March 20, 2017

RE: Proposed Rule: Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act, Docket ID EPA-HQ-OPPT-2016-0636

The Humane Society of the United States (HSUS) and Gradient have collaborated to provide comments to the US Environmental Protection Agency (EPA) on the implementation of the provisions under the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA).

These comments are being submitted on behalf of the members and supporters of HSUS (the nation's largest animal protection organization), who share the common goal of promoting the use of reliable and relevant regulatory chemical testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animal testing to determine chemical toxicity. Gradient, an environmental and risk sciences consulting firm that shares HSUS's commitment to the protection of human health and the environment, worked jointly with HSUS to provide inputs that promotes innovative toxicology strategies that will both improve chemical safety assessment as well as minimize the use of animal testing in such assessments.

We thank EPA for this opportunity to comment on the Proposed Rule. The amended TSCA is an important development for chemical regulation in the US. Under the new TSCA, EPA is tasked with performing affirmative safety evaluations for both new and existing chemicals. In order to meet the new requirements, it will be necessary for companies to produce data that inform toxicity determinations for thousands of chemicals that are currently being manufactured and imported in the US. While we realize that it will be impossible to fully eliminate animal testing and still meet these data needs, we assert that industry, the general public, and animals are best served when the use of animal testing in chemical toxicity evaluations is minimized. The implementation of all aspects of the Proposed Rule offers a tremendous opportunity to advance toxicological analysis through the use of alternative testing methods, including targeted *in vitro* testing, quantitative structure-activity relationship (QSAR) analysis, read-across, and high-throughput screening. Our comments are focused on emphasizing the need for thoughtful chemical characterization strategies that promote the use of non-animal testing alternatives without compromising the reliability of chemical safety evaluations.

In the Proposed Rule, EPA outlines a four-step process for prioritization: (1) Pre-Prioritization, (2) Initiation, (3) Proposed Designation, and (4) Final Designation. EPA is proposing to do the initial prioritization screening, during which most of the information will be gathered, in the Pre-Prioritization phase. The time limit for prioritization is 9-12 months; once prioritization is completed, the substance moves immediately to risk evaluation, which must be completed within three years. Because Pre-Prioritization is outside the legislated time limits, the clock will start with Step 2, Initiation. Public comment is allowed at two points: during the Initiation and Proposed Designation phases. If, after Initiation is completed, EPA finds that the available information is insufficient to make a designation, the substance will default to a high-priority designation. Upon completion of a risk evaluation, EPA must move at least one other high-priority substance into risk evaluation, so that, over time, the number of substances being evaluated never decreases. EPA must designate at least 20 high- and 20 low-priority substances by December 2020 and must have the resources to do so.

Our comments for the "Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act" are summarized below.

General Comments

- The proposed creation of a Pre-Prioritization phase that falls outside of the statutory deadlines largely circumvents the intent of the prioritization process, which is to rapidly identify chemicals in the TSCA universe that require immediate attention, as well as those that require additional information, and to provide public assurance for those chemicals whose detailed assessment is not of immediate concern. Rather than the process described in the prioritization Proposed Rule, EPA would be better aligned with the intent of the legislation by focusing resources in the early years on gathering and evaluating existing information on chemicals on the active TSCA inventory. The Pre-Prioritization process should require no or very little new information generation, and specifically, it should not be necessary for EPA to request any new vertebrate animal testing during the Pre-Prioritization process.
- The identity of chemicals being considered for (Pre-)Prioritization should be public. Additionally, stakeholders should be given the opportunity to submit information on Pre-Prioritization chemicals during a comment period or through other means.
- More transparency is needed in the Pre-Prioritization process. In an effort to be more transparent, EPA could adapt the frameworks similar to those carried out by Canada's Chemical Management Program (CMP) and Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS), or articulated by examples from the RISK21 project. In the RISK21 framework, chemical substances can be screened and mapped according to known information about potential hazard and exposure and bounded by uncertainty stemming both from data variability and from lack of information. This way, substances that are clearly high or low priority can be readily identified. Furthermore, the primary aspect responsible for uncertainty (whether exposure or hazard) is apparent, thus facilitating the gathering of additional information that would be most likely to decrease uncertainty about the risk associated with specific substances.
- Initiation should focus on data-rich compounds, where additional animal testing would likely not be required to make a determination. Exposure information (measured and predicted) could be used to prioritize chemicals within groups of data-rich compounds.
- Once a clearer understanding of high-priority and low-priority criteria are achieved, EPA should focus on developing a robust read-across and chemical-grouping approach, such that the evaluations of data-rich compounds can be leveraged to the extent possible.
- EPA should be balanced in selecting chemicals that will likely be designated low priority (low exposure, low hazard) and those that will be designated high priority (high hazard/high exposure).
- EPA is not adequately addressing the requirement to "reduce and replace, to the extent practicable...the use of vertebrate animals." It would benefit EPA to stress the vital roles of alternative methods, including targeted *in vitro* testing, QSAR analysis, read-across, and high-throughput screening in the prioritization and risk evaluation Proposed Rules.
- EPA should try to develop a standard set of physical-chemical properties, *in vitro* tests, and QSAR methods that could be applied efficiently to most chemicals. The aim would be to provide a means to assure the public that chemicals have not been overlooked in the prioritization process simply because of a lack of understanding of possible effects stemming from lack of testing. The approach would stand in contrast to the European Union's (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) approach, for which the standard and

mandated set of baseline testing includes a great deal of animal testing and considerable expense. The shortcoming of the REACH approach is that a minimum data set mandate, which includes animal testing, is performed before evaluating which specific tests are necessary to establish adequate protection of public health. A well thought-out minimum *in vitro* assay and QSAR array, however, would ensure that indicators of the major toxicity concerns are routinely considered, while leaving animal testing to those cases where it is absolutely necessary.

Comment #1: Pre-Prioritization as described in the Proposed Rule requires significant modification to address legislative intent. EPA needs to provide more transparency on Pre-Prioritization and publicize the identity of chemicals being considered in the Pre-Prioritization process.

Issue: The proposed creation of a Pre-Prioritization process that falls outside of the statutory deadlines and process largely circumvents the intent of the prioritization process, which is to rapidly identify chemicals in the TSCA universe that require immediate attention, as well as those that require additional information, and to provide public assurance for those chemicals whose detailed assessment is not of immediate concern. Furthermore, EPA has proposed that all information necessary for a complete risk assessment be obtained during this Pre-Prioritization phase. This process does not apparently focus resources on chemicals of greatest potential risk and gives no indication whatsoever of the relative potential risk of the vast majority of chemicals.

Other than the criteria in TSCA Sections 6(b)(1)(a) and 6(b)(2) and the mandate to include chemicals from EPA's "Work Plan Methodology for Chemical Assessments" (US EPA, 2012, how is EPA setting priority among the hundreds or thousands of chemicals that may be potentially high or low priority? Additionally, how will industry and the public provide input (*i.e.*, conditions of use) for chemicals being considered in Pre-Prioritization if EPA does not publicize the identities of said chemicals?

Suggestion:

Transparency

Rather than the process described in the Proposed Rule (US EPA, 2017a), EPA would be better aligned with the intent of the Prioritization process by focusing resources in the early years on gathering and evaluating existing information on chemicals on the active TSCA inventory. The Pre-Prioritization phase of the process should require no or very little new information gathering but should rely heavily on existing data, high-throughput analyses including ToxCast™ and ExpoCast, and other modeling techniques. Specifically, the EPA should clarify that the generation of vertebrate animal data will not be required/requested during the Pre-Prioritization process.

Further clarification on how EPA will set priority among the potentially hundreds or thousands of chemicals in the Pre-Prioritization process is needed. This can be achieved by adapting risk matrix processes similar to those carried out under Canada's CMP (Health Canada, 2017) or Australia's NICNAS Inventory of the Multi-tiered Assessment and Prioritization (IMAP) framework (Australia NICNAS, 2016a). Under these frameworks, existing information and modeling are used to identify and prioritize chemicals that present hazard of concern and have a likelihood of high exposure. This is a fairly rough but effective categorization process that ensures that chemicals with the greatest risk are prioritized for further assessment and management, as appropriate.

Another complementary approach that results in a more nuanced prioritization of chemicals has been articulated by the Health and Environmental Sciences Institute (HESI) RISK21 project (Embry *et al*., 2014; Pastoor *et al*., 2014; Wolf *et al*., 2016). RISK21 is the result of a multisector and multinational effort engaging over 120 participants from 12 countries, 20 universities, 15 government institutions, and 2 non-government organizations (Embry *et al.*, 2014). Because the objective is prioritization for evaluation, the RISK21 framework suggests higher tolerance for uncertainty and imprecision in the information, knowing that the detailed assessments will be performed at risk evaluation. This is in line with the intent of and likely level of effort meant for the Pre-Prioritization process. In this way, chemicals with the highest potential risk are assessed first, which ensures public confidence that problematic chemicals are being addressed in the most efficacious way feasible.

The RISK21 framework and web tool allows the user to set priority among the potential substances for Initiation and visualize the uncertainty that drives data gathering on hazard and/or exposure. RISK21 can also help prioritize "candidates for information gathering" into high- or low-risk categories. The RISK21 matrix plots chemicals according to measured and modeled hazard and exposure information, bounded by uncertainty stemming from both data variability and lack of information (Figures 1A-1C). Uncertainties are shown in these figures as gray bands or circles. The plot includes background color coding indicating reasonable (green) and unreasonable (red) risk. The boundaries of reasonable and unreasonable risk can be determined according to a particular decision context set by EPA. As chemicals are mapped to the grid based on the intersection of estimated risk and exposure, substances that are clearly high or low priority can be readily identified. Furthermore, the primary aspect responsible for uncertainty (whether exposure or hazard) is apparent, thus facilitating the gathering of additional information that would be most likely to decrease uncertainty about the risk associated with specific substances.

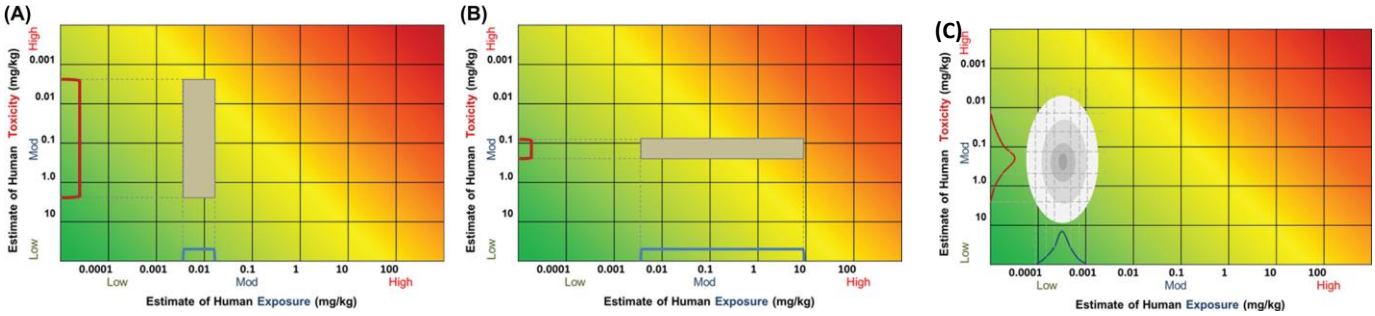

Figure 1 Exposure-Toxicity Intersection Formed from Two Ranges. (A) Illustrates a scenario in which there is a wide range of toxicity values but a fairly narrow range of exposure estimates; (B) Illustrates a scenario in which there is a wide range of exposure values but a fairly narrow range of toxicity estimates; (C) Illustrates that, alternatively, the exposure-toxicity intersection can be formed by mixing two probability distributions showing isoprobability contours (Embry *et al.*, 2014).

Using the RISK21 framework, EPA could perform iterative data-gathering steps to reduce uncertainty where necessary, focusing on the areas where decreasing the uncertainty of an estimate would provide the greatest improvement in risk assessment. For example, Chemical T (in Figure 2B) has sufficient information to demonstrate high exposure and high hazard with low uncertainty, thus making it an ideal candidate for the prioritization process as a high-priority chemical (Embry *et al*., 2014). Chemical U has large uncertainty for both hazard and exposure, and high enough potential for both to present a likely risk, and therefore would be prioritized for more hazard and exposure information gathering. Chemical X is unlikely to present a risk with relatively low uncertainty, and is thus a potential candidate for low-priority designation.

Additionally, as a first pass, a toxicological threshold of concern (TTC) could be applied to the matrix to identify chemicals of low concern (in this case, low priority) (Figure 2A) (Embry *et al*., 2014). The TTC approach requires estimation of a conservative exposure limit below which there is very little possibility of risk. Even if the exposure estimate is not precise, the TTC approach can be used to make decisions about low-exposure chemicals with high confidence. Some applications of TTC involve binning chemicals into three potential hazard classes based on chemical structure, known as Cramer Classes (European Commission, 2017). The European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) (European Commission, 2017) provides the following definitions of the Cramer Classes:

1. **Class I** contains chemicals of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity.
2. **Class II** contains chemicals that are intermediate. They possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3.
3. **Class III** contains substances with a chemical structures [sic] that permit no strong initial impression of safety and may even suggest a significant toxicity.

Figure 2A shows an example of two chemicals, one of which (Chemical Y) falls safely below the TTC cut-off for the most potentially hazardous Cramer Class (Class III) and can therefore be safely considered low priority. The other chemical, Chemical Z requires additional refinement in the estimation before any decision can be confidently made (Embry *et al*., 2014).

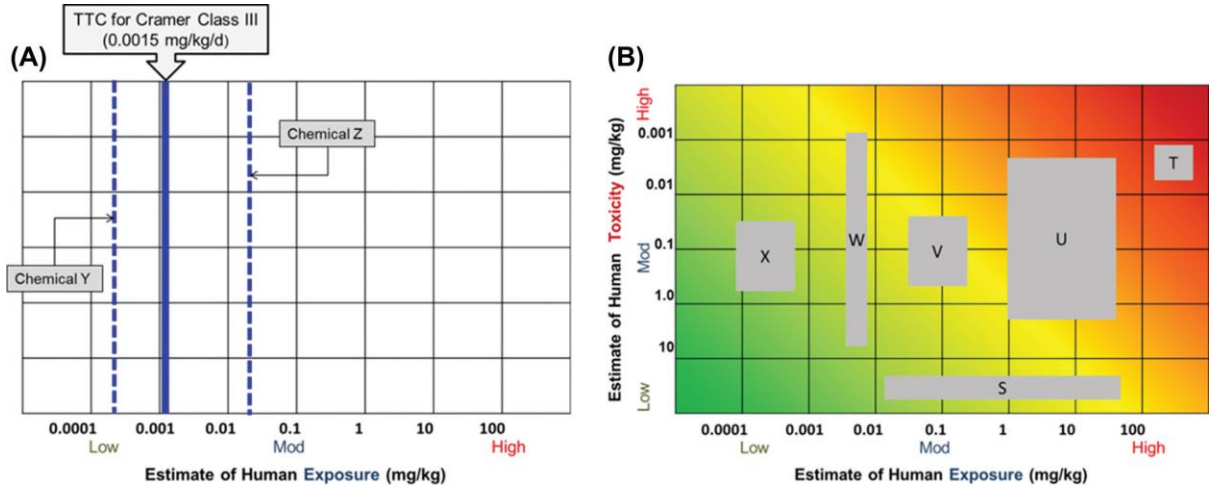

Figure 2 Use in Priority Setting. TTC can be applied as a low tier periodization/screen (Figure 2A). In this example, Chemical Y falls below the TTC, and therefore could be considered low priority; in contrast, Chemical Z could be regulated or prioritized. Another way to prioritize chemicals is shown in Figure 2B, where hazard estimates are plotted along the y-axis and exposure estimates along the x-axis, with uncertainties demonstrated by the gray bands. In this example, Chemical T could likely be initiated, whereas Chemicals U, V, and W may need more toxicity certainty, and S may need more exposure certainty (Embry *et al*., 2014).

Additionally, while there are two comment periods, one during Initiation and another during Proposed Designation, the public and other stakeholders do not have any avenue for input during the selection of chemicals up for Prioritization (*i.e.*, during Pre-Prioritization). EPA should publically identify the chemicals that are being considered for Initiation during Pre-Prioritization. RISK21 would be a valuable

tool for requesting and/or allowing industry to voluntarily provide input on areas of unreasonable uncertainty during a comment period or through other means. By implementing these processes, industry would have some idea of the priority of the chemicals being considered in the Pre-Prioritization process, and the public would be assured that chemicals presenting the highest risk would be addressed first through potential risk management actions.

Criteria

While it is reasonable for EPA to cast a wide net during the Pre-Prioritization process (with a focus on the criteria outlined in the TSCA Work Plan, among others), we recommend that EPA choose chemicals that are data-rich and have well-characterized hazard profiles, comprehensive exposure information, and accurate use information for the next stage of the Prioritization (*i.e*. Initiation).

Additionally, there could be a parallel effort by EPA to identify similar chemicals and perform assessments leveraging data-rich chemicals using a group-type approach. This approach will allow EPA to establish clearer criteria for establishing high and low priorities with existing data in the earlier assessments, as well as refine acceptable read-across strategies. Many existing chemical prioritization schemes across the world allow and encourage the use of alternatives to animal testing including read-across, *in vitro*, and QSAR to inform the prioritization process, such as Australia's NICNAS IMAP (Australia NICNAS, 2016a) and Priority Existing Chemical (PEC) list (Australia NICNAS, 2016b), Canada's CMP existing substances prioritization (Health Canada, 2017), and the REACH Community Rolling Action Plan (CoRAP) (ECHA, 2017a).

Comment #2: EPA should clarify the role of data gaps in the prioritization process.

Issue: As the Proposed Rule is currently written, manufacturers are incentivized to not generate new toxicity information unless requested, since lack of such information is a strategy for manufacturers to "hide" the chemical and avoid having it be chosen for Initiation (and, when it is eventually chosen, it will likely be designated high priority due to the lack of information) (US EPA, 2017a). With that in mind, how does the prioritization process as described, with a strong emphasis on data gathering in an opaque Pre-Prioritization phase, address the role of toxicological or exposure data gaps? EPA's decision on this matter could lead to unnecessary toxicity testing and erroneous labeling of chemicals as high risk simply due to a lack of information. For example, with respect to lack of exposure information, will chemicals with no exposure data automatically be selected for Initiation? Or will EPA assume worst-case scenarios in terms of what is considered "intended, known, or reasonably foreseen" use? Or will these chemicals be passed over by another chemical (of similar toxicity) with demonstrated high and wide dispersive exposure? Will EPA's exposure assessment address all life cycle stages (direct use, indirect emission, ecological receptors), near-field exposure (estimates of exposure to substances found on consumer products and other in-home sources), and far-field exposure (estimates of exposure from chemicals that are released into the environment)?

Suggestions: Further clarification is needed from EPA on the role of data gaps and how EPA will determine what data would be necessary to satisfy its prioritization process. As mentioned in Comment #1, the proposed Pre-Prioritization phase, during which EPA seems to suggest most of the data will be gathered, evaluated, and generated in a process that is undefined, disincentives industry to generate additional information other than what EPA may request. This process of data generation is not efficient or effective unless the process is transparent and guidance describing approaches that EPA will accept is made available.

Toxicity Data Gaps

It could be assumed that EPA will use read-across to address gaps in toxicological data; however, this should be explicitly stated. Furthermore, LCSA specifically calls for further incorporation of *in vitro*, read-across, and high-throughput *in silico* data – "Testing of chemical substances and mixtures" §2603(h)(1)(A) and (2)(A) (US Congress, 2016) – and EPA's 2009 Strategic Plan for Evaluating the Toxicity of Chemicals (US EPA, 2009) discusses the use of high-throughput methods for chemical screening and prioritization. EPA should clarify the types of data and approaches EPA will consider in the Proposed Rule. For additional recommendations on addressing toxicological data gaps, see Comment #5.

Exposure Data Gaps

In the case of data gaps in exposure information, EPA should clarify if chemicals with no exposure data would be automatically initiated or if EPA would assume worst-case scenarios in terms of what is considered "intended, known, or reasonably foreseen" use (US EPA, 2017a, p. 4,829). EPA should also clarify whether all life cycle stages (*i.e.*, direct use, indirect emission, ecological receptors), near-field (*i.e.*, for substances found on consumer products and other in-home sources), or far-field (*i.e.*, for chemicals that are released into the environment) exposure would be considered in the Pre-Prioritization stage. More guidance on the type of exposure data considered will help to integrate a RISK21 approach to the Pre-Prioritization process.

EPA could use modeling software to aid the assessment of exposure risks. Many existing chemical prioritization schemes across the world use exposure modeling tools in their processes, such as Canada's CMP existing substances prioritization (Health Canada, 2017). Examples of available models include:

- EPA's ExpoCast can evaluate both far-field and near-field exposure routes and has been used to develop exposure estimates for approximately 1,900 chemicals (US EPA, 2015).
- EPA's Human Exposure and Dose Simulation High-throughput model (SHEDS-HT), described within EPA's ExpoCast, examines total exposure to a chemical by identifying multiple routes, scenarios, and pathways of exposure. It also examines population and life stage information (US EPA, 2015).
- Canada's Simple Exposure Tool (SimET) identifies chemicals of greatest potential exposure based on three lines of evidence: "1) quantity in commerce in Canada; 2) number of companies involved in commercial activities in Canada; and (3) the consideration by experts of the potential for human exposure based on various use codes" (Health Canada, 2006).
- European Centre for Ecotoxicology and Toxicology of Chemicals' Target Risk Assessment (TRA) tool classifies chemical exposure risk to workers, consumers, and the environment (ECETOC, 2012).

Comment #3: EPA should dedicate significant resources to making low-priority designations.

Issue: EPA is proposing to replace the risk evaluation pipeline with a high-priority chemical whenever a risk evaluation is completed. Unlike the mandate to continually make high-priority assignments, there is no requirement to make low-priority determinations on an ongoing basis. In fact, EPA is mandated to designate no more than 20 low-priority chemicals.

Suggestion: We recommend that EPA dedicate significant resources to the continual identification and determination of low-priority compounds. This is an important function, given EPA's intent to prioritize (high or low) all of the compounds on the existing inventory.

The Proposed Rule states that the prevalence will be a designation of high priority, largely due to a foreseen lack of information (US EPA, 2017a); however, EPA did not define what would be sufficient to establish a chemical as low priority. EPA should be specific about information a manufacturer could compile that would be sufficient to designate a chemical as low priority, which would incentivize manufacturers to submit relevant data. In addition, if a transparent process such as the RISK21 framework were employed, industry could submit such data before being requested by EPA, thereby facilitating and accelerating the prioritization process.

The benefits of an active low-priority designation initiative are manifold. The most immediate benefit is that a "low priority" designation will allow companies that manufacture and/or import the designated chemical to operate effectively without the uncertainty of impending risk mitigation measures. Also, because there will be clear incentives for using low-priority compounds, many companies may look to existing low-priority compounds as possible candidates for replacing chemicals that have a higher potential to receive a "high priority" designation (either from lack of data or higher risk potential), or at least look to develop chemicals with similar chemical and toxicological profiles to low-priority compounds.

In making "low priority" designations, we encourage EPA to prioritize data-rich compounds that clearly have enough existing toxicity information to make confident determinations that a chemical is low priority. Once a significant number of those chemicals have been designated, we recommend that EPA dedicate resources to identifying other chemicals that may have less data but would be expected to have a similar toxicological profile to the designated low-priority compounds. EPA has traditionally provided leadership in read-across approaches, and an active program to identify low-priority compounds allows additional opportunities to expand the science of predictive toxicology, particularly when it can be complemented with *in silico* approaches (*e.g.*, QSAR, high-throughput data). To this end, it would be very useful for EPA to develop a comprehensive framework that emphasizes non-animal testing that could be used to support a low-priority designation. Much of the work that could support such an effort is embodied by the Organization for Economic Cooperation and Development's (OECD) Integrated Approaches to Testing and Assessment (IATA) (OECD, 2016). The OECD's working definition of IATA is, "a structured approach that strategically integrates and weights all relevant data to inform regulatory decisions regarding potential hazard and/or risk and/or the need for further targeted testing and therefore optimising and potentially reducing the number of tests that need to be conducted" (OECD, 2016). Consistent with the OECD IATA approach, we emphasize that no minimum data set be required to make such a determination and that the weight of evidence consider both toxicity and other information that can be garnered from basic physical-chemical and *in silico* information.

Moreover, we support EPA's approach to not only rely on toxicity and chemical characteristics to make designations, but to also include exposure considerations in the low-priority designation. For example, if the only significant route of exposure is dermal and the compound would not penetrate the skin, the compound could be given a low-priority designation. Also, if the compound only involves industrial exposures that would be easily controlled with personal protective equipment (*e.g.*, chemicals with irritative properties controlled with gloves and eye protection), such compounds could also be considered low priority.

Even if a "low priority" designation could not be made fully on the basis of non-animal testing and exposure considerations, it would be useful for EPA to identify non-animal tests and information that would categorically disqualify a substance from being designated a low-priority compound. For example,

if a compound is mutagenic/genotoxic in a certain set of assays and there is a possibility of human exposure, the compound will very likely receive a "high priority" designation. With this information, companies could independently conduct tests and gather information early in the development and formulation process that would provide some indication of the potential of the compound to be designated high priority.

Overall, the designation of chemicals and classes of chemicals as low-priority compounds, in combination with the development of innovative *in vitro* and *in silico* testing strategies that can be used to demonstrate a low risk potential, presents an opportunity to incentivize the use of low-risk chemicals, develop safer alternative chemicals, and advance toxicological assessment with a greater reliance on predictive toxicology and *in vitro* investigations. This will not only be more humane but will also reduce the regulatory and financial burden of chemical companies.

Comment #4: EPA should clarify the role of existing assessments, such as those from the Integrated Risk Information System (IRIS) and the Internal Agency for Research on Cancer (IARC), in the prioritization process.

Issue: Existing assessments are heterogeneous in their standards and may not make an equivalent case for comparison or for any actions that would be needed under TSCA.

Suggestion: EPA needs to clarify the role in prioritization – and eventually in evaluations – played by already existing human health risk assessments from IRIS, IARC, and other bodies.

Existing assessments will generally be heterogeneous in their scope of coverage, in the data available when they were conducted, and in the methods, processes, and standards for drawing conclusions that were employed by the performing organizations at the time the assessments were completed. Some analyses may be out of date and fail to incorporate critical recent findings and scientific insights. Methods and standards of sufficiency of evidence will differ among organizations, and they will have evolved over ongoing practice even within organizations. For all these reasons, the rigor and dependability of identification of "hazards" will be inconsistent among available analyses.

At the same time, the new statute specifically requires that assessments under the LCSA: "shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science" (US Congress, 2016), and consider "the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and…the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models" (US Congress, 2016).

Moreover, the LCSA states that "the Administrator shall make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence." In short, a process should be as rigorous as can be mounted with the latest assessment methods (US Congress, 2016).

Analyses of exposures will be even more heterogeneous among existing analyses, since methods are less codified and standardized, and scopes of interest will differ even more widely.

EPA's challenge will be to conduct the Pre-Prioritization process – and its consideration of hazard and exposure – in an evenhanded way among candidate substances, so that choices for Initiation are not skewed by reliance on differently reliable or tenable past assessments. Priorities need to be decided on comparably rigorous characterizations of the factors that are driving the selection of a substance.

Certainly, once a substance is chosen as a candidate for designation, the assessments forming the basis of its choice need to be up to the standards of assessments that can support its evaluation through the designation and final assessment processes.

For practical reasons, it is understandable (if not optimal) that initial screening and placement in rough categories be done based on already existing evaluations; it is impractical to put all substances in the Pre-Prioritization process through a new state-of-the-art assessment only to find the few initial candidates for early Initiation. But for any substance in the Pre-Prioritization process that is a clear candidate for Initiation, the past assessments need to be reevaluated and reinterpreted to a common and rigorous standard, – one that is truly comparable across chemical substances, is deemed dependable, and that could form the basis for the further analysis of the substance through the balance of the prioritization process.

In order to meet the objective of ensuring to the public and to stakeholders generally that EPA has thoughtfully evaluated the available data and made science-based decisions on its priorities, it is necessary not only that those decision processes in fact be rigorous, but also that the EPA has publicly set out its process and framework for coming to those judgments. This should be clear not only for chemicals selected for further regulatory attention, but also for the bulk of existing chemicals that will not be among the first chosen for "high priority" or "low priority" designation.

Comment #5: EPA should emphasize and discuss the use of alternatives to animal testing as part of information gathering for data gaps during chemical prioritization and risk evaluations processes.

Issue: Since information gathering is an early part of the prioritization process and, as stated in the prioritization rule, will also encompass information that will be necessary for the risk evaluation, the comments below pertain to both the prioritization and risk evaluation Proposed Rules. In the risk evaluation Proposed Rule (US EPA, 2017b, p. 7,565), EPA states with respect to "Other Statutory Requirements" that:

> [A]mendments to TSCA section 4 require EPA to "...reduce and replace, to the extent practicable, [...] the use of vertebrate animals in the testing of chemical substances..." (ellipsis in original) and to develop a strategic plan to promote such alternative test methods. 15 U.S.C. 2603(h). Likewise, TSCA section 26 requires, to the extent that EPA makes a decision based on science under TSCA sections 4, 5, or 6, that EPA uses certain scientific standards and bases those decisions on the weight of the scientific evidence. 15 U.S.C. 2625(h) and (i). While these requirements are relevant to the risk evaluation of chemical substances, EPA is not obliged to repeat them in this proposed rule. As statutory requirements, they apply to EPA's decisions under TSCA section 6. **Moreover, in contrast to TSCA section 6, Congress has not directed EPA to implement these other requirements ''by rule;'' it is well-established that where Congress has declined to require rulemaking, the implementing agency has complete discretion to determine the appropriate method by which to implement those provisions.** (emphasis added)

It may be a positive sign that EPA considers the requirement to minimize vertebrate animal testing to be implicit in its decisions under TSCA Section 6; however, it should be explicitly stated in the Proposed Rule as a reminder that it is a requirement whenever toxicological data gathering is discussed (as it is in the risk evaluation Proposed Rule; US EPA, 2017b, p. 7,570). In addition, submitters of data should be reminded that this requirement extends to them – "Testing of chemical substances and mixtures" §2603(h)(3)(A) (US Congress, 2016).

Additionally, since EPA did not define "sufficiency of information" in the prioritization or risk evaluation Proposed Rules, it is even more important to explain to manufacturers and third-party risk assessors what types of data EPA will consider to be "sufficient" and what role non-animal tests play in that consideration.

Suggestion: Although it is reasonable that EPA does not explicitly describe a plan for minimizing vertebrate animal testing in full in the prioritization and risk evaluation rules, it would be useful to provide a general framework that emphasizes alternatives to animal testing and discuss the types of non-animal tests that EPA will be recommending (*e.g.*, *in vitro* toxicity testing; computational toxicology; data from structure-activity relationships, high-throughput assays, genomic response assays) and the fact that collection of these data will be encouraged rather than the use of animal data, when possible.

Sufficiency of Information

The emphasis on alternatives to animal testing will be important during the data gathering stages of both the risk evaluation and prioritization processes. The risk evaluation Proposed Rule states that "EPA also generally intends to use its authority under TSCA to require the development of new information, as necessary, prior to risk prioritization" (US EPA, 2017b, p. 7,568). This Proposed Rule also states that "EPA will exercise its TSCA information collection, testing, and subpoena authorities, including those under TSCA sections 4, 8, and 11(c) to develop the information needed for a risk evaluation" (US EPA, 2017b, p. 7,568). Given these statements, it is important that manufacturers and third-party risk assessors understand the types of data that will be considered "sufficient." The current risk evaluation Proposed Rule provides little guidance on sufficiency of non-animal testing methods. Given that these methods are often more efficient and cost-effective, stakeholders will need to know to what extent, and in what context, they will also be considered "sufficient."

Note that the risk evaluation Proposed Rule indicates that if the manufacturers' request is considered "insufficient," EPA will require that the information be made available to EPA within 60 days, and if not submitted by then, the request will be considered withdrawn (US EPA, 2017b, p. 7,569). Given this short timeframe to supply missing information, and the fact that it might not be possible to submit the required information within that timeframe, EPA needs to make clear what information is considered "sufficient" early in the process so that manufacturers can collect the relevant information before requesting a risk evaluation.

The LCSA states that EPA:

> shall reduce and replace, to the extent practicable…the use of vertebrate animals in the testing of chemical substances or mixtures under this title by—(A) ***prior to making a request or adopting a requirement for testing using vertebrate animals*** [emphasis added]…reasonably available existing information, including – (i) toxicity information; (ii) computational toxicology and bioinformatics; and (iii) high-throughput screening methods and the prediction models of those methods; and (B) encouraging and facilitating – (i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals…(ii) the *grouping of 2 or more chemical substances* [emphasis added] into scientifically appropriate categories…(iii) the *formation of industry consortia* [emphasis added] to jointly conduct testing to avoid unnecessary duplication of tests… (US Congress, 2016)

EPA does discuss in the Hazard Assessment section of the risk evaluation Proposed Rule that they will consider "[h]uman epidemiological studies; *in vivo* and/or *in vitro* laboratory studies; mechanistic or

kinetic studies in a variety of test systems, including but not limited to toxicokinetics and toxicodynamics, computational toxicology; data from structure-activity relationships, high-throughput assays, genomic response assays, and ecological field data" (US EPA, 2017b, p. 7,570). We agree that it is important to consider all of these data sources in chemical risk evaluations, and particularly non-animal testing methods in the context of the new TSCA's "reduce and replace" requirement for animal testing (US Congress, 2016). There needs to be more discussion of these types of data in the sections of the Proposed Rules that discuss the sufficiency of information for EPA's prioritization and risk evaluation processes.

According to the LCSA, when requesting any new information, EPA "…shall employ a tiered screening and testing process, under which the results of screening-level tests or assessments of available information inform the decision as to whether 1 or more additional tests are necessary…" (US Congress, 2016). This is consistent with EPA's current approach. However, the requirements to "identify the need for the new information, describe how information reasonably available to the Administrator was used to inform the decision to require new information, [and to] explain the basis for any decision that requires the use of vertebrate animals" (US Congress, 2016), and to reduce and replace vertebrate animal testing, necessitates the increased use of tiered screening and testing and implementation of non-animal methods and approaches.

Approaches to Avoid Animal Testing

Since sufficiency of information begins during the Pre-prioritization process, it might be useful for EPA to provide a set of physical-chemical properties, and *in vitro* and QSAR methods that a company could apply to their chemical that would help them determine if their chemical might be considered high priority, or when they may need to consider some form of animal testing. The aim would be to provide a means to assure the public that chemicals have not been overlooked in the prioritization process simply because of a lack of understanding of possible effects stemming from a lack of testing. The approach would stand in contrast to the REACH approach, for which the standard and mandated set of baseline testing includes a great deal of animal testing and considerable expense. The shortcoming of the REACH approach is that animal testing is done, through the minimum data set mandate, before evaluating which specific tests are necessary to establish adequate protection of public health. A well-thought-out minimum *in vitro* assay and QSAR array, however, would add the benefit of ensuring that indicators of the major toxicity concerns are routinely considered, while leaving animal testing to those cases in which it is absolutely necessary.

In scenarios in which new animal testing is necessary, EPA should consider requesting companies to provide proof that they have explored alternatives to animal testing methods (*i.e.*, *in vitro*, QSAR, read-across, data-waiving), leaving animal testing as a last resort. EPA should also encourage joint data submission (and data generation, if warranted) by companies, as indicated in LCSA §2603(h)(1)(B) (US Congress, 2016). Lastly, EPA should encourage collaboration and data sharing among governmental agencies (internal or domestic) for a given chemical.

In addition to saving the lives of many animals, the use of non-animal testing data (*i.e.*, *in vitro* testing; computational toxicology; data from structure-activity relationships, high-throughput assays, genomic response assays, waiving of studies) will allow for faster data gathering and will make it easier to meet the timeline requirements for the prioritization and risk evaluation processes. Several frameworks have recommended approaches that limit animal testing for these reasons. EPA should consider approaches applied by some of these frameworks, as summarized below.

- Australia NICNAS (new chemicals, IMAP, PEC) – These frameworks specify that the use of animal testing may be reduced through data-waiving. NICNAS only requests animal testing if potential risks cannot be evaluated through other means (Australia NICNAS, 2009, 2016a,b).

- EU REACH Existing CoRAP and New Chemical Registration – REACH encourages data sharing among registrants of the same substance. In addition, REACH encourages and provides guidance documents for the use of read-across, data-waiving, and QSAR to inform all human health and aquatic toxicological endpoints, whenever appropriate (ECHA, 2017a,b). Under the REACH legislation, animal testing is only acceptable as a last resort.

Similar to the Australia NICNAS and EU CoRAP approaches, we suggest that EPA require that companies attempt to fulfill data requirements *via* non-animal testing methods and existing animal studies, and only conduct new animal tests if alternative options are not appropriate or sufficient. In addition to considering the Australia and EU approaches, see suggestions below regarding how EPA could implement this approach.

- EU REACH Annex II notes many accepted scenarios where certain tests may be waived (European Union, 2012a):
  - Waiving a short-term, repeated-dose 28-day toxicity study if there is an existing or planned 90-day study.
  - Waiving *in vivo* skin sensitization and acute dermal toxicity tests if the chemical is corrosive or has a pH value <2 or >11.
  - Waiving reproductive and developmental toxicity tests if the chemical is already a genotoxic carcinogen or a known germ cell mutagen. This approach is likely due to the fact that all carcinogens, mutagens, or reproductive toxicants (CMRs) are regulated the same way in the EU.
  - Waiving a reproductive and developmental toxicity test if the chemical has low toxicological activity (*i.e.*, no adverse effects seen in any of the available tests) and it can be proven from toxicokinetic data that no systemic absorption occurs *via* the relevant exposure pathways.
  - Waiving duplicate carcinogenicity and long-term, repeated-dose studies by using a combined carcinogenicity and long-term, repeated-dose study (OECD Test Guideline 453).
  - Waiving a subchronic, repeated-dose 90-day toxicity study if:
    - A 28-day study already showed that the chemical has severe toxicity worthy of it being classified in Globally Harmonized System of Classification and Labelling (GHS) Category 1 or 2, or
    - The chemical undergoes immediate disintegration and there is sufficient data on all of the degradation products, or
    - The chemical is unreactive, insoluble, not inhalable, and showed no toxicity in a 28-day test.
  - Waiving aquatic toxicity testing in crustacean, fish, and algae if the chemical is highly insoluble.
- Other test waiving opportunities:
  - Waiving a second species (mouse) for carcinogenicity test:
    - An assessment of 202 pesticide evaluations from the EU review program under former plant protection products Directive 91/414/EEC indicated that "the mouse carcinogenicity study contributed little or nothing to either derivation of an acceptable daily intake (ADI) for assessment of chronic risk to humans, or hazard classification for labeling purposes. From a pesticide approval perspective, the mouse study did not influence a single

outcome" (Billington *et al*., 2010). This finding echoes that of the International Life Sciences Institute (ILSI)/HESI Agricultural Chemical Safety Assessment Systemic Toxicity Task Force in 2006, which recommended wholesale "elimination of the mouse carcinogenicity bioassay" (Doe *et al*., 2006).

- Waiving an acute oral toxicity test if a 28-day oral study reported a no observed adverse effect level (NOAEL) >1,000 mg/kg-bw:
  - Authors used the European Chemicals Agency (ECHA) REACH Dossier data set and found 1,256 substances that had both a reliable 28-day oral and acute oral study. They found that lack of subchronic oral toxicity (*e.g.*, NOAEL >1,000 mg/kg-bw) was an excellent predictor of low acute oral toxicity (*e.g.*, lethal dose 50 [LD_{50}] >2,000 mg/kg-bw). The accuracy rate was 98%, with nine cases having an incorrect prediction. However, when the authors looked into these nine cases, they found that the data were misrepresented in eight cases, so there was ultimately only one true case. The predictive relationship holds relatively stable for those subchronic studies in which the NOAEL was >500 (96%) and >300 mg/kg-bw (94%) (Gissi *et al*., 2016).
- Waiving an acute dermal toxicity test if an acute oral toxicity test has been performed:
  - A 2007 publication by the United Kingdom Pesticide Safety Directorate examined unpublished acute oral and dermal toxicity data for 195 pesticide active (technical) ingredients and 3,111 formulated products, concluding that "the dermal acute toxicity study adds little if anything to the database on pesticide active substances" and that a "similar result was indicated for formulated products" (Thomas and Dewhurst, 2007). A 2010 update to this analysis, using a slightly expanded data set of 240 pesticide active substances subjected to acute toxicity testing by both oral and dermal routes, found that in only two cases (0.8%) did substances receive a more severe classification when the dermal route was assessed rather than the oral route (Creton *et al*., 2010). Taken together, these analyses clearly illustrate the limited value of acute toxicity testing *via* the dermal route for the purpose of classification and labeling, and call into question the appropriateness of regulations that continue to require redundant dermal route testing when oral data are already available.
  - EU Biocidal Products Regulation 528/2012 Data Requirement 8.7.3 (Annex II) now provides that "Testing by the dermal route is necessary only if: inhalation of the substance is unlikely, or skin contact in production and/or use is likely, and either the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin, or the results of an *in vitro* dermal penetration study (OECD 428) demonstrate high dermal absorption and bioavailability" (European Union, 2012b).
  - EPA's Office of Pesticide Programs also recently published waiver guidance for acute dermal toxicity based on oral data in its "Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis" (US EPA, 2016). Although this guidance was based on a retrospective analysis of formulations, the study and guidance provide further support for waiving dermal studies based on oral data.

References

Australia, Dept. of Health and Ageing (Australia NICNAS). 2009. "Section II - New Chemicals." In *NICNAS Handbook for Notifiers*. 86p.

Australia, Dept. of Health, National Industrial Chemicals Notification and Assessment Scheme (Australia NICNAS). 2016a. "Human Health Assessments: Inventory Multi-Tiered Assessment and Prioritisation (IMAP) Framework." Accessed https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/human-health-assessments.

Australia, Dept. of Health, National Industrial Chemicals Notification and Assessment Scheme (Australia NICNAS). 2016b. "Priority Existing Chemical assessments." November 30. Accessed at https://www.nicnas.gov.au/chemical-information/pec-assessments.

Billington, R; Lewis, RW; Mehta, JM; Dewhurst, I. 2010. "The mouse carcinogenicity study is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides." *Crit. Rev. Toxicol.* 40(1):35-49. doi: 10.3109/10408440903367741.

Creton, S; Dewhurst, IC; Earl, LK; Gehen, SC; Guest, RL; Hotchkiss, JA; Indans, I; Woolhiser, MR; Billington, R. 2010. "Acute toxicity testing of chemicals - Opportunities to avoid redundant testing and use alternative approaches." *Crit. Rev. Toxicol.* 40(1):50-83. doi: 10.3109/10408440903401511.

Doe, JE; Boobis, AR; Blacker, A; Dellarco, V; Doerrer, NG; Franklin, C; Goodman, JI; Kronenberg, JM; Lewis, R; McConnell, EE; Mercier, T; Moretto, A; Nolan, C; Padilla, S; Phang, W; Solecki, R; Tilbury, L; van Ravenzwaay, B; Wolf, DC. 2006. "A tiered approach to systemic toxicity testing for agricultural chemical safety assessment." *Chem. Res. Toxicol.* 36:37-68.

Embry, MR; Bachman, AN; Bell, DR; Boobis, AR; Cohen, SM; Dellarco, M; Dewhurst, IC; Doerrer, NG; Hines, RN; Moretto, A; Pastoor, TP; Phillips, RD; Rowlands, JC; Tanir, JY; Wolf, DC; Doe, JE. 2014. "Risk assessment in the 21st century: Roadmap and matrix." *Crit. Rev. Toxicol.* 44(Suppl. 3):6-16. doi: 10.3109/10408444.2014.931924.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2012. "ECETOC TRA Version 3: Background and Rationale for the Improvements." ECETOC Technical Report No. 114. 120p., July.

European Commission. 2017. "Threshold of Toxicological Concern (TTC)." Joint Research Centre, European Reference Laboratory for Alternatives to Animal Testing (EU ECVAM). Accessed at https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/background/TTC.

European Parliament; Council of the European Union (European Union). 2012a. "Position of the European Parliament adopted at first reading on 22 September 2010 with a view to the adoption of Regulation (EU) No…/2010 of the European Parliament and of the Council concerning the placing on the market and use of biocidal products and repealing Directive 98/8/EC (Text with EEA relevance)." *Off. J. Eur. Union* C 50 E:74-208. P7_TC1-COD(2009)0076. February 21. Accessed at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52010AP0333&qid=1442247797225&from=EN.

European Parliament; Council of the European Union (European Union). 2012b. "Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (Text with EEA relevance)." *Off. J. Eur. Union* L 167:1-123. June 27. Accessed at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:0001:0123:EN:PDF.

European Chemicals Agency (ECHA). 2017a. "Community rolling action plan." Accessed at https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan.

European Chemicals Agency (ECHA). 2017b. "Registration." Accessed at https://echa.europa.eu/regulations/reach/registration.

Gissi, A; Louekari, K; Hoffstadt, L; Bornatowicz, N; Aparicio, AM. 2016. "Alternative acute oral toxicity assessment under REACH based on sub-acute toxicity values." *ALTEX* doi: 10.14573/altex.1609121.

Health Canada. 2006. "The Health-Related Components of Categorization of the Domestic Substances List (DSL): Approach, Results, and Next Steps." 12p. Accessed at http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/contaminants/existsub/categor/approach-approche-eng.pdf.

Health Canada. 2017. "Approach for the Prioritization of Substances on the Revised In Commerce List." Accessed at http://www.chemicalsubstanceschimiques.gc.ca/plan/approach-approche/icl-lsc-eng.php.

Organisation for Economic Co-operation and Development (OECD). 2016. "Report of the Workshop on a Framework for the Development and Use of Integrated Approaches to Testing and Assessment." ENV/JM/MONO(2015)22; OECD Series on Testing and Assessment No. 215. 154p., July 22. Accessed at http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2015)22&doclanguage=en.

Pastoor, TP; Bachman, AN; Bell, DR; Cohen, SM; Dellarco, M; Dewhurst, IC; Doe, JE; Doerrer, NG; Embry, MR; Hines, RN; Moretto, A; Phillips, RD; Rowlands, JC; Tanir, JY; Wolf, DC; Boobis, AR. 2014. "Alternative acute oral toxicity assessment under REACH based on sub-acute toxicity values." *Crit. Rev. Toxicol.* 44(Suppl. 3):1-5. doi: 10.3109/10408444.2014.931923.

Thomas, HD; Dewhurst, IC. 2007. "What does a dermal acute toxicity study add to the information on a plant protection pesticide?" *Toxicology* 231(2-3):114-115. doi: 10.1016/j.tox.2006.11.040.

US Congress. 2016. "An act to modernize the Toxic Substances Control Act, and for other purposes [Frank R. Lautenberg Chemical Safety for the 21st Century Act]." H.R. 2576. 66p., June 22. Accessed at https://www.congress.gov/bill/114th-congress/house-bill/2576/text.

US EPA. 2009. "The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals." Office of the Science Advisor. EPA/100/K-09/001. 35p., March. Accessed at http://insideepa.com/secure/data_extra/dir_09/epa2009_0514.pdf.

US EPA. 2012. "TSCA Work Plan Chemicals: Methods Document." Office of Pollution Prevention and Toxics. 28p., February. Accessed at http://www.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf.

US EPA. 2015. "Exposing the Missing Link: Advancing Exposure Science to Rapidly Evaluate Chemicals." February 2. Accessed at https://blog.epa.gov/blog/tag/expocast/.

US EPA. 2016. "Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis (Final)." Office of Pesticide Programs, 12p., November 9. Accessed at https://www.epa.gov/sites/production/files/2016-11/documents/acute-dermal-toxicity-pesticide-formulations_0.pdf.

US EPA. 2017b. "Procedures for chemical risk evaluation under the amended Toxic Substances Control Act (Proposed rule)." *Fed. Reg.* 82(12):7562-7580. 40 CFR 702. January 19. Accessed at https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01224.pdf.

US EPA. 2017a. "Procedures for prioritization of chemicals for risk evaluation under the Toxic Substances Control Act (Proposed rule)." Fed. Reg. 82(10):4825-4837. 40 CFR 702, January 17. Accessed at https://www.federalregister.gov/documents/2017/01/17/2017-00051/procedures-for-prioritization-of-chemicals-for-risk-evaluation-under-the-toxic-substances-control.

Wolf, DC; Bachman, A; Barrett, G; Bellin, C; Goodman, JI; Jensen, E; Moretto, A; McMullin, T; Pastoor, TP; Schoeny, R; Slezak, B; Wend, K; Embry, MR. 2016. "Illustrative case using the RISK21 roadmap and matrix: Prioritization for evaluation of chemicals found in drinking water." *Crit. Rev. Toxicol.* 46(1):43-53. doi: 10.3109/10408444.2015.1082973.