Toxic Substances Control Act (TSCA) Cumulative Risk Assessment Framework

Introduction

In real world settings, people are continuously subject or exposed to multiple stressors, both chemical and non-chemical, that can cause or otherwise exacerbate adverse health effects resulting from exposure to any particular stressor viewed alone. The National Academy of Sciences has advocated for, and provided recommendations to, advance cumulative risk assessment of chemicals. Cumulative risk assessment considers risks to individuals and the population resulting from to multiple chemical and non-chemical stressors.[1,2,3]

The main U.S. chemical safety law is the Toxic Substances Control Act (TSCA). Originally enacted in 1976, TSCA was reformed in 2016 with the passage of the Frank R. Lautenberg Chemical Safety for the Twenty First Century Act.[4] Among other major improvements, the reforms required for the first time that the U.S. Environmental Protection Agency (EPA) evaluate potential risks presented by most chemicals in commerce and manage risks it determines to be unreasonable, based strictly on scientific criteria and excluding consideration of costs or other non-risk factors.

Core provisions of the 2016 amendments authorize, and compel, EPA to integrate cumulative risk considerations into the identification, evaluation, and management of chemical risks. Specifically, TSCA requires that the agency: (1) identify, assess, and protect against unreasonable risks to potentially exposed or susceptible subpopulations[5]—which effectively requires EPA to account for co-exposures to other chemical and non-chemical stressors that may increase an exposed individual's susceptibility to the chemical subject to risk evaluation; and (2) use best available science[6]—which supports the use of cumulative risk assessment approaches

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[1] Examples of non-chemical stressors include socioeconomic deprivation and other psychosocial stressors, pre-existing health conditions, and excess heat among others (Chari et al. 2012; Fox et al. 2017; Payne-Sturges et al. 2021; Schwartz et al. 2011).

[2] National Research Council. 2008. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

[3] National Research Council. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209 .

[4] 15 U.S.C. §2601, *et seq.*

[5] 15 U.S.C. §§ 2602(12) ("TSCA Section 3(12)"); 2605(b)(4)(A) ("TSCA Section 6(b)(4)(A)").

[6] 15 U.S.C. § 2625(h) ("TSCA Section 26(h)").

where the science is sufficiently developed to do so.[7,8] In addition, TSCA requires the evaluation and management of risks across the full lifecycle of a chemical from all known, intended, and reasonably foreseen uses.[9]

TSCA is unique among U.S. environmental laws in calling for a wholistic consideration of chemical risks—accounting for all sources and pathways of exposure to the general population and those who may be at greater risk because they are more susceptible to a chemical's effects or more highly exposed. In other words, TSCA is one of the most far-reaching opportunities to address the cumulative risks chemicals can pose to public health.

Here we present a TSCA Cumulative Risk Assessment Conceptual Framework (CRA Framework) based on the 4-step regulatory chemical risk assessment paradigm: hazard identification, dose-response characterization, exposure characterization, and risk characterization.[10,11,12] Presented as an inverted pyramid, the CRA Framework describes how the narrow risk evaluations conducted to date under TSCA can scale up incrementally to yield a fully inclusive and comprehensive assessment of cumulative risk, one that considers all relevant stressors (Figure 1). Level 1 represents the narrowest evaluation of chemical risk under TSCA, and is exemplified by the evaluations conducted for trichloroethylene, methylene chloride and N-methyl-2-pyrrolidone by EPA in 2014.[13] On the contrary, Level 5, the outermost, represents a comprehensive and cumulative evaluation of chemical risk under TSCA, cumulative impacts.

Although the CRA Framework is depicted as a series of sequential steps, how they are actually applied will depend on the specific chemical undergoing risk evaluation, available information and methodologies, policy considerations, and other factors. The CRA Framework provides a framework to illustrate how EPA can conceptualize and apply comprehensive cumulative risk

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[7] National Research Council. 2008. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

[8] National Research Council. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

[9] 15 U.S.C. §§ 2602(4) ("TSCA Section 3(4"); 2605(b)(4)(A) ("TSCA Section 6(b)(4)(A)").

[10] National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: The National Academies Press. https://doi.org/10.17226/366.

[11] National Research Council. 1994. *Science and Judgment in Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/2125.

[12] National Research Council 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

[13] These chemicals were listed on the TSCA Work Plan for Chemical Assessments and were completed As these risk evaluations were completed prior to the passage of the amended TSCA, per section 26(l), these evaluations did not need to meet all the requirements for risk evaluations as laid out under section 6 of the law.

evaluations under TSCA in a way that is pragmatic and more protective of public health, especially for those at greatest risk.

Additional Background

Useful background materials on TSCA relevant to the CRA Framework:

- Entry page to TSCA regulation at EPA
- Fact sheet on 2016 reforms made to TSCA
- Side-by-side comparison of the old TSCA and the new amended law
- Final risk evaluations for the first ten chemicals
- Scoping documents for the next 20 chemicals currently undergoing risk evaluation

Glossary

Category of Chemicals Substances- As defined in TSCA, "a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of [the TSCA law], except that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances." [14]

Conditions of use- As defined in TSCA, "circumstances… under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."[15]

Cumulative risk assessment- As defined by the EPA in the Framework for Cumulative Risk Assessment, "is an analysis, characterization, and possible quantification of the combined risks to human health or the environment from multiple agents or stressors." [16] For the purposes of this framework, we choose to define cumulative risk as focusing solely on chemical exposures.

Cumulative impacts- As defined by EPA in the Cumulative Impacts Draft paper, "refers to the total burden – positive, neutral, or negative – from chemical and non-chemical stressors and their interactions that affect the health, well-being, and quality of life of an individual, community, or population at a given point in time or over a period of time."[17]

Exposures - Chemicals that are mediated through a pathway or from a source or condition of use.

> *Pathways of exposure* – The physical course a chemical takes from the source, through various environmental media (e.g., air, water, soil) to the organism exposed.[18] Also see "route of exposure."

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[14] 15 U.S.C. § 2625(c) ("TSCA Section 6(c)").

[15]15 U.S.C. § 2602(4) ("TSCA Section 3(4)").

[16] U.S. EPA. 2003. Framework for Cumulative Risk Assessment. https://www.epa.gov/sites/default/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf.

[17] U.S. EPA 2022 Draft Cumulative Impacts Recommendations for ORD Research. https://www.epa.gov/system/files/documents/2022-01/ord-cumulative-impacts-white-paper_externalreviewdraft-_508-tagged_0.pdf

[18] Adapted from U.S. EPA Exposure Factors Handbook definition for exposure pathway defined as "the physical course a chemical takes from the source to the organism exposed." https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=Exposure%20Factors%20Glossary

Route of exposure - The physical interface through which human exposure to the chemical occurs, i.e., inhalation, oral (ingestion), or dermal contact.[19]

Sources of exposure- Referring to any parts of the natural or built environment that contain chemicals, including air, water, and consumer products.

Frontline communities- People who live, work, play, and learn near thousands of industrial and commercial facilities that use, store, dispose, or release chemicals

Potentially exposed or susceptible subpopulation - As defined in TSCA, "a group of individuals within the general population … who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly."[20] In the CRA Framework, we also refer to potentially exposed or susceptible subpopulations as "vulnerable subpopulations."

Vulnerable subpopulations- A shorthand for potentially exposed or susceptible subpopulations.

[19] Adapted from U.S. EPA Exposure Factors Handbook definition for exposure route, defined as "The way a chemical pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption." Ibid.

[20] 15 U.S.C. § 2602(12) ("TSCA Section 3(12)").

Level 1 – Single-Use Risk: Evaluation of single TSCA chemical use, select sources and vulnerable subpopulations

"Level 1" chemical risk assessments are narrow and examine only a subset of a single chemical's conditions of use,[21] hazards, exposures, and relevant potentially exposed or susceptible subpopulations.[22]

Level 1 risk assessments underestimate single chemical risks by excluding numerous sources of exposure such as from the chemical's release to air, water and land; and from its "legacy" uses and associated disposal. Additionally, sources of exposure are only considered individually; combinations of exposures are not addressed.

These assessments also do not sufficiently consider risks to potentially exposed or susceptible subpopulations, including disproportionately exposed frontline communities and groups more susceptible to a chemical's toxic effects due, for example, to pre-existing health conditions.[23] Often communities or groups are both highly exposed to chemicals and also are more susceptible to their effects.

Relevant Example:
Risk assessments conducted by EPA in 2014 for trichloroethylene (TCE), methylene chloride, and N-methyl-2-pyrrolidone (NMP), chemicals from the TSCA Work Plan for Chemical Assessments, were limited in scope. EPA's risk assessment of TCE excluded environmental releases to groundwater and soil and instead stated that TCE contamination to groundwater and soils will be addressed by other offices within the agency.[24] In its evaluation of NMP, EPA did not consider all relevant vulnerable subpopulations including individuals with existing cardiovascular diseases—only pregnant women and fetuses were considered.[25] Since these risk assessments were completed prior to June 22, 2016 (the passage of the Lautenberg Act) they were not obligated to meet all the requirements laid out in the amended TSCA.[26] On the contrary,

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[21] See "conditions of use" in the Glossary.

[22] See "potentially exposed or susceptible subpopulations" in the Glossary.

[23] McPartland J, Shaffer RM, Fox MA, Nachman KE, Burke TA, Denison RA. Charting a Path Forward: Assessing the Science of Chemical Risk Evaluations under the Toxic Substances Control Act in the Context of Recent National Academies Recommendations. *Environ Health Perspect*. 2022;130(2):25003. doi:10.1289/EHP9649.

[24] Work Plan Risk Evaluation of Trichloroethlyene, finalized June 2014. https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf

[25] Work Plan Risk Evaluation of Methylene Chloride, finalized August 2014. https://www.epa.gov/sites/default/files/2015-09/documents/dcm_opptworkplanra_final.pdf

[26] 15 U.S.C. § 2625(l) ("TSCA Section 6(l)").

risk evaluations conducted during the Trump administration were not only very limited, but also failed to meet the basic requirements under the law.[27]

Analytic Approaches, Methods, and Data Sources:
To date, EPA has taken a limited approach to chemical risk assessments conducted following the 2016 TSCA amendments. While the agency adopted the traditional 4-step regulatory risk assessment framework, [28,29,30] the exposure exclusions and inadequate consideration of vulnerable subpopulations rendered the agency's execution of these steps inadequate to characterize real-world risks from these chemicals.

[27] McPartland J, Shaffer RM, Fox MA, Nachman KE, Burke TA, Denison RA. Charting a Path Forward: Assessing the Science of Chemical Risk Evaluations under the Toxic Substances Control Act in the Context of Recent National Academies Recommendations. *Environ Health Perspect*. 2022;130(2):25003. doi:10.1289/EHP9649.

[28] National Research Council. 1983. *Risk Assessment in the Federal Government*: Managing the Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/366.

[29] National Research Council. 1994. *Science and Judgment in Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/2125.

[30] National Research Council 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

Level 2 – Limited Risk: Full evaluation of risk from combined exposures and considering all vulnerable subpopulations, single chemical

A "Level 2" risk evaluation fully considers a single chemical's conditions of use, hazards, exposures, and relevant potentially exposed or susceptible subpopulations.

Under the 2016 TSCA amendments, the agency is explicitly required to identify, evaluate, and eliminate any unreasonable risks to people, including to vulnerable subpopulations, posed by the conditions of use associated with the chemical undergoing review. This requires EPA to consider all sources and pathways of exposure from individual and combinations of conditions of use, and account for individuals or communities that are more highly exposed (e.g., workers exposed through their occupations and frontline communities). It also requires identification and consideration of those more susceptible to the chemical, such as individuals with pre-existing conditions or genetic differences that increase their susceptibility to a particular chemical exposure or effect, and individuals in sensitive life stages including fetuses, infants, children, and pregnant women. When all relevant conditions of use are considered properly, both the general population and vulnerable subpopulations receive greater protection because these uses contribute to the overall exposures and risks the chemical poses to all.

Relevant Example:
EPA is currently revisiting potential risks posed to frontline communities from environmental releases of a subset of the first 10 risk evaluations—an important step to address the agency's initial policy decision to exclude environmental releases from chemical risk evaluations. In the future, EPA will apply this methodology to the next set of chemicals to be evaluated; 1,3-butadiene is one such chemical. Existing information reveals significant concerns for frontline communities' exposures to this chemical. For example, data from the Toxics Release Inventory reveal that certain residents of the Greater Houston area are disproportionately exposed to 1,3-butadiene relative to the general population because of their proximity to numerous industrial facilities emitting the substance.[31]

Analytic Approaches, Methods, and Data Sources:
Level 2 risk evaluations account for all TSCA exposure sources and relevant vulnerable subpopulations.

In Pullen-Fedinick et al. (2021), the authors describe a conceptual framework that uses publicly available data and GIS to identify high-risk vulnerable subpopulations. These tools can be adapted to identify all potentially exposed or susceptible subpopulations.[32] In MacDonell et al.

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[31] See comments from Earthjustice et al. on Draft Scopes of the Risk Evaluations for the First Twenty High-Priority Substances under the Toxic Substances Control Act. https://earthjustice.org/sites/default/files/files/20_05_26_tx_la_tsca_first_20_hp_appx_rfs.pdf

[32] Pullen Fedinick K, Yiliqi I, Lam Y, Lennett D, Singla V, Rotkin-Ellman M, Sass J. A Cumulative Framework for Identifying Overburdened Populations under the Toxic Substances Control Act: Formaldehyde Case Study. *Int J Environ Res Public Health*. 2021;18(11):6002. Published 2021 Jun 3. doi:10.3390/ijerph18116002.

(2018), the authors provide three approaches for conducting cumulative chemical risk assessments. The approach most applicable to Level 2 involves the calculation of a hazard index that integrates risks for a single chemical resulting from all relevant pathways and sources specific to a geographically defined subpopulation.[33]

Also, see Table 1 for data resources to support the characterization of far-field (outdoor) and near-field (indoor) chemical exposures.

[33] MacDonell MM, Hertzberg RC, Rice GE, Wright JM, Teuschler LK. Characterizing Risk for Cumulative Risk Assessments. *Risk Anal*. 2018;38(6):1183-1201. doi:10.1111/risa.12933.

Level 3 – Aggregate Risk: Expanded evaluation of risk accounting for background exposures from sources outside of TSCA's direct regulatory authority or unidentified sources, single chemical

Expanding on the previous level of analysis, a "Level 3" risk evaluation includes, for a single chemical, background sources of exposure that fall outside of TSCA's direct regulatory authority, such as humans' exposure to the chemical through food packaging or personal care products which are regulated by the U.S. Food and Drug Administration (FDA). Level 3 risk evaluations also consider exposures that cannot be tied directly to a particular source but can nevertheless be identified and characterized through, for example, biomonitoring data. The inclusion of background exposures in the risk evaluation captures relevant, real-world exposures to a chemical that inform the true extent of risk posed by a chemical being evaluated under TSCA.

Relevant Example:
Di(2-ethylhexyl) phthalate (DEHP) is a chemical used in materials and products that fall under TSCA's jurisdiction, including paints and coatings, electronics, construction materials, toys, and playground equipment. However, DEHP is also widely found as a contaminant in foods, particularly in meat and dairy products, and in polyvinyl chloride medical devices and equipment—exposure sources that fall outside of TSCA's direct regulatory authority. Importantly, for DEHP and other ortho-phthalates, diet is a primary source of the exposure for these chemicals. Failing to consider these non-TSCA sources could result in an underestimate of risks, particularly for vulnerable subpopulations.

Analytic Approaches, Methods, and Data Sources:
MacDonell et al (2018) provides an approach for integrating different sources and pathways of exposure to a chemical in a risk evaluation—this method allows for consideration of background exposures.[34] See Table 1 for examples of specific resources to help identify and characterize non-TSCA chemical exposure sources, such as biomonitoring data and EPA's Chemical and Product Database (CPDat).

[34] MacDonell MM, Hertzberg RC, Rice GE, Wright JM, Teuschler LK. Characterizing Risk for Cumulative Risk Assessments. *Risk Anal*. 2018;38(6):1183-1201. doi:10.1111/risa.12933.

Level 4 – Cumulative Risk: Complete evaluation of risk accounting for co-exposures associated with the same health effect(s), multiple chemicals

Building on a Level 3 risk evaluation, a "Level 4" risk evaluation considers co-exposures to other chemicals and pollutants that are associated with the same health effects as the specific chemical undergoing risk evaluation (e.g., other chemicals and pollutants associated with neurodevelopmental effects). Accounting for these co-exposures is important to accurately inform the extent of risk posed by the specific chemical undergoing risk evaluation. This is because these co-exposures may render an individual more susceptible to risks associated with the chemical undergoing risk evaluation. TSCA specifically calls for EPA to identify and eliminate unreasonable risks to such potentially exposed or susceptible subpopulations.

Of particular relevance to Level 4, TSCA specifically authorizes EPA to evaluate and manage risks from a "category of chemical substances".[35] Broadly defined in TSCA, the term allows EPA to define and evaluate a group of substances associated with the same health effects, providing another mechanism for the agency to conduct cumulative risk evaluations under TSCA. Similarly, the National Academy of Sciences has also advocated for, and provided recommendations to, advance cumulative risk assessment of chemicals for which co-exposures are known to occur and which contribute to common adverse health outcomes.[36]

Additionally, the law requires that the agency use the "best available science" in developing chemical risk evaluations, which could be argued to support a cumulative risk approach where the science is sufficient.[37]

Relevant Examples:

- Halogenated flame retardants, such as polybrominated diphenyl ethers, and organophosphate pesticides both harm the developing brain, and co-exposure to these substances is known to occur.[38]
- Formaldehyde, ethylene dibromide, and particulate matter 2.5 (PM2.5) can cause or exacerbate respiratory effects and are of particular concern to communities that are

[35] See "category of chemical substances" in the Glossary.

[36] National Research Council. 2008. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528 ; National Research Council. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209 .

[37] 15 U.S.C. § 2625(h) ("TSCA Section 26(h)").

[38] Gaylord A, Osborne G, Ghassabian A, Malits J, Attina T, Trasande L. Trends in neurodevelopmental disability burden due to early life chemical exposure in the USA from 2001 to 2016: A population-based disease burden and cost analysis. *Mol Cell Endocrinol*. 2020;502:110666.

disproportionately affected by asthma. Air monitoring has detected all three chemicals in the air of the Greater Houston region.[39]

- Di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), di-(2-ethylhexyl phthalate (DEHP), di-isobutyl phthalate (DiBP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), and dicyclohexyl phthalate (DCPH) are part of a group of structurally similar ortho-phthalates that share physical-chemical and toxicological properties.[40] Several ortho-phthalates exert anti-androgen effects leading to defects of the male reproductive tract. Additionally, biomonitoring data indicate that co-exposures to these substances occur across the population.[41] All seven phthalates are currently undergoing risk evaluation by EPA.[42]

Analytic Approaches, Methods, and Data Sources:
Several papers provide background on grouping chemicals based on shared health outcomes and showcase studies that demonstrate the feasibility of conducting a human health risk assessment for combined exposures to chemicals.[43,44,45,46] See Table 1 for specific resources for identifying relevant co-exposures, such as EPA's Computational Toxicology (CompTox) Dashboard, CDC

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[39] Sexton K, Linder SH, Marko D, Bethel H, Lupo PJ. Comparative assessment of air pollution-related health risks in Houston. *Environ Health Perspect*. 2007;115(10):1388-1393. doi:10.1289/ehp.10043.

[40] National Research Council. 2008. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

[41] CDC, *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables,* at 321– 361 (Mar. 2021), https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume2_Mar2021-508.pdf

[42] The seven phthalates currently undergoing risk evaluation under TSCA are assigned as "Phthalates" under the "Chemical Group" column of the table provided by EPA here: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca.

[43] EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bennekou SH, Bragard C, Halldorsson TI, Hernández-Jerez AF, Koutsoumanis K, Naegeli H, Schlatter JR, Silano V, Nielsen SS, Schrenk D, Turck D, Younes M, Benfenati E, Castle L, Cedergreen N, Hardy A, Laskowski R, Leblanc JC, Kortenkamp A, Ragas A, Posthuma L, Svendsen C, Solecki R, Testai E, Dujardin B, Kass GE, Manini P, Jeddi MZ, Dorne JC, Hogstrand C. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA J*. 2019;17(3):e05634. Published 2019 Mar 25. doi:10.2903/j.efsa.2019.5634.

[44] Beronius A, Zilliacus J, Hanberg A, Luijten M, van der Voet H, van Klaveren J. Methodology for health risk assessment of combined exposures to multiple chemicals. *Food Chem Toxicol*. 2020;143:111520. doi:10.1016/j.fct.2020.111520.

[45] National Research Council 2008. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

[46] Kortenkamp A. Which chemicals should be grouped together for mixture risk assessments of male reproductive disorders?. *Mol Cell Endocrinol*. 2020;499:110581. doi:10.1016/j.mce.2019.110581.

NHANES data, and EPA National-scale Air Toxics Assessment (NATA). For example, CompTox can be used to identify chemicals that have similar bioactivity profiles, and NATA can be used to identify geographically co-occurring air pollutants.

Level 5 – Cumulative Impacts: Comprehensive evaluation of risk from co-exposures to non-chemical stressors associated with the same health outcome(s), multiple chemicals

Expanding on the previous level of analysis, a "Level 5" risk evaluation additionally considers co-exposures to non-chemical stressors associated with the same health effects as the chemical undergoing risk evaluation. Non-chemical stressors include experiencing discrimination, having limited financial resources and limited access to education and health care, and being subject to other social inequities and marginalization.[47] Exposure to non-chemical stressors can occur at the individual, community, and macro social scales (e.g., state- or country-wide). Biologically, non-chemical stressors can contribute to the same health effects as chemical stressors and they need to be accounted for in chemical risk evaluations—especially evaluations under TSCA, which calls for consideration of vulnerable subpopulations and the use of the best available science. This comprehensive evaluation of both chemical and non-chemical stressors will result in a realistic evaluation of the risks that individuals and communities face.

Relevant Example:
The systematic disinvestment in communities of color has left residents of these communities stripped of access to healthy food, job opportunities, greenspaces, and safe, non-violent living environments. As a result, residents experience high levels of stress from their social environments while also being exposed to chemicals. For example, people living in the communities with less access to groceries stores selling healthful foods can experience relatively high exposures to ortho-phthalates, such as DEHP and BBzP, which are found in highly processed and packaged grocery and fast-food items.[48, 49] The combined exposure to psychosocial stress and chemical exposures has been associated with adverse pregnancy outcomes such as premature birth.[50]

[47] Barrett ES, Padula AM. Joint Impact of Synthetic Chemical and Non-chemical Stressors on Children's Health. *Curr Environ Health Rep*. 2019;6(4):225-235. doi:10.1007/s40572-019-00252-6.

[48] Goodman M, Lyons S, Dean LT, Arroyo C, Hipp JA. How Segregation Makes Us Fat: Food Behaviors and Food Environment as Mediators of the Relationship Between Residential Segregation and Individual Body Mass Index. *Front Public Health*. 2018;6:92. Published 2018 Mar 29. doi:10.3389/fpubh.2018.00092.

[49] Edwards L, McCray NL, VanNoy BN, et al. Phthalate and novel plasticizer concentrations in food items from U.S. fast food chains: a preliminary analysis. *J Expo Sci Environ Epidemiol*. 2022;32(3):366-373. doi:10.1038/s41370-021-00392-8.

[50] Ferguson KK, Rosen EM, Barrett ES, Nguyen RHN, Bush N, McElrath TF, Swan SH, Sathyanarayana S. Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth. *Environ Int*. 2019;133(Pt B):105254. doi:10.1016/j.envint.2019.105254.

Analytic Approaches, Methods, and Data Sources:
Scientific evidence suggests that non-chemical stressors can increase the adverse health outcomes caused by chemicals,[51] however, there is lack of consensus on how to account for non-chemical stressors in cumulative risk assessments, especially quantitatively. Inconsistencies in the terminology and methodologies used to discuss and measure non-chemicals stressors present challenges for integrating non-chemical stressors into chemical risk evaluation.[52,53,54, 55] Although scientific consensus does not yet exist on the best approach to integrate non-chemical stressors into cumulative risk assessment, several conceptual models are available to support the planning and implementation of this type of cumulative risk assessment process:

- The multiple stressor conceptual model described by Gee and Payne-Sturges (2004) extends the exposure-disease paradigm developed by Sexton et al (1993) by illustrating how disadvantaged populations encounter greater susceptibility to environmental hazards. Included in this stress-exposure disease framework is an emphasis on racial differences in exposure to stress, either on the macro- or micro-level, that contribute to heightened vulnerability to environmental hazards. [56,57]
- The multiple stressor theoretical framework cited by Morello-Frosch and Shenassa (2006) posits that maternal and child health disparities are in part due to the interplay of

[51] Sexton K, Linder SH. Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. *Am J Public Health*. 2011;101 Suppl 1(Suppl 1): S81-S88. doi:10.2105/AJPH.2011.300118.

[52] Crosswell AD, Lockwood KG. Best practices for stress measurement: How to measure psychological stress in health research. *Health Psychol Open*. 2020;7(2):2055102920933072. Published 2020 Jul 8. doi:10.1177/2055102920933072.

[53] Non-chemical stressors have also been referred to as psychosocial or social stressors, social determinants of health, or environmental stressors.

[54] Hibbert K, Tulve NS. State-of-the-Science Review of Non-Chemical Stressors Found in a Child's Social Environment. *Int J Environ Res Public Health*. 2019;16(22):4417. Published 2019 Nov 11. doi:10.3390/ijerph16224417.

[55] Huang H, Wang A, Morello-Frosch R, Lam J, Sirota M, Padula A, Woodruff TJ. Cumulative Risk and Impact Modeling on Environmental Chemical and Social Stressors. *Curr Environ Health Rep*. 2018;5(1):88-99. doi:10.1007/s40572-018-0180-5.

[56] Gee GC, Payne-Sturges DC. Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect*. 2004;112(17):1645-1653. doi:10.1289/ehp.7074.

[57] Sexton K, Olden K, Johnson BL. "Environmental justice": the central role of research in establishing a credible scientific foundation for informed decision making. *Toxicol Ind Health*. 1993 Sep-Oct;9(5):685-727. doi: 10.1177/074823379300900504.

individual and community psychosocial stressors that shape exposures and susceptibility to environmental hazards. These stressors include both racial and economic disparities.[58]

- The social determinant framework from the World Health Organization focuses on global and national structures of social hierarchy and the socially determined conditions these create in which people grow, live, work, and age. These social factors, that are potentially modifiable, lead to differences in exposures and create health disparities. [59]
- deFur et al (2007) developed a conceptual model for incorporating vulnerability into cumulative risk assessments by including psychosocial stressors and human responses. The framework shows how vulnerability factors can act affect how different stressors interact with the individual, community or population or how vulnerability factors can interact with how these groups respond to the stress. [60]

Similarly, a number of applications of cumulative risk assessment for chemical and non-chemical stressors have been proposed, and to some extent utilized, over the years.[61,62] Other examples of available resources and methods include the Cumulative Environmental Hazard Inequality Index (CEHII)[63, 64] and the World Health Organization's (WHO's) Urban Health

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[58] Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. *Environ Health Perspect*. 2006;114(8):1150-1153. doi:10.1289/ehp.8930.

[59] Commission on Social Determinants of Health Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health. Final Report of the Commission on the Social Determinants of Health. Geneva: World Health Organization; 2008. Available at http://whqlibdoc.who.int/publications/2008/9789241563703_eng.pdf

[60] DeFur PL, Evans GW, Cohen Hubal EA, Kyle AD, Morello-Frosch RA, Williams DR. Vulnerability as a function of individual and group resources in cumulative risk assessment. *Environ Health Perspect*. 2007;115(5):817-824. doi:10.1289/ehp.9332.

[61] U.S. EPA. Framework for Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment (CPHEA), formerly known as the National Center for Environmental Assessment (NCEA), Washington Office, Washington, DC, EPA/600/P-02/001F, 2003.

[62] National Research Council 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

[63] Su JG, Morello-Frosch R, Jesdale BM, Kyle AD, Shamasunder B, Jerrett M. An index for assessing demographic inequalities in cumulative environmental hazards with application to Los Angeles, California. *Environ Sci Technol*. 2009;43(20):7626-7634. doi:10.1021/es901041p.

[64] Su JG, Jerrett M, Morello-Frosch R, Jesdale BM, Kyle AD. Inequalities in cumulative environmental burdens among three urbanized counties in California. *Environ Int*. 2012;40:79-87. doi:10.1016/j.envint.2011.11.003.

Equity Assessment and Response Tool (Urban HEART).[65] Table 1 includes several additional data resources to aid in integrating non-chemical stressors into the evaluation of chemical risks such as EJSCREEN.

[65] World Health Organization. Urban HEART: Urban Health Equity Assessment and Response Tool. WHO Center for Health Development. Kobe, Japan: WHO Publications; 2010. https://apps.who.int/iris/handle/10665/79060

Table 1. Available data sources to be used in TSCA cumulative risk evaluations.

Far-Field Exposure Data (outdoor exposures)	Near-Field Exposure Data (indoor exposures)	Biomonitoring Data and/or Health Status	Demographic, economic, and social variables	Biological and Toxicological Properties
U.S. EPA Toxic Release Inventory (TRI) Data OECD Emission Scenario Documents Discharge Monitoring Report (DMR) surface water discharge data from NPDES-permitted facilities National Emissions Inventory (NEI) data National-scale Air Toxics Assessment (NATA) and Air Toxics Screening Assessment, (AirToxScreen) Risk-Screening Environmental Indicators (RSEI) Model	Chemical and Product Database (CPDat) (*part of CompTox Dashboard)* Occupational Safety and Health Administration Chemical Exposure Health Data	National Health and Nutrition Examination Survey (NHANES) Canadian Health Measures Survey State-based biomonitoring programs	U.S. Census Data EJSCREEN: Environmental Justice Screening and Mapping Tool EPA's EnviroAtlas Interactive Map[a] EPA's Exposure Factors Handbook Healthy People 2030 Social Determinants of Health Literature Summaries Centers of Disease Control and Prevention and Agency of Toxic Substances and Disease Registry Social Vulnerability Index Environmental Justice Index	EPA's Toxicity Forecaster (ToxCast) Data Integrated Risk Information Systems (IRIS) Assessments European Chemicals Agency (ECHA) Agency for Toxic Substances and Disease Registry (ATSDR) Tox Profiles

Unregulated Contaminant Monitoring Report (UCMR) for drinking water United States Coast Guard National Response Center (*for chemical spills and accidental releases)*				

Note: All data sources should be used in concert with information from the primary literature.

[a] Also includes far-field exposure information such as NATA data, location data for EPA regulated facilities, and polluted environmental media.

Figure 1. TSCA Cumulative Risk Assessment Framework.