Children's Health Protection Advisory Committee

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Acting Administrator Jane Nishida
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

RE: Protecting children's health under amended TSCA: Chemical prioritization

Dear Acting Administrator Nishida:

The Toxic Substances Control Act (TSCA) was amended in 2016 by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. There was clear consensus and a mandate from Congress that EPA should identify and mitigate risks to human health and the environment from chemicals, with particular emphasis on protecting the most vulnerable populations, including children ("potentially exposed or susceptible sub-populations" in the words of the law).[1] Children's health is uniquely susceptible to adverse impacts from toxic chemicals, and encompasses the health of children as well as people of reproductive age, pregnant people, and the periods of prenatal and postnatal development. The Environmental Protection Agency (EPA) has requested input from the Children's Health Protection Advisory Committee (CHPAC) on TSCA topics that focus on chemical prioritization and data needs to protect children's health (charge provided in July 2020, see Attachment A).

EPA previously developed the TSCA Workplan (referred to as "the Workplan") list of priority chemicals for risk evaluation by considering key hazards, chemical properties, and potential for human exposure as factors of concern for children's health, including: reproductive or developmental effects; probable or known carcinogenicity; persistence; bioaccumulation; use in children's and/or consumer products; and detection in indoor air, dust and environmental media.[2; 3] These priorities and several others were affirmed in the CHPAC's 2011 and 2017 letters and offer a strong scientific foundation for prioritization and consideration of data needs relevant to children's health (Attachment B).[4; 5] An additional guiding priority described herein is the consideration of health equity.

In this letter, CHPAC offers EPA recommendations relevant to children's environmental health in direct response to the four charge questions, which focus on: (1) the evaluation and prioritization of the remaining Workplan chemicals; (2) the evaluation and prioritization of other (non-Workplan) chemicals; (3) identification and addressing of hazard and exposure data gaps; and (4) incorporation of data from New Approach Methods (NAMs). Rather than reviewing specific Workplan or non-Workplan chemicals, we focus on providing frameworks, principles, data sources and methodological approaches whose application will result in chemicals of high concern for children's health being prioritized, with information relevant for risk assessment provided at the same time. CHPAC consensus was that this approach provides more long-term value as EPA can flexibly integrate our recommendations as appropriate and apply them to additional chemicals in the future.

Charge 1: Provide children's environmental health information relevant for prioritization and risk evaluation of the chemicals remaining on the TSCA Workplan.

Recommendations

- Include consideration of social vulnerability and environmental co-exposures as part of 'potentially exposed or susceptible sub-populations' and/or 'other risk-based criteria' in the prioritization process to select high-priority chemicals.
- Prioritize chemicals potentially impacting burdened communities by employing data analysis and visualization to integrate information on chemical and non-chemical stressors.

At present, 53 chemicals remain on the Workplan from which EPA must select at least 50% of high priority chemicals to undergo risk evaluation every three years (Attachment C). As each of the 53 chemicals must eventually undergo risk evaluation, we advise EPA to consider information applicable to both prioritization and risk evaluation. EPA's screening process to create the Workplan list was intended to identify chemicals of concern for children's health and considered a set of key hazard and exposure factors previously identified by CHPAC (Attachment B).[6] As shown in EPA's 2012 and 2014 Workplans, many of the remaining 53 chemicals have hazard and/or exposure profiles suggesting children's environmental health concerns. The data sources and references from the Workplans can serve as a starting point in prioritization.[2; 3]

Considering the prioritization approaches currently used by EPA to identify high priority chemicals, we recommend beginning with chemicals with consumer product use that also affect people in communities most burdened by both environmental health hazards and non-chemical stressors that contribute to social vulnerability.[A] Chemical use in consumer products, including those marketed to children, is a potential exposure factor emphasized in the Workplan process, highlighted previously by CHPAC, and considered under TSCA's Section 6 conditions of use analysis (Attachment B). Social vulnerability and environmental co-exposures are 'other risk-based criteria' whose consideration supports TSCA's mandate to protect susceptible populations and is aligned with EPA's Prioritization Rule criteria.[7] The evaluation of these criteria by EPA is also consistent with Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[8]

Populations of concern for children's health (e.g., children, people of reproductive age, pregnant people) in socially vulnerable groups are more likely to have multiple harmful environmental exposures; higher risks of adverse biological effects, comorbidities and other chronic stressors; and fewer resources for mitigation.[9] Decades of peer-reviewed research demonstrate that chemical exposures can cause more severe adverse health impacts when combined with social stressors. For example, children in poverty were shown to have more severe health outcomes from the same level of lead exposures compared to higher-income children.[10] Studies also document that limiting toxic exposures has long-term benefits for socially vulnerable populations.[11; 12] The ongoing COVID-19 pandemic further highlights how social inequalities profoundly, and unevenly, impact morbidity and mortality. Therefore, we advise EPA to give high priority to preventing harmful exposures in vulnerable communities.[13-17] A strategy prioritizing chemicals disproportionately impacting vulnerable populations helps ensure the opportunity to be healthy is equally available. This approach is also aligned with ongoing efforts across the Agency and within all levels of government to advance health equity, which creates healthier communities and ultimately better health for the entire U.S. population.

[A] CDC defines social vulnerability as "the potential negative effects on communities caused by external stresses on human health. Such stresses include natural or human-caused disasters, or disease outbreaks. Reducing social vulnerability can decrease both human suffering and economic loss." Source: ATSDR

To implement an approach incorporating social vulnerability information into TSCA prioritization, CHPAC recommends prioritizing chemicals with significant overlap of multiple measures of potential risk. Data on social vulnerability, geographic proximity to environmental exposures, potential co-exposures to other chemicals with similar health hazard endpoints, and consumer product use are represented in existing databases and the combined potential risks can be understood through varied data analyses and visualization tools.

As one approach, EPA could begin with the most recent Chemical Data Reporting and Chemical and Product Database information to identify which of the 53 remaining chemicals are used in consumer products including children's products. Then, of the chemicals with consumer product uses, EPA could focus on chemicals with data reported to the Toxics Release Inventory (TRI), as TRI information allows chemical releases to air, land and water to be geographically localized.[18] Such chemical releases could be important contributors to exposures potentially impacting toxicity during preconception, prenatal, postnatal and other sensitive life stages. Attachment C identifies chemical uses from the 2014 Workplan and the chemicals listed in the TRI.

Geographic Information System (GIS) analysis allows overlay of TRI information for a Workplan chemical with consumer product use and other geographic information related to risks. One example is social vulnerability factors in the Centers for Disease Control and Prevention's Social Vulnerability Index.[19;B] Another example is data available in the National Air Toxics Assessment based on emissions modeling of air contaminants that inform potential co-exposures to other contaminants with similar hazard endpoints of concern, such as carcinogenicity or respiratory hazard.[20]

EPA can combine this information with population estimates to prioritize chemicals potentially impacting the greatest number of socially vulnerable people. Attachment D provides an example summing population estimates of counties with both high social vulnerability and high volume of TRI releases for two chemicals to allow comparison. Another approach would be to prioritize chemicals where TRI releases show the greatest potential for co-exposures relevant to the specific health risk(s) of concern for each of the chemicals being evaluated. For example, for a chemical with known respiratory toxicity, extensive co-exposures to other respiratory toxicants may indicate a need for prioritization. General examples of both these approaches are provided in Attachment D. These approaches are not mutually exclusive and can be combined with each other and/or with other relevant data sources to inform prioritization and risk evaluation by providing a more detailed and informative picture of social and environmental factors affecting susceptibility and vulnerability. Examples of resources with relevant data are provided in Attachment E.

As prioritization precedes the more rigorous process of full systematic review, CHPAC believes the recognized limitations in the existing databases (e.g., not all chemicals are in TRI; SVI does not include all social risk factors) need not prevent their utility in establishing the list of priority chemicals. For risk evaluation, EPA would need to refine this analysis with additional data to address limitations (Attachment E). Additional considerations are also needed in risk evaluation. For example, it is critical to consider consumer product exposures in the context of historical or current releases that have led to contaminated air, drinking water and food that contribute to exposures, as highlighted in previous CHPAC recommendations (Attachment B). In addition to considering aggregate exposures to a single chemical across multiple routes and pathways as defined in TSCA regulation,[21] we urge EPA to assess cumulative exposures, the combined exposure to multiple chemical and non-chemical stressors via multiple pathways as outlined in EPA guidance.[22] Our

[B] The Social Vulnerability Index uses 15 metrics to create an index: Below poverty; unemployed; income; no high school diploma; age 65 or older; age 17 or younger; older than age 5 with disability; single parent households; minority; speaks English "less than well"; multiunit structures; mobile homes; crowding; no vehicle; group quarters.

references to "exposure" throughout this letter encompass the concepts of both aggregate and cumulative exposures unless otherwise specified.

In summary, the principles for prioritization that CHPAC recommends can be implemented through employing data analysis and visualization to combine complex and disparate data sources (e.g., chemical use, exposure, hazard/adverse health risks, non-chemical stressors) on the remaining 53 chemicals. Such analyses will support EPA in effectively prioritizing the chemicals most likely to impact children and people of reproductive age in the most burdened communities.

Charge 2: Provide children's environmental health information relevant for prioritization of chemicals not on the TSCA Workplan.

Recommendation

- Evaluate newly available hazard and exposure information periodically during the prioritization process, using the TSCA Workplan method to identify non-Workplan chemicals for prioritization.

TSCA allows consideration of non-Workplan chemicals for priority listing. The Workplan approach originally considered factors relevant to children's environmental health to identify chemicals for screening and selection (Attachment B). CHPAC recommends that EPA continue to build on this foundation and establish specific time frames to re-evaluate current data on chemicals not selected for the Workplan (i.e., non-Workplan chemicals); and use the same process of reviewing authoritative lists to select additional chemicals for screening. Chemicals selected for screening through the process described in this charge response should be prioritized using the same approach as described in the response to charge 1 to ensure decisions are made with full understanding of how they might contribute to environmental health disparities across populations.

Periodic evaluation of non-Workplan chemicals is important because new hazard data may become available and exposures may change, which can impact prioritization. Production can increase or new uses of a chemical may result in increased exposure. Two valuable sources of exposure information to support EPA's screening of non-Workplan chemicals that are updated with a regular frequency include Chemical Data Reporting (CDR) and Toxics Release Inventory (TRI) reporting.

Chemicals screened, but not selected, for the Workplan fell into two categories: (1) "Potential candidates for information gathering" were chemicals without sufficient information on hazard or exposure metrics; and (2) Chemicals ranked "moderate" or "low" in the 2014 Workplan. Attachment F lists the chemicals screened in the Workplan process but not selected for the Workplan.

For Category 1 (insufficient information) chemicals, we advise EPA to seek updated data on hazard, exposure, and adverse human health effects, focusing on the chemical prioritization factors in Attachment B. We recommend that EPA also consider data and findings from epidemiologic studies, several of which are highlighted in Attachment E. EPA should score those chemicals which now have sufficient data and consider those that rank high for earlier prioritization.

For Category 2 (did not rank high in 2014 Workplan process), we recommend EPA evaluate current hazard data and the most recent CDR and TRI data to see if production volume, uses or releases have changed. EPA should update normalized total scores and consider chemicals with a higher ranking for prioritization.

We also recommend that EPA review the authoritative lists used to generate the candidate chemicals screened in the original TSCA workplan process (Attachment G), and additional relevant authoritative lists,

and consider the need to screen relevant chemicals added to each list since 2012. This approach could identify chemicals of emerging concern for prioritization. The data sources and references already gathered from the authoritative listing process may be useful to EPA.

We advise EPA to specifically consider chemical uses in electronics, such as flame retardants, as a relevant consumer and children's product use, especially in light of the rapid expansion of 'distance learning' due to the COVID-19 pandemic and the increased use of computers and electronic devices by children as young as preschool age. We also recommend that EPA analyze biomonitoring data to understand human exposure trends, as well as environmental monitoring data to assess whether occurrence and concentrations are increasing in media such as air, indoor dust, or water.

Charge 3: Provide information on data needs relevant to children's environmental health concerns for prioritization and risk evaluation of the remaining Workplan chemicals.

Recommendations

- Evaluate the completeness of a chemical's database to determine data needs for hazard and exposure data critical for assessing children's health risks, as described below.
- Employ multiple approaches to address gaps in hazard and exposure data needed to ensure robust evaluations that do not underestimate children's health risks.

Hazard and exposure information are necessary to complete both prioritization and subsequent risk evaluations, making it imperative to identify and address data gaps as early in the process as possible. To determine data needs for potential high priority chemicals, we recommend EPA evaluate the completeness of a chemical's database for key hazard and exposure data relevant to children's health as described below. Where data needs are identified, we advise that EPA: (1) use TSCA Section 4 and 8 authorities to collect additional data; and/or (2) determine how adjustment factors, to account for uncertainty, variability, and vulnerability, or other health-protective approaches (e.g., predictive modeling) will be used to address the data gap(s).

TSCA includes the concept of "reasonably available" information which is highly relevant to assessment of children's environmental health impacts. "Reasonably available" data include the full scope of peer-reviewed studies available for individual substances and mixtures. As detailed in a February 2020 CHPAC liaison letter to the EPA Scientific Advisory Board, critical research studies providing key data on children's health risks likely contain protected health information that would prevent raw data from being made public.[23] We advise EPA to include such studies in its evaluations using a validated systematic review method to evaluate and integrate the complete body of relevant scientific evidence, resulting in more robust and reliable evaluations. This recommendation is consistent with the 2020 CHPAC liaison letter which states that "EPA should not exclude high quality research studies."[23]
CHPAC fully supports EPA utilizing TSCA Section 4 and 8 authorities to obtain data, including confidential business information, to inform both the prioritization process and risk evaluations. The TSCA statute allows health and safety studies received in response to such requests to be made available for public review. As industry-sponsored studies do not typically undergo peer review, we recommend that industry-sponsored studies obtained from EPA requests undergo expert review to ensure a full understanding of the findings, strengths, limitations and appropriate use of such data. We also encourage EPA to use relevant data and findings from epidemiologic research (examples in Attachment E).

Multiple approaches to address data needs
In addition to obtaining needed data using TSCA Section 4 and Section 8 authorities, we concur with the National Research Council's recommended use of adjustment factors and other health-protective approaches

to account for "missing defaults" and other data gaps.[24] The need to use adjustment factors that account for life-stage vulnerability is also highlighted in CHPAC's 2017 letter to the EPA on TSCA implementation.[5]

While it is standard to apply adjustment factors to account for inter- and intra-species variability in chemical risk assessment, EPA must consider additional sources of uncertainty, variability, and vulnerability that are pertinent to children's health in non-cancer risk assessment. Some examples include database uncertainty in relation to a critical hazard endpoint or exposure, life stage differences in how a chemical is metabolized, and early life susceptibility such as *in utero* exposure to developmental toxicants. The database uncertainty factor is relevant to the question of data gaps and has not yet been incorporated in TSCA risk assessments. We advise EPA to follow recommendations and established best practices detailed in Agency documents on the use of the database uncertainty factor.[25] Uncertainties, variabilities and vulnerabilities should be quantitatively addressed in risk assessment to avoid underestimating children's health risks.[24]

In general, grouping/categorization approaches to chemicals can be helpful to identify similar data needs, and approaches to addressing them, across similar chemical groups. There are numerous valid approaches to grouping chemicals and we suggest several here, though this is not a comprehensive list.

First, chemicals can be grouped around the potential to increase adverse health impacts, whether through common hazards, exposures, or both. For example, a group could be chemicals with common co-exposures, such as benzene, toluene, ethyl benzene and xylenes (BTEX) related to fossil fuels. A group could also be chemicals with similar adverse health endpoints, such as female reproductive toxicity. Chemicals known to contribute to cumulative impacts in vulnerable populations, which could be identified by approaches outlined in the response to charge question 1, could also be grouped.

Second, chemicals can be grouped according to common chemical characteristics of concern, such as predicted toxicity or chemical properties like persistence and bioaccumulation. For example, several ethanones raise persistence and bioaccumulation concerns.

Third, chemicals can be grouped to support informed substitution and ultimate risk mitigation, when chemicals have similar functional uses and may be used as substitutes for each other. For example, flame retardants used in consumer products could be grouped.

Finally, there may be categories of chemicals where grouping for evaluation may not be helpful, but where the chemicals have similar data needs. For example, several chemicals remaining on the Workplan can be used as components of polymers (bisphenol A, vinyl chloride, styrene) and thus may have similar data needs related to assessing unique hazards and exposures across the chemical life cycle.

<u>Data needed on key hazards relevant to children's health</u>

We concur with previous CHPAC recommendations highlighting the following hazards as of most significant concern for children's health (Attachment B):

- Reproductive toxicity
- Developmental toxicity (including developmental neurotoxicity)
- Carcinogenicity
- Endocrine toxicity, including metabolism disrupting chemicals
- Respiratory toxicity and potential effects on lung development, structure or function
- Immunotoxicity
- Toxicity through preconception and/or *in utero* exposures

The current COVID-19 pandemic highlights the importance of immunotoxicity in contributing to disease risk and reveals how there are often data gaps on how chemical exposures affect the immune system and ultimately, the clinical disease course.[26; 27] There are existing regulatory assays relevant to immunotoxicity which could be utilized.[28]

EPA's existing risk assessment guidelines appropriately outline the type of information needed to evaluate hazards (examples in Attachment H). Ensuring that sufficient information is available on each relevant health endpoint category can provide better grounds for hazard determinations. Regarding endocrine toxicity, we recommend that EPA use the principles outlined by the Endocrine Society as described in CHPAC's 2017 letter.[29] As detailed below, cell-based assays and other high-throughput toxicity tests, often called New Approach Methods (NAMs), have the potential to provide needed data and could be used to establish potential hazards or upgrade overall hazard identification. However, due to important limitations, data from NAMs cannot be used to rule-out a specific hazard.

Research has established how, for certain endpoints, the developing organism can be significantly more sensitive to exposure than the adult organism. Endpoint sensitivity can be determined through dose-response assessment or other approaches, such as outlined by the National Research Council.[30; 31] EPA should prioritize filling data gaps on a chemical's impact on the developing organism for risk assessment. In the event that studies specifically addressing early life sensitivity are not available, adjustment factors should be applied.

Additionally, data needed to integrate life stage susceptibility into the quantitative risk calculation must be identified to set priorities for data requests and examine risk for specific chemicals. The needed data may be chemical-specific, as human variability in response to chemical exposure has been shown to vary widely, and in some cases may exceed the default's maximum 10X value.[32] Data on broader categories of chemicals are also available to inform use of an adjustment factor; for example, adjustment factors for asthma-inducing chemicals.[32] To protect the public, we urge development and use of appropriate adjustment factors for each of the life stages. CHPAC has previously provided data and resources for assessing the susceptibility of different life stages to chemicals or mixtures.[5]

Data needed on key exposures relevant to children's health

Previous CHPAC letters have highlighted the need for the following exposure information relevant for children's health (Attachment B):

- Use in consumer/children's products
- Ubiquitous in environments, foods or products in the U.S.
- Biomonitoring, especially information on chemicals that can cross the blood-brain barrier or placenta, and detection in children, women of reproductive age, cord blood, breast milk and pregnant women
- Presence in drinking water, including private wells
- Presence in breast milk and/or food consumed by infants, children, and women of child-bearing age
- Presence in indoor air and dust, including indoor gyms and places children play indoors
- Presence in outdoor environmental media, especially outdoor soil, and surfaces and structures where children may play or spend time
- Presence inside, outside and adjacent to child care or school settings
- Presence in occupational settings where parents or people of reproductive age work

We advise EPA to determine the completeness of the database on the exposures listed above, including how widespread the use of the chemical is, or is anticipated to be, in the home, schools, parks or other areas where children may spend time.

For key exposures listed above, sufficient data must be available in order to:

- Quantitatively assess each relevant exposure source and pathway
- Understand potential exposures during the chemical's life cycle, including manufacturing, processing, distribution in commerce, use and disposal
- Integrate exposures into a total risk calculation where co-exposures by different routes are expected to occur together (such as inhalation and dermal exposures from product use)
- Integrate exposures into a total risk calculation where exposures from different sources are expected to occur in the same population (such as people of reproductive age who may be exposed to a chemical on the job and also at home from use of a consumer product containing the same chemical)
- Integrate exposures into a total risk calculation where co-exposures to different agents occur and impact similar health endpoints (such as multiple agents with impacts on lung function)

CHPAC therefore urges EPA to consider the data needed to assess each relevant exposure as described above in a risk evaluation. As part of its prioritization strategy, EPA should develop plans to obtain the needed data or utilize adjustment factors or other health-protective approaches. Additionally, exposure assessment should make use of analytic strategies most appropriate for the evaluation of aggregate exposures.

A preliminary review of data on the 53 Workplan chemicals available on PubMed indicates a lack of key hazard and exposure data, highlighted above, for many of the chemicals (Attachment C). CHPAC's review suggests the need for EPA to develop strategies to address these children's health data gaps. For high priority chemicals, EPA should also gather data on common chemical co-exposures and social stressors in exposed populations (resources in Attachment E). Many tribes, states, and local jurisdictions have regional data that may address information gaps and provide data needed for hazard identification, co-exposure and co-stressor impacts. The Committee listed many of these resources in Attachment E and suggests that tribal, state, and local jurisdictions can serve as valuable partners.

Charge 4: Provide information relevant to evaluating children's environmental health concerns with New Approach Methods (NAMs) on EPA's list or in development.

Recommendations

- Limit use of data from New Approach Methods (NAMs) for: screening purposes; indicating hazard; upgrading hazard concern; and adding or increasing adjustment factor(s).
- Use data from NAMs in conjunction with data considering susceptible and vulnerable subpopulations.
- Support independent scientists, public health practitioners and physicians in the collaborative development and review of NAMs specific to children's environmental health.

Section 4(h)(2) (C) and (D) of TSCA requires EPA to develop a list of NAMs that are "scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing" along with criteria "for considering scientific reliability and relevance" of NAMs. Many approaches for the use of NAMs in toxicology are under development.[33-38] Work in this area is rapidly evolving as are the approaches to using these tools in a regulatory context. While the strength of NAMs lies in their ease of use and reduction of animal testing,

CHPAC has not identified any approaches that can currently be paired with NAMs to accurately identify the complex biological responses to chemicals of greatest concern for children's health. Improving EPA's ability to protect children's health through appropriate use of NAMs will require investments in newer methods to better address chronic diseases, developmental disorders, immunologic changes, epigenetic mechanisms, and pre-and perinatal exposures. While EPA awaits the development of methods and regulatory approaches that can utilize NAMs to capture more complex biological processes, we emphasize the NAMs and their development should not hinder the use of existing methods, slow the improvement of traditional methods, or prevent the development of new *in vivo* approaches, which may be more effective in protecting children's health.

Concerns about the ability of current NAMs to inform children's environmental health

In general, EPA's current list of NAMs does not identify which methods, if any, are applicable to assessment of hazards, exposures or susceptibilities relevant to children's health.[39] EPA should clarify how the listed NAMs will be used to provide data on children's environmental health concerns.

There are currently no assays that can capture the most critical hazard endpoints for children's health where complex biological systems are involved (such as reproductive and developmental toxicity; neurodevelopmental toxicity; placental development). The listed NAMs contain some assays relevant to children's health, including estrogen/androgen receptor binding and transactivation, steroidogenesis, and skin/eye irritation. Several of these assays evaluate chemicals for their intrinsic ability to interfere with hormone signaling.

However, the current methods are lacking in key aspects needed to generate data relevant for children's health, such as: assessing non-monotonic dose responses (NMDR); low-dose effects; imbalances and reactive/feedback changes in complex hormonal systems (e.g. hormone synthesis, transport and metabolism); upstream effects that may indicate adversity; sensitivity to exposure during critical developmental stages; and, context dependent features such as tissue, receptor type, and co-factors that may affect hormone signaling.

The development of exposure and hazard models on the TSCA NAMs list, and the assumptions within them, should be transparent. Prior to adding new NAMs to the EPA list, we recommend EPA seek public and expert review of each NAM to ensure a full understanding of the strengths, limitations and appropriate use to inform prioritization and risk evaluation.

Recommendations on using data from NAMs to inform children's health protection and further methods development

Due to the limitations noted above, CHPAC recommends listed NAMs be used for screening purposes and to indicate a hazard or upgrade concern for a hazard, but conclusions about the absence of hazard cannot be drawn solely based on NAMs data. Therefore, we advise that data from these alternative methods should not be used to reduce default adjustment factors but could be used to add or increase such a factor. We also recommend that EPA use the most protective testing strategies to generate information on a broad range of endpoints, including disease-focused endpoints that may include upstream indicators, and not solely the traditional guideline study endpoints which miss many developmental stages and sensitivities.[40]

When applying data from a more studied chemical to a less studied, but related, chemical ("read across"), hazard models should only be used to assume that analogs are at least as toxic as the parent chemical, not to assume that analogs are less toxic. Exposure and hazard models must consider or be used in conjunction with information considering susceptible and vulnerable subpopulations, including developmental stages,

geographic location, environmental justice considerations, sex-specific effects, and other factors known to affect biological susceptibility and vulnerability. Environmental justice considerations include factors outlined in the response to charge 1 above, such as co-exposure to multiple chemical and non-chemical stressors.

We advise EPA to continue considering NAMs approaches that are fully transparent and developed in collaboration with independent scientists, including those in the public health and medical communities. Collaborative development of alternative methods could be more strategically directed if the purpose of the assays were well defined, including how EPA would use the data to inform decisions. We recommend that EPA support the collaborative development and review of NAMs by independent scientists and physicians with expertise in reproductive and developmental biology, endocrinology, hormonal systems, and neuronal development. EPA should also seek input and meaningful involvement from the public, including communities most impacted by the chemicals being assessed.

We emphasize the key characteristics framework for EPA here as it has particular strengths to organize data streams (including data from NAMs) in a clear way, to demonstrate the strength of evidence for different data streams, and to highlight gaps needed to further assess a chemical and its impacts. Essential characteristics have been developed for carcinogens, endocrine disrupters and male and female reproductive toxicants, with additional hazard endpoints in development.[41-45] The key characteristics framework could be utilized independently or in a complementary way with other approaches (e.g., adverse outcome pathways, integrated approaches to testing and assessment, and "-omics" large datasets) and would be directly compatible with a systematic review approach.

In closing, the approaches outlined in our letter will support EPA in strong TSCA implementation, and thus lead to better health protections from toxic chemicals for the most vulnerable population groups and ultimately healthier children and families throughout the U.S. population. Thank you for the opportunity to comment and we look forward to our continued engagement on the protection of children's health.

Sincerely,

Deanna Scher, Ph.D.
Chair

cc: Jeanne Briskin, Director, Office of Children's Health Protection
Michal Freedhoff, Principal Deputy Assistant Administrator, Office of Chemical Safety and Pollution Prevention
Lindsay Hamilton, Associate Administrator, Office of Public Affairs
Nica Louie, CHPAC Designated Federal Official, Office of Children's Health Protection
Dan Utech, Chief of Staff, Office of the Administrator

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Attachments

Attachment A: Amended TSCA Workgroup Charge for the Children's Health Protection Advisory Committee (CHPAC)

SCOPE

OPPT and OCHP are working to establish a new CHPAC workgroup to provide children's environmental health (CEH) expert input on the chemicals remaining in the 2014 TSCA Workplan after the 20 high- and 20 low-priority chemicals were designated in December 2019. Children's health includes the health of pregnant women, prenatal development, and postnatal development from birth through puberty. Under this charge, the CHPAC would identify recommendations for CEH implications for the remaining chemicals on the Work Plan, including which chemicals have children's health relevant data gaps where OPPT could seek reporting or testing under Sections 8 and 4, respectively.

BACKGROUND

TSCA, as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016,) states that "potentially exposed or susceptible subpopulations" ("PESS") be considered in the risk evaluation process.

> *"The Administrator shall conduct risk evaluations pursuant to this paragraph to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use." (Public Law 114-182; 6[b][4][a])*

Further, TSCA amendments specifically calls out infants, children, and pregnant women as examples of PESS:

> *"The term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator 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.'' (Public Law 114-182; Section 3[12])*

Under TSCA, EPA considers PESS, including developmental life stages, in its risk evaluations.

Prioritization

The first step in the TSCA process is prioritization. EPA's process and criteria for prioritization are described in the Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act ("Prioritization Rule"), finalized in June 2017. The Prioritization Rule requires that EPA screen the reasonably available information for chemicals using the following criteria and considerations:

1. *"The chemical substance's hazard and exposure potential;*
2. *The chemical substance's persistence and bioaccumulation;*
3. *Potentially exposed or susceptible subpopulations;*
4. *Storage of the chemical substance near significant sources of drinking water;*
5. *The chemical substance's conditions of use or significant changes in conditions of use;*
6. *The chemical substance's production volume or significant changes in production volume; and*
7. *Other risk-based criteria that EPA determines to be relevant to the designation of the chemical substance's priority."*

The 3rd criterion (above) on PESS has relevance to CEH and the other six criteria (above) have potential relevance to CEH. After public comment on the candidate chemicals, a screening review step results in proposed priority designations. After a public comment period on the screening and priority designations, EPA will designate chemicals either as low-priority substances or as high-priority substances for risk

evaluation. On December 20, 2019, EPA designated 20 high-priority and 20 low-priority substances. Upon completion of each risk evaluation thereafter, EPA must designate another high-priority chemical for risk evaluation. Under TSCA section 6(b)(2)(D) EPA must give preference to chemicals that:

- *have a "persistence and bioaccumulation score of 3"; and*
- *"are known human carcinogens and have high acute and chronic toxicity."*

Chemicals not on the 2014 TSCA Workplan can also be nominated for consideration as high-priority substances under TSCA. However, under TSCA section 6[b][2]B], EPA is required to select at least 50 percent of chemical substances for risk evaluation from the 2014 Workplan:

> *"ADDITIONAL RISK EVALUATIONS.—Not later than three and one half years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, the Administrator shall ensure that risk evaluations are being conducted on at least 20 high-priority substances and that at least 20 chemical substances have been designated as low-priority substances, subject to the limitation that at least 50 percent of all chemical substances on which risk evaluations are being conducted by the Administrator are drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments." (Sec. 6[b][2][B])*

Data Request Authority:

TSCA has provisions for requesting data and requiring reporting from manufacturers and processors under Sections 4 and 8, respectively.

Under TSCA 4[a][1], EPA has "Testing Requirements" in the context of risk evaluations. The language below requires EPA, by rule, order, or consent agreement, to require testing on a substance in certain instances, such as when there is insufficient information and additional data is necessary for risk evaluation purposes. This section on Testing Requirements states-

> *"If the Administrator finds that—*-(A)(i)(I) *the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,*
> *(II) there is insufficient information and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and*
> *(III) testing of such substance or mixture with respect to such effects is necessary to develop such information; or*
> *(ii)(I) a chemical substance or mixture is or will be produced in substantial quantities, and (aaI) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (bbII) there is or may be significant or substantial human exposure to such substance or mixture,*
> *(II) there is insufficient information and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and*
> *(III) testing of such substance or mixture with respect to such effects is necessary to develop such information;" (Sec 4[a][1])*

Under TSCA 4(a)(2)(A)(i), EPA has "Additional Testing Authority" -

"the Administrator may, by rule, order, or consent agreement—

(A) require the development of new information relating to a chemical substance or mixture if the Administrator determines that the information is necessary—

(i) to review a notice under section 5 or to perform a risk evaluation under section 6(b);" (Sec 4[a][2][A][i])

Under TSCA 4[a][2][B], "Additional Testing Authority," in the context of prioritization, states that EPA may –

"require the development of new information for the purposes of prioritizing a chemical substance under section 6(b) only if the Administrator determines that such information is necessary to establish the priority of the substance, subject to the limitations that—

(i) not later than 90 days after the date of receipt of information regarding a chemical substance complying with a rule, order, or consent agreement under this subparagraph, the Administrator shall designate the chemical substance as a high-priority substance or a low-priority substance; and

(ii) information required by the Administrator under this subparagraph shall not be required for the purposes of establishing or implementing a minimum information requirement of broader applicability."

Reporting Authority:

Under Section 8(a), EPA has the authority to write rules to require manufacturers and processors to maintain records and submit reports in order to enforce TSCA.

"The Administrator shall promulgate rules under which—

(A) each person (other than a small manufacturer or processor) who manufactures or processes or proposes to manufacture or process a chemical substance (other than a chemical substance described in subparagraph (B)(ii) shall maintain such records, and shall submit to the Administrator such reports, as the Administrator may reasonably require, and

(B) each person (other than a small manufacturer or processor) who manufactures or processes or proposes to manufacture or process—

(i) a mixture, or

(ii) a chemical substance in small quantities (as defined by the Administrator by rule) solely for purposes of scientific experimentation or analysis or chemical research on, or analysis of, such substance or another substance, including any such research or analysis for the development of a product, shall maintain records and submit to the Administrator reports but only to the extent the Administrator determines the maintenance of records or submission of reports, or both, is necessary for the effective enforcement of this Act." (Sec. 8[a][1])

"The Administrator may require under paragraph (1) maintenance of records and reporting with respect to the following insofar as known to the person making the report or insofar as reasonably ascertainable:

> *(A) The common or trade name, the chemical identity, and molecular structure of each chemical substance or mixture for which such a report is required.*
>
> *(B) The categories or proposed categories of use of each such substance or mixture.*
>
> *(C) The total amount of each substance and mixture manufactured or processed, reasonable estimates of the total amount to be manufactured or processed, the amount manufactured or processed for each of its categories of use, and reasonable estimates of the amount to be manufactured or processed for each of its categories of use or proposed categories of use.*
>
> *(D) A description of the byproducts resulting from the manufacture, processing, use, or disposal of each such substance or mixture.*
>
> *(E) All existing information concerning the environmental and health effects of such substance or mixture.*
>
> *(F) The number of individuals exposed, and reasonable estimates of the number who will be exposed, to such substance or mixture in their places of employment and the duration of such exposure.*
>
> *(G) In the initial report under paragraph (1) on such substance or mixture, the manner or method of its disposal, and in any subsequent report on such substance or mixture, any change in such manner or method." (Sec. 8[a][2])*

Alternative Test Methods:

Section 4[h] of TSCA directs the reduction of testing on vertebrates (Sec 4[h][1]) and the implementation of "alternative test methods," (Sec 4[h][2]) defined as those that are scientifically valid and not based on vertebrate species. These alternative methods could include -

"(i) computational toxicology and bioinformatics;
(ii) high-throughput screening methods;
(iii) testing of categories of chemical substances;
(iv) tiered testing methods;
(v) in vitro studies;
(vi) systems biology;
(vii) new or revised methods identified by validation bodies such as the Interagency Coordinating Committee on the Validation of Alternative Methods or the Organization for Economic Co-operation and Development; or
(viii) industry consortia that develop information submitted under this title." (Sec. 4[h][2])

CHARGE QUESTIONS

1) Referring to the text from TSCA and the Prioritization Rule (above), please review the remaining TSCA Workplan chemicals for potential CEH concerns (e.g., exposure, effects, and emerging issues).
    a. Please provide a compilation of the scientific information supporting potential CEH concerns, including data sources and references for the remaining chemicals on the TSCA workplan.

b. For any chemical with information that indicates a potential CEH concern, please specify and comment on whether the available information is relevant for the intended use of risk evaluation. If criteria #7 (above) is a consideration, please describe the "Other risk-based criteria..." used to justify the CEH level of concern.
c. Please provide a narrative regarding the degree of clarity and completeness of the documentation associated with the generation of the provided information.

2) While EPA is required to select 50% of their priority chemicals from the 2014 Workplan (see above), other chemicals can be nominated for high and low priority chemicals under TSCA. Are there chemicals beyond those remaining on the Workplan that should be considered for prioritization? If so, provide a list of these non-Workplan chemicals along with the information indicated in question 1 above for consideration.

3) Referring to the text on EPA's authority to request new data and report on existing data from a manufacturer in Sections 4 and 8 (see above), among the remaining Work Plan chemicals, which ones with potential CEH concern have significant data gaps which could be addressed by obtaining data, including through either the Section 4 or Section 8 mechanisms?

a. For example, are there chemicals currently on the workplan list to which children have high exposure but for which additional health effects data may be needed (or vice versa)?
b. For the specific chemicals on the workplan, what assays or types of studies may be needed to adequately assess CEH exposure or effects in order to prioritize chemicals on the Work Plan list or to conduct the Risk Evaluation?

4) Referring to the text on alternative test methods (above) from Section 4[h] of TSCA, EPA has published a List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs] (see: https://www.epa.gov/sites/production/files/2018-06/documents/alternative_testing_nams_list_june22_2018.pdf)). EPA has also committed to updating this list periodically as new methods become available. Are there any alternative test methods, either currently available (on EPA's current list) or under development, that are relevant to developmental life stages and could be used for testing TSCA chemicals for CEH exposure or effects? If so, please provide as much information as possible about these methods, and how they are particularly relevant to CEH concerns.

Attachment B: Table of chemical prioritization factors

Factor	TSCA workplan[C]	CHPAC 2011 letter[D]	CHPAC 2017 letter[E]	TSCA regulation[F]
Hazards				
Reproductive or developmental effects	X	X[1]	X[2]	
Probable or known carcinogens	X	X		X
Endocrine disruption		X	X	
Respiratory toxicity/effects on lung development, structure or function		X		
Immunotoxicity		X		
Presents hazard to children through preconception and/or *in utero* exposures		X		
High acute and chronic toxicity				X
Chemical Properties				
Persistence	X	X		X
Bioaccumulation	X	X		X
Exposure Potential				
Used in children's products	X	X	X	X[3]
Used in consumer products	X	X	X	X[3]
Ubiquitous in environments, foods or products in the US		X	X[4]	
Detected in biomonitoring	X	X[5]	X[6]	
Detected in biota	X			
Detected in drinking water	X	X		
Detected in food consumed by infants, children, pregnant and/or lactating women		X		
Detected in indoor air	X	X		
Detected in indoor dust	X	X		
Detected in environmental media	X	X[7]		
Detected in childcare and/or school settings		X		
Detected in occupational settings where children, parents, reproductive age people work		X		
Volume of releases reported to Toxics Release Inventory	X			
Production volume	X			X[8]
Storage near significant sources of drinking water				X
Misc.				
Other risk-based criteria determined to be relevant to the designation of the chemical substance's priority				X

[1]Highlights developmental neurotoxicity
[2]Highlights developmental toxicity
[3]Criteria are "exposure potential" and "conditions of use or significant changes in the conditions of use"
[4]Highlights "chemicals children are likely to encounter"
[5]Highlights chemicals that can cross placenta or blood-brain barrier
[6]Highlights chemicals detected in children, women of reproductive age, cord blood, pregnant women
[7]Highlights outdoor soil, surfaces and structures where children may play or spend time
[8]Criteria are "Production volume or significant changes in production volume"

[C] US EPA, TSCA Workplan Chemicals: Methods Document. (2012)
[D] CHPAC, Criteria for identifying chemicals of concern for children (including prenatal and preconception exposures. (March 2011)
[E] CHPAC, Protecting children's health under amended TSCA. (March 2017)
[F] 82 FR 33753

Attachment C: 53 remaining TSCA workplan chemicals: Initial review of children's environmental health information and data gaps
A more detailed Excel file of this attachment is available upon request.

N/A= Not available; No relevant studies were identified in the PubMed search findings (see search terms used in footnote 2).
Yellow highlighted cells = few or no studies identified in PubMed search (see search terms used in footnote 2).

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	**CEH Exposure**			**CEH Effects**	
	Exposure information[2]	**Human biomonitoring data[2]**	**Breastmilk Detection/Levels[2]**	**Human Health Outcome Data[2]**	**Animal Effects Data[2]**
Acetaldehyde (75-07-0) Consumer; Industrial TRI: Y	Adolescents: e-cigarettes, waterpipe smoking, and alcohol; outdoor air pollutant generated by industrial and road traffic; pediatric surgical smoke; childcare facilities	N/A	N/A	Associations: e-cigarettes and asthma; alcohol-based mouthwash and oral cancer; alcohol and Fetal Alcohol Spectrum Disorders; in utero acetaldehyde and PNET in children	N/A
Acrylonitrile (107-13-1) Consumer; Dispersive; Industrial TRI: Y	Indoor environmental tobacco smoke as a VOC metabolite; production of synthetic fibers, rubber, plastics including plasticizer in toys; exposure as a VOC in cribs at neonatal intensive care units	Smoking was positively associated with metabolites of the tobacco constituents including acrylonitrile in pregnant women; acrylonitrile metabolites associated with ETS; Children 6-11 yrs (NHANES) had statistically significantly higher levels of the metabolite acrylonitrile-vinyl chloride-ethylene oxide than nonsmoking adults.	N/A	Associations: Occupational exposure and menstrual disorder and dysgenesis in female workers and the wives of male workers.	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
tert-Amyl methyl ether (994-05-8) Consumer; Industrial TRI: N	Gasoline additive	N/A for children's studies. Blood and urine concentrations measured in healthy male volunteers (not known whether adolescents included) exposed to tert-Amyl methyl ether (TAME) via inhalation of gasoline; Driver studies of TAME in blood and urine.	N/A	N/A	Developmental toxicity: rat, mice, zebrafish. Effects after gestational exposure include fetal deaths, reduced fetal bodyweight, increased cleft palate incidence, enlarged lateral ventricles of the cerebrum, and craniofacial abnormalities.
Antimony and Antimony Compounds (category) Consumer; Industrial TRI: Y	Children dietary exposure (China): average exposure of the population on antimony in 3 age groups exceeded WHO ADI (0. 86µg/kg BW); Prenatal exposure to antimony (Japan).	Identified in maternal blood, cord blood, and placenta (Japan); Hair levels significantly higher in girls than boys (Iran); High blood levels in children (Uganda, Romania); levels in urine higher in children who ate more vegetables (Spain).	Detected- levels varied.	Associations: Antimony exposure and ADHD; Prenatal exposure and birth outcomes and development, including cellular function, aging, girl's puberty, and disease susceptibility.	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Arsenic and Arsenic Compounds (category) Consumer; Industrial TRI: Y	Arsenic (As) in drinking water (Mexico); Dietary exposure of inorganic arsenic (iAs) in children (Spain).	Equivalent (BE) value for As of 15 µg/L in children's urine (Mexico); urinary iAs detected (Spain); geometric mean (GM) for total As in urine 33.82 µ/L for school children aged 6 - 11 years (Spain); GM for total arsenic was 12.9 µg/L in urine for 7 year old children (Italy).	Detected- levels varied	Associations: Neuropsychological development (Spain); possible kidney damage in children (Mexico); diabetes-related outcomes 14+ yrs old (American Indian tribes); adverse pregnancy outcomes (e.g., spontaneous abortion, stillbirth and low birth weight); genetic damage in children exposed to As in drinking water (West Bengal, India).Review by Young et al. suggests in utero and postnatal As exposure could increase risk of adult disease (e.g., cancer, cardiovascular disease, non-alcoholic fatty liver disease, and diabetes).	Developmental neurotoxicity; male reproductive toxicity
Barium Carbonate (513-77-9) Consumer; Industrial TRI: N	Pesticide; Used in cement production; laboratory worker exposure.	N/A for children's studies	N/A	N/A for children's studies. Ingestion and hypokalemia that can lead to tachycardia, hypertension or hypotension, muscle weakness, and paralysis.	N/A
Benzenamine (62-53-3) Consumer; Industrial TRI: Y	Sparse information. Dyes: Case report of 16 yr old girl exposed in paint and dye-casting factory using aniline dyes.	No children's studies. Biomonitoring studies: aniline urinary studies and levels higher from occupational exposure.	N/A	Case report: 16 yr old girl working in a paint and dye-casting factory of aniline dyes presented with cyanosis, fever and altered sensorium; Parental occupational aniline exposure increased risk of acute lymphocytic leukemia in children.	Developmental toxicity; Developmental neurotoxicity, Reproductive toxicity.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Benzene (71-43-2) Consumer; Dispersive; Industrial TRI: Y	Tobacco smoke; air pollutants; and in polymers, resins, synthetic fibers; 6-12 yr old children exposed while working with solvents (Mexico); Parental occupational exposure for machine or engine mechanics, in the shoe industry, or in nail salons.	Elevated levels of benzene in blood and urine of children (Kinshasa/DRC).	Detected- levels varied	Associations: Kidney damage in children (Mexico); childhood exposure and risk of acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML); Air pollution, including benzene, increases ADHD risk; Nail salon occupational exposure (could include adolescents 16+ yrs old) to volatile organic compounds like benzene can lead to cancers (e.g., squamous cell carcinoma, nasopharyngeal cancer, Hodgkin's lymphoma, and leukemia) (Colorado); Maternal and paternal occupational benzene exposure increased risk for childhood cancer.	N/A
Bisphenol A (BPA) (80-05-7) Consumer; Industrial TRI: Y	Used to synthesize polycarbonate plastics and epoxy resins, including in dental sealants.	83% of hair samples at concentrations 24 to 1427 ng/g (Spain); BPA urinary concentrations detected in nearly all children sampled (Europe); children 6 to 8 yrs old had higher BPA levels than older children (Canada).	Detected- levels varied	Associations: increased risk of obesity, AD/hyperactivity and/or ASD in children; disrupts placental epigenetics; prenatal urinary BPA concentration associated with child behavior and cognitive abilities (associations stronger for boys than girls).	Effects on steroid hormone and vitamin D3 metabolism in rats after postnatal developmental exposure.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Butanamide, 2,2'-[(3,3'- dichloro[1,1'-biphenyl]- 4,4'-diyl)bis(azo)]bis[N-(4-chloro-2,5 -dimethoxyphenyl)-3-oxo- (Pigment Yellow 83) (5567-15-7) Consumer; Industrial	Search results for "pigment yellow" since no results for pigment yellow 83: Exposure through tattooing in young adults; Azo colorant dyes exposure in workers	N/A	N/A	N/A	N/A
Butanamide, 2-[(4-methoxy-2-nitrophenyl) azo]-N-(2-methoxyphenyl)-3-oxo- (Pigment Yellow 65) (6528-34-3) Consumer TRI: N	Search results for "pigment yellow" since no results for pigment yellow 65: Exposure through tattooing in young adults; Azo colorant dyes exposure in workers	N/A	N/A	N/A	N/A
4-sec-Butyl-2,6-di-tert-butylphenol (17540-75-9) Consumer; Industrial TRI: N	N/A	N/A	N/A	N/A	N/A
Cadmium and Cadmium Compounds (category) Consumer; Industrial TRI: Y	Prenatal and postnatal exposure (e.g., coal smoke) (Bangladesh); Dietary exposure in infants (France); e-waste recycling exposure in children; Coal smoke as airborne cadmium source from heating stoves (Mongolia).	Measured Cd in blood, feces, and urine (Zambia); Metal levels higher in 0-3 yr old children than 4-7 year old children; Cadmium detected in maternal blood and their children's blood (Europe);	Detected- levels varied	Associations: childhood exposure and several bone-related biomarkers (Bangladesh); Childhood exposure (prenatal or postnatal) and lower IQ in boys and altered behavior in girls; children's e-waste exposure and hearing loss; dietary exposure in children <3 yrs old and potential nephrotoxicity effects.	Human and zebrafish comparative study suggests cadmium exposure increases the risk of juvenile obesity.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Chromium and Chromium Compounds (category) Industrial TRI: Y	Hexavalent chromium present in house dust; Applications in industries, homes (house dust), agriculture (pesticides) and medicine; contaminated wastewater; found in tobacco producing regions.	Detected in placenta; Median urinary chromium level in children aged 1-17 years was 0.54 µg/g of creatinine (Buenos Aires); Urinary chromium concentrations detected in children 3 months to 6 yrs old (NJ, US) with median uncorrected urinary chromium concentration of 0.19 µg/l (0.22±0.16).	Detected- levels varied	Associations: Gestational exposure to chromium and fetal growth effects; childhood exposure and kidney injury molecule-1; postnatal exposure and neuropsychological development in school-aged children.	N/A
Cobalt and Cobalt Compounds (category) Industrial TRI: Y	Children exposure through e-waste recycling regions, shoes, and personal care products.	Urinary levels measured in children >7 yrs old (Taiwan), children had higher levels of than adults; high urinary levels of cobalt in workers and people living nearby mines or smelters (<3 km) (DRC).	Detected- levels varied	Associations: Cobalt in footwear in children and allergic contact dermatitis.	N/A
Creosotes (8001-58-9) Industrial TRI: Y	Creosote is a complex mixture, containing over 200 constituents (NIOSH, 1977); neighborhood air, water, and soil around wood treatment plants contaminated with wood preserving chemicals; contaminated groundwater from the American Creosote Works Superfund site (Pensacola, FL); Occupational dermal and inhalation exposure to workers using creosote as wood protectant to produce railway sleepers, utility poles and marine pilings.	PAH urinary biomarkers were identified in soil remediation workers (smokers and nonsmokers) on former creosote wood impregnation site polluted w/creosote oil; dermal and respiratory exposure in creosote workers: urinary metabolites excretion of 1-hydroxypyrene as good biomarker for PAHs. Workers can be adolescents.	N/A	Associations: Paternal occupational exposure and increased odds ratios for neuroblastoma; Potential parental occupational exposure to creosote and brain cancer (five cases); Exposed residents (adults and some children) near wood treatment plant had significantly more cancers and respiratory, skin, and neurological health outcomes than unexposed matched controls.	Developmental toxicity (e.g., embryonic cardiac deformities in Atlantic killfish; Pacific herring embryos near 100-yr old creosote-treated pilings exhibited higher Cyp1a gene expression than embryos from reference areas; teratogenicity of groundwater at American Creosote Works Superfund site, Pensacola, Fla).

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Cyanide Compounds (Limited to dissociable compounds) (category) Consumer; Industrial TRI: N	Food contaminant (e.g., cyanide in cassava); Preterm infants in NICU often placed in incubators that may increase exposure to VOCs, including cyanide; Air fresheners, aerosols, paint or varnish, organic solvents, and passive/active smoking (ETS)	Urinary metabolites of cyanide higher in infants in NICU incubators.	Detected- levels varied	Associations: Dietary cyanogen exposure associated w/1-4 yr olds neurodevelopmental effects (cognitive and motor) (DRC, Africa).	N/A
3,3'-Dichlorobenzidine (91-94-1) Industrial TRI: Y	Occupational exposure - production of colorants.	N/A for children. Biological monitoring of workers used hemoglobin adducts and spot samplings of urinary 3,3'-DBZ excretion; urinary mutagenicity determination assay found that 11% of workers (who could be adolescents) in azo dye manufacturing had exposure higher than nonworkers.	N/A	N/A for children's studies. Mutagen.	N/A
3,3'-Dichlorobenzidine dihydrochloride (612-83-9) Consumer; Industrial TRI: Y	Occupational exposure - production of colorants	N/A for children's studies. Effective biological monitoring was achieved w/hemoglobin adducts and spot samplings of urinary 3,3'-DBZ excretion in workers (who could be adolescents). (who could be adolescents)	N/A	N/A for children's studies. Mutagen.	Androgen Receptor EcoScreen assessed androgen receptor (AR) agonist and antagonist activity of 253 test compounds: identified 3,3'-dichlorobenzidine dihydrochloride as potent AR antagonist.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
1,2-Dimethoxyethane (Monoglyme) (110-71-4) Consumer; Industrial TRI: N	Occupational exposure- used as solvent in batteries	N/A for children's studies. Higher urinary levels of MAA metabolite of EGdiME among occupationally exposed workers (who could be adolescents) than controls.	N/A	N/A	Developmental and Reproductive Toxicity (e.g., testicular atrophy, embryotoxic effects).
2-Dimethylaminoethanol (DMAE) (108-01-0) Industrial TRI: N	DMAE and its salts have been used in medicine; consumer products; related compounds used in gas purification; used in label printing plants	N/A	N/A	N/A for children's studies. Associations: workers (some could be adolescents) and blurry, halo, and blue-grey vision.	Developmental toxicity (DMAE inhibits choline uptake and metabolism during neurulation resulting in growth retardation and neural tube and facial defects; increased fetal body wt and increased incidence of 6 skeletal variations but no malformations).
Di-n-octyl phthalate (DnOP) (1,2-Benzenedicarboxylic acid, 1,2- dioctyl ester) (117-84-0) Industrial; Commercial; Consumer TRI: N	Occupational; Indoor dust; Consumer products	MnOP detected in urine of pregnant women; Children's urinary MnOP not above limits of quantification; not identified in urine samples of children or adolescents (Germany); not detected in urine from mothers and their school-aged children in Duisburg birth cohort study.	N/A	Associations: Urinary metabolite of DNOP exposure in late pregnancy and lower nonverbal IQ scores in children; urinary metabolites from maternal third trimester DNOP concentration and lower bone mineral concentration at 10 yrs old but associations did not remain statistically significant after multiple testing correction; DnOP levels in overweight children compared to nonoverweight.	Developmental toxicity (in utero exposure led to significant increase in rudimentary lumbar ribs but no increase in the incidence of fetal malformations or external and visceral variations).

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Ethylbenzene (100-41-4) Consumer; Industrial TRI: Y	Air pollution as VOC (burning fossil fuels, waste emission, coal industry); Occupational exposures including oil and natural gas development and operations and composting facilities; Indoor air contaminant; Traffic air pollution; Tobacco smoke; Diet.	NHANES children ≥6 yrs old: consuming vegetables and fruit associated w/decreased urinary metabolites; tobacco smoke as a major source of ethylbenzene exposure for the general U.S. population; Urine samples collected from composting facilities workers.	Detected (Pellizzari et al. 1982) but concentrations not reported	Associations: Pregnant women with high exposure 5 days prior to delivery and cardiovascular events; Annual 2008 asthma rates positive correlation with total benzene, toluene, ethylbenzene and xylene (BTEX) at 5-digit zip code scale spatial resolution in children (5+ yrs old) and adults (Detroit); Children with higher BTEX compound exposure more likely to receive academic support services later in childhood (NYC).	N/A
bis(2-Ethylhexyl) adipate (103-23-1) Consumer; Industrial TRI: N	Plasticizer in food packaging (e.g., cereal based food, some PVC-based plastic wrap); consumer products (e.g., deodorant); plastic medical devices used in pediatric intensive care units; and occupational exposure (e.g., DEHA is used as hydraulic fluid, component of aircraft lubricants).	Infants urine samples had median dietary intake of DEHA over 7 consecutive days of 1.0 µg/kg b.w. Urine samples analyzed for DEHA metabolites in healthy adults was highest in those consuming food wrapped in cling film. Detected urinary metabolites in pregnant women; Healthy subjects aged 14-60 years measured for urinary DEHA metabolites from food intake over 7 consecutive days - median is 0.7 (2.2) microg/kg b.w.	N/A	N/A	Reproductive toxicity e.g., ovarian toxicity, female fertility); peroxisome proliferator; Genotoxicity: one study found no genotoxicity in primary cultures of adult rat hepatocytes; Another study found DNA damage in cells of zebrafish larvae.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
2-Ethylhexyl 2,3,4,5-tetrabromobenzoate (TBB) (183658-27-7) Consumer; Industrial TRI: N	Flame retardants and polyurethane foams exposure occupational or in home (indoor dust, furniture, cat hair); children's hand wipes; Potential through dietary intake from e waste sites.	Detected in serum and milk in nursing women; in hair and fingernail samples of U.S. college students (some adolescents).	Detected- levels varied	N/A	Developmental toxicity (e.g., exposure to TBB may activate an antioxidant response and alter behavior during early zebrafish development); Endocrine toxicity (e.g., liver gene transcription analysis using RNA-sequencing indicated that 28-d dietary exposure of trout to EH-TBB down-regulated a gene that mediates endocrine processes in Rainbow trout); Reproductive toxicity (e.g., fecundity effects in adult zebrafish study).
bis(2-Ethylhexyl) - 3,4,5,6-tetrabromophthalate (TBPH) (26040-51-7) Consumer; Industrial TRI: N	Flame retardants and polyurethane foams; indoor dust (ingestion and dermal); dust of commercial airplanes; children's hand wipes.	Detected in maternal serum and milk; Correlation between fingernail levels and dust observed; Hair and fingernail samples analyzed in university students, concentrations of 20-240ng/g in hair, <17-80ng/g in nails.	Detected- in 32.4% of milk samples	N/A	Reproductive toxicity (e.g., TBPH can be metabolized by porcine esterases to TBMEHP and induced MNGs in the fetal testes in a rat model). PPAR agonist in mouse cells. Hepatic effects.
2,5-Furandione (108-31-6) Industrial TRI: Y	N/A	N/A	N/A	N/A	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
1-Hexadecanol (36653-82-4) Consumer; Dispersive; Industrial TRI: N	N/A	N/A	N/A	Sparse information on children. "Exosurf neonatal," synthetic surfactant used to treat respiratory distress syndrome in newborns, assessed lung and neuro outcomes in clinical trials: found no adverse effects at 1 or 2 yrs old. Did not follow to later ages.	N/A
2-Hydroxy-4-(octyloxy) benzophenone (1843-05-6) Consumer; Commercial TRI: N	N/A	N/A	N/A	N/A	N/A
Lead and Lead Compounds (category) Consumer; Industrial TRI: Y	Lead-based paint in old homes and schools (e.g., house dust); air; soil; pellet guns; jewelry.	Detected in blood (cord and maternal), placenta, teeth, and urine; Numerous studies serum levels of lead in children (e.g., NHANES 2011).	Detected- levels varied	Associations: Developmental neurotoxic health outcomes even at low doses; Thyroid impacts; Male reproductive outcomes (e.g., sperm quality).	Neurodevelopmental toxicity (rats, mice, zebrafish); male reproductive toxicity (mice); Transgenerational effects on brain transcriptome (zebrafish).
Long-chain chlorinated paraffins (C18-20) (category) Industrial; Dispersive TRI: N	N/A	N/A	Detected- mean concentration of 19.1 (<LOD-184) ng g-1; detected in 86% of the human milk samples	N/A	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Medium-chain chlorinated paraffins (C14-17) (category) Consumer; Dispersive; Industrial TRI: N	Food, dust; in adhesives; plastic sports courts and synthetic turf; indoor air environments (e.g., residential houses, malls, offices, and student dormitories); Indoor dust and indoor air posed high risks for toddlers and infants.	Lactational transfer. Study of short and medium chain CPs found levels of both ∑SCCP and ∑MCCP were present in: maternal serum > breast milk > cord serum > placenta.	Detected- levels varied	N/A	N/A
4,4'-Methylene bis(2- chloroaniline) (101-14-4) Consumer; Industrial TRI: Y	Occupational exposure: polyurethane workers; plastic product manufacture.	N/A for children's studies. Case report of accidental spill resulting in dermal exposure to worker: serial urinary MBOCA samples from the worker over a 2 week period allowed calculation of biological half-life for MBOCA in urine of approximately 23 hours.	N/A	No human data; suspected human carcinogen	No info on dev and repro tox; known animal carcinogen
Molybdenum and Molybdenum Compounds (category) Consumer; Industrial TRI: N	Mining and living near mining areas; personal care products (e.g., colored cosmetics); diet (e.g., vegetables); cobalt-chromium-molybdenum (CoCrMo) metal-on-metal prosthetics.	Detected in urine, amniotic fluid, cord blood, pregnant women maternal serum, children's nails, and placenta; Mo concentration in urine was 52.1+/-29.3 microg/L for children living near mine (Mexico). Children who ate more vegetables had higher levels Mo (NHANES; Spain)	Detected- levels varied	Associations: higher Mo in umbilical cord and higher risk for cleft lip or cleft palate; higher urinary Mo level in children and DNA and lipid damage; Concentrations above the median and increased risk for NTDs.	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Naphthalene (91-20-3) Consumer; Industrial TRI: Y	Incomplete combustion of organic materials; traffic emissions; smoked or barbecued food; leafy vegetables; mothballs; indoor air (e.g., tobacco smoke); crabs of polluted waters; gas stations and gas filler occupational exposure.	Metabolites detected in urine, serum, breast milk; Urinary metabolites: 3 yr olds with hydroxynaphthalenes predominant (Poland); higher levels in adolescents and adults than young children (Australia); preschool air levels and children's urinary levels correlate; high metabolite levels in mothers and their newborns (Czech Republic).	Detected- levels varied	Poisoning incidents of children from mothballs leads to acute intravascular hemolysis leading to anemia, hemoglobinuria, methemoglobinemia, and acute kidney injury (AKI); Associations: Highest napthalene metabolite in urine and increased risk of obesity in children (Canada); Maternal air emission exposure and low birth weight in offspring; prenatal exposure and adverse brain development (Taiwan). Serum metabolite levels and asthma biomarkers in children.	Developmental toxicity (juveniles exposed to NA induced lung cytotoxicity [mice]; increased rates of embryonic mortality and malformation, and decreased hatchability [zebrafish]); Developmental neurotoxicity in PAH mixture study including napthalene (zebrafish).
2-Naphthalenecarboxylic acid, 4-[(4-chloro-5- methyl-2-sulfophenyl) azo]-3-hydroxy-, calcium salt (1:1) (Pigment Red 52) (17852-99-2) Consumer; Industrial TRI: N	N/A	N/A	N/A	N/A	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Nickel and Nickel Compounds (category) Consumer; Industrial TRI: Y	Consumer products (e.g., jewelry, coins, zippers, belts, tools, toys, chair studs, cases for cell phones and tablets); dental appliances; Contamination of air, food, and water; naturally occurring in rock and soil; Occupational exposure and fence-line communities (e.g., mining; oil refineries; non-ferrous metal plants.	Detected in serum, urine, and hair of children.	Detected- levels varied	Associations: Allergic contact dermatitis (ACD) in children; most frequent cause of contact allergy worldwide; higher maternal urinary nickel and increased risk of preterm delivery; maternal levels and congenital heart defects in offspring; in utero levels and slower progression of breast development in offspring; Ni levels negatively associated with testosterone in girls 8-13 yrs old.	Developmental toxicity (e.g., embryonic effects [sea urchin])
N-Nitrosodiphenylamine (86-30-6) Consumer; Industrial TRI: Y	N/A	N/A	N/A	N/A	Cytotoxicity in hamster ovary cells; Carcinogen
Nonylphenol and Nonylphenol Ethoxylates (NP/NPEs) (category) Commercial; Industrial TRI: Y	Consumer products; food (grains, livestock, and seafood); industrial applications; soil.	Detected in serum, urine, cord blood in children.	Detected- levels varied	Associations: ADHD in children 4-15 yrs old; maternal 4-n-nonylphenol exposure and spontaneous abortion	Developmental neurotoxicity (e.g., CNS molecular changes after in utero exposure, involved in RXRα/PXR/CAR signaling pathways [mouse primary neuronal cell cultures]; NP developmental exposure leads to hyperadrenalism [rat]); Reproductive toxicity (4-Nonylphenol effects on rat testis; Transcriptomic analysis found genes in gene ontologies related to germ cell development and reproduction).

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
4-tert-Octylphenol (4-(1,1,3,3-Tetramethylbutyl)-phenol) (140-66-9) Consumer; Industrial TRI: N	Industrial chemicals used in the manufacture of nonionic surfactants (tOP)	Urine levels of tOP: young children had higher concentrations than adolescents; and adolescents higher concentrations than adults (NHANES).	Detected- levels varied	Associations: Significant negative associations between maternal urinary tOP concentrations and neonatal sizes at birth (males more sensitive than females).	Endocrine disruptor (e.g., decrease in circulating thyroxine, increase in thyroid follicular cell hypertrophy, hyperplasia during metamorphosis and Müllerian duct development effects [frogs]; some males exhibit testicular oocytes [fish]; estrogen action increased the percentage primordial and developing follicles and cell proliferation in neonatal ovaries [pigs]; positive correlation with feminization indicators in males and masculinization indicators in females [fish]).
Octamethylcyclotetrasiloxane (D4) (556-67-2) Consumer; Dispersive; Industrial TRI: N	Consumer products (e.g., personal care products); indoor air: infants had highest levels and adults had lowest levels of D4; medical devices (e.g., breast implants).	Detected in serum of pregnant women.	N/A	N/A	Female reproductive toxicity (delays ovulation by delay of LH surge; estrogenic and antiestrogenic activity; dopamine agonist-like activity; 2-gen reproductive study found female effects on fertility and litter size; acceleration of onset of female reproductive senescence (rat).
p,p'-Oxybis(benzenesulfonyl hydrazide) (80-51-3) Consumer TRI: N	N/A	N/A	N/A	N/A	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Styrene (100-42-5) Consumer; Industrial TRI: Y	Plastics manufacturing; Food (e.g., migration from polystyrene-based food packaging; consumer products (e.g., air fresheners, aerosols, paint/varnish, organic solvents, scented products); formation during the biodegradation of a wide variety of naturally occurring compounds with structures similar to styrene; Air exposure (e.g., tobacco smoke is major route).	Individuals with high vegetable and fruit intake had lower urinary metabolite levels (NHANES , ≥6 years old); detected in pregnant women urine and higher in smokers; urinary metabolites of children 6-11 yrs old decreased with age and overall, children had higher levels than nonsmoking adults (NHANES).	Detected- median value of 0.129 ng mL(-1) (also detected in Pellizzari et al. 1982 and modeled in Fisher et al. 1997)	Associations: Childhood obesity; low birth weight in offspring (Texas); in utero exposure and increased risk of ASD (PA; NATA data); Birth cohort of premature children and children with allergic risk factors - Higher styrene levels in home associated with increased risk of pulmonary infections in six-week-old infants (LARS)	Developmental toxicity (embryotoxic [Mediterranean mussel]; polystyrene nanoparticle studies found decreased heart rate and altered larval behavior (Zebrafish), delayed gonad maturation and decreased fecundity of female and decreased the hatching rate, heart rate, and body length of offspring [Medaka]; and no effects on growth or swimming activity [frog tadpoles]).
Tribromomethane (Bromoform) (75-25-2) Consumer; Industrial TRI: Y	Air toxic; Water disinfection byproduct (product of chlorination); Children exposure via showering, bathing, swimming, and drinking water.	Maternal blood bromoform (TBM) detected in pregnant women.	N/A	Associations: perinatal exposure to bromoform and ASD diagnosis; in utero exposure may be associated with impaired neonatal neurobehavioral development of offspring; blood levels of total trihalomethanes during late pregnancy and lower mean birth weight of offspring.	Developmental toxicity (embryo-larval developmental toxicity [sea urchin]); cytotoxicity; genotoxicity; and mutagenicity.
Triglycidyl isocyanurate (2451-62-9) Consumer; Industrial TRI: N	Epoxy derivative, mainly in polyester powder paints; occupational air exposure; no children's exposure studies identified.	N/A	N/A	N/A for children's health outcome studies; Studies of workers (which can include adolescents), exposure associated with allergic contact dermatitis and asthma.	N/A

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Vinyl chloride (75-01-4) Consumer; Industrial TRI: N	Petrochemical occupational exposure and proximity to complex; indoor environmental tobacco smoke; polyvinyl chloride (PVC) in children's products (play mats, etc.); NJ vinyl chloride release incident (2012).	Urinary metabolite studies: thiodiglycolic acid (TDGA), potential vinyl chloride monomer (VCM) biomarker, measured in children living near petrochemical complex; vinyl chloride metabolites identified in pregnant women; detected in children 6-11 yrs old (NHANES); metabolites of VOC in neonates in intensive care units at 2X levels reported for children in NHANES.	N/A	Associations: Studies in workers (some of whom may be adolescents): liver effects; Children with higher urinary TDGA levels had associations with hepatic function and fibrosis index and increased risk of pediatric non-alcoholic fatty liver disease (NAFLD); pregnancy drinking water contaminants, including vinyl chloride, and neural tube defects in children (Camp LeJeune).	Genotoxicity; Developmental toxicity differed by route of exposure: No effects observed on embryonic or fetal development after inhaled vinyl chloride monomer (mouse, rat and rabbit) vs. injection during early pregnancy increased incidence of malformations, esp. NTDs in embryos (mice).
m-Xylene (108-38-3) Consumer; Industrial TRI: Y	Outdoor air (e.g., traffic); Indoor air (cooking/cleaning, childcare facilities, smoking, higher levels in houses with attached garage); consumer products; occupational exposure; municipal solid waste composting facility; drinking water.	Urine concentration measured in municipal solid waste composting facility workers (can be adolescents or adults) for m-/p-/o-xylene; Blood concentrations of m-/p-/o- xylene measured in children (Mn; 150 children from two low income, minority city neighborhoods);	N/A	Associations: High pregnancy exposure and cardiovascular events in pregnant woman; Interaction between asthma and air exposure to m-/p-/o- xylene in pregnant women increased risk of preeclampsia; indoor air levels and nasal obstruction in children; o-xylene exposure during pregnancy and occurrence of wheezing symptoms in infant;	N/A for developmental or reproductive studies; cytotoxicity
o-Xylene (95-47-6) Consumer; Industrial TRI: Y			Detected- median value of 0.159 ng mL(-1)		No rodent developmental or reproductive toxicity studies identified; embryonic growth and development effects found in ecological toxicity study (marsh frog).

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
p-Xylene (106-42-3) Consumer; Industrial TRI: Y		blood levels in children (NHANES)	Detected- median value of 0.539 ng mL(-1)	among children with asthma m,p-xylene, or o-xylene exposure associated with asthma symptoms; xylene exposure may contribute to risk of allergic sensitization to food allergens milk and egg white (LARS); Primary school children residing near oil terminal with VOC exposure - exposure to o-xylene and respiratory symptoms.	One dev study identified: Prenatal exposure to p-xylene and no effects noted (rat)
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl) (54464-59-4) Consumer; Industrial TRI: N	In fragrances; personal care products; Detection in the environment (e.g., sludge, wastewater, river water, and house dust samples)	N/A	N/A	N/A	Sparse data. Gavage study in rats: Fetal body weights were reduced by 480 mg/kg/d, but not to a statistically significant degree.
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) (54464-57-2) Consumer; Industrial TRI: N	In fragrances; personal care products; Detection in the environment (e.g., sludge, wastewater, river water, and house dust samples)	N/A	Detected- in 34% of breast milk samples; median concentration value <1.5 ng/g lipid	N/A	Sparse data. Gavage study in rats: Fetal body weights were reduced by 480 mg/kg/d, but not to a statistically significant degree.
Ethanone, 1-(1,2,3,4,6,7,8,8aoctahydro- 2,3,8,8-tetramethyl-2-naphthalenyl) (68155-67-9) Consumer; Industrial TRI: N	In fragrances; personal care products; Detection in the environment (e.g., sludge, wastewater, river water, and house dust samples)	N/A	N/A	N/A	Sparse data. Gavage study in rats: Fetal body weights were reduced by 480 mg/kg/d, but not to a statistically significant degree.

Chemical Name (CAS) and Use[1] Found on Toxics Release Inventory (TRI): Y/N	CEH Exposure			CEH Effects	
	Exposure information[2]	Human biomonitoring data[2]	Breastmilk Detection/Levels[2]	Human Health Outcome Data[2]	Animal Effects Data[2]
Ethanone, 1-(1,2,3,5,6,7,8,8aoctahydro- 2,3,8,8-tetramethyl-2-naphthalenyl) (68155-66-8) Consumer; Industrial TRI: N	In fragrances; personal care products; Detection in the environment (e.g., sludge, wastewater, river water, and house dust samples)	N/A	N/A	N/A	Sparse data. Gavage study in rats: Fetal body weights were reduced by 480 mg/kg/d, but not to a statistically significant degree.

[1]Information from the 2014 TSCA Workplan: https://www.epa.gov/sites/production/files/201501/documents/tsca_work_plan_chemicals_2014_update-final.pdf

[2] OCHP Staff performed searches for literature in PubMed in July 2020. Children's exposure search terms: children AND (<chemical name> OR <CAS number>) AND exposure; children's biomonitoring search terms: children AND (<chemical name> OR <CAS number>) AND biomonitoring; Children's human health outcome search terms: (Children OR Develop*) AND Human Health Outcome (Data OR study) AND (<chemical name> OR <CAS number>); Children's relevant effects: (Children OR Develop*) AND Animal Effect (Data OR study) AND (<chemical name> OR <CAS number>); Breast milk search terms: (human milk OR breast milk) AND (<chemical name> OR <CAS number>).

Attachment D: Example GIS Analysis

Here we present examples of GIS analysis illustrating our recommendations for charge question 1. These examples are not mutually exclusive and can be combined with each other and/or with other relevant data sources to inform prioritization and risk evaluation by providing a more detailed and informative picture of social and environmental factors that affect susceptibility and vulnerability.

Data Sources and Method

Toxics Release Inventory (TRI): 2016 TRI data on air, water and land releases reported for benzene or ethylbenzene were aggregated to the county level, summing the release data wherever more than one facility reported releases in a county.

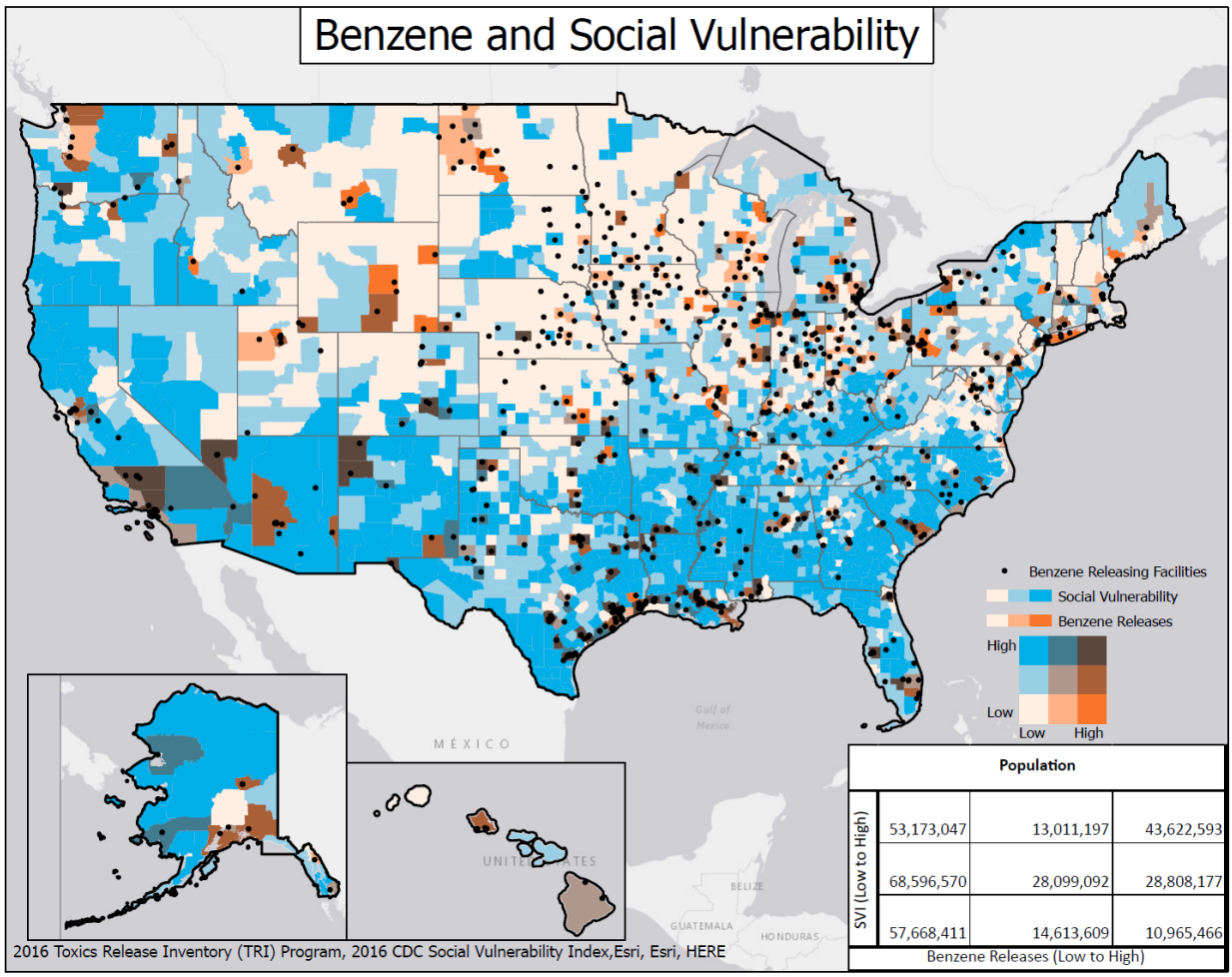
Social Vulnerability Index (SVI): 2016 county level data for population and overall SVI were used.

National Air Toxics Assessment (NATA): 2014 cancer risk data were aggregated to the county level, averaging the cancer risk data of the census tracts that make up each county. NATA data from Excel files were merged with shapefiles of counties by FIPS code.

NATA cancer risk values are calculated by the EPA based on emissions data and modeling for all carcinogenic Hazardous Air Pollutants (HAPs). For the TSCA Workplan chemicals, we recommend analyzing co-exposures with HAPs that affect the relevant related health endpoint(s). NATA estimates include total respiratory hazard indexes as well as other endpoints relevant for children's health.

On request of the CHPAC TSCA Workgroup, ICF created the bivariate choropleth maps included here. More information about the maps and visual analysis is available upon request.

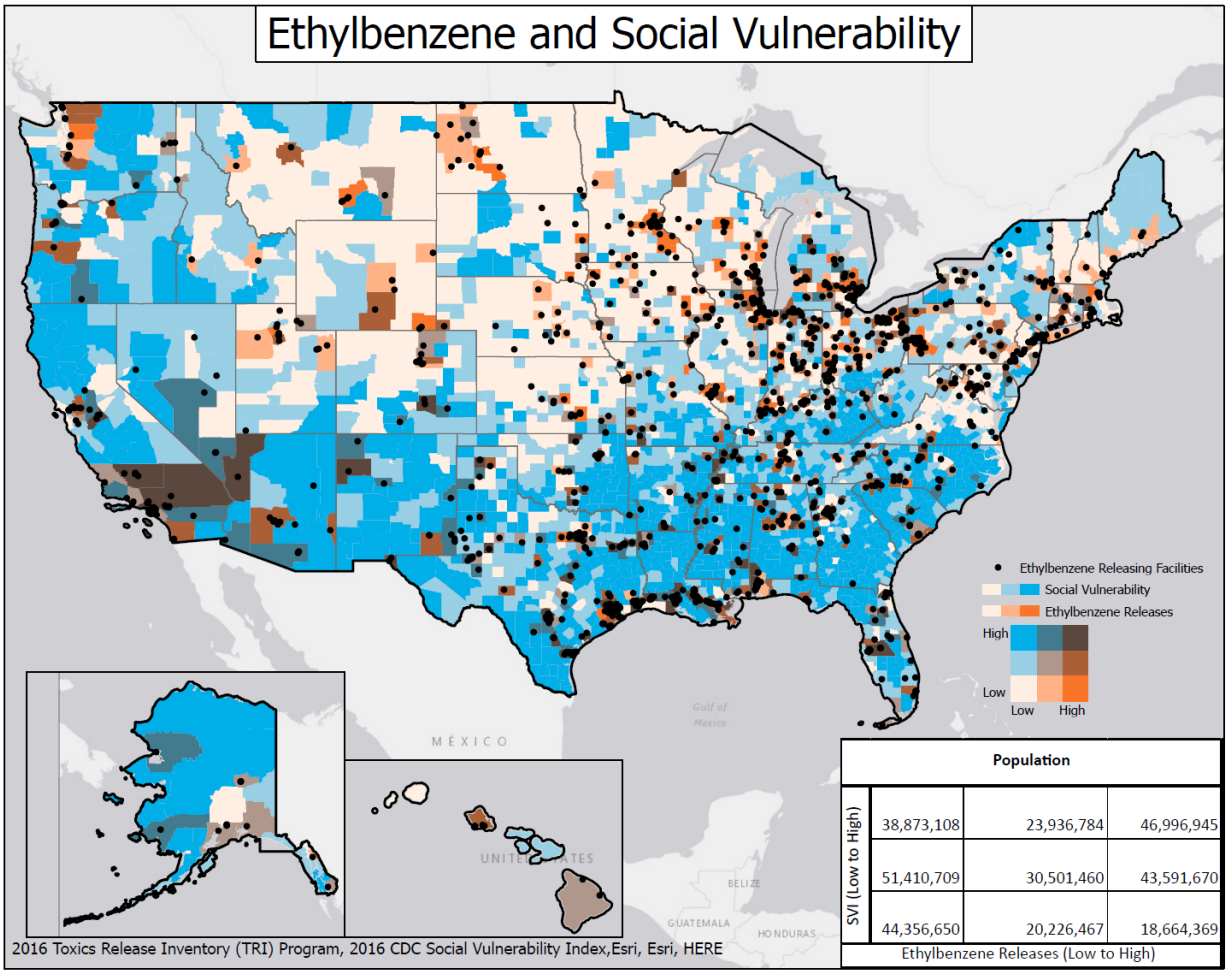
Map: Benzene TRI data and SVI



	Population		
SVI (Low to High)	53,173,047	13,011,197	43,622,593
	68,596,570	28,099,092	28,808,177
	57,668,411	14,613,609	10,965,466
	Benzene Releases (Low to High)		

Counties with highest Social Vulnerability Index and highest benzene releases are indicated by the darkest color. Table contains summed population numbers for each combination of exposure and SVI.

Map: Ethylbenzene TRI data and SVI



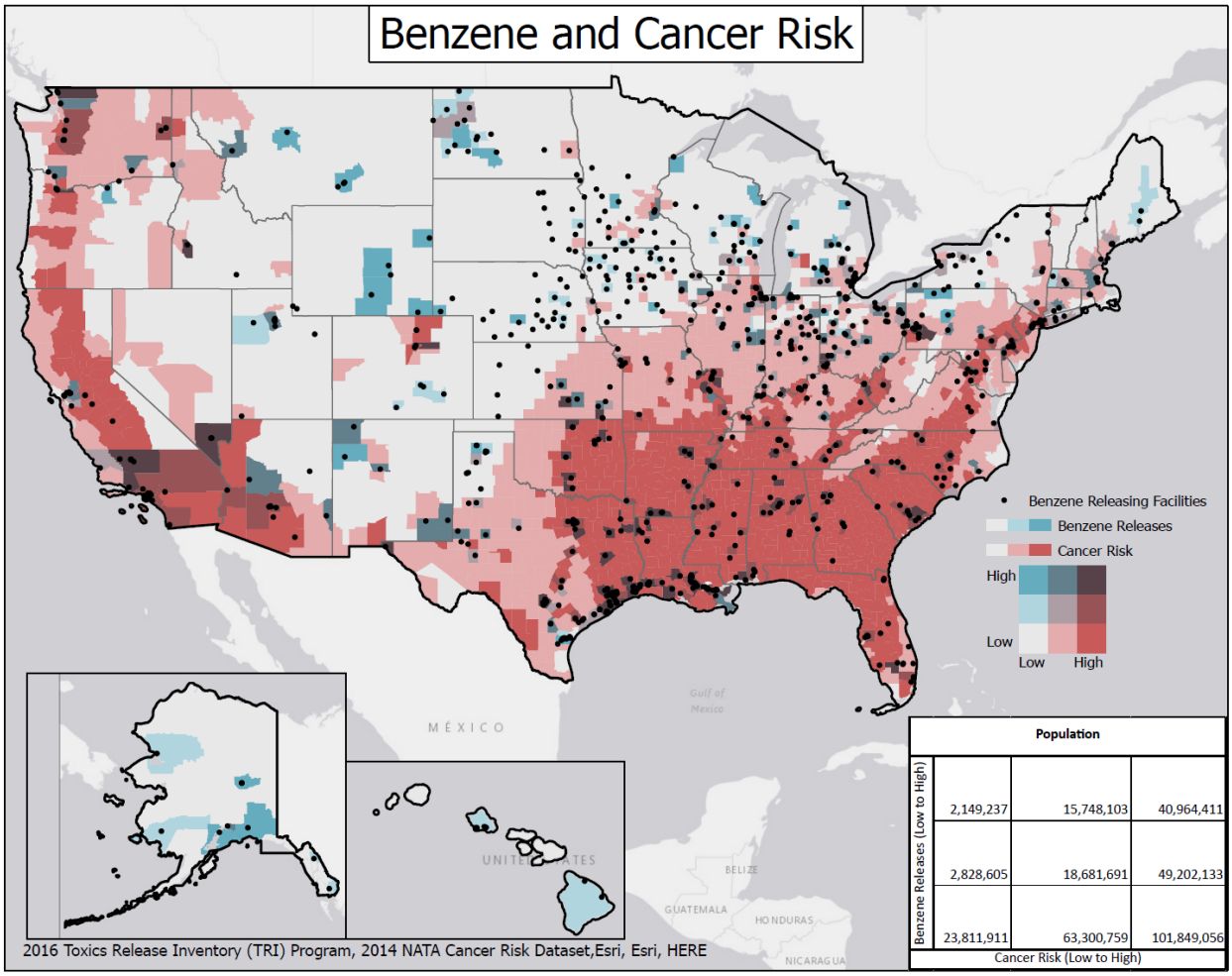
	Population		
SVI (Low to High)			
	38,873,108	23,936,784	46,996,945
	51,410,709	30,501,460	43,591,670
	44,356,650	20,226,467	18,664,369

Ethylbenzene Releases (Low to High)

Counties with highest Social Vulnerability Index and highest ethylbenzene releases are indicated by the darkest color. Table contains summed population numbers for each combination of exposure and SVI.

This information could be used in a variety of ways to inform prioritization. For example, EPA can identify counties with both high volume of TRI releases and high social vulnerability for each remaining chemical on the workplan (high/ high counties), and also quantify the number of people in such counties by summing high/high county population estimates for each chemical. The number of people in high/high counties can then be compared for each chemical to help direct prioritization. Different chemicals can be compared to each other and used to identify where multiple exposures may be occurring to the same vulnerable population. Potential co-exposures could also be evaluated by considering TRI releases in combination with other types of environmental exposures, such as hazardous air pollutants as in the following example.

Map: Benzene TRI data and NATA total cancer risk



Counties with highest total cancer risk due to Hazardous Air Pollutant emissions and highest benzene releases are indicated by the darkest color. Table contains summed population numbers for each combination of exposure and cancer risk.

The example presented in this map shows NATA total cancer risk as a general example. CHPAC notes that consideration of co-exposures should be focused on chemicals that affect related health endpoints, such as affecting the same body system or association with increased risk of related types of cancer.

Additionally, this type of analysis could be performed for any of the critical health endpoints highlighted in the letter:

- Reproductive toxicity
- Developmental toxicity (including developmental neurotoxicity)
- Endocrine toxicity, including metabolism disrupting chemicals
- Respiratory toxicity and potential effects on lung development, structure or function
- Toxicity to the immune system, including immunosuppression and excessive activation
- Toxicity that through preconception and/or in-utero exposures

Attachment E: Resources for social vulnerability and environmental co-exposure information

Resource	Type of information	Agency/ Source
National		
Superfund National Priorities List sites	Environmental co-exposures	US EPA
Toxics Release Inventory	Environmental co-exposures	US EPA
Methods for modeling TRI emissions at different levels of geographic resolution	Environmental co-exposures	Dolinoy, D. C., & Miranda, M. L. (2004). GIS modeling of air toxics releases from TRI-reporting and non-TRI-reporting facilities: Impacts for environmental justice. *Environmental Health Perspectives*, *112*(17), 1717–1724. https://doi.org/10.1289/ehp.7066
National Health and Nutrition Examination Survey (NHANES)	Environmental co-exposures and social vulnerability	Centers for Disease Control and Prevention (CDC)
National Air Toxics Assessment	Environmental co-exposures	US EPA
EJ Screen	Environmental co-exposures and social vulnerability	US EPA
National Toxic Substance Incidents Program (NTSIP)	Environmental co-exposures	Agency for Toxic Substances and Disease Registry (ATSDR)
American Community Survey	Population characteristics and demographics	US Census Bureau
US census data	Population characteristics and demographics	US Census Bureau
National Electronic Injury Surveillance System (NEISS)	Chemical co-exposures	Consumer Product Safety Commission (CPSC)
National Poison Data System	Chemical co-exposures	American Association of Poison Control Centers
Household Products Database	Chemical co-exposures	National Institutes of Health
Social Vulnerability Index	Social vulnerability	Centers for Disease Control and Prevention (CDC)
National Environmental Public Health Tracking	Environmental co-exposures and social vulnerability	Centers for Disease Control and Prevention (CDC)
Facility Registry Service (FRS)	Environmental co-exposures	US EPA
Product testing data	Chemical co-exposures	Washington State Department of Ecology
High Priority Chemicals Data System (HPCDS)	Chemical co-exposures	Interstate Chemicals Clearinghouse
County Health Rankings	Population health metrics	University of Wisconsin/ Robert Wood Johnson Foundation
Contaminant Occurrence and Related Data for Six-Year Review of Drinking Water Standards	Chemical co-exposures	US EPA

Resource	Type of information	Agency/ Source
America's Children Report	Environmental co-exposures and social vulnerability	Federal Interagency Forum on Child and Family Statistics
America's Children and the Environment Report	Environmental co-exposures	US EPA
EnviroAtlas	Environmental co-exposures	US EPA
State/ Local		
CalEnviroScreen	Environmental co-exposures and social vulnerability	California EPA
California Pesticide Use Reporting (PUR)	Environmental co-exposures	California EPA
California air toxics monitoring information	Environmental co-exposures	California Air Resources Board
Washington state social vulnerability mapping	Environmental co-exposures and social vulnerability	Washington Department of Health
Washington state lead and arsenic smelter data	Environmental co-exposures	Washington Department of Ecology
Washington state Toxics Clean Up Program	Environmental co-exposures	Washington Department of Ecology
Minnesota Areas of Environmental Justice Concern GIS-based screening tool	Environmental co-exposures and social vulnerability	Minnesota Pollution Control Agency
New York state Maps & Geospatial Information System (GIS) Tools for Environmental Justice	Social vulnerability	New York Department of Environmental Conservation
New York City Environment and Health Data Portal	Environmental co-exposures and social vulnerability	NYC Department of Health and Mental Hygiene
State Environmental Public Health Tracking Programs (25 states, funded by CDC)	Environmental co-exposures and social vulnerability	Specific to state
City Health Dashboard	Environmental co-exposures and social vulnerability	New York University/ Robert Wood Johnson Foundation
State Biomonitoring Programs	Environmental co-exposures	Specific to state; Association of public health laboratories has a current list
Protecting the health of children: National snapshot of environmental health services	Environmental co-exposures and social vulnerability	American Public Health Association

Resource	Type of Information	Agency/ Source
Tribal		
Great Lakes region	Environmental co-exposures	Great Lakes Indian Fish & Wildlife Commission
National	Environmental co-exposures	Northern Arizona University Institute for Tribal Environmental Professionals
National- Environmental Protection in Indian Country	Environmental co-exposures	EPA
National	Environmental co-exposures	Tribal Court Clearinghouse for Environmental Resources
Native American Lands Environmental Mitigation Program	Environmental co-exposures	Department of Defense
Longitudinal children's health studies		
Environmental Influences on Child Health Outcomes (ECHO) program, bringing together about 70 existing cohorts of children, with aim to enroll 50,000 participants	Environmental co-exposures and social vulnerability	National Institutes of Health
Project VIVA	Environmental co-exposures and social vulnerability	Harvard Medical School
Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study	Environmental co-exposures and social vulnerability	UC Berkeley
Columbia Center for Children's Environmental Health	Environmental co-exposures and social vulnerability	Columbia University

Attachment F: Chemicals not on TSCA Workplan to consider for prioritization
This is a list of chemicals entering Step 2 of 2012 TSCA workplan process that were potential candidates for information gathering or that did not meet scoring criteria for inclusion on 2012 or 2014 Workplan.

Source: To generate the list of 267 chemicals presented here, we started with the table of 345 chemicals in this document: US EPA, TSCA Work Plan: 2012 Scoring of Potential Candidate Chemicals Entering Step 2.[7] We then removed the chemicals that were included on the 2014 TSCA Workplan from the table.

An Excel file of this attachment is available upon request.

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
(1,1-Dimethylethyl)-4-methoxyphenol	25013-16-5	3	2	1
(13Z)-Docosenamide	112-84-5	1	3	1
(1-Methylethenyl)benzene	98-83-9	3	2	1
(Chloromethyl)benzene	100-44-7	3	2	1
(Dichloromethyl)benzene	98-87-3	3	1	1
(Z)-1,2-Dichloroethylene	156-59-2	1	3	2
[1,1'-Biphenyl]-4,4'-diamine	92-87-5	3	1	1
[1,1'-Biphenyl]-4,4'-diamine, 3,3'-dimethyl-	119-93-7	3	2	1
[1,1'-Biphenyl]-4-amine	92-67-1	3	1	1
1-(1,1-Dimethylethyl)-3,4,5-trimethyl-2,6-dinitrobenzene	145-39-1	3	3	2
1-(2-Phenyldiazenyl)-2-naphthalenol	842-07-9	3	*	2
1,1,1,2,2,2-Hexachloroethane	67-72-1	2	1	2
1,1,1,3,3,3-Hexafluoro-2-propanone	684-16-2	3	1	2
1,1,1-Trichloroethane	71-55-6	2	2	2
1,1,2,2-Tetrachloroethane	79-34-5	3	1	2
1,1'-Oxybis[1-chloromethane]	542-88-1	3	1	1
1,2,3-Propanetricarboxylic acid, 2-(acetyloxy)-, 1,2,3-tributyl ester	77-90-7	2	2	1
1,2,3-Propanetricarboxylic acid, 2-hydroxy-,lithium salt (1:3)	919-16-4	2	*	*
1,2,3-Propanetricarboxylic acid, 2-hydroxy-,potassium salt (1:3)	866-84-2	2	3	1
1,2,3-Propanetricarboxylic acid, 2-hydroxy-,sodium salt (1:3)	68-04-2	1	3	1

[7] Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-2012-scoring-potential-candidate

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
1,2,3-Propanetriol, 1,2,3-triacetate	102-76-1	2	2	1
1,2,3-Trichloropropane	96-18-4	3	1	2
1,2,4,5-Tetrachlorobenzene	95-94-3	3	1	3
1,2,4-Benzenetricarboxylic acid, 1,2,4-tris(2-ethylhexyl) ester	3319-31-1	2	3	1
1,2,4-Benzenetricarboxylic acid, mixed branched tridecyl and isodecyl esters	70225-05-7	3	*	1
1,2-Benzenedicarboxylic acid, 1,2-diethyl ester	84-66-2	1	3	1
1,2-Benzenedicarboxylic acid, 1,2-diheptyl ester, branched and linear	68515-44-6	3	2	1
1,2-Benzenedicarboxylic acid, 1,2-dimethylester	131-11-3	2	3	1
1,2-Benzenedicarboxylic acid, 1,2-diundecylester, branched and linear	85507-79-5	1	3	1
1,2-Benzenedicarboxylic acid, 1-heptyl 2-nonyl ester, branched and linear	111381-89-6	1	2	1
1,2-Benzenedicarboxylic acid, 1-heptyl 2-undecyl ester, branched and linear	111381-90-9	1	2	1
1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear	111381-91-0	1	2	1
1,2-Benzenedicarboxylic acid, di-C6-14-branched and linear alkyl esters	309934-69-8	1	3	2
1,2-Ethanediol	107-21-1	1	2	1
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione1,3,5-tris[[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]methyl]-	40601-76-1	1	3	2
1,3,5-Tribromobenzene	626-39-1	3	1	2
1,3-Benzenediamine, 4-methyl-	95-80-7	3	1	1
1,3-Dichloro-1-propene	542-75-6	3	2	1
1,3-Dichlorobenzene	541-73-1	2	2	2
1,3-Dinitrobenzene	99-65-0	1	1	2
1,3-Dioxolane	646-06-0	2	3	*
1,4-Benzenedicarboxylic acid, 2,5-bis(phenylamino)-	10109-95-2	*	2	1

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
1,4-Benzenedicarboxylic acid, 2,5-bis[(4-methylphenyl)amino]-	10291-28-8	*	2	2
1,4-Dinitrobenzene	100-25-4	3	1	2
1,4-Dioxacyclohexadecane-5,16-dione	54982-83-1	2	3	1
1,6-Octadien-3-ol, 3,7-dimethyl-	78-70-6	1	3	1
1,8-Dihydroxy-4-nitro-5-(phenylamino)-9,10-anthracenedione	20241-76-3	3	2	2
1-[2-(2,4-Dinitrophenyl)diazenyl]-2-naphthalenol	3468-63-1	3	2	2
1-[2-(2-Chloro-4-nitrophenyl)diazenyl]-2-naphthalenol	2814-77-9	3	2	2
1-[2-(4-Methyl-2-nitrophenyl)diazenyl]-2-naphthalenol	2425-85-6	3	2	2
1-Butanol	71-36-3	2	3	1
1-Decanaminium, N-decyl-N,N-dimethyl-, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonate (1:1)	251099-16-8	*	*	3
1-Decanol	112-30-1	1	3	1
1-Dodecanol	112-53-8	1	3	1
1-Eicosanol	629-96-9	1	3	2
1H-Benz[de]isoquinoline-1,3(2H)-dione	81-83-4	*	3	1
1-Hexanol	111-27-3	1	3	1
1-Methoxy-4-[(1E)-1-propen-1-yl]benzene	4180-23-8	2	3	1
1-Methyl-2,4-dinitrobenzene	121-14-2	3	1	2
1-Methyl-2-nitrobenzene	88-72-2	3	1	1
1-Naphthalenemethanol, .alpha.,.alpha.-bis[4- (diethylamino)phenyl]-4-(ethylamino)-	1325-86-6	*	*	3
1-Naphthalenemethanol, .alpha.,.alpha.-bis[4- (dimethylamino)phenyl]-4-(phenylamino)-	6786-83-0	*	2	3
1-Naphthalenemethanol, α,α-bis[4-(dimethylamino) phenyl]-4-(methylphenylamino)-	1325-85-5	3	*	2
1-Naphthalenesulfonic acid, 2-[2-(2-hydroxy-1-naphthalenyl)diazenyl]-, barium salt (2:1)	1103-38-4	1	3	2

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
1-Naphthalenesulfonic acid, 2-[2-(2-hydroxy-1-naphthalenyl)diazenyl]-, calcium salt (2:1)	1103-39-5	*	3	2
1-Octadecanol	112-92-5	1	3	2
1-Octanol	111-87-5	3	3	1
1-Propanol	71-23-8	2	2	1
1-Tetradecanol	112-72-1	1	3	1
2-(1,3-Dihydro-3-oxo-2H-indol-2-ylidene)-1,2-dihydro-3H-indol-3-one	482-89-3	3	3	1
2-(Butoxymethyl)oxirane	2426-08-6	2	3	1
2-(Chloromethyl)-oxirane (Epichlorohydrin)	106-89-8	3	2	1
2-(Phenoxymethyl)oxirane	122-60-1	2	2	1
2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoroheptanoic acid	375-85-9	*	*	3
2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Tricosafluorododecanoic acid	307-55-1	1	2	3
2,2'-[(3,3'-Dichloro[1,1'-biphenyl]-4,4'-diyl)bis(2,1-diazenediyl)]bis[3-oxo-N-phenylbutanamide	6358-85-6	1	3	2
2,2'-[(3,3'-Dichloro[1,1'-biphenyl]-4,4'-diyl)bis(2,1-diazenediyl)]bis[N-(2,4-dimethylphenyl)-3-oxobutanamide	5102-83-0	1	3	2
2,2'-[Oxybis(methylene)]bisoxirane	2238-07-5	3	*	1
2,2-Dichloroacetic acid	79-43-6	3	3	1
2,3,4,5,6-Pentabromophenol	608-71-9	3	2	2
2,3-Dibromo-1-propanol phosphate	126-72-7	3	2	2
2,3-Dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-1H-indene	116-66-5	3	*	2
2,4-Dichlorophenol	120-83-2	3	1	2
2,4-Pentanedione	123-54-6	3	3	1
2,5-Dichlorophenol	583-78-8	1	2	2
2,5-Dimethylfuran	625-86-5	1	3	1
2,6-Dimethyl-2-octanol	18479-57-7	*	3	1
2-[(2-Propen-1-yloxy)methyl]-oxirane	106-92-3	2	2	1
2-[2-(2-Methoxy-4-nitrophenyl)diazenyl]-N-(2-methoxyphenyl)-3-oxobutanamide	6358-31-2	1	3	2
2-[3-(3-Chlorophenyl)propyl]pyridine	101200-53-7	*	*	2

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
2-[4,6-Bis(2,4-dimethylphenyl)-1,3,5-triazin-2-yl]-5-(octyloxy)phenol	2725-22-6	1	2	2
2-Bromopropane	75-26-3	2	1	1
2-Butanone	78-93-3	1	3	1
2-Buten-1-ol, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-	28219-61-6	3	3	2
2-Butenedioic acid (2Z)-, 1,4-bis(2-ethylhexyl)ester	142-16-5	3	3	1
2-Chloro-6-(trichloromethyl)pyridine	1929-82-4	2	2	2
2-Chlorophenol	95-57-8	3	1	1
2-Chloropropanoic acid	598-78-7	3	*	1
2-Ethoxy-2-methylpropane	637-92-3	1	2	1
2-Ethoxyethane	110-80-5	1	3	1
2-Ethoxyethyl acetate	111-15-9	3	2	1
2-Ethylhexanoic acid	149-57-5	1	3	1
2-Hexanone	591-78-6	2	1	1
2-Methoxy-2-methylpropane	1634-04-4	1	3	1
2-Methoxyethanol	109-86-4	2	2	1
2-Methoxyethyl acetate	110-49-6	3	1	1
2-Methyl-1,3-dinitrobenzene	606-20-2	1	1	2
2-Methylbenzylamine	95-53-4	3	1	1
2-Naphthalenecarboxylic acid, 3-hydroxy-	92-70-6	2	2	1
2-Naphthalenecarboxylic acid, 3-hydroxy-4-[2-(4-methyl-2-sulfophenyl)diazenyl]-, calcium salt (1:1)	5281-04-9	2	3	2
2-Naphthalenecarboxylic acid, 4-[2-(5-chloro- 4-methyl-2-sulfophenyl)diazenyl]-3-hydroxy-, calcium salt (1:1)	7023-61-2	1	3	2
2-Naphthalenol, 1-[2-(2,4-dimethylphenyl)diazenyl]-	3118-97-6	1	2	3
2-Naphthalenol, 1-[2-(2-methoxyphenyl)diazenyl]-	1229-55-6	2	*	2
2-Naphthylamine	91-59-8	3	*	2
2-Oxetanone	57-57-8	3	2	1
2-Oxiranemethanol	556-52-5	3	1	1
2-Phenyloxirane	96-09-3	3	1	1

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
2-Propanone	67-64-1	1	3	1
2-Propenamide	79-06-1	3	2	1
2-Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethylhexyl ester	5466-77-3	1	3	1
2-Propenoic acid, butyl ester	141-32-2	2	2	1
3-(2-Oxiranyl)-7-oxabicyclo[4.1.0]heptane	106-87-6	2	*	1
3,7-Dimethyl-6-octen-1-ol	106-22-9	2	3	1
3-Chloro-1-propene	107-05-1	3	2	1
3-Methylphenol	108-39-4	3	2	1
3-Oxo-N-phenylbutanamide	102-01-2	2	2	1
4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	31906-04-4	2	3	1
4,4'-(1,1-Dioxido-3H-2,1-benzoxathiol-3-ylidene)bis[2,5-dimethylphenol]	125-31-5	3	*	2
4,4'-(1,1-Dioxido-3H-2,1-benzoxathiol-3-ylidene)bis[2,6-dibromophenol]	115-39-9	1	*	3
4,4'-(1,1-Dioxido-3H-2,1-benzoxathiol-3-ylidene)bis[2-bromo-6-methylphenol]	115-40-2	*	*	2
4,7-Methano-1H-indenol, 3a,4,5,6,7,7a-hexahydro-, acetate	54830-99-8	3	3	1
4,7-Methano-1H-indenol, 3a,4,5,6,7,7a-hexahydro-, propanoate	68912-13-0	1	3	1
4-Chloro-2-methylbenzylamine	95-69-2	3	2	2
4-Chlorobenzylamine	106-47-8	3	1	1
4-Ethenylcyclohexene	100-40-3	2	2	1
4-Hydroxybenzoic acid	99-96-7	2	2	1
4-Hydroxybenzoic acid, ethyl ester	120-47-8	1	3	1
4-Octylphenol	1806-26-4	3	3	1
9,10-Anthracenedione, 1,4-bis[(4-methylphenyl)amino]-, sulfonated, potassium salts	125351-99-7	*	*	*
9H-Fluorene	86-73-7	3	2	2
9-Methoxy-7H-furo[3,2-g][1]benzopyran-7-one	298-81-7	3	*	1
9-Octadecenoic acid (9Z)-, barium salt (2:1)	591-65-1	*	2	2

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
Amides, coco, N,N-bis(hydroxyethyl)	68603-42-9	3	3	1
Anthracene	120-12-7	2	2	2
Benz[a]anthracene	56-55-3	3	2	3
Benzenamine, 4,4'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bis-	13080-86-9	3	1	3
Benzeneethanamine, .alpha.-methyl-	300-62-9	2	2	1
Benzeneethanol	60-12-8	3	2	1
Benzenepentanol, .gamma.-methyl-	55066-48-3	1	3	1
Benzenepropanal, 4-(1,1-dimethylethyl)-alpha-methyl-	80-54-6	2	3	1
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1'-[(1,2-dioxo-1,2-ethanediyl)bis(imino-2,1-ethanediyl)]ester	70331-94-1	3	2	2
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1'-[2,2-bis[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]- 1-oxopropoxy]methyl]-1,3-propanediyl] ester	6683-19-8	1	3	2
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester	2082-79-3	2	3	1
Benzenesulfonamide, N-(4-amino-9,10-dihydro-3-methoxy-9,10-dioxo-1-anthracenyl)-4-methyl-	81-68-5	3	2	2
Benzenesulfonic acid, [[4-[[4-(phenylamino)phenyl][4-(phenylimino)-2,5-cyclohexadien-1-ylidene]methyl]phenyl]amino]-	1324-76-1	*	3	3
Benzenesulfonic acid, 2-amino-5 methyl-	88-44-8	2	3	2
Benzenesulfonic acid, 5-chloro-2-[2-(2-hydroxy-1-naphthalenyl)diazenyl]-4-methyl-,barium salt (2:1)	5160-02-1	1	3	2
Benzenesulfonic acid, C10-16-alkyl derivs.	68584-22-5	1	3	1
Benzenesulfonic acid, mono-C10-16-alkyl derivs., sodium salts	68081-81-2	*	3	1
Benzo[a]pyrene	50-32-8	3	2	3

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
Benzoic acid, 2-[(3,5-dibromo-4-hydroxyphenyl)(3,5-dibromo-4-oxo-2,5-cyclohexadien-1-ylidene)methyl]-, ethyl ester	1176-74-5	3	*	2
Benzoic acid, 2-[2-[1-[[(2,3-dihydro-2-oxo-1H- benzimidazol-5-yl)amino]carbonyl]-2-oxopropyl]diazenyl]-	31837-42-0	1	3	2
Benzoic acid, 4-hydroxy-, butyl ester	94-26-8	1	3	1
Benzoic acid, 4-hydroxy-, propyl ester	94-13-3	2	3	1
Benzoyl chloride	98-88-4	3	2	1
Bis(2,4-dihydroxyphenyl)methanone	131-55-5	3	*	1
Boric acid (H3BO3)	10043-35-3	2	3	1
Bromodichloromethane	75-27-4	3	1	2
Bromoethene	593-60-2	3	1	2
Bromomethane	74-83-9	2	2	1
Butanedioic acid, 2-sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (1:1)	577-11-7	2	3	1
C.I. Pigment Green 7	1328-53-6	*	3	2
C.I. Sulphur Orange 1	1326-49-4	3	*	2
Carbamic acid, ethyl ester	51-79-6	3	1	1
Carbon disulfide	75-15-0	2	3	1
Chloramide	10599-90-3	3	3	1
Chlorine oxide (ClO2)	10049-04-4	3	2	1
Chlorobenzene	108-90-7	2	3	1
Chloromethane	74-87-3	2	2	1
Chloromethoxymethane	107-30-2	3	1	1
Cyclohexanol, 2-(1,1-dimethylethyl)-, 1-acetate	88-41-5	2	3	1
Cyclohexanol, 4-(1,1-dimethylethyl)-, 1-acetate	32210-23-4	2	3	1
Decanedioic acid, 1,10-bis(1,2,2,6,6-pentamethyl-4-piperidinyl) ester	41556-26-7	3	3	2
Decanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluoro-	335-76-2	1	2	3

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
D-Glucitol, 1,3:2,4-bis-O-[(3,4-dimethylphenyl)methylene]-	135861-56-2	*	2	2
Dibenz[a,h]anthracene	53-70-3	3	2	2
Dibromochloromethane	124-48-1	3	2	2
Dibromomethane	74-95-3	2	1	1
Dihydro-3-(octen-1-yl)-2,5-furandione	26680-54-6	*	3	1
Dimethylbenzene	1330-20-7	1	3	1
Dinitrotoluene (technical grade)	99749-33-4	*	*	*
Dodecanoic acid	143-07-7	2	3	1
Ethanaminium, N,N,N-triethyl-, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonate (1:1)	56773-42-3	3	*	3
Ethanol, 2,2'-(methylimino)bis-	105-59-9	1	3	1
Ethanol, 2,2'-iminobis-, N-coco alkyl derivs.	61791-31-9	3	3	1
Fluoroethene	75-02-5	3	1	2
Hexabromo-1,1'-biphenyl	36355-01-8	3	2	3
Hexachlorocyclohexane	608-73-1	3	2	3
Hexanedioic acid, 1,6-diisononyl ester	33703-08-1	1	3	1
Indium phosphide (InP)	22398-80-7	3	*	2
Isocyanatomethane	624-83-9	1	1	1
Mercury and Mercury Compounds	7439-97-6	3	3	3
Methanamine, N-methyl-N-nitroso-	62-75-9	3	3	2
Methanesulfonic acid, methyl ester	66-27-3	3	*	1
Methanol	67-56-1	2	3	1
Methylbenzene	108-88-3	2	3	1
Methylium, [4-(dimethylamino)phenyl]bis[4-(ethylamino)-3-methylphenyl]-, acetate (1:1)	72102-55-7	3	2	2
N-(2-methylphenyl)-3-oxobutanamide	93-68-5	2	2	1
N-(4-Chlorophenyl)-2-hydroxy-9H-carbazole-3-carboxamide	132-61-6	3	*	2
N-(4-ethoxyphenyl)acetamide	62-44-2	3	2	1
N,N,N',N',N'',N''-Hexamethylphosphoric triamide	680-31-9	2	1	1
N,N-Dimethylacetamide	127-19-5	1	2	1
N,N-Dimethylcarbamyl chloride	79-44-7	3	1	1

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
N-[2-[2-(2-Bromo-4,6-dinitrophenyl)diazenyl]- 5-(diethylamino)phenyl]acetamide	52697-38-8	3	2	2
N-[4-(Acetylamino)phenyl]-4-[2-[5-(aminocarbonyl)-2-chlorophenyl]diazenyl]-3-hydroxy-2-naphthalenecarboxamide	12236-64-5	3	*	2
N-[5-[Bis[2-(acetyloxy)ethyl]amino]-2-[2-(2-bromo-4,6-dinitrophenyl)diazenyl]-4-ethoxyphenyl]acetamide	12239-34-8	3	2	2
Neodecanoic acid, barium salt (2:1)	55172-98-0	*	2	3
N-ethyl-N-nitroso-ethanamine	55-18-5	3	2	2
Nitrobenzene	98-95-3	2	2	1
N-Methyl-N-[(9Z)-1-oxo-9-octadecen-1-yl]glycine	110-25-8	3	*	2
N-methyl-N'-nitro-N-nitrosoguanidine	70-25-7	3	*	1
N-Methyl-N-nitrosourea	684-93-5	3	1	1
N-nitroguanidine	556-88-7	1	*	1
Octadecanoic acid	57-11-4	1	3	2
Octadecanoic acid, 1,1'-[2,2-bis[[(1-oxooctadecyl)oxy]methyl]-1,3-propanediyl ester	115-83-3	*	3	1
Octadecanoic acid, calcium salt (2:1)	1592-23-0	*	3	1
Octadecanoic acid, magnesium salt (2:1)	557-04-0	1	3	1
Octadecanoic acid, methyl ester	112-61-8	*	2	1
Octadecanoic acid, tridecyl ester	31556-45-3	*	3	1
Octanoic acid	124-07-2	1	3	1
O-Dinitrobenzene	528-29-0	1	1	2
Oxirane	75-21-8	3	2	1
Oxirane, 2,2',2'',2'''-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis-	7328-97-4	3	3	3
Perchloric acid	7601-90-3	3	1	1
Peroxide, 1,1'-(1,1,4,4-tetramethyl-1,4-butanediyl)bis[2-(1,1-dimethylethyl)	78-63-7	3	2	3
Peroxide, 1,1'-(1,1,4,4-tetramethyl-2-butyne- 1,4-diyl)bis[2-(1,1 dimethylethyl)	1068-27-5	3	1	3

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
Peroxide, 1,1'-(3,3,5-trimethylcyclohexylidene)bis[2-(1,1-dimethylethyl)	6731-36-8	3	2	3
Peroxide, 1,1'-[1,3(or 1,4) phenylenebis(1-methylethylidene)]bis[2-(1,1-dimethylethyl)	25155-25-3	3	2	3
Phenanthrene	85-01-8	2	2	2
Phenol	108-95-2	2	3	1
Phenol, 2,4-bis(1,1-dimethylethyl)-, 1,1',1''-phosphite	31570-04-4	1	3	2
Phosphonic acid, P-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1)	65140-91-2	*	2	2
Phosphoric acid, 2-ethylhexyl ester, potassium salt	68550-93-6	*	*	1
Phosphoric acid, diethyl ester	598-02-7	1	2	1
Phosphoric acid, dimethyl ester	813-78-5	*	1	1
Phosphorodithioic acid, O,O-diethyl ester	298-06-6	3	1	1
Phosphorodithioic acid, O,O-dimethyl ester	756-80-9	3	2	1
Polychlorinated Naphthalenes (PCNs)	NOCAS	1	3	3
Propanenitrile, 3-[[2-(acetyloxy)ethyl][4-[(6,7-dichloro-2-benzothiazolyl)azo]phenyl]amino]-	127126-02-7	3	*	*
Propanenitrile, 3-[[2-(acetyloxy)ethyl][4-[2-(2,6-dichloro-4-nitrophenyl)diazenyl]phenyl]amino]	5261-31-4	3	2	2
Propanenitrile, 3-[[4-[2-(2,6-dibromo-4-nitrophenyl)diazenyl]phenyl]ethylamino]	55281-26-0	*	2	2
Propanoic acid, 3,3'-thiobis-, 1,1'-didodecylester	123-28-4	3	2	1
Propanoic acid, 3,3'-thiobis-, 1,1'-dioctadecylester	693-36-7	2	2	1
Pyrene	129-00-0	2	1	2
Quartz (SiO2)	14808-60-7	3	3	2
Quino[2,3-b]acridine-7,14-dione, 5,12-dihydro-	1047-16-1	1	3	2

Chemical Name	CASRN	2012 Hazard Score	2012 Exposure Score	2012 Persistence/ Bioaccumulation Score
Quino[2,3-b]acridine-7,14-dione, 5,12-dihydro-2,9-dimethyl-	980-26-7	2	3	2
Quinoline	91-22-5	3	2	1
Retinoic acid	302-79-4	3	*	2
Sulfuric acid monododecyl ester sodium salt (1:1)	151-21-3	2	2	1
Sulfuric acid, diethyl ester	64-67-5	3	2	1
Sulfuric acid, dimethyl ester	77-78-1	3	1	1
Sulfuric acid, mono-C10-16-alkyl esters, ammonium salts	68081-96-9	3	3	1
Tributylstannane	688-73-3	3	*	3
Trichloromethyl benzene	98-07-7	3	1	1
Urea, N-ethyl-N-nitroso-	759-73-9	3	1	1
Zinc oxide (ZnO)	1314-13-2	1	2	3

Attachment G: Authoritative sources used to generate candidate chemicals for the TSCA Workplan method

Source: US EPA, TSCA Workplan Chemicals: Methods Document. Pg. 3-4 (2012)

Prioritization Factor	Sources
Carcinogens	• IRIS: 1986 Class A, B1; 1996 Known or Probable; 1999 or 2005 Carcinogenic • IARC Carcinogens, Group 1, 2A • NTP Known Carcinogens
Persistent, Bioaccumulative, Toxic (PBT)	• TRI PBT Rule • Great Lakes Binational PBT • Canadian P, B, and T (all three criteria met) • LRTAP POPS • Stockholm POPs
Children's Health	• IRIS: Repro/Dev (RfD or RfC for repro or dev) • NTP CERHR: Infants any effect or pregnant women any effect • Cal Prop 65 Reproductive
Children's Product Use	• Reported in products intended for use by children in 2020 CDR* • Washington State Children's List
Neurotoxicity	• IRIS
Biomonitoring	• NHANES • Drinking water contaminant monitoring • Fish tissue studies

*For the 2012 TSCA Workplan, EPA used the 2006 Inventory Update Reporting (IUR); more current use data are available to EPA in the most recent Chemical Data Reporting (CDR).

Attachment H: Excerpts from EPA risk assessment guidelines

We note here the principles outlined in EPA's risk assessment guidelines for determining a potential hazard:

- EPA's Guidelines for Developmental Toxicity Risk Assessment note that "The minimum evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single, appropriate, well-conducted study in a single experimental animal species."
- EPA's Guidelines for Reproductive Toxicity Risk Assessment: "The minimum evidence necessary to determine if a potential hazard exists would be data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species."

We note here the principles outlined in EPA's risk assessment guidelines to judge the lack of a hazard:

- EPA's Guidelines for Developmental Toxicity Risk Assessment: "The minimum evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult."
- EPA's Guidelines for Reproductive Toxicity Risk Assessment: "The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect."
- EPA Guidelines for Carcinogen Risk Assessment: A determination of "Not Likely to Be Carcinogenic to Humans" requires robust evidence as follows:

  "This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be based on data such as:

    - animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),
    - convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans,
    - convincing evidence that carcinogenic effects are not likely by a particular exposure route (see Section 2.3), or
    - convincing evidence that carcinogenic effects are not likely below a defined dose range.

  A descriptor of "not likely" applies only to the circumstances supported by the data. For example, an agent may be "Not Likely to Be Carcinogenic" by one route but not necessarily by another. In those cases that have positive animal experiment(s) but the results are judged to be not relevant to humans, the narrative discusses why the results are not relevant.