BIOMARKERS, OMICS, AND THE CURVE¹

Wayne G Landis,*† and David R Fox‡

†Institute of Environmental Toxicology, Huxley College of the Environment, Western Washington University, Bellingham, Washington, USA

‡Environmetrics Australia, Beaumaris, Victoria, Australia

wayne.landis@wwu.edu

DOI: 10.1002/ieam.4030

Our point of departure is Leung (2018), “Joining the dots between omics and environmental management.” The paper is a useful overview of the state of biomarkers, omics, and adverse outcome pathways and their potential applications to risk assessment and environmental management. Since the 1980s, biomarkers and now omics have been part of the toxicological literature. Adverse outcome pathways form an organizing cause–effect model and have been widely adopted. The question remains how to effectively match this body of research to current tools in ecological risk assessment, decision making, and adaptive environmental management.

Current ecological risk assessment and environmental management use probabilistic tools such as Monte Carlo modeling and Bayesian approaches (Landis et al. 2017; Carriger et al. 2018). Bayesian networks and influence diagrams can incorporate a diverse array of information to estimate risk and generate management options. Also, Bayesian networks have the ability to accommodate a variety of types of data into the same model (environmental DNA [eDNA], acetylcholinesterase [AChE] inhibition, population modeling) and to innately incorporate uncertainty. It is also possible to use Bayesian networks to search for patterns in large datasets, using case-learning to derive relationships between the input and output nodes (Graham 2016). Case-learning is a type of machine learning noted by Leung (2018) as a possible application of omics.

The issue is not whether biomarkers and omics can be useful to risk assessment and environmental management. The issue is how to incorporate the entirety of this information into the estimation of risk and effective environmental management. In 2018, that answer means a probability distribution describing an exposure–effect relationship, which will result in a probability distribution describing risk to an endpoint. The risk estimate should include descriptions of uncertainty and an understanding of model sensitivity. To adequately describe exposure–effect for biomarkers or other omic applications to estimate risk, we have argued that this means that a regression or curve-fitting approach be applied to experimental design and data analysis (Fox and Landis 2016). After all, toxicity is a curve and not a *p*-value, a continuous response and not a binary effect–no effect boundary.

¹ This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:[10.1002/ieam.4030](https://doi.org/10.1002/ieam.4030)

The difficulty is that in observations of omics papers and posters at the recent Society of Environmental Toxicology and Chemistry (SETAC) North America conference in Minneapolis, Minnesota, USA, and in surveying the literature, is that biomarker and omics studies often are reported using the null hypothesis significance testing approach. The results are published as a set of test concentrations, together with the mean response of a set of replicates, a standard deviation, and the p -value for that exposure. The p -values decrease as exposure increases, but not always. Using the typical design of exposure doses increasing by a factor of 10 for each treatment means that for many chemicals the transition from no effect to maximum effect will be underdescribed. This type of analysis is not a complete description of exposure–response.

In contrast, and more than a decade ago, Sandahl et al. (2005, 2007) presented examples of exposure–response curves being used to describe toxicity with a biomarker. Sandahl et al. (2005) describe the relationships between AChE activity and chlorpyrifos activity for coho salmon in a study relating AChE activity to swimming and feeding behaviors. Figure 1 in Sandahl et al. (2005) plots the relevant data sets, shows the curves, and estimates an effect concentration, in this case a benchmark concentration (BMC). Data sets are available for additional analyses. Sandahl et al. (2007) also employed curve fitting to describe the change in response of electro-olfactograms (smell response) to Cu. As in the 2005 paper, the data are made available for further analysis. In both Sandahl et al. papers, the test concentrations were appropriate to cover the entire exposure–response relationship, including points that document the portions of the curve describing the transition from no measured effect to a maximum effect. In the 2005 and 2007 figures, the confidence intervals are not shown but were calculated and used in the estimation of a BMC.

Compared to computational tools of the mid-2000s, it is now routine to perform curve fitting to describe exposure–response relationships. There are numerous programs and the dose–response curve (drc) package in R is freely available for estimating the parameters of a variety of concentration–response models as well as providing measures of uncertainty. Fox and Landis (2016) have demonstrated how similarity measures can be used for categorical information to estimate exposure–response relationships. This type of tool could be used for situations in which multiple markers are being used and the measurement is an up or down regulation.

If biomarkers and omics are to be incorporated into risk assessment, decision making, and adaptive management, it is vital that we not make the error of designing experiments and reporting data for binary outcomes. It is imperative in the biomarker–omics field to design experiments and conduct analyses in a manner that describes the entire exposure–response relationship for use in the most current methods for quantifying ecological risk and evaluating management options.

References

Carriger JF, Dyson BE, Benson WH. 2018. Representing causal knowledge in environmental policy interventions: Advantages and opportunities for qualitative influence diagram applications. *Integr Environ Assess Manag* DOI 10.1002/ieam.2027

Fox DR, Landis WG. 2016. Don't be fooled—A no-observed-effect concentration is no substitute for a poor concentration–response experiment. *Environ Toxicol Chem* 35:2141–2148.

Graham SE. 2016. Predicting risk to estuary water quality and patterns of benthic environmental DNA in Queensland, Australia using Bayesian networks [Masters thesis]. Bellingham (WA): Western Washington Univ. [cited Year Month Day]. <http://cedar.wwu.edu/wwuet/511>

Landis WG, Markiewicz AJ, Ayre KK, Johns AF, Harris MJ, Stinson JM, Summers HM. 2017. A general risk-based adaptive management scheme incorporating the Bayesian network Relative Risk Model with the South River, Virginia, as case study. *Integr Environ Assess Manag* 13:115–126.

Leung KM. 2018. Joining the dots between omics and environmental management. *Integr Environ Assess Manag* 14:169–173.

Sandahl JF, Baldwin DH, Jenkins JJ, Scholz NL. 2005. Comparative thresholds for acetylcholinesterase inhibition and behavioral impairment in coho salmon exposed to chlorpyrifos. *Environ Toxicol Chem* 24:136–145.

Sandahl JF, Baldwin DH, Jenkins JJ, Scholz NL. 2007. A sensory system at the interface between urban stormwater runoff and salmon survival. *Environ Sci Technol* 41:2998–3004.

Author Manuscript

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Landis, WG;Fox, DR

Title:

BIOMARKERS, OMICS, AND THE CURVE

Date:

2018-05-01

Citation:

Landis, W. G. & Fox, D. R. (2018). BIOMARKERS, OMICS, AND THE CURVE. INTEGRATED ENVIRONMENTAL ASSESSMENT AND MANAGEMENT, 14 (3), pp.419-420. <https://doi.org/10.1002/ieam.4030>.

Persistent Link:

<http://hdl.handle.net/11343/283883>