Supplemental Material

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Table S1. Governmental Partners

- Army Corps of Engineers
- California Environmental Protection Agency, Office of Environmental Health Hazard Assessment
- European Chemicals Agency
- European Joint Research Centre
- Health Canada
- L'Institut National de l'Environnement Industriel et des Risques
- U.S. Food and Drug Administration (National Center for Toxicological Research)
- U.S. Centers for Disease Control and Prevention, National Center for Environmental Health, and Agency for Toxic Substances and Disease Registry
- U.S. Department of Defense
- U.S. National Center for Advancing Translational Science
- U.S. National Institute of Environmental Health Sciences and National Toxicology Program
- U.S. National Institute for Occupational Safety and Health

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Table S2: An Illustrative Framework for Evidence Integration Focusing on New Data Types Presented in the NexGen Report. This causal determination framework illustrates how evidence integration and inferences about causality could be made using new data types. The left column summarizes the prototype results, the middle column presents evidence for causality exemplified by the prototypes, and the right column illustrates how such prototypic evidence might be integrated and weighed. The first set of prototypes is unique in that the prototypes have known human health effects and well-documented public health risks. For these prototypes, the "Evidence Integration" column evaluates how successful new data types were in predicting known outcomes (criteria for study selection, evidence integration and causal determination considered here are discussed in DHHS 2014; EPA 2013a; McConnell et al. 2014; Meek et al. 2014; NRC 2014; Rhomberg et al. 2013). Modifications of the Bradford-Hill criteria (e.g., consistency, coherence, biologic plausibility) continued to be useful in the evaluation of new data types. As presented here, confidence in causality ranges from suggestive to likely, largely based on the understanding of the biologic context in which new data types are embedded. "Likely" is generally for the limited number of cases where the new data types are well anchored to adverse outcomes by a combination of observational and experimental data, and include mechanistic and systems biology understanding. Biologic context need not be chemical specific but can be derived from disease-/disorder-specific knowledge or from analogy with related chemicals. In practice, much of the new datatypes are anticipated to be suggestive for the near-term and most appropriate for screening and prioritization and, perhaps, limited-scope assessments. Of note is that, contrary to traditional approaches, some new approaches can be used to estimate relative potencies or toxicity values in the absence of clearly identified hazards. Major assessments are anticipated to be augmented by new data types but, for the near term, continue to be based on traditional data. To simplify the table, similar prototypes with shared attributes are aggregated where possible.

Table S2: An Illustrative Framework for Evidence Integration Focusing on New Data Types Presented in the NexGen Report.

Prototypes	Evidence for Causality	Evidence Integration

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Tier 3	**Molecular epidemiology and clinical studies:** • Illustrated that new data types (when properly collected, analyzed, and reported) appear to provide results comparable to robust, traditional human data, and could be used, when linked to mechanistic information, to: (1) evaluate potential hazard posed by chemicals with no or limited traditional data, (2) augment traditional assessments, or (3) better inform traditional risk assessment issues, such as human variability and susceptibility, cross-species and *in vivo*-to-*in vitro* comparisons, cumulative risk, and low exposure-dose-response relationships.	• **Specific pattern alterations in molecular events appear consistently and strongly associated with known intermediate events and known hazards at environmental exposure levels** (EPA 2013b, 2015a; McCullough et al. 2014; McHale et al. 2009; McHale et al. 2012; Smith et al. 2011; Thomas et al. 2014). Data for tobacco smoke were reported in the Gene Expression Omnibus (GEO) or ArrayExpress (AE). Also see Cooper et al. (2013). • Exposure-dose was measured for benzene and ozone using urinary biomarkers and radiolabeled ozone, respectively (Hatch et al. 2014; McHale et al. 2009; Thomas et al. 2014). Tobacco-smoke exposures were self-reported, substantially increasing uncertainty for exposure-dose-response characterization and highlighting the need for accurate exposure characterization (EPA 2015a). • Dose-dependent alterations are observed in concomitantly collected molecular events and adverse effects, in the range of environmental exposure (benzene and ozone). Some molecular pathways are altered at all concentrations; other molecular and toxicological effects emerge with increasing dose. Molecular patterns that occur consistently across all concentrations appear preferable as biomarkers (EPA 2013b; Hatch et al. 2014; McCullough et al. 2014; Thomas et al. 2014). • Pharmacological interventions have been shown to modify identified AOPs, and, concomitantly, the incidence or severity of the adverse outcomes (Cooper et al. 2013; Hatzimichael and Crook 2013; McCullough et al. 2014).	**Suggestive to likely:** Evidence is consistent, coherent, and biologically plausible that the observed molecular events are causally related to adverse effects. Implications are based on comparisons to robust traditional risk assessments: • For benzene and ozone, identified molecular events are likely causally related to known adverse outcomes in a dose-dependent fashion. Mechanistic links between molecular events, intermediate effects, and adverse outcomes are well understood. Pharmacologic intervention that blocks implicated pathways also blocks or ameliorates adverse effects. • In comparison, the molecular data for PAH are considered suggestive of a causal association between PAH and lung cancer due to a lack of an observed exposure-dose-response relationship (likely due to uncertainties in exposure characterization), and data quality, analysis, and reporting limitations. Only about 8% of studies in GEO and AE met study selection criteria.

		• Additional evidence for the involvement of specific pathways in disease is provided by identification of naturally occurring human gene variants in the AOP network that alter susceptibility and risks (Cooper et al. 2013; Hatzimichael and Crook 2013; Moreno-Macias et al. 2013; Schlenk et al. 2008; Shen et al. 2011; Sillé et al. 2012; Smith et al. 2011; Vawda et al. 2014; Zhuo et al. 2012). • Adverse outcome pathway (AOP) networks are also disrupted by other chemical and nonchemical stressors known to alter the incidence of the specific disease/disorder under consideration; thus, AOP networks provide a tool for evaluating cumulative risks based on mechanistic commonalities (IARC 2012; Smith et al. 2011; R Thomas et al. 2012). • Supporting data are provided by multiple molecular epidemiology and clinical studies and chronic animal bioassays and coherence with other systems biology data (NIH BioSystems: acute myeloid leukemia, lung cancer (small cell, non-small cell); Comparative Toxicogenomics Database: PAHs and cancer: (EPA 2013a, b): BaP and cancer, ozone and respiratory disease). • Although species and *in vitro* differences exist, these examples provide consistent, coherent biologically plausible data linking specific omic alterations with specific diseases.	**Suggestive vs. likely:** In general, molecular data alone associated with adverse outcomes are expected to be only suggestive or inadequate for causal determination. To rise to likely, the following are generally necessary: multiple, consistent, high-quality observational studies with similar results; understanding of the cascade of events between molecular events to adverse outcomes, and experimental evidence showing that reversal of pathway alterations blocks or ameliorates adverse outcome; or naturally occurring experiments where gene variants alter incidence or characteristic of disease. Important variables such as experimental paradigm (e.g., *in vivo* vs. *in vitro*), cell type, tissue type, and species also require consideration. Suggestive data are likely to be most useful for hypothesis generation, discovery, screening and prioritization, and potential augmentation of traditional data.
Tier 2	**Knowledge mining and meta-analysis** prototype illustrated how large searchable databases can be used to identify, organize, integrate, and analyze existing data in an automated (computerized) fashion to discover new insights into public health risks.	• **Knowledge mining and meta-analysis discovered associations between known exposures (biomonitoring) to several environmental agents** (e.g., metals and persistent organics chemical) with prediabetes/diabetes using the Centers for Disease Control and Prevention's National Health Assessment Examination Survey. Human tissue biomarker and clinical outcome data are from the same individuals (EPA 2015a; Patel et al. 2012; Patel et al. 2013a). • Supporting data are found elsewhere in the literature (NIEHS 2015b; Thayer et al. 2012). • No systems biology context or AOP is available for data from NHANES. Information on biological context is available from the literature but currently not easily accessible in high- or medium-throughput approaches (Audouze et al. 2013; Inadera 2013). • Prototype also explored possible links among site-specific chemical exposures, ethnicity, genetic variants, and diabetes risks (Dimas et al. 2014; EPA 2015a; Patel and Cullen 2012).	**Suggestive:** Could rise to likely with the types of supporting data noted above under "Suggestive vs. likely." Associative data generally most useful for hypothesis generation.

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	Short-duration *in vivo* exposure bioassays data use in either alternative or rodents species is illustrated in two prototypes.	**Short-duration, *in vivo* exposure bioassays—alternative (nonmammalian) species prototype included example zebrafish developmental assay results, characterization of thyroid-specific mechanisms, and predictive modeling of complex dose-response phenomena.** Padilla et al. (2012) reported AC_{50}s in a zebrafish developmental assay for 305 chemicals. Potencies for individual chemicals and chemical classes were shown to range over several orders of magnitude (1 nM–80 µM). For certain classes of chemicals, 80–100% of the chemicals in a class tested positive (embryo death or structural defects). Perkins et al. (2013) illustrated the use of alternative species to help articulate mechanisms showing an AOP network for thyroid disruption with example toxicants and alternative models applicable to both human and ecological hazard assessment. Also discussed are how predictive models coupled to mechanistic understanding can be used to better characterize dose-response (Sipes et al. 2011b), circadian variations (Eisenberg et al. 2008), and exposure window-response relationships (DeWoskin et al. 2014). For more details on alternative species bioassays see Ankley and Gray (2013), Perkins et al. (2013), and Villeneuve et al. (2014).	**Suggestive to likely** for consistent, coherent, biologically plausible adverse phenotypic outcome data from nonmammalian, vertebrate species. Confidence is generally higher for evolutionarily conserved processes. **Suggestive:** For transcriptomic changes correlated to adverse outcomes studies and coupled to AOPs. High-content assays with measurable adverse outcomes (e.g., zebrafish developmental assay) generally have greater evidentiary weight than initiating event assays (e.g., transcriptomic assays). Some systems biology context is needed for limited-scope assessments for human risk (e.g., cross-species conservation, AOPs). Alternative species outcome data alone are sufficient for ecologic risk assessment. Cross-species extrapolation and subchronic measurement of indicators introduces additional uncertainties as compared to human data discussed above data. Reverse toxicokinetic models are needed to estimate equivalent human doses.
		Short-duration, *in vivo* exposure bioassays—rodent prototype correlated transcriptomic alterations with adverse outcomes, as determined in traditional bioassays for 10 chemicals (Thomas et al. 2011; RS Thomas et al. 2012; Thomas et al. 2013c). Consistency of the correlation between transcriptional changes and adverse effects across different exposure periods was also demonstrated (5 days to 13 weeks) (Thomas et al. 2013c). Transcriptional changes appeared at somewhat lower concentrations than traditional effects. Transcriptomic studies alone cannot predict specific hazards but might be useful to relatively ranking chemical potencies to induce biologic alterations that might precede adverse outcomes. In general, transcriptomic data require some biologic context (e.g., AOPs) to increase confidence of biologic significance.	

Tier 1	**QSAR and molecular docking models** are used to generate potency estimates and, with less confidence, hazards. Read-across is also considered (i.e., filling data gaps for data-poor chemicals by analogy with structurally related, more data-rich chemicals).	**QSAR models can predict chemical-specific toxicity values based on chemical inherent properties for several data-poor chemicals.** • Models are developed based on chemical structures and known outcomes for data-rich chemicals. • Organisation for Economic Co-operation and Development (OECD) is harmonizing international use of QSAR hazard models and read-across in the OECD QSAR toolbox (OECD 2014, 2015a, b). • Often, the consensus of a suite of appropriate models is the preferred approach. • Often, models better predict potency than specific effects. • Issues exist around characterizing the uncertainty in QSAR and related read-across approaches and in the transparency of some models [see Ball et al. (2014) and Patlewicz et al. (2013)].	**Suggestive to Likely:** TOPKAT Model predictions of potency when model is appropriate for chemicals evaluated; not generally predictive of dose-response for specific hazards; does generate a lowest-observed-adverse-effect level for a subset of the data-poor chemicals that meet confidence criteria. Additional OECD models and read-across can improve confidence in hazard characterization.
	High-throughput, *in vitro* bioassays and virtual tissue models are discussed.	**High-throughput *in vitro* assays** based on biological process disruptions are interpreted in systems biology and AOP contexts, and associated with adverse outcomes (Attene-Ramos et al. 2013; EPA 2015a; Judson et al. 2014; Tice et al. 2013). **Virtual tissue modeling** provides additional tools for evaluating data-limited chemicals (Knudsen et al. 2013).	**Suggestive:** When coupled with understanding of the AOP(s). Could rise to likely with the types of supporting data noted above under "Suggestive vs. likely."

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