Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

Mechanistic integration of exposure and effects: advances to apply systems toxicology in support of regulatory decision-making

Annie M. Jarabek[1] and David E. Hines[2]

Abstract

Modernizing risk assessment methods that underlie risk management decisions developed to protect public and environmental health will require interdisciplinary dialog and communication. Alignment of exposures across traditional data streams such as data from *in vivo* laboratory animal and epidemiological or clinical studies, as well as integration of novel data types from emerging testing technologies and new methods of analysis, will improve causal inference. We propose a mechanistic scaffold that supports a source-to-outcome structure and an associated workflow pipeline which facilitates needed data curation and transparency regarding operational assumptions. The scaffold and workflow components enhance the utility and repurposing of data with the flexibility to support regulatory decision-making in a fit-for-purpose fashion. Efficient use of data based on this scaffold across various modeling approaches will promote "one health" characterization to improve, promote, and protect the health of all species and the environment. Associated data standards to facilitate leveraging and sharing of data will increase communication and collaboration across different disciplines to enable that end.

Addresses

[1] National Center for Environmental Assessment (NCEA), Office of Research and Development (ORD), U.S. Environmental Protection Agency (US EPA), Research Triangle Park, NC, USA

[2] National Health and Environmental Effects Research Laboratory (NHEERL), Office of Research and Development (ORD), U.S. Environmental Protection Agency (US EPA), Research Triangle Park, NC, USA

Corresponding author: Jarabek, Annie M (jarabek.annie@epa.gov)

Current Opinion in Toxicology 2019, **16**:83–92

This review comes from a themed issue on **Systems Toxicology**

Edited by **Stephen Edwards** and **Yu-Mei Tan**

Available online 14 September 2019

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2019.09.001

2468-2020/Published by Elsevier B.V.

Keywords

AEP, Aggregate exposure pathway, AOP, Adverse outcome pathway, CRA, Cumulative risk assessment, Evidence integration, FAIR (Findable, Accessible, Interoperable, and Reusable) principles, Mechanistic modeling.

Acronyms

AEP, Aggregate exposure pathway; AOP, Adverse outcome pathway; CEA, Comprehensive environmental assessment; CRA, Cumulative risk assessment; CSM, Conceptual site model; DAG, Directed acyclic graphs; EBT, Evidence-based toxicology; FAIR, (Findable Accessible Interoperable and Reusable); HTS, High-throughput screening; IATA, Integrated assessment and testing approach; IBE, Inference to the best explanation; MOA, Mode of action; MIE, Molecular initiating event; MCDA, Multi-criteria decision analysis; RWE, Real-world evidence; SEND, Standard for Exchange of Nonclinical Data (SEND); TSE, Target site exposure.

Introduction: Modernizing assessment methods

It has long been recognized in the practice of risk assessment for public health protection that the cumulative risk of disease in a population or community results from aggregate exposures to multiple agents or stressors [61]. Multiple chemical, physical, biological, and psychosocial agents or stressors, as well as potential buffers or mitigating factors, combine to determine the actual vulnerability to disease. For example, environmental factors such as toxic chemical emissions to air, water, or soil all impact both human and ecological systems, and superimpose on physiological background (e.g., intrinsic traits such as race, gender, age; behavior, and genetic sensitivities) and lifestyle conditions (e.g., socioeconomic status and health care access). Conceptual site models used in cumulative risk assessment attempt to capture those complexities by mapping stressors and the propagation of their impacts through various media and receptors, and strategies for problem formulation and data sources have been provided [38,43,62]. However, most of these approaches are not mechanistically based and focus on identifying qualitative associations and patterns of evidence rather than causal interactions. While some approaches such as directed acyclic graphs, a type of graphical causal model comprising nodes connected by unidirectional arrows to depict relationships, can be used to represent elements in a conceptual site model and purport to inform causality [10], narratives that provide the ability to integrate more and various data types are often preferred to arrive at inference to the best explanation regarding the causes of observed effects [76]. However, commonly used qualitative frameworks that apply a weight of evidence approach to inference to the best explanation (e.g., those regarding a mode of action for risk

assessment of a chemical [37,75]) often do not consider exposures relevant to the problem formulation or align exposures across the various experimental platforms that underlie the different types of data. Toxic effects, or more recently key characteristics [57], may be listed as a sequence of likely events based on current understanding of various target toxicities (e.g., cancer, reproductive toxicity) but the relationship among them is not quantified (e.g., how much of one event is necessary to observe the next) nor are dose—response relationships evaluated within a biological system or source-to-outcome construct.

More recent guidance has acknowledged that emerging technologies allow the measurement of toxicant concentrations in both media and various biological samples, so that the next generation of exposure science to inform risk assessment aims at comprehensive characterization of exposures and effects in an integrated fashion [36,44,52]. This characterization should include integration of biomarker measures and "-omic" technologies to describe the exposome [14,16,35]. Emphasis is now on proper alignment of various exposure platforms (e.g., in vitro, in vivo, and epidemiological) to support quantitative evaluation of the interactions between relevant physical, chemical, or biological stressors and receptors, thereby facilitating inferences for risk assessment [46].

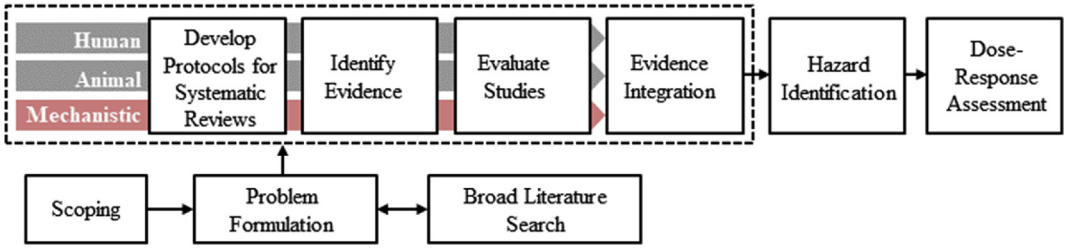
Realizing the promise that comprehensive exposures and effects characterization would bring to improve risk assessment through the integration of evolving exposure measures with emerging biomedical resources also requires coherent application of diverse data that reflect rapid advances in novel measurement technologies and computational modeling. For example, operational procedures in risk assessment aimed at environmental and public health protection are increasingly utilizing systematic review to identify relevant studies and foresee the application of artificial intelligence approaches to increase their efficiency and scope [6,26,27,68]. These practices were originally developed in the clinical arena; adopting them to toxicological questions requires addressing the challenges of integrating data from multiple evidence streams, multiple animal species (and strains), and multiple outcomes and endpoints that characterize hazards. In addition, this adoption must also address evaluating exposures to complex mixtures and accounting for the frequent lack of human data that necessitates extrapolation from other species to human outcomes [26,69].

Current approaches to hazard identification use systematic review and criteria for data relevance that consider the contributions of human health, experimental animal, and mechanistic data streams according to separately defined PECO (Population, Exposure, Comparator, Outcome) statements. These PECO statements reflect problem formulation [26,68]; and these data streams are processed in a somewhat hierarchical (e.g., preference placed on human data when available) and parallel approach (Figure 1). While systematic review is a needed advancement to formalize and structure the evaluation of study quality and relevance, the parallel approach to different data streams currently practiced precludes the necessary alignment across exposure and experimental platforms that is requisite to achieve a quantitative description of the pathogenic processes for various disease outcomes. Furthermore, interdisciplinary dialog is not fostered which prevents critical data integration.

The adverse outcome pathway (AOP) framework provides a mechanistic description of toxicity pathways within organisms that evolves with current knowledge to characterize disease pathogenesis as a biological signature involving key events as sequelae in response to a molecular initiating event or molecular initiating event (MIE) [4]. Owing to its chemical-agonistic nature [65,66], this tool has gained global traction as a framework for organizing and evaluating mechanic information [31] and can be used to guide workflows for the application of high-throughput screening data and other emerging data into regulatory risk assessment [1,15]. The aggregate exposure pathway (AEP) framework has been proposed as an analogous structure to AOPs that organizes exposure data and predictions to provide a mechanistic description of exposure pathways [60]. AEPs are broader than other targeted exposure frameworks [40] in that they encompass the environmental transport and transformation of chemicals as well as toxicokinetic interactions within organisms leading to the target site exposure as the concentration at the biological location of the MIE in an AOP. Thus, coupling the AEP and AOP frameworks together provides a source-to-outcome continuum that enables risk-based, hazard-based, or exposure-based decision-making [16,58,59]. Network structures such as AOPs and AEPs are useful for risk assessments because they can provide comprehensive representation of organisms within their environments as complex systems [23].

While hazard assessment and prioritization of chemicals for further testing can make direct use of descriptive (qualitative) AOPs, risk assessment requires quantitative relationships from exposure to effect timing and magnitude [13,47,73]. Quantitation of the AEP and AOP components is the needed next step to advance their use in regulatory risk assessment. Applications range from prioritization to dose—response analyses, as well as to position assessment approaches to integrate the data generated by new alternative methods with traditional *in vivo* testing, and best bridge with systems biology and computational models of virtual tissues. As new research continues to expand scientific knowledge of exposure and toxicity pathways, transparent

Figure 1



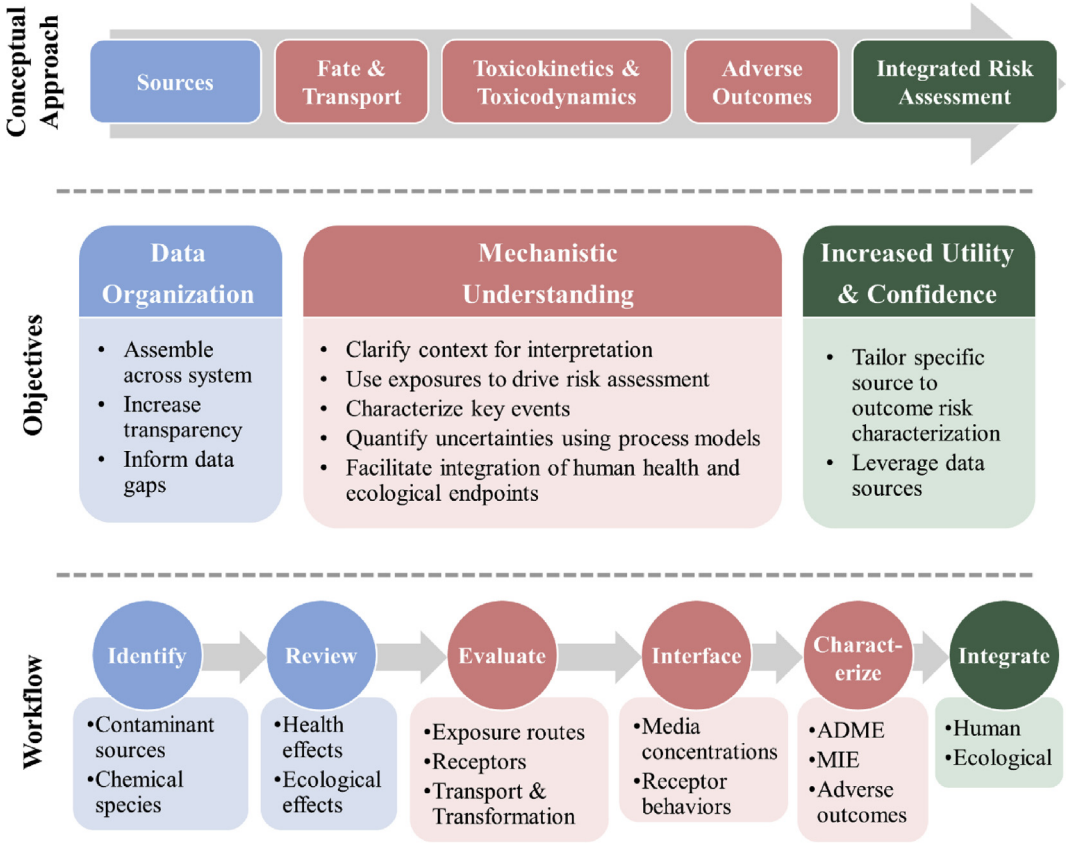
Schematic of systematic review and evidence integration for human health risk assessment in the Integrated Risk Information Systems (IRIS) at the US EPA [45]. Mechanistic data stream highlighted for emphasis.

workflows for the collection, alignment, and integration of exposure and effects data will be crucial for using this information to effectively inform various risk assessment applications.

Mechanistic modeling as a systems scaffold

To advance cumulative risk assessment approaches to take advantage of emerging data streams and apply

Figure 2



Mechanistic scaffold encompassing components of a comprehensive "source-to-outcome" conceptual model structure and an associated workflow using process elements consistent with objectives of systematic review and combined AEP:AOP frameworks. The workflow provides data assembly and organization to align exposure and effects data in support of integrated analyses across species to characterize and quantify key events and key event relationships. Each major action area (e.g., review, evaluate) across the workflow facilitates multiple data streams to be considered in an integrated fashion. Consideration of mechanistic data and an underlying understanding of the pathogenic process is emphasized to provide quantitation (e.g., data on transport and transformation measurements; receptor behaviors; absorption, distribution, metabolism, and elimination [ADME]; dose–response and time course data for key events). Quantitation is necessary to describe components of the continuum in a causal description of pathogenesis across species.

systems biology, we thus propose mechanistic process modeling as a scaffold for a systems toxicology workflow (Figure 2). Mechanistic process modeling is defined as quantitative description of the determinants dictating development of a disease process due to the interaction of various receptors (e.g., organisms or test systems) with determinants that dictate environmental exposures. Process modeling was advocated originally by the NRC to capture the current understanding of disease processes and advance the application of biomarker data [41,55,56]. The utility of process modeling to both the organization and evaluation of data for the application of DNA adducts to assess human risk has been demonstrated [29,48]. Recently, efforts to directly link mechanistic toxicity pathways with relevant environmental exposure pathways have been proposed as a tool for prioritizing compounds for further evaluation and to identify potential risks to both human health and ecological outcomes [16], and a tiered workflow has been proposed for improving the acquisition and application of exposure data [40]. The use of integrated approaches to testing and assessment to provide mechanistic evidence for supporting safety assessments has demonstrated the benefits of a mechanistic approach [64,53]. For example, mechanistic modeling has been used to translate individual-based toxic effects data into endpoints meaningful at the population level (i.e., magnitude of mortality and reproductive impairment) in an assessment of the environmental fate and risk of insecticides applied by aerial spraying to control corn pests on nontarget avian species [17].

Constructing a comprehensive mechanistic scaffold can act as an organizing framework to inform ontologies or evidence maps, leverage data sources, and facilitate quantitative characterization of key events of transport and transformation used in exposure models or of disease pathogenesis. The emphasis on quantitation for each major action area of the workflow facilitates interdisciplinary dialog to enhance evidence integration in a coherent fashion thereby also increasing transparency about assumptions that may be used. Use of the scaffold also advances the harmonization of "noncancer" and "cancer" assessment approaches by integrating all relevant scientific information into a biologically coherent mode of action to improve the scientific basis of assessments [8,7]. Furthermore, coherence and consistency among the components are highlighted and can be used to leverage data. For example, key physicochemical characteristics are inherent in both environmental transport and transformation and ADME processes. The scaffold and associated workflow advance risk assessment by providing the following features: 1) highlighting data gaps and deficiencies in mechanistic understanding for both exposure and toxicity pathways, 2) accounting for chemical- and receptor-specific toxicokinetic properties, 3) providing a context for the interpretation of toxicity assays, and 4) leveraging available data to enhance their utility. For example, a recent case study demonstrated how an AOP could be used to organize mechanistic toxicity data across multiple species for supporting a site-based cumulative risk assessment [20]. In this case study, an AOP was used to assemble data from mechanistic toxicity assays, whereas an AEP provided the exposure context for interpreting the data and identifying at-risk organisms [21].

The proposed mechanistic scaffold and associated workflow pipeline address needs identified in a survey of academic, government, and business communities which indicated that identifying relevant exposure pathways and developing techniques for evaluating exposure and effects were among the 10 most important questions for researchers to address for advancing risk assessment [9]. The workflow is also consistent with a framework to catalyze the generation and utilization of real-world evidence standards and calls for improved data quality and curation, data access, and improved analytical methods and research methods to strengthen causal inference in drug safety and development [74]. Calls for evidence-based toxicology have included assessment of test performance characteristics, mechanistic understanding, extended quality assurance, formal validation, and the use of integrated testing strategies to increase the quality of results and facilitate their interpretation [25].

The use of a mechanistic scaffold provides a basis for this interpretation of results through integration of various approaches to hazard identification and risk prediction, affording the flexibility to apply different modeling techniques in a fit-for-purpose fashion commensurate with the available data. For example, prioritization may be based on large-scale predictions from HTS data of a chemical database. Mechanistic models can provide insights into the mechanistic functions of chemical properties or the exposure treatments, which are necessary to understand and overcome the limitations of data mining or machine learning predictions when applied to limited chemical domains or to extrapolate the data to address different exposure durations and concentrations. One can imagine in the future the realization of a generalized biologically based dose–response model where individual parameter calibration and model refinement would rely on a machine learning layer overtop the mechanistic framework to tailor the predictions to various exposure use cases that require characterization in the regulatory arena. Machine learning research could be harnessed to overcome the current scalability limitations of mechanistic modeling, whereas mechanistic models could be used by machine learning algorithms both as transient inputs and as a validating framework [5]. A modular approach to assembly of data and quantitative AOPs would facilitate rapid development of biological pathway models [18]. The proposed workflow based on the mechanistic

scaffold is modular and can embrace the complementary strengths of mechanistic modeling and machine learning approaches to provide, for example, the critical link between an adverse outcome prediction and the mechanistic understanding of disease pathogenesis and progression. Thus, this approach provides a basis for improved integration through hybrid observational and interventionist or experimental approaches [5,16,74]. Eventually, comprehensive characterization of "one health" to encompass and integrate all potential detrimental outcomes in the environment, including research and data from human, veterinary, wildlife, and environmental disciplines at multiple levels, is envisioned to improve the health of humans, animals, and the environment [3,22].

Supporting data quality and reporting standards

Scientific inquiry and research productivity in this evolving era of technological advances has been described as relying on observations related to the "3 V's": "Volume" (big), "Velocity" (fast—both with respect to measurement and computing), and Variety (multiple sources) and has recently focused attention on needed "rigor and reproducibility" [67]. Thus, good data management is foundational to supporting discovery, innovation, knowledge, and subsequent reuse and translation to actionable information. Beyond proper collection, quality control, curation, annotation, and archiving, it is now necessary to extend principles of reporting such as that of the Standard for Exchange of Nonclinical Data (SEND) and the Minimum Information about Microarray Experiment (MIAME) standard, to the characterization of metadata that describe the components of the "cyberinfrastructure" and elucidate details of "what, how, and why" the experimental data or models were designed, created, and used in analysis [51]. Reporting standards increase the reliability and reproducibility of results, as well as transparency when interpreting findings, and are essential for supporting regulatory decision-making [2]. Standardizing collection and reporting techniques can improve the reproducibility, transparency, and efficiency of collecting data as well as their reliability and relevance for evaluations, thus increasing their utility for informing regulatory risk assessment by ensuring that necessary information is reported [39,40]). Developing reporting standards for both exposure and effects data is a critical task because consistent data are necessary to quantitatively link results from different studies. For example, data from multiple toxicokinetic studies can be combined to parameterize models that describe a quantitative, mechanistic link between environmental exposures and the concentrations inside an organism, and therefore can inform predictions of toxic effects based on an anticipated exposure [11,32]. Risk assessment typically requires overcoming the challenge of repurposing of data from experiments that were not necessarily designed to support the inferences of interest. These data sets are typically disparate and heterogeneous, use different diagnostic categories and outcome measures including both genotypic and phenotypic information, and are based on different principles of organization, providing further issues for data integration [74]. Data management now encompasses maintaining metadata describing curation histories. For example, a repository for biological models has been developed to encourage, facilitate, and promote model dissemination and reuse once they are extensively tested and encoded in standardized formats [33]. A systems biology markup language has been developed as a file format for computational models describing biological processes so that different tools can all operate on identical representations of models, thereby removing translation errors and assuring a common starting point for analyses [28]. Taxonomies and ontologies are now being developed to facilitate reporting standardization, data sharing, translation, and analysis based on the same mechanistic principles proposed herein [19,50,72].

Clear documentation of the motivation (why), experimental design (how), and methodologies (what) used to collect exposure and effects data can facilitate their interpretation in a regulatory context [2]. For example [34], note that fix-interval monitoring techniques may not detect pulses of highly transient environmental contaminants, making it challenging to relate regulatory limits based on dose—response toxicity data from experimental testing protocols to real-world exposures. Furthermore, consistent reporting of units and assumptions can allow for integration of exposure and effects data from multiple experiments across a mechanism. Hines et al [20] adjusted dosing data to account for differences in administered doses of perchlorate salts based on the molecular weight of specific salts used in each experiment to assemble and align mechanistic effects data across an AOP. Developing an agreed-on set of reporting standards for exposure and effects data should be a priority for risk assessors to ensure that research efforts have the highest possible impact.

The proposed mechanistic emphasis for components in the scaffold and associated workflow also provides a systematic construct for stakeholder communities to both understand components of risk characterization and voice valuation preferences, regarding either exposures or species and endpoint of interest, so that decision makers can be afforded a more comprehensive characterization of alternatives and their performance. Stakeholder engagement is critical for acceptance of new technologies and approaches [63]. Thus, the approach readily informs decision support tools such as multicriteria decision analysis [30] and can help accelerate understanding and acceptance of systematic

review and computational approaches by facilitating stakeholder-specific interactions, demonstrating translation into application, and illustrating with case studies based on sites of interest [12]. Comprehensive environmental assessment has called for both a means of organizing complex environmental information from various inputs including life cycle assessment, environmental conditions, and impacts on humans and other biota, together with a structured process to engage stakeholders for reaching transparent judgments [49]. Both aspects of that assessment construct would benefit from the transparency afforded by more explicit mechanistic evaluations and documentation.

Fostering FAIR principles

The acquisition of exposure and effects data is costly. Furthermore, data sharing that enables interdisciplinary collaboration among epidemiologists, clinicians, experimental biologists, toxicologists, statisticians, and computational modelers is key to making effective use of such data to enable improved predictive capacities. Guiding principles (FAIR – Findable, Accessible, Interoperable, and Reusable) that support both manual or automated discovery and exploration have been proposed and are evolving to support good data stewardship [70,71]. Proper documentation of code and open access to models, including software for systematic review, to support interoperability is another burgeoning need to advance their acceptance and application in risk assessments. Data formats, description of the data pipeline, and workflows are recognized as a means to implement these principles, increase the utility of data, and sustain databases and repositories. More recently, Holub et al [24] have called for extension of these principles to ensure complete coverage of the provenance information for biological materials and associated data, from the physical material and all preanalytical steps, including sample stabilization and biobanking, through to the data generated and published. It is now recognized that data generated from samples (e.g., omics or imaging data) is becoming increasingly critical for creating context, ensuring reproducibility, and understanding analyses. As mentioned previously, reusability is a critical aspect for assessment applications, and reproducibility needs a clear link to reusability because, with the exception of some dedicated data registries, the data were not originally created for the specific application (e.g., evaluation of the safety or effectiveness of drugs), so their value for such secondary uses is often unreliable [74]. Mechanistic workflows and data standards can best inform this principle.

Finally, although it is now widely recognized that data sharing will accelerate discovery and innovative solutions to benefit decision-making in public health at the local, national, and global levels by enhancing transparency and cooperation, reproducibility of research, cost-efficiency, and preventing redundancies, several barriers exist to its acceptance and wide applicability [63]. Barriers fall into the following major areas: technical (e.g., lack of metadata and standards), motivational (e.g., lack of incentives), economic, political (e.g., lack of trust), legal (e.g., privacy), and ethical [63].

The proposed scaffold and explicit considerations of the components in the associated workflow will facilitate needed documentation and transparency to address several technical issues, as well as provide for communication and building trust among users. For example, at each step in the workflow, the scaffold provides a mechanistic platform to perform the specific action (e.g., review, evaluate, interface, characterize, etc.). The initial review across data types together can organize the data and provide context, highlighting similarities and differences across species regarding exposure routes and effects. Evaluating data within the mechanistic structure provides for interdisciplinary dialog regarding the nature and quantitation of the effects, so that the interfacing of the exposure data with the receptor concentrations best represents a coherent understanding across different data streams (e.g., ecological, human studies, *in vitro* assays) regarding the critical fate and transport and then ADME processes. Mechanistic understanding of physicochemical characteristics can enhance both exposure and ADME descriptions. This results in the needed alignment of experimental platforms, resulting in consistent doses at the MIE and perturbation of pathways. Consistent internal dosimetry across data types then facilitates coherent characterization of key events and dose–response analyses, again allowing for both quantitation and leveraging of data. For example, data from laboratory animals can be extrapolated using physiologically based pharmacokinetic (PBPK) models to inform dose–response analyses of human studies. Standards are anticipated to follow that will enhance reporting and incentivize populating the workflow, thereby addressing several of the technical barriers identified previously. And as the workflow is implemented, interdisciplinary dialog will build bridges and engender trust in the resultant applications and assessments. In particular, combining data within the mechanistic scaffold based on specific workflow tasks will build confidence in and accelerate the application of new technologies such as NAMs and integrated approaches to testing and assessment into the assessment process.

Summary

Understanding exposure and effects mechanisms can facilitate data organization and interpretation in support of quantitative evidence integration, as well as identify gaps in current knowledge, and is essential for regulatory applications of the Tox21 vision [42] and more recent calls for the advancement of risk assessment with

emerging technologies [46]. The current challenge facing the risk assessment community with regard to integrating mechanistic exposure and effects data is to develop workflows and reporting standards for gathering this information and applying them to systems toxicology [54]. Mechanistic modeling can serve as the basis of comprehensive characterization from stressor source to adverse outcome, and thereby supports needed exposure alignment, data organization, study quality and data relevance evaluation, and quantitative evidence integration in a transparent fashion across different exposures or experimental platforms and test species. Developing these mechanistic approaches will help to drive interdisciplinary dialog and data sharing that can advance applications of exposure and effects data in future regulatory risk assessments to better target exposures, evaluate the relevant dose of a contaminant, and characterize toxic effects with confidence across species.

Disclaimer

This article has been subjected to review by the Office of Research and Development and approved for publication. The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Drs. William Boyes and Rory Conolly for their careful reviews and constructive comments on the article. This work was funded wholly by the U. S. Environmental Protection Agency.

References

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Adeleye Y, Andersen M, Clewell R, Davies M, Dent M, Edwards S, Fowler P, Malcomber S, Nicol B, Scott A, Scott S: **Implementing Toxicity Testing in the 21st Century (TT21C): making safety decisions using toxicity pathways, and progress in a prototype risk assessment**. *Toxicology* 2015, **332**: 102–111.

2. •• Ågerstrand M, Christiansen S, Hanberg A, Rudén C, Andersson L, Andersen S, Appelgren H, Bjørge C, Clausen IH, Eide DM, Hartmann NB: **A call for action: improve reporting of research studies to increase the scientific basis for regulatory decision-making**. *J Appl Toxicol* 2018, **38**:783–785.
Authors articulate the needs of consistent and detailed reporting which will improve systematic review. Reporting standards will also improve data reliability which will be reflected in any resultant inferences.

3. Aguirre AA, Beasley VR, Augspurger T, Benson WH, Whaley J, Basu N: **One health-Transdisciplinary opportunities for SETAC leadership in integrating and improving the health of people, animals, and the environment**. *Environ Toxicol Chem* 2016, **35**:2383–2391.

4. Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, Serrrano JA: **Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment**. *Environ Toxicol Chem* 2010, **29**:730–741.

5. •• Baker RE, Peña J-M, Jayamohan J, Jérusalem A: **Mechanistic models versus machine learning, a fight worth fighting for the biological community?** *Biol Lett* 2018, **14**:20170660.
Paper describes the important features of different types of mathematical models and how they might be applied in a coherent, complimentary approach to characterize biological systems.

6. Beller E, Clark J, Tsafnat G, Adams C, Diehl H, Lund H, Ouzzani M, Thayer K, Thomas J, Turner T, Xia J, Robinson K, Glasziou P, founding members of the ICASR group: **Making progress with the automation of systematic reviews: principles of the international collaboration for the automation of systematic reviews (ICASR)**. *Syst Rev* 2018, vol. 7(1):77.

7. Boobis AR, Daston GP, Preston RJ, Olin SS: **Application of key events analysis to chemical carcinogens and non-carcinogens**. *Crit Rev Food Sci Nutr* 2009, **498**:690–707.

8. Bogdanffy MS, Daston GP, Faustman EM, Kimmel CA, Kimmel GL, Seed J, Vu V: **Harmonization of cancer and noncancer risk assessment: proceedings of a consensus-building workshop**. *Toxicol Sci* 2001, **61**:18–31.

9. Boxall AB, Rudd MA, Brooks BW, Caldwell DJ, Choi K, Hickmann S, Innes E, Ostapyk K, Staveley JP, Verslycke T, Ankley GT: **Pharmaceuticals and personal care products in the environment: what are the big questions?** *Environ Health Perspect* 2012, **120**:1221–1229.

10. Brewer LE, Wright JM, Rice G, Neas L, Teuschler L: **Causal inference in cumulative risk assessment: the roles of directed acyclic graphs**. *Environ Int* 2017, **102**:30–41.

11. Brock TC: **Priorities to improve the ecological risk assessment and management for pesticides in surface water**. *Integr Environ Assess Manag* 2013, **9**:e64–e74.

12. Carusi A, Davies MR, De Grandis G, Escher BI, Hodges G, M.Y. Leung K, Whelan M, Willett C, Ankley GT: **Harvesting the promise of AOPs: an assessment and recommendations**. *Sci Total Environ* 2018, vols. 628–629:1542–1556.

13. Conolly RB, Ankley GT, Cheng W, Mayo ML, Miller DH, Perkins EJ, Villeneuve DL, Watanabe KH: **Quantitative Adverse Outcome Pathways and their application to predictive toxicology**. *Environ Sci Technol* 2017, **51**:4661–4672.

14. DeBord G, Carreón T, Lentz TJ, Middendorf PJ, Hoover MD, Schulte PA: **Use of the "exposome" in the practice of epidemiology: a primer on -omic technologies**. *Am J Epidemiol* 2016, **184**:302–314.

15. Edwards SW, Tan Y-M, Villeneuve DL, Meek M, McQueen CA: **Adverse outcome pathways—organizing toxicological information to improve decision making**. *J Pharmacol Exp Ther* 2016, **356**:170–181.

16. • Escher BI, Hackermüller J, Polte T, Scholz S, Aigner A, Altenburger R, Böhme A, Bopp SK, Brack W, Busch W, Chadeau-Hyam M: **From the exposome to mechanistic understanding of chemical-induced adverse effects**. *Environ Int* 2017, **99**: 97–106.
A comprehensive landscape of emerging computational tools is presented. Discussion of how they can be seamlessly integrated from exposure to predict adverse outcome pathways is illustrated.

17. Etterson M, Garber K, Odenkirchen E: **Mechanistic modeling of insecticide risks to breeding birds in North American agroecosystems**. *PLoS One* 2017, **12**. e0176998.

18. Foran CM, Rycroft T, Keisler J, Perkins EJ, Linkov I, Garcia-Reyero N: **A modular approach for assembly of quantitative adverse outcome pathways**. *ALTEX* 2019, **36**:353–362.

19. • He Y, Xiang Z, Zheng J, Lin Y, Overton JA, Ong E: **The eXtensible ontology development (XOD) principles and tool**

implementation to support ontology interoperability. *J Biomed Semant* 2018, **9**:3.
Interoperability among ontologies is requisite for coherent data management and systematic review in support of public health. This paper discusses critical concepts and necessary tools.

20. •• Hines DE, Edwards SW, Conolly RB, Jarabek AM: **A case study application of the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)**. *Environ Sci Technol* 2018, **52**:839–849.
This case study is the first to apply the aggregate exposure pathway (AEP) and adverse outcome pathway (AOP) frameworks in an integrated fashion to achieve a comprehensive source to outcome description to inform cumulative risk assessment. It focuses on the AOP component and illustrates how data on both human and ecological endpoints can be integrated.

21. •• Hines DE, Conolly RB, Jarabek AM: **A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks**. *Environ Sci Technol* 2019. https://doi.org/10.1021/acs.est.9b04639 [Epub ahead of print].
This paper focuses on the AEP component of a case study that illustrates integration of the AEP and AOP frameworks. Important considerations of transport and transformation as well as of receptor behavior (e.g., diet) and of how quantitative AEP analysis of these processes propagate across to the AOP component of a comprehensive source-to-outcome conceptual model is illustrated.

22. • Hitziger M, Esposito R, Canali M, Aragrande M, Häslerd B, Rüegga SR: **Knowledge integration in One Health policy formulation, implementation and evaluation**. *Integration* 2018, **96**.
One health is an important emergent concept in public health protection. This paper provides definition and discusses challenges of data integration to advance policy implementation.

23. Hoeng J, Talikka M, Martin F, Sewer A, Yang X, Iskandar A, Schlage WK, Peitsch MC: **Case study: the role of mechanistic network models in systems toxicology**. *Drug Discov Today* 2014, **19**:183–192.

24. • Holub P, Kohlmayer F, Prasser F, Mayrhofer MT, Schlünder I, Martin GM, Casati S, Koumakis L, Wutte A, Kozera Ł, Strapagiel D, Anton G, Zanetti G, Sezerman OU, Mendy M, Valík D, Lavitrano M, Dagher G, Zatloukal K, van Ommen GB, Litton JE: **Enhancing reuse of data and biological material in medical research: from FAIR to FAIR-health**. *Biopreserv Biobank* 2018, **16**:97–105.
An important extension of FAIR principles to accompanying biomaterials and data such as image analysis necessary to understand context and applicability domain. These extensions provide important and forward-looking requirements regarding how to best use and repurpose (if necessary) data found in various and increasingly available repositories.

25. Hoffmann S, Hartung T: **Toward an evidence-based toxicology**. *Hum Exp Toxicol* 2006, **25**:497–513.

26. Hoffmann S, de Vries RBM, Stephens ML, Beck NB, Dirven HAAM, Fowle 3rd JR, Goodman JE, Hartung T, Kimber I, Lalu MM, Thayer K, Whaley P, Wikoff D, Tsaioun K: **A primer on systematic reviews in toxicology**. *Arch Toxicol* 2017, **91**:2551–2575.

27. Hooijmans CR, de Vries RBM, Ritskes-Hoitinga M, Rovers MM, Leeflang MM, IntHout J, Wever KE, Hooft L, de Beer H, Kuijpers T, Macleod MR, Sena ES, Ter Riet G, Morgan RL, Thayer KA, Rooney AA, Guyatt GH, Schünemann HJ, Langendam MW, GRADE Working Group: **Facilitating healthcare decisions by assessing the certainty in the evidence from preclinical animal studies**. *PLoS One* 2018, **13**.e0187271.

28. • Hucka M, Bergmann FT, Chaouiya C, Dräger A, Hoops S, Keating SM, König M, Novère NL, Myers CJ, Olivier BG, Sahle S, Schaff JC, Sheriff R, Smith LP, Waltemath D, Wilkinson DJ, Zhang F: **The systems biology markup language (SBML): language specification for level 3 version 2 core release 2**. *J Integr Bioinform* 2019:16.
As computational models become more prevalent in public health applications, a markup language will ensure their consistent use across various venues. The markup language also facilitates sharing of models which provides for efficient use of resources.

29. Jarabek AM, Pottenger LH, Andrews LS, Casciano D, Embry MR, Kim J, Preston RJ, Reddy MV, Schoeny R, Shuker D, Skare J, Swenberg J, Williams G, Zeiger E: **Creating context for the use of DNA adduct data in cancer risk assessment: I. Data organization**. *Crit Rev Toxicol* 2009, **39**:659–678.

30. Kiker GA, Bridges TS, Varghese A, Seager TP, Linkov I: **Application of multicriteria decision analysis in environmental decision making**. *Integr Environ Assess Manag* 2005, **1**:95–108.

31. LaLone CA, Ankley GT, Belanger SE, Embry MR, Hodges G, Knapen D, Munn S, Perkins EJ, Rudd MA, Villeneuve DL, Whelan M: **Advancing the adverse outcome pathway framework—an international horizon scanning approach**. *Environ Toxicol Chem* 2017, **36**:1411–1421.

32. Leonard JA, Tan YM, Gilbert M, Isaacs K, El-Masri H: **Estimating margin of exposure to thyroid peroxidase inhibitors using high-throughput *in vitro* data, high-throughput exposure modeling, and physiologically based pharmacokinetic/pharmacodynamic modeling**. *Toxicol Sci* 2016, **151**:57–70.

33. Li C, Donizelli M, Rodgriquez N, Dharuri H, Endler L, Chelliah V, Li L, He E, Henry A, Stefan M, Snoep JL, Hucka M, LeNovère, Laibe C: **BioModels Database: an enhanced, curated and annotated resource for published quantitative kinetic models**. *BMC Syst Biol* 2010, **4**. Article number: 92.

34. Lorenz S, Rasmussen JJ, Süß A, Kalettka T, Golla B, Horney P, Stähler M, Hommel B, Schäfer RB: **Specifics and challenges of assessing exposure and effects of pesticides in small water bodies**. *Hydrobiologia* 2017, **793**:213–224.

35. • Manrai AK, Cui Y, Bushel PR, Hall M, Karakitsios S, Mattingly CJ, Ritchie M, Schmitt C, Sarigiannis DA, Thomas DC, Wishart D, Balshaw DM, Patel CJ: **Informatics and data analytics to support exposome-based discovery for public health**. *Annu Rev Public Health* 2017, **38**:279–294.
This paper provides an update to the concept of the exposome proposed in 2012. New tools developed to deploy the concept in the context of public health are presented.

36. Mattingly CJ, McKone TE, Callahan MA, Blake JA, Hubal EAC: **Providing the missing link: the exposure science ontology ExO**. *Environ Sci Technol* 2012, **46**:3046–3053.

37. Meek ME, Palermo CM, Bachman AN, North CM, Jeffrey Lewis R: **Mode of action human relevance (species concordance) framework: evolution of the Bradford Hill considerations and comparative analysis of weight of evidence**. *J Appl Toxicol* 2014, **34**:595–606.

38. Menzie CA, MacDonell MM, Mumtaz MA: **A phased approach for assessing combined effects from multiple stressors**. *Environ Health Perspect* 2007, **115**:807–816.

39. Moermond CT, Kase R, Korkaric M, Ågerstrand M: **CRED: criteria for reporting and evaluating ecotoxicity data**. *Environ Toxicol Chem* 2016, **35**:1297–1309.

40. Money C: **Improving the relevance and efficiency of human exposure assessments within the process of regulatory risk assessment**. *Environ Sci: Process Impacts* 2018, **20**:12–19.

41. NRC, National Research Council: *Environmental epidemiology, committee on environmental epidemiology*. Washington, DC: National Academy Press; 1991.

42. NRC, National Research Council: *Toxicity testing in the 21st century: a vision and a strategy*. National Academies Press; 2007.

43. NRC, National Research Council: *Science and decisions: advancing risk assessment*. National Academies Press; 2009.

44. NRC, National Research Council: *Exposure science in the 21st century: a vision and a strategy*. National Academies Press; 2012.

45. NRC, National Research Council: *Review of EPA's integrated risk information system (IRIS) process*. National Academies Press; 2014.

46. NRC, National Research Council: *Using 21st century science to improve risk-related evaluations*. National Academies Press; 2017.

47. •• Perkins EJ, Ashauer R, Burgoon L, Conolly R, Landesmann B, Mackay C, Murphy CA, Pollesch N, Wheeler JR, Zupanic A, Scholz S: **Building and applying quantitative adverse outcome pathway models for chemical hazard and risk assessment**. *Environ Toxicol Chem* 2019. https://doi.org/10.1002/etc.4505 [Epub ahead of print] Review. PubMed PMID: 31127958.

To best impact risk assessment, the adverse outcome pathway (AOP) construct must be quantitative. This paper shows how response-response relationships among the key events of an AOP can be used to develop a quantitative construct.

48. Pottenger LH, Andrews LS, Bachman AN, Boogaard PJ, Cadet J, Embry MR, Farmer PB, Himmelstein MW, Jarabek AM, Martin EA, Mauthe RJ, Persaud R, Preston RJ, Schoeny R, Skare J, Swenberg JA, Williams GM, Zeiger E, Zhang F, Kim JH: **An organizational approach for the assessment of DNA adduct data in risk assessment: case studies for aflatoxin B1, tamoxifen and vinyl chloride**. *Crit Rev Toxicol* 2014, **44**: 348–391.

49. Powers CM, Dana G, Gillespie P, Gwinn MR, Hendren CO, Long TC, Wang A, Davis JM: **Comprehensive environmental assessment: a meta-assessment approach**. *Environ Sci Technol* 2012, **46**:9202–9208.

50. Price P, Leonard J: **A proposal for creating a taxonomy of chemical interactions using concepts from the aggregate exposure and adverse outcome pathways**. *Curr opin Toxicol* August 2019, **16**:58–66. https://doi.org/10.1016/j.cotox.2019.05.007.

51. Quackenbush J: **Data reporting standards: making the things we use better**. *Genome Med* 2009, **25**:111. 11.

52. • Rappaport SM: **Redefining environmental exposure for disease etiology**. *NPJ Sys. Biol. Appl* 2018, **3**:30. https://doi.org/10.1038/s41540-018-0065-0.

This paper updates the concept of the exposome to articulate how it might be utilized in discerning environmental causality for different experimental designs.

53. Rovida C, Alépée N, Api AM, Basketter DA, Bois FY, Caloni F, Corsini E, Daneshian M, Eskes C, Ezendam J, Fuchs H: **Integrated testing strategies (ITS) for safety assessment**. *ALTEX-Altern Anim Experimentations* 2015, **32**:25–40.

54. Sauer JM, Hartung T, Leist M, Knudsen TB, Hoeng J, Hayes AW: **Systems toxicology: the future of risk assessment**. *Int J Toxicol* 2015, **34**:346–348.

55. Schulte PA: **Methodologic issues in the use of biologic markers in epidemiologic research**. *Am J Epidemiol* 1987, **126**: 1006–1016.

56. Schulte PA: **A conceptual framework for the validation and use of biologic markers**. *Environ Res* 1989, **48**:129–144.

57. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K: **Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis**. *Environ Health Perspect* 2016, **124**:713–721.

58. • Tan YM, Leonard JA, Edwards S, Teeguarden J, Egeghy P: **Refining the aggregate exposure pathway**. *Environ Sci: Process Impacts* 2018a, **20**:428–436.

This paper provides important refinements to the concept and discusses applications of the aggregate exposure pathway (AEP). The additional context in this paper is useful to help accelerate the application and decrease confusion regarding its use for exposure assessment as one aspect of risk assessment.

59. Tan YM, Leonard JA, Edwards S, Teeguarden J, Paini A, Egeghy P: **Aggregate exposure pathways in support of risk assessment**. *Curr opin Toxicol* 2018b, **9**:8–13.

60. Teeguarden JG, Tan Y, Edwards SW, Leonard JA, Anderson KA, Corley RA, Kile ML, Simonich SM, Stone D, Tanquay RL, Waters KM, Harper SL, Williams DE: **Completing the link between exposure science and toxicology for improved environmental health decision making: the Aggregate Exposure Pathway framework**. *Environ Sci Technol* 2016, **50**:4579–4586.

61. U.S. EPA: *Framework for cumulative risk assessment*. Washington, DC: U.S. EPA/ORD/RAF; 2003. EPA/600/P-02/001F. Available at: http://www.epa.gov/raf/publications/framework-cra.htm.

62. U.S. EPA: *Concepts, methods, and data sources for cumulative health risk assessment of multiple chemicals, exposures and effects: a resource document (final report, 2008)*. Washington, DC: U.S. Environmental Protection Agency; 2008:2007. EPA/600/R-06/013F.

63. van Panhuis WG, Paul P, Emerson C, Grefenstette J, Wilder R, Herbst AJ, Heymann D, Burke DS: **A systematic review of barriers to data sharing in public health**. *BMC Public Health* 2014, **14**:1144.

64. Van Leeuwen CJ, Patlewicz GY, Worth AP: **Intelligent testing strategies**. In *Risk assessment of chemicals*. Dordrecht: Springer; 2007:467–509.

65. Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, Landesmann B, Lettieri T, Munn S, Nepelska M, Ottinger MA, Vergauwen L, Whelan M: **Adverse outcome pathway (AOP) development I: strategies and principles**. *Toxicol Sci* 2014a, **142**:312–320.

66. Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, Landesmann B, Lettieri T, Munn S, Nepelska M, Ottinger MA, Vergauwen L, Whelan M: **Adverse outcome pathway development II: best practices**. *Toxicol Sci* 2014b, **142**:321–330.

67. Waller LA, Miller GW: **More than manuscripts: reproducibility, rigor, and research productivity in the big data era**. *Toxicol Sci* 2016, **149**:275–276.

68. Whaley P, Halsall C, Ågerstrand M, Aiassa E, Benford D, Bilotta G, Coggon D, Collins C, Dempsey C, Duarte-Davidson R, FitzGerald R, Galay-Burgos M, Gee D, Hoffmann S, Lam J, Lasserson T, Levy L, Lipworth S, Ross SM, Martin O, Meads C, Meyer-Baron M, Miller J, Pease C, Rooney A, Sapiets A, Stewart G, Taylor D: **Implementing systematic review techniques in chemical risk assessment: challenges, opportunities and recommendations**. *Environ Int* 2016, **92–93**: 556–564.

69. Wikoff DS, Britt JK: **The Role of systematic review in the practice of toxicology and risk assessment—an appreciation for the primary tool in evidence-based practice**. *Toxicol open access* 2006, **2**:110.

70. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J, Brookes AJ, Clark T, Crosas M, Dillo I, Dumon O, Edmunds S, Evelo CT, Finkers R, Gonzalez-Beltran A, Gray AJ, Groth P, Goble C, Grethe JS, Heringa J, Hoen PA, Hooft R, Kuhn T, Kok R, Kok J, Lusher SJ, Martone ME, Mons A, Packer AL, Persson B, Rocca-Serra P, Roos M, van Schaik R, Sansone SA,, Schultes E, Sengstag T, Slater T, Strawn G, Swertz MA, Thompson M, van der Lei J, van Mulligen E, Velterop J, Waagmeester A, Wittenburg P, Wolstencroft K, Zhao J, Mons B: **The FAIR Guiding Principles for scientific data management and stewardship**. *Sci Data* 2016:160018. https://doi.org/10.1038/sdata.2016.18. Erratum in: Sci Data. 2019 Mar 19;6(1):6.

71. •• Wilkinson MD, Dumontier M, Jan Aalbersberg I, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J, Brookes AJ, Clark T, Crosas M, Dillo I, Dumon O, Edmunds S, Evelo CT, Finkers R, Gonzalez-Beltran A, Gray AJG, Groth P, Goble C, Grethe JS, Heringa J, Hoen PAC', Hooft R, Kuhn T, Kok R, Kok J, Lusher SJ, Martone ME, Mons A, Packer AL, Persson B, Rocca-Serra P, Roos M, van Schaik R, Sansone SA, Schultes E, Sengstag T, Slater T, Strawn G, Swertz MA, Thompson M, van der Lei J, van Mulligen E, Velterop J, Waagmeester A, Wittenburg P, Wolstencroft K, Zhao J, Mons B: **Addendum: the FAIR Guiding Principles for scientific data management and stewardship**. *Sci Data* 2019, **6**:6. Mar 19.

The FAIR principles have been instrumental in promoting scientific data sharing and management in this era of "big data". The addendum in an important update and illustrates that these principles are an evolving, "living" coda being deployed by the scientific community across various disciplines.

72. •• Yu MK, Ma J, Ono K, Zheng F, Fong SH, Gary A, Chen J, Demchak B, Pratt D, Ideker T: **DDOT: a Swiss army knife for investigating data-driven biological ontologies**. *Cell Syst* 2019, **8**:267–273. e3.
The data-driven ontology toolkit (DDOT) is a software library developed to facilitate assembly and analysis of ontologies together with a web application to visualize them. The paper illustrates how the toolkit can organize data into a structured hierarchy of cellular components and pathways and provides a good example of how evidence will be utilized in the future to support public health decision making.

73. •• Zgheib E, Gao W, Limonciel A, Aladjov H, Yang H, Tebby C, Gayraud G, Jennings P, Sachana M, Beltman JB, Bois FY: **Application of three approaches for quantitative AOP development to renal toxicity**. *Comput Toxicol* 2019, **11**:1–13.
This paper articulates the need for quantitative analyses of dose–response for health risk assessment and then discusses the features of three different approaches currently being used to advance quantitative adverse outcome pathways (AOPs). The case study aptly depicts the diverse types of data typically encountered when attempting evidence integration for health risk assessment.

74. Oye KA, Jain G, Amador M, Arnaout R, Brown JS, Crown W, Ferguson J, Pezalla E, Rassen JA, Selker HP, Trusheim M, Hirsch G: **The next frontier: fostering innovation by improving health data access and utilization**. *Clin Pharmacol Ther* 2015 Nov, **98**:514–521. https://doi.org/10.1002/cpt.191. Epub 2015 Sep 10. Review. PubMed PMID: 26234275; PubMed Central PMCID: PMC5052021.

75. Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice J, Younes M: **IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis**. *Regul Toxicol Pharmacol* 2001, **34**:146–152.

76. Krieger N, Davey Smith G: **The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology**. *Int J Epidemiol* 2016 Dec, **45**:1787–1808. https://doi.org/10.1093/ije/dyw114. PubMed PMID: 27694566.