United States
Environmental Protection Agency

September 27, 2018
Office of Chemical Safety and
Pollution Prevention

A Working Approach for Identifying Potential Candidate Chemicals for Prioritization

September 2018

1. Introduction

The information set forth in this document is intended to describe the general approaches EPA may consider to identify existing chemicals as potential candidates for prioritization. The ultimate goal of these approaches is to identify potential candidates from which EPA will select candidates for prioritization, consistent with its regulations at 40 C.F.R. § 702.5.

This document describes the near-term and proposed longer-term approaches that EPA is developing to identify potential chemicals as candidates for prioritization. First, the document describes the near-term approach, EPA anticipates using to inform the identification of potential candidates for the initial 20 high-priority and 20 low-priority chemical substances that must be identified pursuant to section 6(b)(2)(B). In Section 7, the document presents a proposed longer-term approach that EPA is considering to "bin" chemicals on the TSCA active inventory, meaning that EPA would loosely group chemicals on the Inventory into pools that could inform potential prioritization based on risk-based data and information availability. This white paper is intended to begin a public discussion, beginning in late 2018, regarding the implementation of this longer-term approach. EPA has opened a docket to accept initial comment on this longer-term approach that will inform expansion of this approach and proof of concept. When complete, the binning approach will help inform which chemicals EPA may chose for prioritization.

This document merely presents internal approaches for EPA, and neither constitutes rulemaking by the U.S. EPA, nor can be relied on to create a substantive or procedural right enforceable by any party in litigation with the United States. Non-mandatory language such as "should" provides recommendations and does not impose any legally binding requirements. Similarly, statements about what EPA expects or intends to do reflect general principles to guide EPA's activities and are not judgments or determinations as to what EPA will do in any particular case.

2. Background

2.1 Evaluating Existing Chemicals under TSCA

Under Section 6(b) of the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (P.L. 114-182), EPA is required to prioritize and evaluate the risks of existing chemical substances.[1] The law contains deadlines and minimum requirements for the number of chemicals that must undergo risk evaluation, and provides the general process and criteria by which prioritization and risk evaluation must be conducted (*Figure 1*).

Prioritization[2] is a 9- to 12-month public process during which a chemical substance or category of chemicals is designated as either high-priority or low-priority for risk evaluation.

[1] Unless otherwise indicated, any references to "chemical" or "chemical substance" throughout this document means a "chemical substance" as defined in TSCA Section 3(2).

[2] Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act. (40 CFR 702) Final Rule, https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2016-0636.

High-priority chemical, as defined in TSCA is "a chemical substance that the Administrator concludes, without consideration of costs or other nonrisk factors, may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to potentially exposed or susceptible subpopulations identified as relevant by the Administrator". A low-priority substance is one that "if the Administrator concludes, based on information sufficient to establish, without consideration of costs or other nonrisk factors, that such substance does not meet the [High-Priority] standard" A chemical designated as low-priority indicates a risk evaluation is not warranted at that time, but this is not a finding of low or no risk. Final designation of a chemical or chemical category as a high-priority immediately begins the risk evaluation process laid out by rule.[3] TSCA requires that high-priority chemicals undergo risk evaluation to determine whether a chemical 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[4] identified as relevant to the risk evaluation by the Administrator, under the conditions of use[5]. The risk evaluation must take no longer than three years with a possible six-month extension. If unreasonable risks are identified, EPA has two years with a possible extension of two addition years to address those risks by regulation.

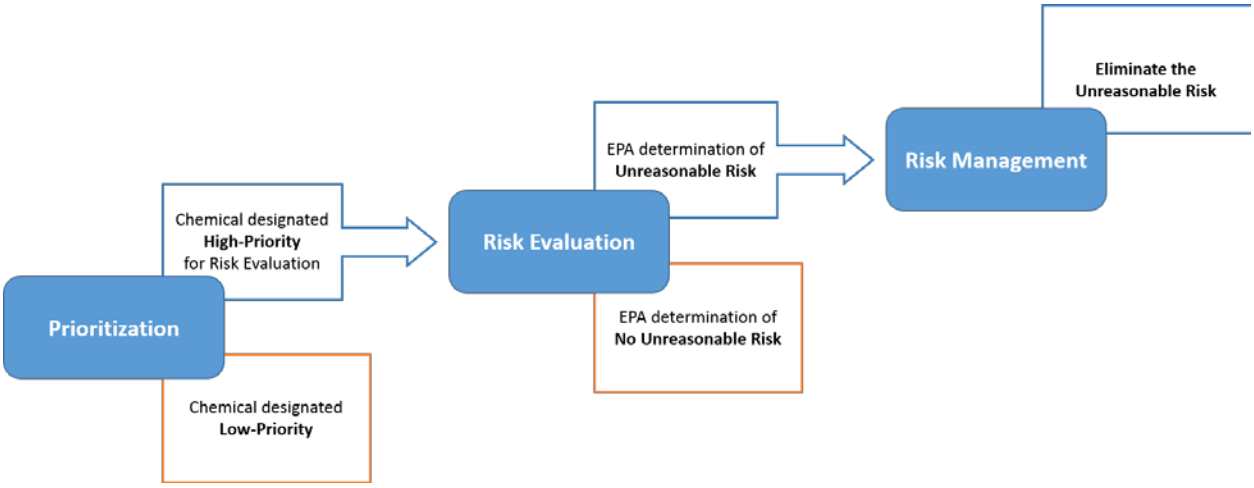

Figure 1. Process for evaluating the risks of existing chemicals.

[3] "Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act," (40 CFR 702) Final Rule, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0654-0108.

[4] "Potentially exposed or susceptible subpopulation," as defined in TSCA Section 3(12), 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 (15 U.S.C. 2602).

[5] "Conditions of use" under TSCA means "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of" (15 U.S.C. 2602). For purposes of prioritization, the Administrator may determine that certain uses fall outside the definition of "conditions of use".

TSCA requires EPA to make continued progress in prioritizing and reviewing existing chemicals to determine which of those chemicals merit further evaluation and to manage identified unreasonable risks. TSCA gives EPA discretion to choose which chemical substances to put into the prioritization process. With the approaches presented here-in, EPA is developing internal recommendations to develop a process to implement its approach using sound science.

2.2 Public Engagement

On December 11, 2017 EPA held a public meeting to gain input regarding identifying potential candidates for prioritization.[6] In preparation for this meeting EPA published a discussion document including possible approaches to inform the dialogue at the meeting.[7] EPA has considered the oral and written comments received at the public meeting and comments provided to the Agency via the docket (EPA-HQ-OPPT-2017-0586) in the development of the approaches discussed in this document. A Response to Comment document has been developed to address the comments provided.

EPA received 43 relevant comments in the docket associated with the public meeting.[8] There was consensus in the comments that EPA should proceed in a transparent manner with opportunities for public participation. However, there was no consensus around one or more of the proposed approaches the Agency presented. Use of the 2014 Update to the TSCA Work Plan (2014 Work Plan) as the starting point for identifying high-priority candidates was the approach with the most consistent support. Some commenters saw value in grouping chemicals in categories, such as their use in a particular sector, similar toxicological profiles, or by chemical class for pre-prioritization, prioritization, and risk evaluation. For low-priority chemicals, there was some support for using the Safer Chemicals Ingredient List (SCIL) chemicals as a starting point. There were opposing views with respect to the number of low-priority chemicals (beyond the mandated first 20) that should be identified, and the resources that the Agency should devote to going beyond the statutory requirement.

There was general support for the integration of New Approach Methods (NAMs)[9] for filling information gaps during the process to identify potential candidates for prioritization,

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[6] EPA included a pre-prioritization process in the proposed Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act. In response to public comment, EPA removed this process from the final rule and began a public process to further refine the Agency's pre-prioritization approach. The proposed rule and the Agency's response to comments can be found in docket EPA-HQ-OPPT-2016-0636. https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2016-0636

[7] Meeting materials for the December 11, 2017 Possible Approaches for Identifying Potential Candidates for Prioritization Public meeting can be found here: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/possible-approaches-identifying-potential-candidates .

[8] The public comments received following the December 11, 2017 public meeting are available at www.regulations.gov in docket EPA-HQ-OPPT-2017-0586. https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2017-0586

[9] The term NAMs was recently introduced to cover any *in vitro, in silico*, or *in chemico* technique used to provide data or information for regulatory decision making (ECHA, 2016). https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

however, there was some concern regarding the readiness of these approaches for decision-making on prioritization for risk evaluation. There were opposing views regarding filling information gaps and EPA's authority to request submission of information, the use of voluntary submissions, when to request information, the quality of information, and how to use information from other jurisdictions (e.g., EU REACH).

Accompanying this white paper is a response to comment document in which EPA has provided responses to the comments received orally during the December 11, 2017 public meeting and to the comments submitted to the docket after the meeting.

2.3 Statutory Timelines and Chemical Substance Considerations

In the development of a process for identifying potential candidates for prioritization several statutory timelines and requirements must be considered.

TSCA mandates the minimum number of chemical substances that must be undergoing risk evaluation at a given time. Section 6(b)(2)(B) requires that no later than three and a half years after the date of enactment (December 22, 2019) the Agency must have at least 20 high-priority chemical substances undergoing risk evaluation. Additionally, by this date, at least 20 chemical substances must have been designated as low-priority substances. In addition, to continue the existing chemicals risk evaluation program, the Agency must designate at least one high-priority chemical substance upon the completion of each subsequent risk evaluation (other than a manufacturer-requested risk evaluation).

TSCA mandates timelines for both prioritization and risk evaluation. Prioritization must take between 9- and 12-months (Section 6(b)(2)(C)) and risk evaluation must be completed within three years, with a potential six-month extension. Given this timing, EPA intends to begin prioritization for 40 chemicals (20 high-priority and 20 low-priority candidates) between December 2018 and March 2019.

In light of deadlines it is important that the Agency generally understand the sufficiency of the information, including the conditions of use, for prioritization of a given chemical prior to initiation of prioritization. As stated in the final Prioritization rule preamble, "EPA intends to resolve any concerns it may have about the sufficiency of information about a given chemical substance for purposes of prioritization…before subjecting that chemical substance to the prioritization process".[10] When information gaps are identified, ideally those gaps would be filled early in the process to allow EPA to complete its screening review by the statutory deadline. Identifying information gaps and needs before a chemical enters prioritization is an

[10] Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act. (40 CFR 702) Final Rule, https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2016-0636.

important component of pre-prioritization and prioritization. The Agency has authorities under TSCA sections 4, 8, and 11 to gather information and request data to fill data gaps.

TSCA requires that at least 50% of the chemicals undergoing risk evaluation must come from the 2014 Update to the TSCA Work Plan (6(b)(2)(B)). In 2012, EPA used a two-step screening process to identify potential candidate chemicals for assessment under TSCA.[11] EPA identified an initial group of candidate chemicals for review using a specific set of sources and certain factors, such as: potentially of concern for children's health, persistent, bioaccumulative and toxic, probable or known carcinogens, use in consumer products, and detected in biomonitoring programs. During this step, chemicals were excluded if they: did not meet the intent of the Work Plan process, were not subject to TSCA, if they were already the subject of TSCA action, or due to other chemical properties (e.g., complex process streams, bioproducts not commercially produced, naturally occurring). These chemicals were then screened and sorted into four categories: high, moderate, low and information gathering. EPA used information from additional exposure and hazard data sources in a second step. EPA identified 83 chemicals receiving high scores and those became the focus of the 2012 Work Plan.[12] The list was re-screened using the same scoring methodology in 2014 with updated industry data submitted to EPA through the 2011 Toxics Release Inventory and the 2012 Chemical Data Reporting requirements, resulting in 90 chemicals listed in the 2014 Update to the TSCA Work Plan. EPA has risk evaluations under way for an initial group of 10 chemicals from the Work Plan as per section 6(b)(2)(A). Seven other Work Plan chemicals are persistent, bioaccumulative, and toxic (PBT), of which 5 PBT chemicals are being addressed through expedited rulemaking under TSCA section 6(h) without a risk evaluation. Manufacturers of the other 2 PBT chemicals on the Work Plan requested that EPA conduct a risk evaluation pursuant to section 6(h)(5). Seventy-three chemicals remain to be prioritized from the 2014 Update to the TSCA Work Plan.[13]

[11] TSCA Work Plan Methods Document 2012 https://www.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf.

[12] 2012 TSCA Work Plan Chemicals https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/2012-tsca-work-plan-chemicals

[13] The 2014 Work Plan chemicals list consists of 90 chemicals. With the passage of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, EPA was required to select the first 10 chemicals to undergo risk evaluations from the 2014 Update to the TSCA Work Plan. These 10 chemicals were announced on December 16, 2016. TSCA section 6(h) requires EPA to take expedited regulatory action under section 6(a) without a risk evaluation for PBT chemicals from the 2014 Update of the Work Plan Chemicals. Seven 2014 Work Plan chemicals are being addressed as PBTs under Section 6(h) or through self-nominations received as part of the Section 6(h) identification process. Manufacturers for two of the chemicals submitted timely requests to EPA for risk evaluations pursuant to section 6(h)(5) and are therefore not subject to the rulemaking effort. This leaves 73 more chemicals that need to undergo prioritization.

3. General Approaches to Identifying Potential Candidates for Prioritization

Considering the above statutory requirements for prioritization and risk evaluation, as well as public comments received, EPA has developed a near-term general approach to identifying potential candidates for prioritization. This approach is focused on identifying potential candidates for the initial 20 high- and 20 low-priority chemical substances as required in section 6(b)(2)(B).

EPA expects its approach for identifying candidates for prioritization to evolve over time as it develops expertise in identifying chemicals to enter prioritization, as well as in conducting prioritization and risk evaluations. EPA looks to preserve its flexibility in the approach used to identify potential candidates for prioritization, to ensure that EPA can incorporate newly developed and updated information, including analytical methods, and consider policy developments, including any future Agency or other Federal Agency, and U.S. government priorities. EPA expects to use these lessons learned from the process of selecting the first 40 chemicals, for the next set of chemicals.

EPA is considering a longer-term approach to bin the remaining chemicals (those not included on the 2014 TSCA Work Plan) on the TSCA active inventory. EPA currently expects to use an approach that integrates available information from both NAMs and traditional approaches, covering the domains of hazard, exposure, persistence, and bioaccumulation for human and ecological domains, to group chemicals based on information availability and hazard and exposure potential. What is described in this document is the first step of developing this approach. Subsequent steps will include a white paper and future public workshops and discussion.

4. Near-term Approach for Identifying Potential Candidate Chemicals for High-Priority Designation

4.1 Working Approach

EPA's working approach is to primarily look to the 2014 Work Plan for high-priority potential candidates as TSCA requires that at least 50% of the chemicals undergoing risk evaluation as of December 2019 must come from the 2014 Work Plan.

EPA considered several approaches and tools for identifying potential candidate chemicals for prioritization. These approaches were presented at a December 11, 2017 public meeting. As noted previously, there was general support for using the 2014 Work Plan chemicals as the starting point for identifying potential high-priority candidates.

As explained during the meeting, use of the 2014 Work Plan does not constitute a finding of risk. The chemicals on this list will be subject to the prioritization process for determination of high-priority designation. If designated as high-priority, the chemical will undergo risk

evaluation. TSCA requires EPA to evaluate the chemicals on the 2014 Work Plan as part of prioritization and risk evaluation; however, EPA is not bound by the findings of the 2014 Work Plan. EPA recognizes that science approaches have evolved and additional information has been developed for chemicals on the 2014 Work Plan. When a chemical is considered for prioritization, EPA will identify and review reasonably available information[14], including any new information.

In addition, if chemicals are identified as potential candidates that are not on the 2014 Work Plan, EPA's intends to select chemicals on the TSCA Active Inventory (as of April 2018 or the most recent).

EPA generally intends to consider the three factors, described below, for selecting potential chemicals for prioritization.

a. Priorities

In selecting chemicals as potential candidates for prioritization EPA expects to consider overarching Agency priorities. This may include, but is not limited to, a chemical or group of chemicals that are priorities for the Agency, including chemicals that other EPA program offices have deemed a priority for their program and suitable for current prioritization.

In addition, EPA is committed to engaging and collaborating with partner federal agencies prior to and during the prioritization process (82 FR 33754). EPA is required to consult with other federal agencies during both prioritization and risk evaluation. In addition, EPA intends to consult with other federal agencies on the identification of potential candidate chemicals for the prioritization step. EPA will also collaborate with other federal agencies to identify any information that may be useful in the selection of candidate chemicals, and during prioritization and risk evaluation. Additionally, TSCA section 26(a) specifically allows other federal agencies, at EPA's request, to (i) make their services, personnel, and facilities available to the Agency, (ii) provide information, data, estimates, and statistics to the Agency, and (iii) grant EPA access to all information in their possession as the Agency may reasonably determine to be necessary for the administration of the statute.

While EPA intends to look first to the 2014 Work Plan for potential high-priority chemical candidates, EPA acknowledges that consistent with the criteria in its prioritization regulation, chemicals not listed on the 2014 Work Plan may also be selected as candidates for prioritization in cases where other federal agencies, public input, or the EPA administrator have identified these chemicals as particularly suitable. 40 C.F.R. §702.5. Consultation with both intra- and interagency partners may aid in the identification and information gathering of a non-listed candidate

[14] "Reasonably available information" means information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation. Information that meets the terms of the preceding sentence is reasonably available information whether or not the information is confidential business information, that is protected from public disclosure under TSCA section 14. (40 CFR Part 702.3)

chemical, and EPA will open dockets for all potential candidate chemicals not listed on the Work Plan

EPA will also consider public input received, such as during any public consultations and through the dockets, for each of the 2014 Work Plan chemicals and chemicals not included on the Work Plan (see section 4.2).

b. Quantity and Quality of Information

EPA intends to consider the quantity and quality of information when identifying potential candidate chemicals for prioritization and risk evaluation.

EPA intends on surveying the information and checking quality data elements in a step-wise approach that ensures responsible and timely completion of the process according to TSCA timelines. The approach is intended to screen out information-deficient candidate chemicals that would hinder EPA's ability of performing scientifically sound risk evaluations from the initial selection of 20 high and 20 low-priority candidates. The scientific underpinnings of a risk evaluation need to be strong enough to support a risk determination and inform potential future risk management activities.

Additional information may need to be developed for information-deficient chemical substances. To support this information development, EPA may provide public notification of any Work Plan chemicals found to have insufficient information to undergo prioritization. EPA's information gathering authorities include public notification processes, and may be used to develop necessary information for a chemical substance or chemical category. Once generated, the new information will feed into analyses and decisions supporting the selection of candidate chemicals beyond the initial 20 high-and low-priority candidates and the prioritization process within the statutory timeframes.

c. Work Load

As EPA explained during the December 11, 2017 public meeting, the Agency must be mindful of its workload and resource constraints, given the statutory deadlines and other requirements. Once a chemical is designated high-priority for risk evaluation, the three-year statutory deadline for completing the risk evaluation begins with no opportunity for interruption. However, EPA can extend up to six additional months under the statute.

To address workload issues, EPA could use diverse approaches to consider current expertise or facilitate the analysis of candidate chemicals. For example, EPA could identify potential candidate chemicals that share certain characteristics with the first 10 chemical substances undergoing risk evaluation,[15] such as solvents, since focusing

[15] On December 19, 2016, EPA published a list of 10 chemical substances that are the subject of the Agency's initial chemical risk evaluations, as required by TSCA § 6(b)(2)(A).

on the solvents remaining on the 2014 Work Plan would take advantage of the expertise developed on the six solvents currently undergoing risk evaluation (e.g., development of exposure scenarios).

EPA could also consider selecting a category of chemicals for prioritization[16]. As stated in the *Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act* Final rule (82 FR 33753-33764) preamble "TSCA section 26 provides EPA with authority to take action on categories of chemical substances. Furthermore, "…should EPA determine to prioritize a category of chemical substances, EPA would describe the basis for such a determination in the Federal Register notice published to initiate prioritization" and "EPA will provide an explanation of the rationale for initiating the process on the chemical substance, thus ensuring the public has notice and an opportunity to comment on any decision to prioritize a category of chemical substances."

4.2 Transparency and Public Participation

In addition, as explained in the *Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act* Final rule (82 FR 33753-33764), EPA intends to foster a dialogue with stakeholders by publishing a notice explaining why it chose to initiate the prioritization process on a particular chemical substance and seeking relevant information from the public. EPA also intends to publish a proposed priority designation along with an identification of the information, analysis, and basis supporting the proposed designations.

To facilitate the sharing of information by stakeholders and the public which could update the information EPA currently has on the 2014 Work Plan chemicals, EPA is opening dockets for each of the 2014 Work Plan chemicals that are not the subject of ongoing risk evaluations or risk management actions.[17] EPA may will also open dockets for other potential candidate chemicals for those not on the Work Plan. EPA expects that the dockets will also increase transparency of the process.

[16] The term "category of chemical substances" means a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some way suitable for classification as such for purposes of this Act, expect that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances. TSCA § 26(b).

[17] The total number of dockets is 75, since it includes the two PBT chemicals for which manufacturers requested risk evaluations pursuant to section 6(h)(5).

5. Near-term Approach for Data Landscaping and Determining Information Readiness

The purpose of this section is to describe the near-term approach EPA generally intends to follow for identifying relevant information on the 73 remaining chemicals listed under the 2014 Work Plan and that could be candidates for prioritization. EPA's general goal at this stage is to determine whether the information is sufficient and relevant to 1) evaluate information availability for prioritization and risk evaluation and 2) identify gaps that may be filled through future information gathering activities. We use, "data landscape" to refer to a high-level survey of the available information or evidence obtained from a variety of data sources. The survey is only meant to identify data availability and gaps, and to assess whether the amount of data available is sufficient for prioritization and risk evaluation of candidate chemicals. This process and the data surveyed are not meant to supplant the prioritization process or the risk evaluation process.

5.1 Long- vs. Near-term Approach for Identifying Potential Candidate Chemicals for Prioritization

For the long-term, EPA's goal is to develop a procedure to inform selection of candidates for prioritization that integrates information from NAMs[18] and information from traditional studies (e.g., hazard, exposure, engineering, fate), and builds on the 2014 Work Plan methodology. Section 7 of this document describes in more detail EPA's approach to inform priorities within the TSCA program and the use of alternative testing data (i.e., NAMs).

For both strategies, it will be important for EPA to identify data availability and sufficiency for potential candidate chemicals for prioritization. Therefore, before initiating the prioritization process, EPA generally intends to review available hazard and exposure-related information, and evaluate whether that information would be sufficient to allow EPA to complete prioritization and risk evaluation within the statutory deadlines. To the extent the information is not currently available or is insufficient, EPA plans to determine whether and how information can be developed and collected, reviewed and incorporated into analyses and decisions and in what timeframe. EPA believes it is most prudent to identify gaps as early as possible in the process to ensure statutory deadlines are met and decisions to inform public health decisions and protections are supported by the scientific evidence.

[18] The Strategic Plan to Promote the Development of Alternative Test Methods provides information on and examples of NAMs vs. traditional studies. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

5.2 Identification of Information

EPA intends to actively begin gathering information for the 73 remaining chemicals listed under the 2014 Work Plan. EPA generally plans to utilize reasonably available and frequently used data sources including but not limited to those already identified in the TSCA 2012 Work Plan Methods document[19], public literature and gray literature sources as deemed necessary. Gray literature refers to sources of scientific information that are not formally published and distributed in peer reviewed journal articles. These references are still valuable and consulted in the TSCA risk evaluation process. Examples of gray literature are theses and dissertations, technical reports, guideline studies, conference proceedings, publicly-available industry reports, unpublished industry data, trade association resources, and government reports.

The proposed approach to identify information is depicted in *Figure 2*. This approach highlights three types of information sources that can be used and considers *accessibility* of data. *Data accessibility* refers to the extent to which information can be readily obtained – i.e., through direct data queries and/or additional extraction from relevant data sources. Information provided from each source builds upon existing information from all information sources to provide a holistic information landscape required to identify information availability and gaps. The proposed approach for data landscaping purposes consists of:

(i) Type 1 sources: data sources storing reasonably available and relevant information that is readily queryable and extractable in a structured manner. This includes existing databases (and dashboards) that allow the user to sift through information using a graphical user-interface, a direct query such as SQL[20], or webservice APIs[21]. EPA's National Center for Computational Toxicology's Chemistry Dashboard[22] is one of the several examples of a Type 1 source. The Chemistry Dashboard integrates information across various sources mapped to an expert-reviewed chemical structure[23] and includes information from various state, national, and international sources. Information relating to physicochemical properties, hazard, exposure, persistence and bioaccumulation are identified and reviewed for relevancy.

(ii) Type 2 sources: additional details are obtained on existing information from public and non-public (i.e., confidential business information) sources that are maintained by

[19] TSCA Work Plan Chemicals: Methods Document https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-methods-document
[20] SQL: Structured Query Language
[21] API: Application Programming Interface
[22] Williams, A. J., Grulke, C. M., Edwards, J., McEachran, A. D., Mansouri, K., Baker, N. C., Patlewicz, G., Shah, I., Wambaugh, J. F., Judson, R. S., *et al.* (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. *J Cheminform* **9**(1), 61 (https://comptox.epa.gov/dashboard).
[23] Richard, A. M. (2004). DSSTOX website launch: Improving public access to databases for building structure-toxicity prediction models. *Preclinica* **2**(2), 103-108.

competent authorities[24] – this includes supporting information from other EPA program offices, state and federal agencies including assessments or evaluations from various US and international organizations (e.g., including but not limited to EPA/IRIS,[25] EPA/OW,[26] EPA/OAR,[27] EPA/HPV program,[28] IARC,[29] NTP,[30] NIOSH, OECD,[31] ATSDR,[32] TSCATS,[33] Cal EPA).[34]

(iii) Type 3 sources: initial broad searches are performed to identify additional sources of information within the public and gray literature domains that are not available from Type 1 and 2 sources (e.g., searches in PubMed, ToxNet, other US government and international websites). Examples of available Type 3 information sources can be found in the supplemental document to the TSCA scope documents for the first ten chemicals identified for risk evaluation.[35]

[24] The terminology competent authority is used by OECD and represents any national or local agency, authority, department, inspectorate, minister, ministry official, parliament or public or statutory person of any government of any country that has the delegated or invested authority, capacity, or power to perform a designated function.
[25] EPA/IRIS: EPA Integrated Risk Information System Assessments: https://cfpub.epa.gov/ncea/iris2/atoz.cfm
[26] EPA/OW: EPA Office of Water: https://www.epa.gov/aboutepa/about-office-water
[27] EPA/OAR: EPA Office of Air and Radiation: https://www.epa.gov/aboutepa/about-office-air-and-radiation-oar
[28] PA/HPV Challenge Program: EPA High Production Volume Challenge Program
[29] IARC: International Agency for Research on Cancer: https://www.iarc.fr/
[30] NTP: National Toxicology Program: https://ntp.niehs.nih.gov/
NIOSH: National Institute for Occupational Safety and Health: https://www.cdc.gov/niosh/
[31] OECD: Organization for Economic Co-operation and Development: http://www.oecd.org/
[32] ATSDR: Agency for Toxic Substances and Disease Registry: https://www.atsdr.cdc.gov/
[33] TSCATS: Toxic Substances Control Act Test Submissions
https://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=2855
[34] CalEPA: California Environmental Protection Agency: https://calepa.ca.gov/
[35] First Ten Chemicals for Risk Evaluation. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca#ten

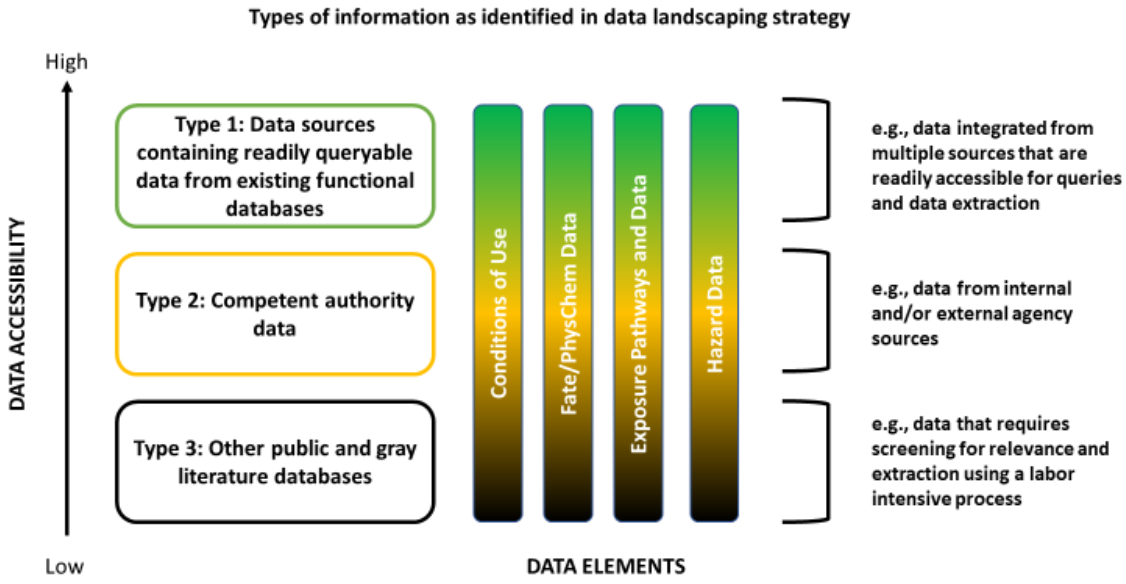

Figure 2. Approach to Identifying Information on Potential Candidate Chemicals. *Type 1 data sources refer to previously extracted and available information residing within existing databases. Competent Authority (Type 2) data refer to information such as that found internal and/or external to the Agency for regulatory purposes. Type 3 databases refer to information that may require additional efforts for screening and extraction. Data accessibility is defined by the extent to which information can be readily obtained. The data elements are examples of data/information streams that would be collected to develop the data landscape including, but not limited to, conditions of use, fate/physical chemistry, exposure and hazard data.*

TSCA requires that EPA use information in a manner consistent with the best available science and that EPA base decisions on the weight of the scientific evidence. Through the prioritization and risk evaluation process, EPA plans to use a step-wise approach that is consistent with the TSCA science standards. When gathering information to support the priority designation, EPA plans to integrate elements of quality in the data eligibility criteria during the screening process.

The initial emphasis will be the exclusion of unacceptable data sources based on data quality criteria outlined in the *Application for Systematic Review in TSCA Risk Evaluations* EPA document.[36] Specifically, these criteria identify serious flaws that would make the information unreliable to use for risk evaluation purposes.[37] This increases the efficiency of EPA's

[36] Application of Systematic Review in TSCA Risk Evaluations, 2018, pending publication, EPA Document# 740-P1-8001.

[37] Evaluation Method for First Ten Chemicals for Risk Evaluation. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca#ten

systematic review efforts by excluding unacceptable data sources early in the process for those chemical substances that may enter risk evaluation through a high-priority designation.

Furthermore, EPA may find information gaps due to lack of extracted information from available information sources. In such cases, gaps would also be filled with additional information as deemed necessary. It may also require analysis of additional data that were not previously extracted or evaluated for relevancy and quality (e.g., Type 3 information through title and abstract screening with the assistance of machine learning[38] for literature prioritization to assess relevant information availability).

EPA will refine and improve this process as necessary based on the state of the science, available information, and data readiness, as well as Agency capacity and statutory deadlines.

5.3 Integration of Information and Identification of Data Landscape Gaps

As depicted in *Figure 2*, it will be important to identify the data elements such as conditions of use, exposure and hazard information necessary to assess availability and relevance of information for prioritization and risk evaluation.[39] For example, hazard information availability will be assessed for preliminarily identified use/exposure scenarios. EPA anticipates using, in most cases, a combination of submitter information, market analysis, as well as relevant information from various frequently used sources to determine use scenarios and identify relevant exposure pathways information, which includes both pathway and route information. Exposure information (e.g., route and pathway) will be combined with relevant hazard information (e.g., dermal, inhalation) to support the identification of data availability. Identified gaps in the information will be flagged for further review. EPA's information gathering authorities include public notification processes, and may be used to develop necessary information for a chemical substance or chemical category. Once generated, the new information will feed into analyses and decisions supporting the selection of subsequent candidate chemicals.

6. Near-term Approach for Low-Priority Chemical Substance Selection

As described previously, in order to implement section 6 of the Lautenberg Amendments to TSCA, EPA must designate 20 low-priority chemical substances by December 2019. EPA intends to select candidates that appear to be most suitable for low-priority designation. The most suitable candidates are those likely to be favored by the considerations in the act (Section

[38] EPA/OPPT is exploring automation and machine learning tools for data screening and literature prioritization activities (e.g., SWIFT-Review, SWIFT-Active Screener, Dragon, DocTER). SWIFT is an acronym for "Sciome Workbench for Interactive Computer-Facilitated Text-mining".

[39] These efforts are not meant to replace the risk evaluation process which will involve a more exhaustive search and full systematic review of available data, including any new information that becomes available during the prioritization process.

6(b)(1)(A)) [and the regulations at 40 CFR 702.5]. In identifying potential candidates for low-priority chemical designation, EPA will use the best available science, consistent with section 26(h) of the statute.

EPA may identify substances from multiple sources, including one or more of the following chemical information resources (described below): EPA's Safer Chemical Ingredients List (SCIL); EPA's Chemical Assessment Management Program (ChAMP); and Organization for Economic and Co-Operation Development (OECD) Screening Information Data Sets (SIDS) assessment documents. These resources reference useful information on chemical hazard and, in some cases, on conditions of use and exposure. Using all resources is important, since the different sources will provide different information to support assessment of the elements in the prioritization process (40 CFR §702.9 (a)).

The SCIL is a continuously updated list of chemicals that meet low-concern Safer Choice criteria for both human health and ecological hazard endpoints. Through reviews to list these chemicals on SCIL, EPA has found these chemicals to be relatively rich in information on hazard, and, to some degree, on conditions of use information. Through public meetings and comments, EPA stakeholders indicated support for use of SCIL as a starting point for identifying potential low-priority candidate chemicals.

Under ChAMP, EPA scientists performed interim evaluations of hazard, use, and exposure of high- and medium-production volume chemicals (HPV and MPV, respectively). Screening-level risk-based prioritizations were developed as interim evaluations that constituted neither a final Agency determination on risk nor a determination as to whether sufficient data were available to characterize risk. However, chemicals determined to be low concern through the ChAMP evaluations may serve as a useful source for identifying potential low-priority candidate chemicals.

SIDS Initial Assessment Reports (SIARs) and SIDS Initial Assessment Profiles (SIAPs) are prepared by OECD member nations in collaboration with industry sponsors and represent a systematic investigation of the potential hazards to human health and the environment associated with HPV chemicals. SIDS documents include a base set of hazard information for each chemical substance, known as the SIDS elements, and incorporate available information on use patterns and exposure (limited information) to put hazard(s) into context (http://www.oecd.org/chemicalsafety/risk-assessment/1947541.pdf). SIDS documents range from targeted assessments or reports on a subset of endpoints to full risk screening assessments.

At this time, EPA intends to select low-priority candidate chemicals from the TSCA Active Inventory (as of April 2018 or the most recent version). In general, EPA intends to preferentially select CAS numbers that represent discretely defined structures, which can be more confidently associated with information on hazard, conditions of use, and exposure. An ethoxylated and/or propoxylated surfactant is an example of a CAS-number-defined substance on the TSCA inventory with a structure that is not precisely defined. Surfactants under a given CAS number may have a range of ethoxylation (EO) and/or propoxylation (PO), where different

ranges of EO and/or PO may be associated with different hazard characteristics as well as differing use and exposure patterns. This approach does not preclude EPA from considering chemical categories[40] for prioritization. In the long-term, EPA may make greater use of category approaches to include non-discrete substances if sufficient information is available.

TSCA requires low-priority substance designation to be based on sufficient information. EPA will ensure designations are based on an adequate quantity and quality of information, and at the same time do not overly tax Agency capacity. Sections 4.1b and 4.1c of this paper already addressed information sufficiency and workload issues. EPA intends to select candidate low-priority chemicals with robust data sets for hazard and exposure, with respect to the range of the substances' conditions of use.

EPA has the flexibility to identify any subsequent low-priority chemical substance candidates beyond the required 20 chemicals. EPA will gain experience through the process leading to designation of 20 low-priority substances.

Stakeholders suggested that, after information from designating the required 20 low-priority chemicals is publicly available, they may wish to volunteer to sponsor the development of information that could be used by EPA to identify candidates that may be designated as low-priority chemicals, beyond the required 20. The experience that EPA and stakeholders gain in designating the first 20 low-priority chemicals could set the stage for an enhanced stakeholder role in designation of additional substances. Similarly, the experiences EPA and stakeholders gain in designating the first 20 high-priority chemicals could also set the stage for an enhanced stakeholder role.

7. Binning the TSCA Inventory

This section describes a longer-term, risk-based approach for parsing the chemical on the TSCA Active Inventory that are not currently on the TSCA Work Plan into bins that can be used to inform multiple activities and priorities throughout EPA, including within the TSCA program. Stakeholders within and outside the federal family have suggested that an approach to bin the remaining active chemicals would be useful. Other countries (e.g., Canada) are undertaking similar exercises. The bins will be defined using a combination of binning scores and information availability. The binning scores included in the approach will incorporate human hazard relative to exposure, ecological hazard, genotoxicity, persistence, and bioaccumulation, further building upon prioritization approaches used in the TSCA 2012 Work Plan process[41] and the objectives identified for integrating NAMs in the Canadian Chemicals Management Plan (CMP)[42]. Consistent with stakeholder feedback, this approach integrates NAMs to fill gaps when

[40] As defined in TSCA Section 26(c).
[41]TSCA Work Plan Methods Document 2012 https://www.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf.
[42]Chemicals Management Plan Science Committee Objectives Paper for Integrating New Approach Methods http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=172614CE-1.

traditional testing data are not available. For example, *in vitro* bioactivity measurements are used when *in vivo* toxicity studies are not available. The information availability scores are intended to reflect the likelihood that a substance has sufficient information for risk evaluation. The approach relies on a large data infrastructure that stores information from NAMs as well as traditional toxicology, exposure, and environmental fate-related studies. The information will be integrated using a web-based decision support workflow to calculate the binning and information availability scores and enable decision makers to perform expert review of the information. Implementation is anticipated to occur in three stages, with near-, intermediate-, and long-term goals.

While the approach of binning the TSCA inventory will help to reduce the size of the pool from which the EPA will draw chemicals for potential prioritization, its purpose is not to identify a list of high-priority candidates. Nor is its purpose to signal that the EPA has concerns with particular chemicals or categories of chemical substances. The starting point of the TSCA Active Inventory is still a large set of tens of thousands of chemicals. Through the approach, EPA will attempt to identify a portion of the Active Inventory that can be set aside as not containing candidates for high-priority designation, so that EPA can focus on chemicals that are most likely to meet the statutory standard of high priority chemicals.

EPA will be transparent in its implementation of the binning approach, and will actively engage with the public on both the application and interpretation of the results of the approach. EPA intends to hold public meetings, provide comment opportunities, and employ other engagement activities to ensure that stakeholders' expertise and perspectives are considered. The anticipated process in the development and implementation of this approach includes the following:

- Public release of this document that outlines the higher-level strategy for parsing the chemicals on the TSCA active inventory into bins. EPA will also be opening a docket (EPA-HQ-OPPT-2018-0659) to take initial high-level comment on this approach. EPA will also take comment on how the resulting bins and the remaining Work Plan chemicals will inform selection of the next chemical for prioritization, as well as a methodology to address information gaps identified during the binning process. These initial comments will inform a white paper/proof-of-concept.

- Release of a white paper that describes a proof-of-concept for the binning approach using a relatively small number of substances. The white paper will provide additional details on the data integration and scoring, how the resulting bins will inform selection of candidate chemicals, and how information gaps identified during the binning process will be addressed

- Public meeting to discuss and receive feedback on the planned approach, as will be described in a forthcoming white paper, and to also discuss the results of a proof-of-concept exercise .

- Application of the binning approach to the active TSCA inventory.

7.1 Chemical Structures, Identifiers, and Mapping

Over the near-term (FY 2019), EPA expects that the substances evaluated in the binning approach will include the non-confidential active TSCA inventory. Provisional substances would be removed and the remaining substances mapped to Distributed Structure-Searchable Toxicity (DSSTox) identifiers.[43,44] Any substances with conflicts between the TSCA identifiers and DSSTox records (e.g., discrepant CAS numbers or chemicals names) would be placed in a queue for mapping review by trained chemists. Currently, the mapped, non-confidential active TSCA inventory contains ~10,000 substances.[45]

7.2 Binning Score Calculation

The binning score would be informed by human hazard relative to exposure, ecological hazard, genotoxicity, susceptible populations, persistence, and bioaccumulation. Calculation of the binning score (Figure 3) would incorporate elements of both the TSCA 2012 Work Plan scoring method and the process identified for integrating NAMs into the Canadian CMP[46]. The five components would be numerically scored and then combined to provide an overall binning score.

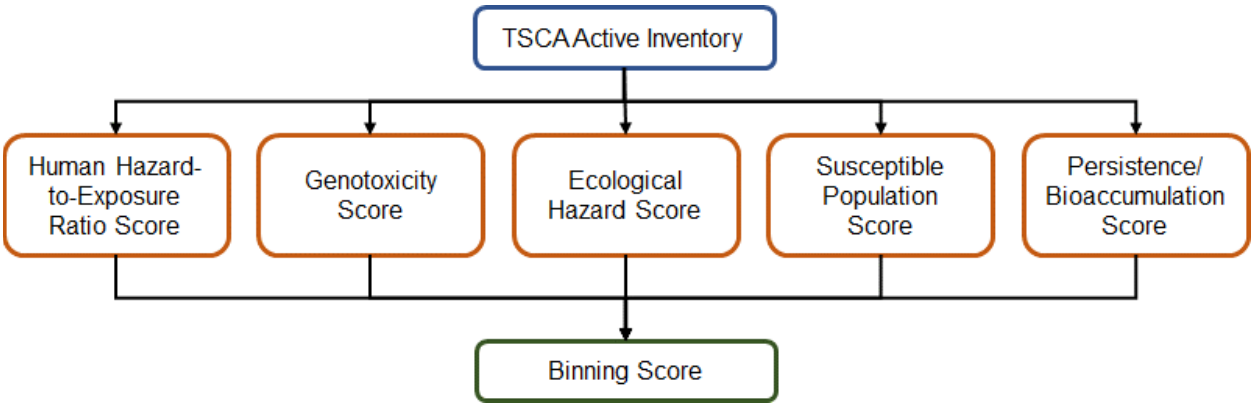

Figure 3. Flow diagram identifying the individual components and the process for calculating the binning scores assigned to individual substances. The overall binning score will be a function of the individual component scores.

[43] Richard, A. M. (2004). DSSTOX website launch: Improving public access to databases for building structure-toxicity prediction models. *Preclinica* **2**(2), 103-108.
[44] Williams, A. J., Grulke, C. M., Edwards, J., McEachran, A. D., Mansouri, K., Baker, N. C., Patlewicz, G., Shah, I., Wambaugh, J. F., Judson, R. S., *et al.* (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. *J Cheminform* **9**(1), 61.
[45] Curated list of non-confidential substances on the active TSCA inventory https://comptox.epa.gov/dashboard/chemical_lists/tscaactivenonconf.
[46] Chemicals Management Plan Science Committee Objectives Paper for Integrating New Approach Methods http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=172614CE-1.

7.3 Human Hazard-to-Exposure Ratio Component

The calculation of the human hazard-to-exposure ratio component score would be based on a decision tree that incorporates a tiered hazard selection process as well as exposure estimates from the EPA ExpoCast modeling effort (Figure 4). The ExpoCast exposure estimates incorporate production volume and conditions of use and are calibrated based on biomonitoring data for the general population.[47] Over the intermediate term, EPA anticipates that the ExpoCast models will be extended to also incorporate occupational exposure estimates (see Intermediate-Term Goals and Improvements section). Under this approach, EPA would then consider two primary paths based on volatility as a surrogate for route of exposure. For non-volatile substances, points-of-departure (PODs) from traditional oral *in vivo* repeat dose toxicity studies would be divided by the median ExpoCast exposure estimate to provide a hazard-to-exposure ratio (HER). When *in vivo* studies are not available, *in vitro* bioactivity estimates from ToxCast would be converted into an oral dose equivalent using high-throughput toxicokinetic approaches[48] and divided by the ExpoCast exposure estimate to provide a bioactivity-to-exposure ratio (BER). Finally, when both *in vivo* and *in vitro* studies are not available, a Threshold of Toxicological Concern (TTC) would be calculated when appropriate[49, 50] and divided by the ExpoCast exposure estimate to provide a TTC-to-exposure ratio (TER). A human hazard exposure ratio component score will be assigned in a tiered fashion based on the magnitude of the HER, BER, or TER value. The order of preference is HER > BER > TER (i.e., if the HER is available, it is used over BER and TER). For volatile substances, PODs from traditional *in vivo* repeat dose toxicity studies would be utilized followed by *in vitro* bioactivity estimates from ToxCast. EPA does not initially anticipate incorporating any TTC value since there is not a widely adopted approach for estimating TTC values for the inhalation route.[51] Over the intermediate term, the database for repeat-dose inhalation studies will be updated and EPA anticipates that TTC values would be derived for volatile substances with inhalation as the primary route of exposure (see Intermediate-Term Goals and Improvements section). If no HER, BER, or TER values can be estimated, the substance is flagged for future information gathering or information request.

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[47] Wambaugh, J. F., Wang, A., Dionisio, K. L., Frame, A., Egeghy, P., Judson, R., and Setzer, R. W. (2014). High throughput heuristics for prioritizing human exposure to environmental chemicals. *Environ Sci Technol* **48**(21), 12760-7.

[48] Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., *et al.* (2015). Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. *Toxicol Sci* **148**(1), 121-36.

[49] Kroes, R., Renwick, A. G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J. G., *et al.* (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem Toxicol* **42**(1), 65-83.

[50] Munro, I. C., Ford, R. A., Kennepohl, E., and Sprenger, J. G. (1996). Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. *Food Chem Toxicol* **34**(9), 829-67.

[51] Dewhurst, I., and Renwick, A. G. (2013). Evaluation of the Threshold of Toxicological Concern (TTC)--challenges and approaches. *Regul Toxicol Pharmacol* **65**(1), 168-77.

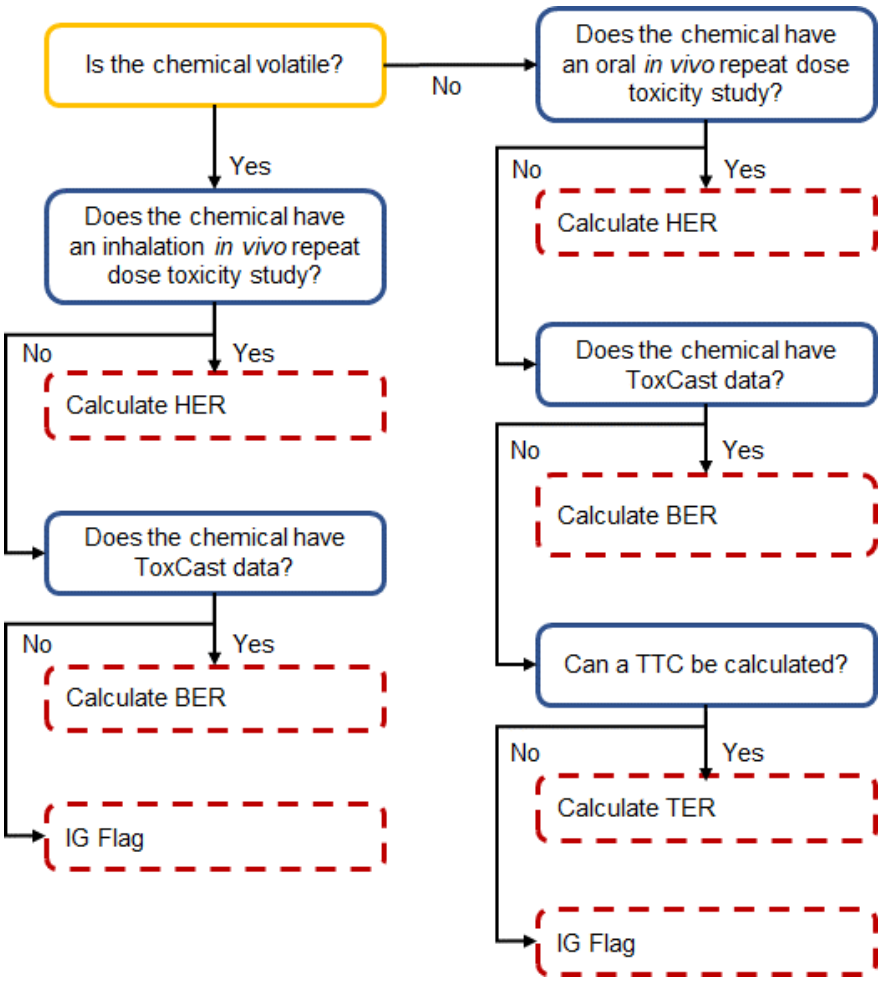

Figure 4. Decision tree associated with the human hazard-to-exposure ratio component. The decision tree begins with the yellow box in the upper left-hand corner and ends at one of the red, dashed line boxes. Blue, solid line boxes represent intermediate decision points. HER, hazard-to-exposure ratio calculated based on in vivo repeat dose toxicity studies divided by the median ExpoCast exposure estimate; BER, bioactivity-to-exposure ratio calculated based on in vitro bioactivity estimates divided by the median ExpoCast exposure estimate; TER, TTC-to-exposure ratio calculated based on the TTC divided by the median ExpoCast exposure estimate; and IG Flag, information gathering flag.

The data sources used for identifying the *in vivo* toxicity studies would include ToxRefDB[52], the European Chemicals Agency via eChem Portal[53], the European Food Safety Agency[54], COSMOS[55], Provisional Peer Reviewed Toxicity Values for Superfund[56], Hazard Evaluation Support System (HESS) database[57] , EPA Integrated Risk Information System (IRIS)[58], High Production Volume Information System (HPVIS)[59], and the Hazardous Substances Data Bank (HSDB)[60]. The data sources for the *in vitro* bioactivity estimates would come from ToxCast[61] and the high-throughput toxicokinetic data are compiled from the HTTK R-package[62]. The TTC values would be calculated using the ToxTree software application.[63]

7.4 Genotoxicity Component

The calculation of the genotoxicity component score would involve two, tiered evaluation processes that are based on the type of DNA damage (e.g., mutagenicity, clastogenicity) and the typical genotoxicity tests used in regulatory assessment (Figure 5). The first tiered process evaluates the mutagenicity and DNA damaging potential of a substance. The standard *in vivo* studies would be used in the first tier (e.g., the transgenic rodent somatic and germ cell gene mutation test and the *in vivo* mammalian alkaline comet test). If no *in vivo* studies are available, the standard *in vitro* studies would be used as the second tier (e.g., bacterial reverse mutation assay [Ames], the *in vitro* mammalian cell gene mutation test [HPRT or MLA/tk]). Finally, if no *in vivo* or *in vitro* studies are available, potential mutagenicity would be predicted using the Toxicity Estimation Software Tool (TEST)[64]. Substances with no *in vivo, in vitro,* or *in silico* data would be flagged for future information gathering.

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[52] Martin, M. T., Judson, R. S., Reif, D. M., Kavlock, R. J., and Dix, D. J. (2009). Profiling chemicals based on chronic toxicity results from the U.S. EPA ToxRef Database. *Environmental health perspectives* **117**(3), 392-9.
[53]OECD eChem Portal. https://www.echemportal.org/echemportal/index.action.
[54]European Food Safety Agency Chemical Hazards Data – OpenFoodTox https://www.efsa.europa.eu/en/data/chemical-hazards-data.
[55]Cosmetics Ingredients Safety Database (COSMOS) https://cosmosdb.eu/cosmosdb.v2/accounts/login/?next=/cosmosdb.v2/.
[56]Provisional Peer Reviewed Toxicity Values for Superfund https://hhpprtv.ornl.gov/.
[57]Hazard Evaluation Support System (HESS) https://www.nite.go.jp/en/chem/qsar/hess-e.html.
[58]EPA Integrated Risk Information System https://www.epa.gov/iris.
[59]High Production Volume Information System (HPVIS) https://www.epa.gov/chemicals-under-tsca.
[60]Hazardous Substances Data Bank (HSDB) – A ToxNet Database https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
[61]ToxCast data from invitrodb_v2 https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data.
[62]High-Throughput Toxicokinetics R package https://cran.r-project.org/web/packages/httk/index.html.
[63] Patlewicz, G., Jeliazkova, N., Safford, R. J., Worth, A. P., and Aleksiev, B. (2008). An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR QSAR Environ Res* **19**(5-6), 495-524.
[64]EPA Toxicity Software Estimation Tool (TEST) https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test.

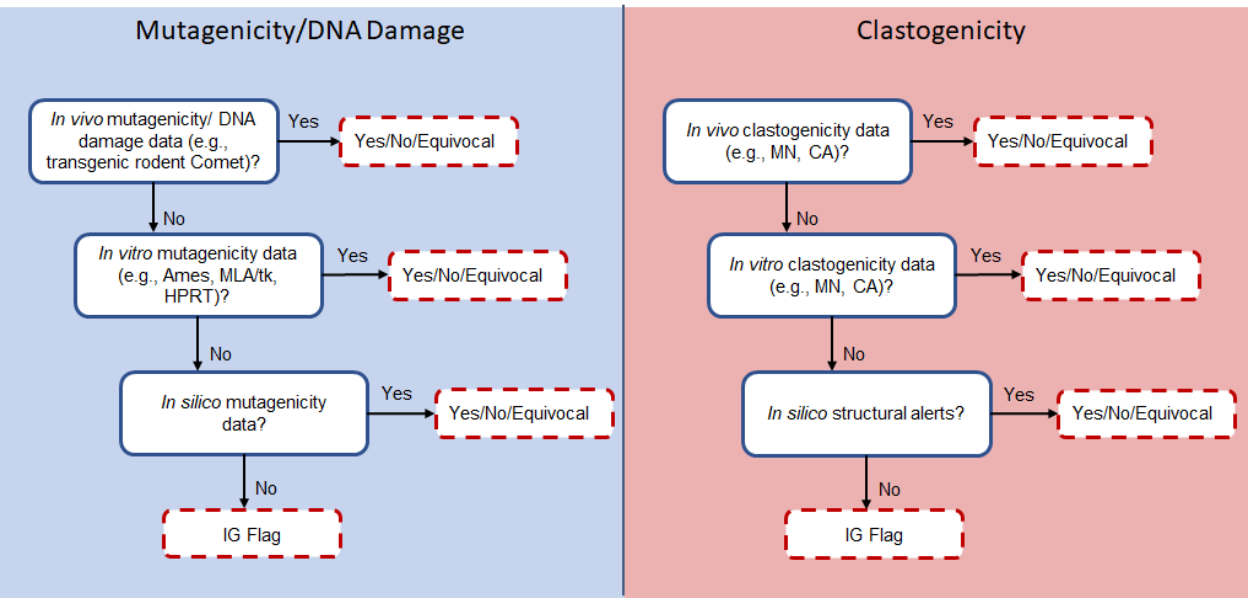

Figure 5. Tiered evaluation process associated with the genotoxicity component. The process in the blue shaded area evaluates the potential mutagenicity and DNA damaging potential of a substance while the process in the red shaded area evaluates the potential clastogenicity. The evaluation process in each shaded area begins with the blue box and ends at one of the red, dashed line boxes. MLA/tk, mouse lymphoma assay, thymidine kinase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; MN, micronucleus; CA, chromosomal aberrations; IG, information gathering.

The second process evaluates the potential clastogenicity of a substance. The standard *in vivo* studies would be used in the first tier (e.g., mammalian erythrocyte micronucleus test and the mammalian bone marrow chromosomal aberration test). If no *in vivo* studies are available, the standard *in vitro* studies would be used as the second tier (e.g., *in vitro* mammalian cell micronucleus assay and *in vitro* mammalian chromosomal aberration assay). Finally, if no *in vivo* or *in vitro* studies are available, potential clastogenicity would be predicted using structural alerts from the Organization for Economic Cooperation and Development (OECD) QSAR Toolbox[65]. Substances with no *in vivo, in vitro,* or *in silico* data will be flagged for future information gathering. The overall genotoxicity component score would be calculated using both the mutagenicity/DNA damage and clastogenicity calls.

7.5 Ecological Hazard Component

The calculation of the ecological hazard component score would initially involve the acute and chronic aquatic toxicity similar to that performed for the TSCA 2012/2014

[65]OECD QSAR Toolbox http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm.

Workplan[66]. The experimental data would be derived from both the EPA ECOTOX database[67] and from the European Chemicals Agency via eChem Portal[68] and include mortality, reproductive, and growth endpoints. For each substance, lethal concentration required to kill 50% of the population (LC50) or effective concentration at half maximal response (EC50) value and no observable effect concentration (NOEC) or low observable effect concentration (LOEC) would be identified for the acute and chronic endpoints, respectively. When experimental data are not available, the LC50 or EC50 value for acute aquatic toxicity would be predicted using the EcoSAR[69] model and the Toxicity Estimation Software Tool (TEST)[70], respectively. The ecological hazard component score would be calculated as a function of the measured or predicted potency values. When no experimental data or model predictions are available, the substance would be flagged for future information gathering. In addition, the experimentally measured potency values would be compared with the water solubility of the chemical. Potency values that are greater than the water solubility would be flagged for further consideration. Over the intermediate term, quantitative ecological exposure models would be developed and integrated with the potency values for aquatic toxicity to facilitate calculation of an ecological hazard-to-exposure ratio similar to the human hazard component.

7.6 Susceptible Human Population Component

Calculation of the susceptible population component score would be based on the potential for exposure to children. The presence in children's products would be identified based on both the EPA Consumer Product Database (CPDat)[71] and the EPA Chemical Data Reporting (CDR) results. Substances with no CPDat or CDR data available will be flagged for future information gathering.

[66]TSCA Work Plan Methods Document 2012 https://www.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf.
[67]EPA ECOTOXicology knowledgebase (ECOTOX). https://cfpub.epa.gov/ecotox/.
[68]OECD eChem Portal https://www.echemportal.org/echemportal/index.action.
[69]EPA Ecological Structure Activity Relationships (ECOSAR) Predictive Model https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model.
[70]EPA Toxicity Software Estimation Tool (TEST) https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test.
[71] Dionisio, K. L., Phillips, K., Price, P. S., Grulke, C. M., Williams, A. J., Biryol, B., Hong, T., and Isaacs, K. K. (2018). The chemical and products database, a resource for exposure-relevant data on chemicals in consumer products. *Scientific Data* **In Press**.

7.7 Persistence and Bioaccumulation Component

Calculation of the persistence and bioaccumulation component score will be based on the potential for organisms to be exposed for an extended period and for potential accumulation up the food chain. Persistence is evaluated based on the potential half-life in air, water, soil, and sediment while factoring in the partitioning characteristics of the substances and all potential removal pathways based on standard physical-chemical properties and environmental fate parameters[72]. Bioaccumulation is represented based on bioaccumulation factors (BAF) or bioconcentration factors (BCF). When experimental data are not available, the persistence and bioaccumulation potential would be predicted using EpiSuite[73] and OPERA models.[74]

7.8 Information Availability Score Calculation

The amount of hazard- and exposure-related information that is sufficient to perform a risk evaluation is typically context specific and informed by expert judgement. However, an expert-driven approach is not readily scalable for evaluating the thousands of substances in the active TSCA inventory. To attempt to achieve these incongruent aims, a relatively simple set of three criteria were developed that inform the set of potentially relevant human health and ecological toxicity information. The criteria include a combination of primary use as a chemical intermediate, environmental half-life, water solubility, molecular weight, and whether the chemical is an exempt polymer (Figure 6). Following application of the criteria, the information availability score is calculated as a function of the potentially relevant information in the associated list that is available for a specific substance. Missing information will be flagged for potential future information gathering.

[72]TSCA Work Plan Methods Document 2012 https://www.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf.
[73]EPI Suite™-Estimation Program Interface https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.
[74] Mansouri, K., Grulke, C. M., Judson, R. S., and Williams, A. J. (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. *J Cheminform* **10**(1), 10.

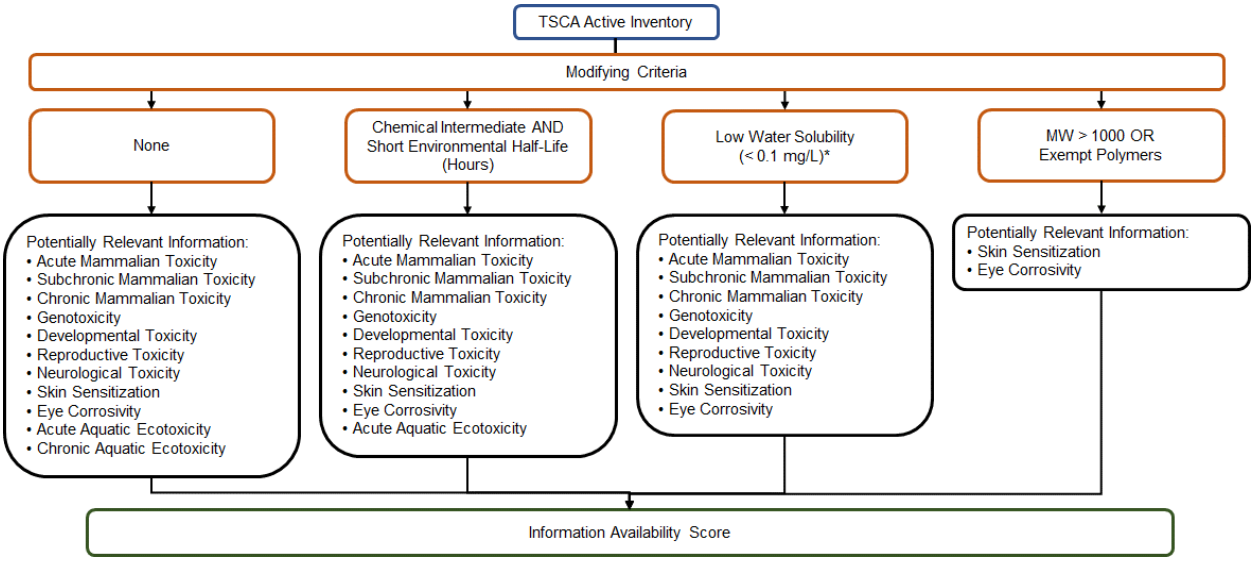

Figure 6. Flow chart for calculating the information availability score for each substance based on a small number of physico-chemical and use criteria for identifying potentially relevant human health and ecological toxicity information.
** The criteria for determining low water solubility is based on Sustainable Futures Manual (EPA-748-B12-001).*

7.9 Substance Binning Process

Following the calculation and assignment of both the overall binning score and information availability score, the substances would be parsed into multiple bins (Figure 7). The two-dimensional scoring matrix can be parsed into many different combinations and bin sizes depending on program needs. The bins shown serve as only one example. Bins 1 through 3 are designed to be enriched in substances whose potential risks are higher than chemicals in bins 4-7 with differing degrees of information availability. As one progresses to Bins 2 and 3, the potentially relevant missing information is flagged for potential information gathering. Bins 4 and 5 are designed to contain substances whose potential risks are lower than those in bins 1-2 and higher than those in bins 6-7 and high information availability to provide a broader pool of substances for additional consideration. Bin 6 is designed to contain potentially lower risk substances with high information availability. Finally, Bin 7 contains substances with potentially lower risk that may need targeted studies or information gathering. Note that neither a chemical's score nor the bin in which it is placed would determine whether a chemical is a good candidate for prioritization or whether it will be selected for prioritization. Rather, the score is intended only to reflect the synthesis of a substantial volume of information and to allow EPA to loosely group chemicals into pools of potential candidates for further evaluation. This process would inform EPA's decision, but would not be determinative. The forthcoming white paper on the binning process will further describe how the bins will inform selection of candidate chemicals for prioritization, in combination with the remaining Work Plan chemicals, Administrator priorities, and other considerations.

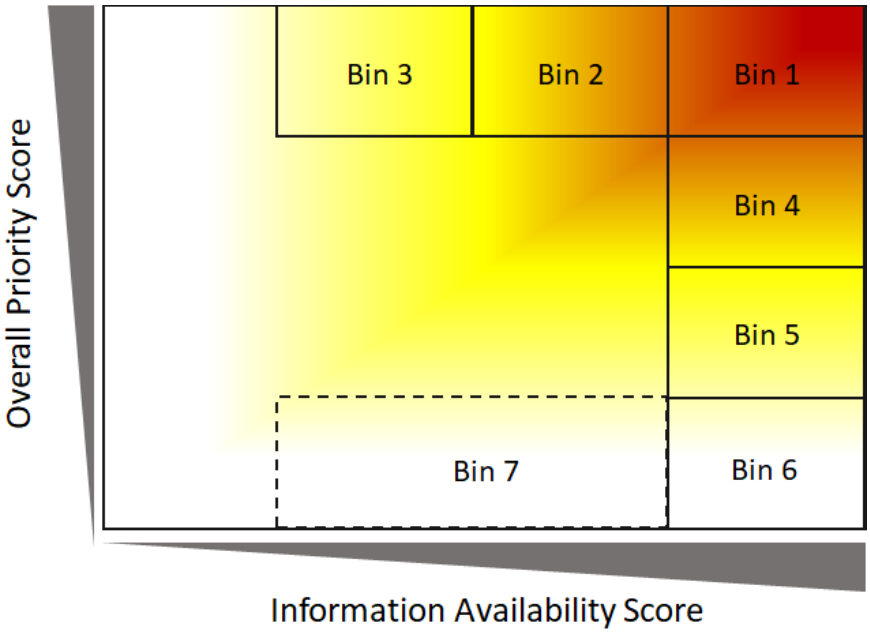

Figure 7. Graphical representation of the scoring matrix used to define the bins for parsing the active TSCA inventory. The red color represents substances with high overall binning and information availability. The yellow color represents substances with moderate overall binning and information availability scores and white represents substances with low overall binning and information availability scores. The bins shown serve as only one example.

The binning process utilizes a large scientific computing and data management infrastructure that runs predictive models and stores information from NAMs as well as traditional toxicology studies, exposure information, experimental measurements of persistence and bioaccumulation, and presence in products. The model results and information are integrated using a web-based decision support workflow to calculate the binning and information availability scores and enable users to efficiently perform expert review of the available information prior to selecting candidates or identifying gaps. The workflow also provides flexibility to expand or shrink the TSCA inventory or alter the scoring and binning process based on scientific improvements or policy changes.

7.10 Intermediate-Term Goals and Improvements

It is anticipated that the binning approach may be iteratively improved as more experience is gained with the process and other sources of relevant data are incorporated. Over the intermediate time frame (FY 2020-2021), the following improvements are expected to be made:

- Substances evaluated in the binning approach will be modified to incorporate changes based on the TSCA Inventory Notification Rule[75]. The updated inventory is expected to include over 38,000 substances.

- Approximately half of the active TSCA inventory are mixtures or substances of unknown or variable composition, complex reaction products, and biological materials (UVCBs). The computational modeling and scoring and binning process will be adapted to accommodate mixtures and UVCBs.

- Occupational exposure is an important pathway to assess under TSCA. The ExpoCast models will be updated and improved to provide occupational exposure estimates.

- In the proposed approach, the TTC approach forms the baseline for estimating potential hazardous concentrations for substances with no traditional *in vivo* toxicity studies or *in vitro* bioactivity measurements. The database for repeat-dose inhalation studies will be updated and TTC values will be derived for volatile substances with inhalation as the primary route of exposure.

- Incorporate consideration of *in vitro* assay data into ecological hazard component scoring in cases where *in vivo* acute and chronic data are lacking. This would allow consideration of evidence for potential specifically-acting modes of action in cases where otherwise only non-specific (narcosis-type) toxicity would drive the prioritization.

- Combine quantitative ecological exposure models with ecological hazard to facilitate integration of the ecological hazard-to-exposure ratio into the binning score.

7.11 Long-Term Goals and Improvements

Over the long-term (beyond FY2021), the strategy is expected to evolve to incorporate information from NAMs that meet the criteria for reliability and relevance outlined in the draft "Strategic Plan to Promote the Development and Implementation of Alternative Test Methods"[76].

[75]TSCA Inventory Notification (Active-Inactive) Rule https://www.epa.gov/tsca-inventory/tsca-inventory-notification-active-inactive-rule.
[76]Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing in TSCA https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce.

7.12 Caveats and Potential Limitations

The caveats and potential limitations of the proposed strategy:

- In order to bin the thousands of chemicals on the Active Inventory, the calculation of the binning and information availability scores would be performed using an automated process that may not account for all potential exceptions or contexts that may occur for a specific chemical or chemical group. Expert review of the chemicals and associated bins will be an integral part of the process.

- The initial strategy does not fully account for all routes of exposure (e.g., dermal) or all populations (e.g., elderly). Other routes of exposure and potentially susceptible populations may be added over time.

- The binning and scoring strategy relies on a large database of chemical properties, hazard, exposure, persistence, and bioaccumulation information that have been integrated from multiple sources and models. Although efforts have been taken to ensure the accuracy of the information, the database may contain errors propagated from the source databases. The cleaning and curation of the information will be an ongoing process.

7.13 Summary

A longer-term, risk-based strategy is proposed for enabling the efficient binning of chemicals on the active TSCA inventory. The strategy parses a very large chemical space into more manageable pieces based on both potential risks and information availability. The strategy integrates NAMs as well as traditional toxicology and experimental information to calculate binning scores while information availability enriches for chemicals with the highest likelihood for potentially successful risk evaluation. The proposed strategy utilizes a large scientific computing and data management infrastructure to enable systematic and reproducible binning of the thousands of substances that fall under the TSCA legislation. The information is integrated using a web-based decision support workflow to enable expert review prior to selecting candidates and the flexible adaptation of the process based on scientific or policy changes. The bins will be useful to inform priorities within the TSCA program and potentially throughout the EPA for consideration by program offices. Stakeholders will also benefit by understanding the data available for a particular chemistry, where gaps may exist, and where the chemical falls within the screening level risk continuum.

8. Conclusion

This document describes the near-term approach that EPA anticipates using to inform the identification of potential candidates for the initial 20 high-priority and 20 low-priority chemical substances that must be identified pursuant to section 6(b)(2)(B). The document also presents a

proposed longer-term approach that EPA is considering to bin the TSCA inventory to begin to identify potential candidates for the prioritization of subsequent chemicals. EPA expects to begin, a public discussion regarding the implementation of this longer-term approach will be required. The EPA intends to hold public meetings, provide comment opportunities, and employ other engagement activities to ensure that stakeholders' expertise and perspectives are considered in the implementation of this approach.