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Providing the Missing Link: the Exposure Science Ontology ExO

Carolyn J. Mattingly,*[,†] Thomas E. McKone,[‡] Michael A. Callahan,[§] Judith A. Blake,[∥] and Elaine A. Cohen Hubal[⊥]

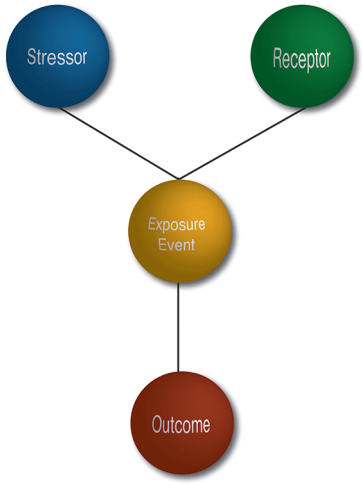
[†]North Carolina State University, Raleigh, North Carolina 27695, United States

[‡]University of California, School of Public Health and Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States

[§]MDB, Inc., Durham, North Carolina 27713, United States

[∥]The Jackson Laboratory, Bar Harbor, Maine 04609, United States

[⊥]National Center for Computational Toxicology, U.S. EPA, Research Triangle Park, North Carolina 27711, United States



Environmental health information resources lack exposure data required to translate molecular insights, elucidate environmental contributions to diseases, and assess human health and ecological risks. We report development of an Exposure Ontology, ExO, designed to address this information gap by facilitating centralization and integration of exposure data. Major concepts were defined and the ontology drafted and evaluated by a working group of exposure scientists and other ontology and database experts. The resulting major concepts forming the basis for the ontology are "exposure stressor", "exposure receptor", "exposure event", and "exposure outcome". Although design of the first version of ExO focused on human exposure to chemicals, we anticipate expansion by the scientific community to address exposures of human and ecological receptors to the full suite of environmental stressors. Like other widely used ontologies, ExO is intended to link exposure science and diverse environmental health disciplines including toxicology, epidemiology, disease surveillance, and epigenetics.

Significant progress has been made over the past decade in collecting and improving access to genomic, toxicology, and health data. The resulting information resources, however, lack extensive and reliable exposure data required to translate molecular insights, elucidate environmental contributions to diseases, and assess human health risks at the individual and population level. Recent advances in a range of fields provide an important opportunity to extend and integrate the field of exposure science with other research activities linked to occupational and community environments, genomics, medical research, urban systems studies, and ecosystems science. Many fields are developing ontologies and knowledge systems as a way of organizing and analyzing large amounts of complex information from multiple scientific disciplines to provide unprecedented perspective and enable more informed hypothesis development . Here we report on the development of an Exposure Ontology, ExO, to formalize conceptualization of exposure science and extend the ability to integrate and analyze exposure information within the broader context of environmental health.

WHAT IS EXPOSURE SCIENCE?

Exposure is the contact between a stressor and a human or ecological receptor.[1] Exposure science focuses on understanding and characterizing receptor interactions with one or more environmental stressor of concern. Although the primary focus of exposure science for human-health risk assessment has involved an individual or human population as a receptor of exposure and a chemical as an stressor of exposure, these concepts can be more broadly defined.[2] For example, the receptor can be an organ, tissue or cell, and the stressor can be a biological, physical, or psychosocial agent. Exposure assessment may include estimating the magnitude, frequency, and duration of an exposure, along with characteristics of the receptor.[1] For chemical stressors, exposure information is required to understand a system-level response to chemical perturbations and implications at the individual and population levels, as well as to link information on potential toxicity of environmental contaminants to health outcomes.

In a recent report by the National Research Council (NRC) of the National Academy of Sciences (NAS), "Toxicity Testing in the 21st Century: A Vision and a Strategy," the authors noted that population-based data and human exposure information are required at each step of their vision for toxicity testing.[3] Exposure needs highlighted in the NRC report include (1) human exposure data to select doses for toxicity testing facilitating development of environmentally relevant hazard information; (2) biomonitoring data to relate real-world human exposures with concentrations that perturb toxicity pathways

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(i.e., biologically relevant exposures); and (3) information on host susceptibility and background exposures to interpret and extrapolate (i.e., translate) in vitro test results for risk assessment.

Exposure information is also integral for understanding interactions among the environment, genetics, and health.[4,5] Common complex diseases such as asthma, autism, diabetes and obesity arise from the combined effects of both genetics and environmental exposures.[6] As genomic research advances, there is increasing recognition that understanding the contribution of environmental factors to disease etiologies will require a more comprehensive view of exposure and biological response than has traditionally been applied.[7]

A number of recent advances in a range of scientific fields make possible significant growth of the role of exposure science in health studies. These advances include (a) rapidly expanding biomarkers based on tissue residues, metabolomics, and other "omics", (b) exposure surveys that provide useful but incomplete data on links between tissue levels and chemical loads in food, air, soil, and indoor environments, (c) the growing availability of geographical positioning and geographical information technologies to track both people and pollutants, and (d) advances in the theory and applications for environmental chemistry.[8] However, the ability to obtain, evaluate and integrate information about exposures to harmful agents that arise from diverse sources remains inadequate. The National Institutes of Health (NIH) reported that recent increases in the incidence of chronic diseases, such as diabetes, childhood asthma, obesity, or autism are likely due to changes in our environments, diets, or activity levels. In defining the goals of its Exposure Biology Program, the National Institute of Environmental Health Sciences states that "understanding the contribution of environmental factors to disease susceptibility will require a more comprehensive view of exposure and biological response than what has traditionally been applied".[6] Addressing these challenges requires a more formal integration of exposure science with advances in related fields so that it can be leveraged more effectively for regulation, prevention, and risk management.

DOES THE FRAMEWORK EXIST FOR INTEGRATION OF EXPOSURE DATA?

Recognizing the critical need for exposure information to inform chemical design, evaluation and health risk management, the ExpoCast program was initiated to meet challenges posed by new toxicity testing approaches.[9] The goal of this research initiative is to advance characterization of exposure required to translate findings in computational toxicology to information that can be directly used to support exposure and risk assessment for decision- making and improved public health. Broadly and long-term, the ExpoCast program will foster novel exposure science research to link information on potential toxicity of environmental contaminants to real-world health outcomes. Significant progress has been made in collecting and enabling wide access to genomic, toxicology, and health data.[10−12] For example, the Comparative Toxicogenomics Database (CTD; http://ctdbase.org) promotes understanding about the effects of environmental chemicals on human health through literature curation and integration of data describing chemical interactions with genes and proteins as well as chemical- and gene-disease relationships.[10] Outstanding needs identified under the ExpoCast program by the environmental health, exposure research and risk assessment communities include (a) centralizing and contextualizing exposure data into a broader biological framework that includes disease- and mechanism-based information and (b) provide novel resources for developing predictive models and hypotheses about the complex connections between "real-world" environmental exposures and human health effects. Meeting these outstanding needs will require comprehensive exposure data curation and integration initiatives. A current roadblock to implementing such initiatives has been the lack of an exposure ontology.

ONTOLOGIES AND THEIR STATUS IN EXPOSURE SCIENCE

An ontology is a formal representation of knowledge within a domain. It typically consists of a structured set of terms, their definitions and an explanation of the relationships between the terms.[13] Ontologies are critically important for specifying data of interest in a consistent manner, thereby enabling unambiguous data aggregation, analysis and exchange. Currently, the most widely implemented ontology in biomedical research is the Gene Ontology (GO), which provides hierarchical controlled terms that describe the biological processes, molecular functions and cellular components of gene products.[14] Widespread use of GO for functional annotation has been invaluable for facilitating querying, analysis and interpretation of molecular information from diverse genome data repositories and high-throughput data sets.[15]

Several exposure glossaries have been developed.[16−19] Most recently, the International Programme for Chemical Safety (IPCS), as part of the World Health Organization's (WHO's) Harmonization Project, compiled 57 glossaries containing at least one exposure-related term into a larger glossary of several hundred terms with the definitions from each of the glossaries retained under each term.[16,17] From these varied definitions, the IPCS committee identified about 20 important terms and developed consensus definitions for these,[1] which were then adopted by the International Society of Exposure Science for use in society publications.[18] While the glossaries identify major concepts, these are not sufficiently detailed or formally structured to enable comprehensive exposure data curation, integration and analysis. An exposure ontology, consistent with those being used in toxicology and other health sciences, is required to formally represent exposure concepts, the relationships between these concepts and most important, the relationships between exposure, susceptibility, and toxicology information.[19]

DEVELOPMENT OF AN EXPOSURE ONTOLOGY (EXO) TO FACILITATE CENTRALIZATION AND INTEGRATION OF EXPOSURE SCIENCE

A successful exposure ontology must facilitate the semantic retrieval of exposure data in the context of environmental health science, medical surveillance, disease control, health tracking, risk assessment, and other public health and environmental science endeavors. Its implementation will enable biocurators to generate standardized annotations from the published literature and experimental data sets and connect these annotations to broader-based biological data, similar to what has been achieved in other biomedical fields. To facilitate improved integration of and access to exposure information, we initiated development of an exposure ontology with an *initial* focus on human exposure to chemicals. However, the ultimate intent is to provide classes that can be extended to encompass exposure data for the full range of stressors and receptors.

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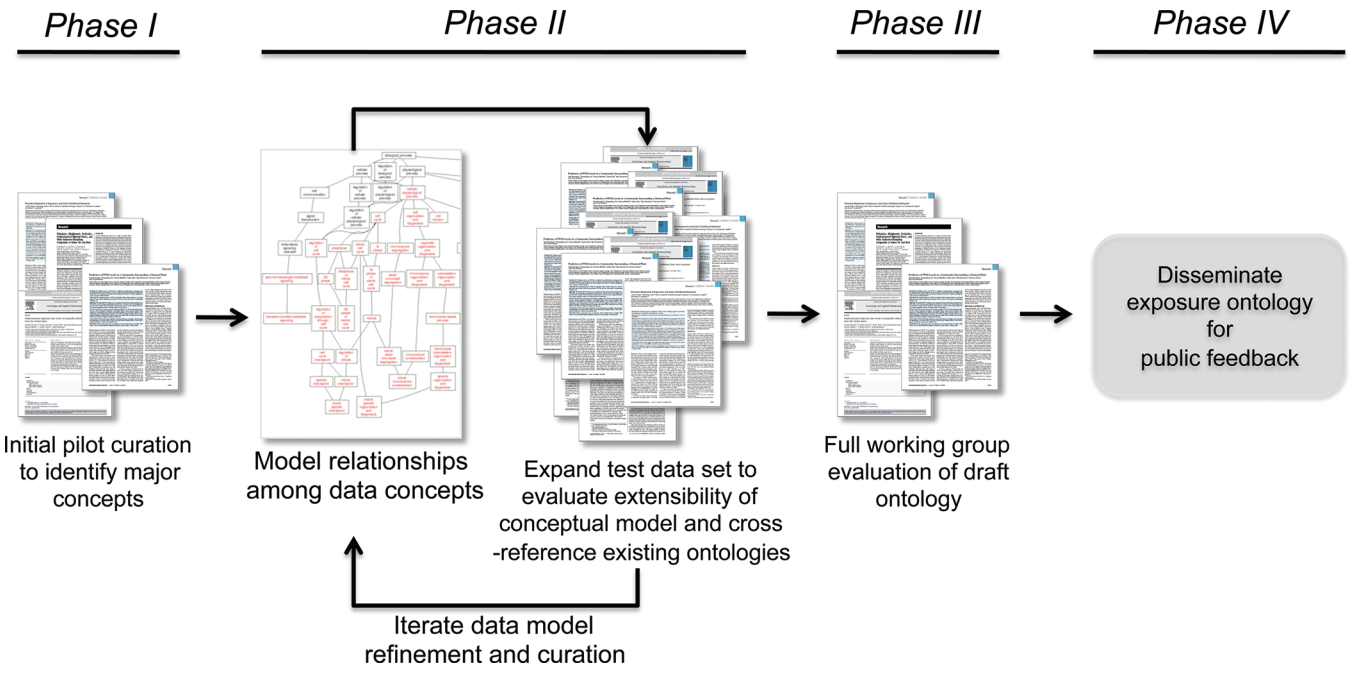

Figure 1. Phases of exposure ontology development. ExO was developed using a phased approach. During phase I, the exposure science working group defined major concepts for the ontology based on a pilot curation project and by leveraging prior glossary development efforts. In phase II, the ontology draft was developed. The draft was reviewed and tested by the working group during phase III. Phase IV launches the public release of the draft ontology for community feedback and expansion.

We used the Gene Ontology project as model for our ontology development process[20] but also assured broad participation from fields linked to exposure science. We formed an exposure ontology working group that included the authors of this paper along with ten other scientists selected to broadly represent the community of exposure science, experts in database and ontology development, as well as expertise from the complementary fields of genetics, molecular biology, computational toxicology, clinical medicine, regulatory scientists, environmental chemistry, air quality science, indoor environmental science, and environmental health sciences. The working group included research, academic, regulatory, industrial, and nongovernment organizations. The authors sought input from the working group in preparing both the manuscript and the case-study curations. We implemented a phased strategy for developing the ontology, which we call ExO.

Phase I: Define Major Concepts for the Ontology. To identify the major biological concepts and frame the exposure ontology, working group members conducted a pilot curation of a common set of four publications selected to be broadly representative of exposure science literature. On the basis of the results from the first round of this pilot curation, the group defined major concepts or root classes on which to build a draft ontology, namely exposure stressor, exposure receptor, exposure event and exposure outcome.

Phase II: Draft the Ontology. Once the root classes were outlined and defined, we began structuring these classes into a hierarchy that consisted of more specific subclasses (often referred to in hierarchical taxonomies as child terms), as well as the relationships between these levels of classes or terms. This process involved iterative rounds of pilot curation to test whether the terms were relevant and could effectively represent the critical information in the studies evaluated. Definitions of terms throughout the hierarchy were also created to ensure clarity and consistency of use. To avoid duplication with existing ontologies, and to maximize the potential for data aggregation in the future, we cross-referenced our terms with other ontologies using the OBO Foundry (http://www.obofoundry.org/) and National Center for Biomedical Ontology's (NCBO) BioPortal (http://bioportal.bioontology.org/) sites. These sites provide query mechanisms for accessing terms within available biomedical ontologies. Among the 80 terms in the draft ontology, 34 mapped to terms from a total of 15 existing ontologies, and the IDs, terms, and definitions from these ontologies were adopted and database cross-references (dbxref) were established.

Phase III: Review and Test the Ontology. To ensure that the draft ontology adequately reflected diverse areas of exposure research, it underwent rigorous review by the full working group. This process required that each working group member identify and curate approximately three additional manuscripts each in his/her specific area of expertise. This round of pilot curation results was evaluated as a group and used to make necessary refinements to the ontology.

Phase IV: Disseminate the Ontology. To maximize the utility of the exposure ontology, we invite feedback from the public. To facilitate this process, we formatted the draft ontology using the standard Open Biomedical Ontologies (OBO) format and made it available at multiple sites, including CTD (http://ctdbase.org/downloads/#exposures), OBO Foundry (http://www.obofoundry.org/), and NCBO BioPortal (http://bioportal.bioontology.org/). Each of these sites provides a mechanism for the community to submit feedback to the developers. On a bimonthly basis, feedback will be incorporated into ExO in a version-controlled manner in coordination with the CTD project. Modified versions will be appropriately designated and updated on each of the aforementioned sites for ongoing public review and development.

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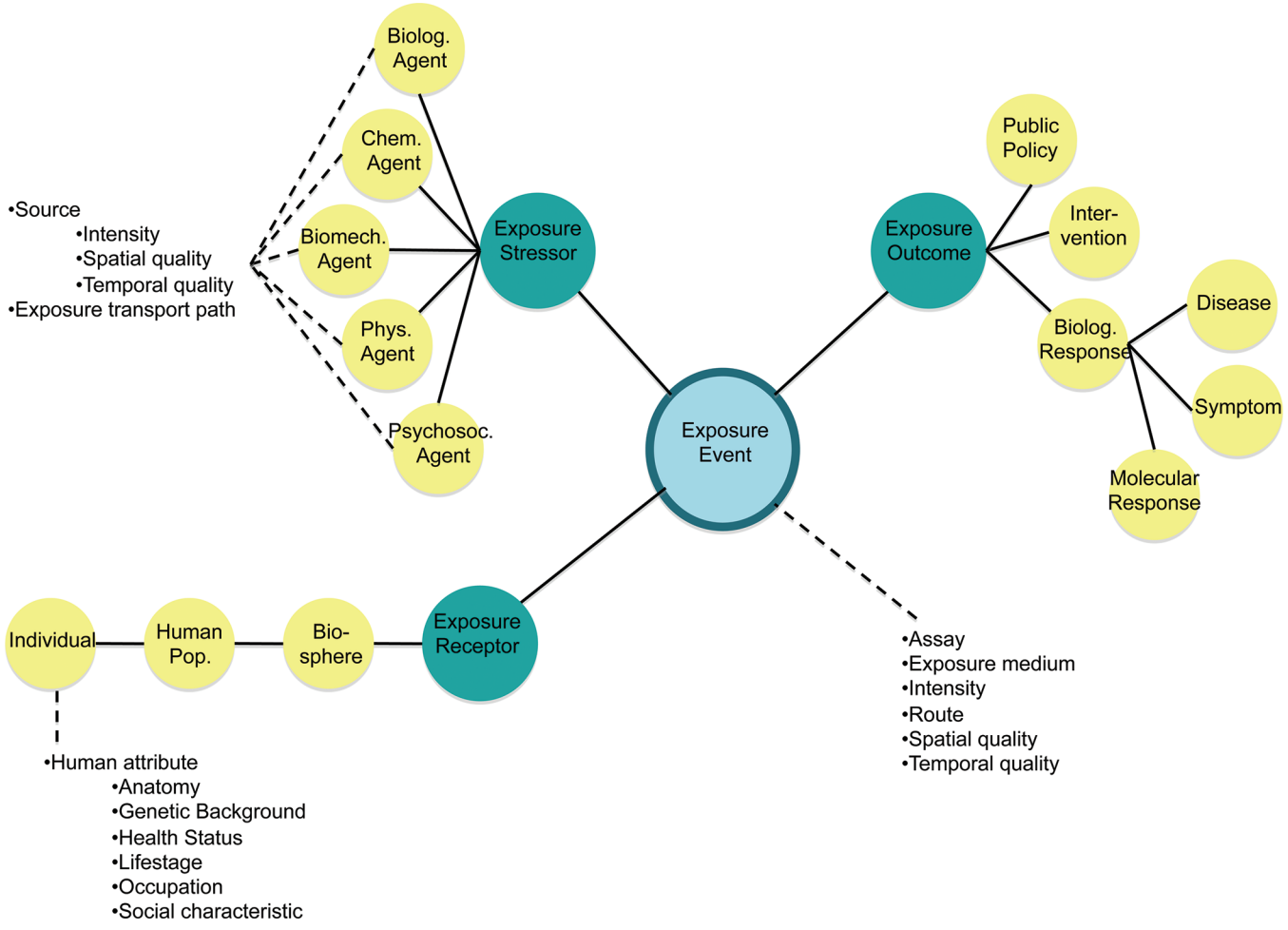

Figure 2. Relational view of ExO concepts (classes). The central concepts of ExO are shown in relation to an Exposure Event and include Exposure Stressor, Exposure Receptor, and Exposure Outcome (green circles). Select child terms (yellow circles) and attributes of these terms (bulleted lists connected by dashed lines) are also included to provide a high-level view of the ExO structure.

THE EXO FRAMEWORK

ExO is anchored by four major concepts or root classes that were identified by the working group as key to capturing exposure information. These concepts are (1) exposure event, (2) exposure stressor, (3) exposure receptor, and (4) exposure outcome. They are generically related in that an "exposure stressor interacts with an exposure receptor via an exposure event resulting in an exposure outcome." We defined these terms as follows or through cross-references to other ontologies (ontology name, ID):

- Exposure Stressor: An agent, stimulus, activity, or event that causes stress or tension on an organism and interacts with an exposure receptor during an exposure event.
- Exposure Receptor: An entity (e.g., a population, organism, tissue, cell) that interacts with an exposure stressor during an exposure event.
- Exposure Event: An interaction between an exposure stressor and an exposure receptor.
- Exposure Outcome: An entity that results from the interaction between an exposure receptor and an exposure stressor during an exposure event (e.g., asthma, metabolite formation, oxidative stress, upregulation of a gene).

ExO is structured hierarchically to allow representation of data related to or characteristic of these concepts at varying levels of detail. Although aspects of these classes are represented in other ontologies, to our knowledge they are not related in an existing ontology with the structure and format required by the exposure science community. The root classes of ExO, as well as select child terms are illustrated hierarchically in Figure 2. Shown here, biological, chemical, biomechanical, physical, and psychosocial agents are types, or children, of exposure stressors. Each stressor can then be further defined with additional child terms or attributes through development of novel terms or by leveraging terms from existing ontologies as needed (not shown in depth here for simplicity). For example, in a particular context, a specific chemical agent, such as bisphenol A (BPA), may have a known source, as well as a designated intensity and associated spatial and temporal qualities. The ontology aims to represent the *possible* spectrum and granularity of data involved in an exposure event or study.

The development and use of terminology that is both accepted and widely used by exposure practitioners is critical for integration and future growth of the exposure science field. In this work, we found that the essence of exposure science is the study of the co-occurrence of a stressor and a receptor. Exposure science provides the spatial/temporal narrative of the intensity (e.g., concentration) of a stressor at the boundary between two systems, one functioning as an "environment" and one functioning as a target (receptor). Exposure science explains and describes these processes with respect to an outcome.

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Table 1. ExO Terms Invoked to Curate Two Exposure Reports[21,22]

Braun et al. (2009)			
exposure stressor	**chemical agent**		
	bisphenol A		
exposure receptor	**human population/lifestage**	**human population/location**	
	mothers	Cincinnati, OH	
	2-year old children	Cincinnati, OH	
exposure event	**location**	**assay/medium**	**assay/method**
	gestation environment	maternal urine	HPLC
			behavioral assessment system for children (BASC-2)
exposure outcome	**biological response/symptom**		
	neurodevelopment		
Rudel et al. (2003)			
exposure stressor	**chemical agent**		
	phthalates		
	o-phenylphenol		
	4-nonylphenol		
	4-*tert*-butylphenol		
exposure receptor	**human population**	**location**	
	residents	Cape Cod	
exposure event	**assay medium**	**assay/location**	
	air	indoor	
	dust	indoor	

These core concepts are widely employed in the exposure science literature, but often with inconsistent descriptions/definitions. In order to make the exposure ontology compatible with international norms for concepts and terminology, we started with the IPCS glossary to seed a library of terms. Because the IPCS glossary is limited, we found it necessary to generalize, extend and update terminology, an effort that was informed by the numerous rounds of pilot curation that were carried out by the working group during ontology development.

TWO EXAMPLES OF EXO APPLICATIONS

Example 1: Biomedical Literature Curation. The goal of a biomedical curation project is to identify the major concepts of a scientific study in the published literature and annotate these concepts concisely and reproducibly using standardized terms, which can then be leveraged to analyze these concepts within or across many studies and other research areas. To demonstrate how ExO can be used to facilitate curation, we summarize the content of two different exposure studies and present the terms used to capture the major concepts.[21,22]

- Braun et al. examined the association between prenatal BPA exposure and behavior changes in 2-year-old children.[22] Exposure is believed to result from BPA polymers that can be hydrolyzed and leach from products like food containers and baby bottles. The authors used data from 249 mothers and their children in Cincinnati, Ohio. Maternal urine was collected at ∼16 and 26 weeks of gestation and at birth. BPA concentrations were quantified using high-performance liquid chromatography−isotope-dilution tandem mass spectrometry. Child behavior was assessed at 2 years of age using the second edition of the Behavioral Assessment System for Children. Results suggested that that prenatal BPA exposure may be associated with externalizing behaviors in 2-year-old children, especially among female children.
- Rudel et al. sampled indoor air and dust in 120 homes from Cape Cod, Massachusetts in which they analyzed 89 organic chemicals identified as endocrine-disrupting compounds (EDCs).[21] The authors detected 52 compounds in air and 66 in dust. The most abundant compounds in air included phthalates (plasticizers, emulsifiers), *o*-phenylphenol (disinfectant), 4-nonylphenol (detergent metabolite), and 4-*tert*-butylphenol (adhesive) with typical concentrations of 50−1500 ng/m^3. Penta- and tetrabrominated diphenyl ethers (flame retardants) were frequently detected in dust, and 2,3-dibromo-1-propanol was detected in air and dust. Twenty-three pesticides were detected in air and 27 were detected in dust, the most abundant included permethrins and piperonyl butoxide. For virtually all target compounds, levels detected in indoor air were higher than those previously reported. This study provides a basis for prioritizing exposure research for individual EDCs and mixtures and new tools for exposure assessment in health studies.

Table 1 illustrates how the terms currently defined in ExO were used to effectively capture the major concepts of these two very different studies. The power of this exercise becomes apparent in the context of a large-scale curation and integration effort because these terms can then be used to query and aggregate data *across* studies in ways that are not otherwise possible from free-text summaries or abstracts. The importance of flexible query and analysis capacities is continually demonstrated through the increasing reliance of the research community on large-scale public biological database projects: all of which rely on ontologies and controlled vocabularies to store and manage the underlying data. Notably, the NIEHS awarded funds to support comprehensive curation and integration of exposure data into the existing, freely available Comparative Toxicogenomics Database (http://ctd.mdibl.org). Specifically, this project will use ExO to (a) curate, centralize and contextualize exposure data into a broader biological framework that includes

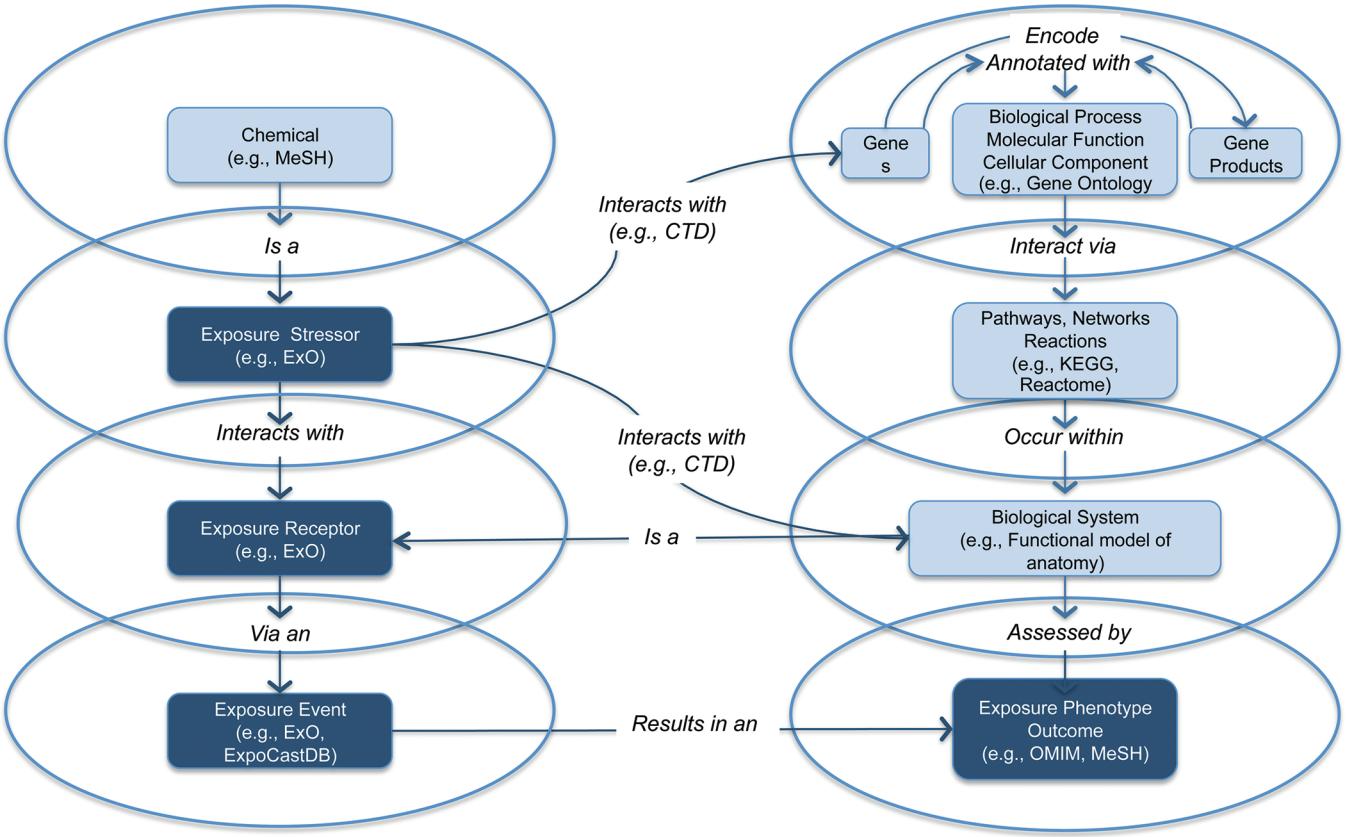

Figure 3. High-level schematic of ExO integration within a broader biological context. ExO will enable curation, aggregation and integration of exposure data with other important aspects of environmental health research such as, but not limited to chemical stressors, disease outcomes and molecular pathways. Such integration will expand the impact of exposure data and inform existing environmental health data by providing associated real-world exposure context. Light blue boxes show existing, relevant data sets and ontologies. Dark blue boxes highlight new data representations and associations made possible with an exposure ontology, ExO (Figure was modified from ref 24).

disease- and mechanism-based information and (b) develop predictive models and hypotheses about the complex connections between real-world environmental exposures and human health effects.

Example 2: Development of Linked Computational Toxicology Data Resources. The ACToR system was developed by the U.S. Environmental Protection Agency to make data on health effects and exposure potential for environmental chemicals readily accessible and to provide a resource for model-building to fill gaps in environmental health risk information.[23] The ACToR system is comprised of four interacting databases: core ACToR (includes chemical identifiers and summary data on hazard, exposure, use); ToxRefDB (a compilation of in vivo toxicity data from guideline studies); ExpoCastDB (human exposure measurement data from observational studies); and ToxCastDB (data from high-throughput screening [HTS] programs).[11]

ExpoCastDB was developed to improve access to human exposure data from observational studies, and currently houses results for a set of studies funded by EPA's National Exposure Research Laboratory. Data currently include amounts of study chemicals found in food, drinking water, air, dust, indoor surfaces and urine. ExpoCastDB is tied into the ACToR system through generic chemical linkages to facilitate integration of exposure measurement data with data on chemical toxicity, environmental fate, manufacture and use, and ToxCast HTS results. Within ExpoCastDB, controlled vocabularies are used to facilitate searching and analyses across data sets. The ExpoCastDB conceptual data model is designed to eventually capture key information for characterizing exposure, details of study design, and metadata associated with sample analysis. The controlled vocabulary and data model for ExpoCastDB are being developed to be consistent with ExO to facilitate linkages with other information resources required to support computational toxicology and chemical risk assessment as well as to encourage standardized reporting of observational exposure information.

The current version of ExO includes very high-level (i.e., more general) concepts and an expanding foundation of child (i.e., more specific) terms. Through future development and with input from the scientific community, these branches will be further specified. In keeping with an open source approach, we anticipate that existing ontologies will be leveraged heavily for this purpose (e.g., CHEBI and MeSH for "Chemical agent" Stressors; DO, OMIM and MeSH for "Disease" Outcomes). Such cross-referencing will underscore where ExO and exposure science fits into a broader knowledge space and where it may add value to existing ontologies and biomedical resources. Consistent use of ExO in efforts such as ACToR and CTD will provide increasing opportunities for collaboration, diverse cross-referencing of data and analyses of exposure information in a broader context than was previously possible.

FUTURE APPLICATIONS AND CONCLUSIONS

Similar to other biomedical ontologies, the potential applications for ExO are far-reaching and include (a) capturing

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and centralizing exposure data, (b) facilitating exchange and integration of exposure data, (c) developing exposure-relevant text mining tools (natural language processing or other approaches), and (d) leveraging comprehensive exposure information for computational analysis and modeling.[15] Figure 3 provides a high-level view of the major exposure concepts (root classes) in ExO that are not currently represented among available ontologies and how these concepts can be integrated into a knowledge system with a broader spectrum of biological data. ExO will enhance access to exposure data sets through community adoption of these terms and contribute to the needed centralization by enabling consistent curation, integration and aggregation of exposure data (see application examples described above).

Although knowledge-discovery tools are new to the exposure science community, these tools are critical for leveraging exposure information to design health studies and interpret results for improved public health decisions. Standardized ontologies define relationships, allow for automated reasoning, and facilitate meta-analyses. ExO will facilitate development of biologically relevant exposure metrics, design of in vitro toxicity tests, and incorporation of information on susceptibility and background exposures for risk assessment. In this approach, there are multiple levels of organization, from the global environment down through ecosystems, communities, indoor spaces, populations, organisms, tissues, and cells. We anticipate that the exposure science and environmental health community will adopt and contribute to this work, as wide acceptance is key to integration and federated searching of exposure data to support environmental and public health research. In particular, we anticipate acceptance of the concept that exposure science provides the spatial/temporal narrative about the intensity (concentration) of a stressor at the boundary between two systems: one functioning as an "environment" (stressor) and one functioning as a target (receptor). An agreed-upon exposure ontology with clear definitions and relationships should help to facilitate decision-making, study design and prioritization of research initiatives by enhancing the capacity for data collection and analysis in a manner that has not been possible previously. Because the exposure narrative informs research, policy, and regulation, the exposure ontology will significantly benefit these different activities as the exposure literature grows and diversifies. We encourage members of the community to review the ontology and provide comments and term additions as needed.

AUTHOR INFORMATION

Corresponding Author

*Phone: 919-515-1509. E-mail: cjmattin@ncsu.edu.

Notes

The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

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ABBREVIATIONS AND DEFINITIONS

BPA	bisphenol A
CTD	Comparative Toxicogenomics Database
ExO	exposure ontology
EDC	endocrine-disrupting compounds
GO	gene ontology
IPCS	International Programme for Chemical Safety
NAS	National Academy of Sciences
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NRC	National Research Council
WHO	World Health Organization

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