dose to target(s), comprised of chemicals or metabolites arising through multiple routes, suggests a complexity that must be understood for risk assessment to be useful to and reliable for decision-makers. Portal of entry effects often demonstrate increased local concentrations which damage cells directly or overwhelm protective, homeostatic mechanisms and lead to adverse outcomes at the site of contact. Systemic effects are more difficult to assess with regard to contributions from target dose without improved understanding of pharmacokinetics of both exogenous and endogenous chemicals and their relative accessibility to targets. Assuming response-additivity for incremental exposures based on an unknown contribution to total dose in populations of animals or humans who are either "exposed" or "unexposed" is no longer scientifically defensible. Toxicological principles require that we know where we are on the dose-response curve and whether incremental risks are significant, for regulatory purposes, compared to background. Reviewers of a recent IRIS assessment of methanol raised the question of whether a reference dose premised on potential for a pharmacokinetically-based shift in blood levels was overly conservative and counterintuitive, given what is known about population background exposures (USEPA 2013). Small incremental cancer risks illustrate a similar problem. These are often based on high dose studies where observed cancer risk in animal studies is 1% or greater, while the shape of the cancer dose-response at lower, more environmentally relevant, doses is unknowable. Such characterizations of safety or risk make the risk manager's job in assessing the potential impact of regulatory action that much more difficult. If this is the case, a thorough awareness of the accompanying uncertainty of the outcome is critical to understanding the impact of their actions.

6. Putting risk from exogenous exposures in context

Both risk assessors and risk managers should place greater emphasis on the importance of understanding risk in context as a feature of problem formulation. When considering specific exogenous exposures, the determination of characteristics like attributable risk, relative risk, and manageable risk can provide such context. These characteristics provide risk managers important information to frame the discussion of risk priorities and regulatory options.

Risk assessments attempt to quantify the impact of a specific level of exposure on individuals and populations. In epidemiology, attributable risk is the difference in rate of a condition between an exposed population and an "unexposed population," and is mostly calculated in cohort studies, where individuals are assembled and grouped based on exposure status and followed over a period of time. While background may be represented in "unexposed" populations, normal variability in background exposures can push results of such studies toward the null and present a "signal to noise" problem, as mentioned above. This issue of attributable risk is exacerbated when relying on animal studies where background levels in animals may differ markedly from those in humans, based on such things as diet, metabolism, and elimination kinetics. Use of high doses in experimental studies likely reduces this concern, since, under these conditions, exogenous exposures are very much higher than endogenous levels, and would typically exceed ranges of total dose to targets in the human situation; however, this does not match with "real world" situations. Indeed, top-down dose-response assessment has been shown to significantly overestimate attributable risk of low doses (Slikker et al., 2004). A better understanding of background concentrations in populations and their influence on disease risk is necessary to determine attributable risk in a meaningful, quantitative way, especially given that for some chemicals, endogenous exposures exceed exogenous ones in the dose-range of interest (e.g., ammonia, certain aldehydes, EtO).

Another useful concept to put exposures in context is relative risk. Relative risk describes how much risk can be attributed to a particular increment of exposure compared to that from background concentrations of the same or similar chemicals or, at best, from all sources affecting disease incidence. Quantifying an upper bound on a risk-specific dose as one in a million (10^{-6}) or as one in ten thousand (10^{-4}) is best understood if the total disease risk in the population is considered. Understanding the relative magnitude of the risk under consideration should also factor into decisions for prioritizing resources for both research and regulation to help ensure that we are addressing the most important problems.

A third concept that should play into scoping and problem formulation is manageable risk. Manageable risk invokes the recognition that background concentrations of chemicals have a role to play in disease etiology, which allows one to take a holistic view of risk management. Addressing relatively small increments of risk will have greater benefits if knowledge gleaned in their assessment suggests that further risk reduction is possible, for instance, through dietary intervention or promotion of healthy microbiota. Beyond the use of regulatory tools, risk managers can promote other approaches to environmental and public health for managing endogenous (background) chemicals with exogenous exposures.

7. Conclusions

The risk assessment process continues to evolve. The concept of the exposome has highlighted the need to address individual exposures in the broader context of a lifetime of endogenous and exogenous exposures. One area clearly needing additional attention is the approach to assessing risk from endogenous chemicals with exogenous exposures. Current practice typically fails to adequately consider or address this challenge. Little guidance is available to assist risk assessors in tackling the complexities of this task, although some progress is being made. Recent examples of such risk assessments may be instructive in developing an appropriately designed problem formulation for such assessments to ensure that the necessary information: is developed when needed; is considered in systematic reviews; is incorporated into risk assessments; and is presented to risk managers who can then better evaluate their risk management options for such situations. The set of questions gleaned from these examples and proposed for use (Table 1) and, where needed, the development of specific information available to address them, offers a starting point for further improvements in the process of addressing this risk assessment challenge.

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