A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP12596.

Invited Perspective: Mixtures—Are They Worth the Risk (Assessment)?

Lesliam Quiros-Alcala[1] and Dana Boyd Barr[2]

[1]Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[2]Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

https://doi.org/10.1289/EHP12596

Refers to https://doi.org/10.1289/EHP11899

Historically, environmental health research has focused on studying exposure to a single chemical or chemical class and its relation to a single health outcome. In reality, exposures do not occur alone but involve a complex milieu of chemicals that may result in one or more health risks. With the advent of exposomic techniques for measuring a wide array of chemicals simultaneously[1–4] and mixtures analysis techniques for evaluating the contributions of multiple chemicals to health outcomes,[5–7] a more comprehensive and holistic evaluation of exposure and disease is now possible. Given this realization, it is not unreasonable to assume our current risk assessment techniques evaluating risk on a single chemical basis is outdated and likely an inaccurate representation of the true risk from complex chemical exposures.

In the commentary by Savitz and Hattersley,[8] the authors address a complex issue in exposure science and epidemiology—mixtures—and how data on mixtures can be used to inform and maximize their usefulness in regulatory decision-making. As more epidemiologic studies integrate mixtures analyses using advanced statistical approaches, such as quantile g-computation,[7] Bayesian kernel machine regression,[5] or weighted quantile sum regression,[6] data on individual chemical effects are often relegated to less critical findings of these studies. To update the risk assessment paradigm, Savitz and Hattersley present a framework for decision-making for evaluating chemical mixtures.[8]

The proposed framework suggests common mixture groupings based on product or exposure sources or common modes of action or effects. The authors examine the advantages and disadvantages of conducting studies on mixtures for advancing knowledge to inform policies, and they offer a strategy for epidemiologists and regulators to use in considering when and how to assess chemical mixtures. The authors conclude that conventional methods for assessing individual effects of chemicals remain preferable in certain situations. However, if the complexity and loss of generalizability that may occur when considering mixtures in a risk assessment are justified by dramatic improvements in the assessment, a mixtures approach may be warranted, especially if it is hypothesis-driven rather than data-driven exploration.

As the authors indicate, a critical need still exists to examine the individual effects of single chemicals to help discern the constituents of exposure mixtures that could be the "bad actors" (or main drivers associated with health end points) and to better inform further mixtures analyses. However, this approach may be inadequate given that the total risk of multiple chemicals may not be the sum of their individual risks. In fact, the few instances where risk has been evaluated with simple mixtures, the combination of chemicals appear to synergistically increase or attenuate associated end points.[9] Individual chemicals may behave differently when present in a complex mixtures, which could enhance exposure, uptake, or intake or alter distribution, metabolism, elimination, or internal biological activity. These changes would not be captured by simply adding risk. In these situations, exposomics or data-driven techniques may be useful in identifying common metabolic pathways affected by observed chemical mixtures in individuals, especially when repeated temporal samples are measured. Many mediating pathways, such as oxidative stress, inflammation, and protein function, have been identified as common targets for many environmental chemicals that may ultimately drive potential adverse outcomes.

To illustrate, neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, are believed to have common pathogenic pathways, such as generation of reactive oxygen species (ROS), oxidative stress, or altered protein structures especially with misfolding, faulty degradation, DNA damage/mutations, mitochondrial dysfunctions, and neuroinflammatory processes.[10] Different chemicals, such as rotenone and dieldrin, may cause epigenetic changes; manganese may alter protein folding; vanadium may produce excess ROS; and 1,1,1-trichloro-2,2-bis (*p*-chlorophenyl)ethane (DDT) may induce oxidative stress. However, they all synergistically work to alter mitochondrial performance that may lead to disease development or exacerbation.[10] Exposomics may be able to identify chemicals that may contribute to these alterations and may further impact disease development. In ideal practice, all of the chemical contributors would be considered when evaluating risk.

Adding to the complexity of using mixtures analysis in risk assessment, Savitz and Hattersley highlight that significant spatial and temporal variation in exposures occur. Current exposure assessment methods may not adequately capture all exposures to all subpopulations, limiting the generalizability of these findings for risk assessment. For example, a mixtures approach could be effective in a worker population experiencing similar primary exposures, such as hairdressers who may come into contact with hair products containing similar classes of chemicals. Still, such results may not apply to the general population. Regardless, analyses of multiple serial samples collected across broad regions or populations may enable scientists to overcome this limitation.

Consideration of chemicals individually for risk assessments also has the advantage of potentially identifying "regrettable substitutions" that may otherwise go unnoticed. For example, di-2-ethylhexyl phthalate has been linked to adverse respiratory effects, including increased risk of asthma morbidity, as has its replacement product, di-2-ethylhexyl terephthalate.[11] But realistically, these substitutions would be present in mixtures that may have synergistic biological effects as well.

Individual chemical risk assessment will always be necessary to fully characterize a given chemical's harm. However, it is important to consider mixtures in risk assessment because they are more representative of real-world exposures and likely work collectively to induce a disease state. Application of advanced

Address correspondence to Dana Boyd Barr, 1518 Clifton Rd., CNR7007, Emory University, Rollins School of Public Health, Gangarosa Department of Environmental Health, Atlanta, GA 30322 USA. Email: dbbarr@emory.edu

The authors declare they have no real or apparent conflicts of interest.

Received 14 December 2022; Revised 21 February 2023; Accepted 28 February 2023; Published 6 April 2023.

statistical methods and exposomic techniques for mixtures will continue to be useful and should be fully considered in the risk assessment process. Savitz and Hattersley have thrown down the gauntlet, and it is time for U.S. regulators to take up the challenge.

References

1. Barouki R, Audouze K, Becker C, Blaha L, Coumoul X, Karakitsios S, et al. 2022. The exposome and toxicology: a win–win collaboration. Toxicol Sci 186(1):1–11, PMID: 34878125, https://doi.org/10.1093/toxsci/kfab149.
2. Kalia V, Belsky DW, Baccarelli AA, Miller GW. 2022. An exposomic framework to uncover environmental drivers of aging. Exposome 2(1):osac002, PMID: 35295547, https://doi.org/10.1093/exposome/osac002.
3. Price EJ, Vitale CM, Miller GW, David A, Barouki R, Audouze K, et al. 2022. Merging the exposome into an integrated framework for "omics" sciences. iScience 25(3):103976, PMID: 35310334, https://doi.org/10.1016/j.isci.2022.103976.
4. Vermeulen R, Schymanski EL, Barabási AL, Miller GW. 2020. The exposome and health: where chemistry meets biology. Science 367(6476):392–396, PMID: 31974245, https://doi.org/10.1126/science.aay3164.
5. Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, et al. 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16(3):493–508, PMID: 25532525, https://doi.org/10.1093/biostatistics/kxu058.
6. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. 2015. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J Agric Biol Environ Stat 20(1):100–120, PMID: 30505142, https://doi.org/10.1007/s13253-014-0180-3.
7. Schmidt S. 2020. Quantile g-computation: a new method for analyzing mixtures of environmental exposures. Environ Health Perspect 128(10):104004, PMID: 33074735, https://doi.org/10.1289/EHP7342.
8. Savitz DA, Hattersley AM. 2023. Evaluating chemical mixtures in epidemiological studies to inform regulatory decisions. Environ Health Perspect 131(4):045001, https://doi.org/10.1289/EHP11899.
9. Martin O, Scholze M, Ermler S, McPhie J, Bopp SK, Kienzler A, et al. 2021. Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. Environ Int 146:106206, PMID: 33120228, https://doi.org/10.1016/j.envint.2020.106206.
10. Huang M, Bargues-Carot A, Riaz Z, Wickham H, Zenitsky G, Jin H, et al. 2022. Impact of environmental risk factors on mitochondrial dysfunction, neuroinflammation, protein misfolding, and oxidative stress in the etiopathogenesis of Parkinson's disease. Int J Mol Sci 23(18):10808, PMID: 36142718, https://doi.org/10.3390/ijms231810808.
11. Fandiño-Del-Rio M, Matsui EC, Peng RD, Meeker JD, Quirós-Alcalá L. 2022. Phthalate biomarkers and associations with respiratory symptoms and healthcare utilization among low-income urban children with asthma. Environ Res 212(pt B):113239, PMID: 35405131, https://doi.org/10.1016/j.envres.2022.113239.