Comments from U.S. Academic Scientists on Amended TSCA Implementation

Public Comment to Obtain Input on Risk Evaluation Processes under the Amended TSCA

Docket EPA-HQ-OPPT-2016-0400

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We, the undersigned academic and clinical scientists from universities across the U.S., appreciate the opportunity to provide comments to the U.S. Environmental Protection Agency (EPA) on its implementation of the Amended Toxic Substances Control Act (TSCA) risk evaluation process.

The new amendments to TSCA represent an important opportunity for EPA to update their scientific approaches to evaluating the potential risks posed by industrial chemicals in commerce. Furthermore, EPA's decisions on risk evaluation under TSCA will have implications for future assessments of environmental chemicals more broadly. We welcome EPA's engagement with the public in this process.

We recommend that 1) in the rulemaking for the risk evaluation process EPA should issue a description of the process only; and 2) that EPA specify how it will implement its risk evaluations through a guidance process, which should be separate from the rulemaking. We recommend that within that guidance process EPA state that it will adhere to a transparent process that reflects the most current scientific methods for risk evaluation.

We are making the following recommendations for EPA to incorporate into the risk evaluation that will ensure that EPA guidance aligns with EPA's overall mission of protecting human health and the environment. The outline of our comments are below, followed by further detailed comments on each of these recommendations.

We recommend that as part of EPA guidance, EPA should:

1. **Utilize science in a way that supports timely decision-making about toxic chemicals.**
2. **Incorporate only modern scientific approaches to chemical hazard and risk assessment. In particular:**
   - Treat cancer and non-cancer health endpoints in a scientifically equivalent manner. Do not assume a 'threshold' response exists for non-cancer outcomes unless there is strong scientific evidence to demonstrate a threshold;
   - Assess aggregate risk and cumulative risks to ensure hazard and risk assessment reflect the reality of people's exposures; and,
   - Use science-based defaults and incorporate factors that reflect the range of variability and susceptibility in the population to ensure that risks are not underestimated.
3. **Apply systematic and transparent review methods for evidence evaluation. In particular:**
   - EPA should assess the strength of the evidence using systematic review approaches and not 'weight of the evidence' approaches; and,
   - Do <u>not</u> require knowledge of mechanism by which a chemical exerts its toxicity as criteria for determining toxicity.
4. **Clarify that determination of "unreasonable risk"** can be based on qualitative findings, i.e., any chemical with the documented potential to produce harm (i.e., hazard data) and for which there is also potential for exposure. EPA guidance should reflect that risk, by definition, is the possibility of harm, not the certainty of harm. Numerical estimates of risk should be addressed in the risk management phase *after* a chemical is deemed to be of unreasonable risk.
5. **Match the evidence needed to the decision to be made.** Once a chemical has been designated high priority, meaning EPA has concluded that it "may present an unreasonable risk," EPA should require strong, affirmative data in the risk evaluation phase to conclude that a chemical does not pose an "unreasonable" risk.

EPA needs to expeditiously incorporate the best available science in its methods and approaches and at the same time make timely decisions based on evaluating the strengths and limitations of available data. Delays in decision making come at a cost, as exposures to toxic chemicals mount faster than science accumulates. <u>Further, methods and approaches for each of these recommendations are available and have been demonstrated, so that EPA does not have to reinvent the wheel but can proceed immediately to improving the basis of their decision-making.</u> Below are our detailed comments with references to both methods and findings that can be implemented into the risk evaluation so

that EPA can adequately characterize and address risks from toxic chemical exposures in our children and families and for future generations.

We thank you for considering these comments, and we welcome the opportunity to discuss them further.

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Recommendations for EPA risk evaluation guidance

Recommendation 1. Utilize science in a way that supports timely decision-making about toxic chemicals.

A critical objective of a chemical assessment process should be to identify the highest quality evidence on which to base a decision in the shortest period of time. At the same time, the best science should drive the decisions to be made. Unfortunately, due to the limitations of the regulation of chemicals in commerce under past and amended TSCA, the vast majority of high-use chemicals in commerce have little to no hazard or risk data. This data void will create challenges in evaluating the toxicity of chemicals that are now in our environment and bodies, many of which will persist for generations to come. However, as stated by Sir Austin Bradford Hill, who is recognized as one of the world's greatest medical statisticians, incompleteness of science "…does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time" [1]. EPA must anticipate when data voids will be problematic—through scoping activities and topic expertise—and develop clear, transparent, and consistent rules beforehand about how to handle situations where limited data exist. In particular, EPA should make clear that **absence of data does not mean there is no hazard or risk.** The only appropriate interpretation of a data void is that the hazards and risks are "unknown." In this case, EPA's goal should be to explicitly specify how it will address chemicals with "unknown" toxicity and obtain the data needed to make a scientifically based decision.

To ensure the timely assessment of chemicals EPA should utilize existing knowledge documented in risk or hazard evaluations completed by EPA itself (for example, by the Integrated Risk Information System program) and other government agencies (i.e., National Toxicology Program) or authoritative bodies (i.e., the International Agency for Research on Cancer and the California Environmental Protection Agency's Prop 65 List). These assessments provide evidence summaries and integration of existing data and can provide a critical immediate source of data on recognized hazards.

Recommendation 2. Incorporate modern scientific methods and approaches.

The TSCA amendments provide an opportunity for EPA to update their chemical assessment methods and approaches to incorporate modern scientific knowledge gained in the past several decades. Modern methods and approaches have been recommended in detail by the National Academy of Sciences (NAS) in several landmark publications, *Science and Decisions*, *Phthalates and Cumulative Risk,* and *Review of EPA's Integrated Risk Information System (IRIS) Process* [4-6]. These approaches have been developed and promoted by leading clinical and scientific communities, including doctors and academics in the U.S. and around the world. These publications compile a wealth of expertise and the most current state of the science that can be specifically and efficiently integrated into EPA's chemical assessments. Further, these methods and approaches have already been developed and evaluated, by U.S. government agencies like the National Toxicology Program [7] and the European Union in its implementation of REACH [See: http://ec.europa.eu/environment/chemicals/reach/reach_en.htm]. EPA can utilize this existing knowledge and practice and not have to reinvent the wheel, but instead immediately begin incorporating these best practices and lessons learned from other government bodies. This will maximize efficiency and expedite the implementation process, allowing EPA to focus on other aspects of chemical assessment that warrant further attention.

We highlight below several key recommendations that encompass these most current scientific methods and approaches.

A. Treat cancer and non-cancer health endpoints in a scientifically equivalent manner. Do not assume a 'threshold' response for non-cancer outcomes, unless strong scientific evidence exists to demonstrate that it exists.

The NAS has recommended a unified approach to cancer and non-cancer health assessment, based on understanding of the underlying biology and the lack of a scientific reason supporting the approach to handle the evaluation of these health endpoints differently [4]. For example, under a unified approach EPA would develop risk estimates for non-cancer health outcomes across the spectrum of potential exposures as it does for carcinogens and not assume that a threshold exists for a chemical unless there is strong evidence documenting that one does. Currently, EPA does not consistently develop risk estimates for non-cancer health effects. The NAS has identified this weakness, noting "… current RfD-based risk characterizations do not provide information on the fraction of the population adversely affected by a given dose or on any other direct measure or risk." This is problematic because these qualitative results "…are inadequate for benefit-cost analyses or for comparative risk analyses. MOEs and RfDs as currently defined do not provide a basis for formally quantifying the magnitude of harm at various exposure levels… A probabilistic approach to non-cancer assessment,

similar to how cancer risks are expressed, would be much more useful in risk-benefit analysis and decision-making" [4]. EPA should provide quantitative estimates of the potential risks posed across the range of exposure scenarios, for both cancer and non-cancer outcomes, in order to ensure the true value of preventing or reducing health risks is brought to bear on decision-making under the new TSCA amendments. The feasibility of calculating non-cancer risk estimates has been demonstrated [4, 8-10].

The NAS has also recommended use of a continuous dose-response approach that can default to linear model, specifically recommending "linear conceptual models unless data are sufficient to reject low-dose linearity; and nonlinear conceptual models otherwise" [4] that do not assume a threshold for real world exposure levels and below. With this approach, the default is to assume that no "threshold" or "safe" level of exposure exists below which there is no harm unless strong scientific evidence exists to demonstrate otherwise. Data show that chemicals can increase the risk of many non-cancer health effects (such as reproductive harm and neurological effects) even at very low doses. Further, people are exposed to multiple chemicals simultaneously, many of which can increase the risk of similar adverse health outcomes. Additionally, vulnerabilities in the population may occur due to life stage, genetics, disease status, or other exogenous factors (e.g. poverty), and these vulnerabilities can contribute to adverse health outcomes. Together, these factors have the effect of lowering any potential threshold in the population that may have theoretically existed in a one-chemical-at-a-time exposure model among healthy individuals to levels of exposure that are trivial or insignificant, thereby essentially negating the existence of a "safe" threshold. In general, current science shows that the real world scenario of simultaneous exposures to multiple chemicals at current environmental levels and even at several orders of magnitude below are unlikely to reflect a "safe threshold." This is not to say that thresholds might not exist for some chemicals; it means that within the narrow window between current population exposure levels and slightly lower exposures, such potential thresholds are not relevant to a regulatory decision.

Additionally, EPA should not use Margin of Exposure (MOE) approaches, as these are simply the point of departure (e.g., LOAELs, NOAELs or BMDLs) divided by exposure values and compared to a combination of the uncertainty factors. The MOE is not an actual estimate of risk, as it does not provide any information about the potential risk at various exposure estimates. Rather, it is another version of the "bright line" approach similar to the RfD, which the NAS recommended moving away from [4]. Furthermore, the EPA cannot conduct a benefits analysis using solely the MOE because there is no accompanying dose-response information. We strongly advise against representing the MOE as an estimate of risk and encourage EPA to utilize available analytical methods to develop quantified estimates of risk that can be of use to both risk managers and decision-makers.

B. Assess aggregate risk and cumulative risks to ensure hazard and risk assessment reflect the reality of people's exposures.

People are simultaneously exposed to a multitude of chemicals in the real world, many of which contribute to similar adverse health effects, and they can be exposed to the same chemical through multiple exposure pathways. Not accounting for these well-documented scientific facts inherently biases EPA's assessment, in the direction of systematic underestimation of individual and population risk, which in turn undermines science-based decisions. The federal pesticide law passed in 1996 and the European framework for chemical management (REACH) require aggregate risk assessments. Under these laws, regulators must consider all sources of possible exposure to a chemical even when only considering the risk from any one source of that chemical. Assessing "cumulative exposures," i.e., accounting for the fact that people are exposed to a multitude of chemicals simultaneously, because these exposures can have (an) additive effect(s) on increasing the risk of an adverse health effect, was codified in Food Quality Protection Act (FQPA) and recommended by the NAS in 2008 [5]. This concept was expanded on in *Phthalates and Cumulative Risk* in which NAS recommended that chemicals that contribute to the same common adverse health outcome (not just the same - mechanism) should be considered as additive to the risk. While *Phthalates and Cumulative Risk* focused on the need to do this for phthalates, the NAS did not limit its recommendation to phthalates. For example, it pointed to the fact that lead and mercury can have an additive effect collectively on brain development. Biomonitoring data clearly support that people are exposed to a myriad of chemicals simultaneously—for instance NHANES data has documented that virtually 100% of pregnant women in the U.S. are simultaneously exposed to measurable levels of at least 43 different chemicals [11]. However, current EPA practices fail to consistently aggregate cancer or non-cancer risks over different exposure pathways (inhalation, ingestion, etc.). EPA should incorporate practices to consider aggregate exposures from all relevant pathways to develop risk metrics that are adequately representative of the true risks faced by the population. When data are lacking, EPA should rely on a default approach to account for all chemicals that contribute to the same

common adverse health outcome considered as additive to the risk. The EPA has broached this issue in the past in their draft dioxin risk assessment, which considered the impact of background and cumulative exposure to dioxin-like compounds and the potential impact on low-dose response [12]. We recommend that EPA begin routinely incorporating these considerations on in all their chemical assessments.

C. Use science-based defaults as recommended by the NAS in 2008 and incorporate factors that reflect the range of variability and susceptibility in the population to ensure risks are not underestimated.

The use of defaults is typically a component of risk assessment, as a way to handle the common issue of missing data. Historically, EPA has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. However, science has since evolved and there are now more scientifically-based values that can be used when specific information is missing. For example, science has shown that developmental life stages, including the fetus, infancy, and childhood, are more vulnerable periods of exposure to chemicals. However, typical EPA age-dependent adjustment factors account for other life stages but NOT fetal exposures. This is a critical point to address, as fetal development is the most sensitive time period of one's life and has implications for healthy development and outcomes that can persist into adulthood. EPA should evaluate this rich body of literature to identify the most up-to-date scientific knowledge regarding human variability and susceptibility and incorporate these scientifically-based default values in their assessments when specific data are lacking. For example, the California EPA has developed child-specific risk values for chemicals (i.e., atrazine, chlorpyrifos, lead, nickel, manganese, heptachlor, etc.) that specifically address child-specific routes of exposure and differences in children's susceptibility compared to adults. EPA should review this body of evidence and incorporate these values as appropriate (See: http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds). Furthermore, a default guidance principle should be that animal findings are relevant to humans unless there is sufficient and compelling information to support otherwise.

As described above, risk assessments under a unified approach need to quantitatively incorporate factors that influence the likelihood of disease which is influenced by both personal factors, such as life stage, genetics, underlying disease status, external factors including social and life circumstances (such as poverty and life stress), and exposures to other chemicals. Often times these factors are not addressed quantitatively in risk assessments and even those that are may be insufficient. Newer science demonstrates that the typical safety factor of 10 is insufficient to account for variability due to life stage, genetics, underlying disease status, external stressors that may be due to poverty or other difficult life conditions. It has been proposed that although this susceptibility variable is distributed broadly in the human population, a factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses [4]. For cancer, the NAS found that differences in median versus higher-end response to carcinogens differ by a factor of 25.7.

EPA should also incorporate the real-world experience and perspective of communities who are overburdened by pollution, environmental hazards, and social and economic stressors. These communities are exposed to a disproportionate share of pollution and subsequent adverse health impacts. These communities are often made up of people of color and lower income who are exposed to a multitude of pollution exposures that collectively increase the risk of harm, combined with synergistic effects with other health stressors in their daily lives such as limited access to quality health care [14]. EPA should incorporate guidance for their risk assessments that advance environmental justice and truly protect the whole of public health by reducing environmental exposures and resulting health impacts in these overburdened communities. At a minimum, this includes updating risk assessment guidelines to account for cumulative impacts of multiple exposures and underlying vulnerabilities, in particular by incorporating alternate methods to assess risk that better capture and represent those faced by overburdened and underserved communities.

Recommendation 3. Apply systematic review methods for evidence evaluation.

EPA should assess the strength of the evidence using systematic review approaches and not 'weight of the evidence' approaches. While the term "weight of the scientific evidence" language is used several times throughout the bill (investigating cancer clusters, allocating discretionary exemptions, Administrator decisions in TSCA bill sections 4-6), we recommend that EPA clarify the term, and further, the clarification should be based on systematic review methods as recommended by the House report and NAS. The House Report [Report 114-176] which accompanies the TSCA amendment states that ''[t]he term 'weight of evidence' refers to a systematic review method that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream

of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance…." The NAS published in their 2014 report in review of the EPA IRIS program that the term "weight of evidence" is misunderstood, has 'become too vague and is of little scientific use' [6], and they recommend systematic review approaches.

Systematic review methodology includes developing a protocol for the assessment, identifying evidence, evaluating studies, integrating the evidence, and making systematic and transparent conclusions about the strength of the scientific evidence related to the health hazards of exposure to environmental chemicals. Systematic review methods for environmental health have been developed through both the National Toxicology Program's Office of Health Assessment and Translation (OHAT) and the Navigation Guide methodology. OHAT has published a handbook specifying how to conduct a robust review. Further, a number of case studies using systematic reviews have been published in the literature demonstrating the efficacy and advantages of this approach [15-19]. Further, systematic review methods have been recommended by the NAS as "…an approach that would substantially strengthen" EPA chemical assessments [6]. These modifications are critical improvements that will benefit EPA and help to decrease the time required for completing these assessments.

EPA can take advantage of the experience and tools that have been developed for systematic reviews, including structured searches, publicly available protocols registered online on the database PROSPERO, tools for literature review (Distiller) and data extraction and visualization (HAWC) [20-22].

Furthermore, we recommend that EPA: **does <u>not</u> require knowledge of the mechanism by which a chemical exerts its toxicity as criteria for determining toxicity.** A chemical's mechanism of action or mode of action is not a requirement for science-based decision making. The benefits of hand washing in surgical suites were well described before we understood the underlying mechanism of germs. Similarly, we lack knowledge on the mechanism for the vast majority of pharmaceutical drugs, but this is not a requirement for allowing their use by millions of people. We therefore recommend EPA consistently utilize mechanistic knowledge, when available, but only to upgrade and support evidence of toxicity, NOT to downgrade the strength of evidence.

The principles of systematic reviews should be applied to all evidence streams, including *in vitro* model systems, and predictive modeling of exposure.

It is very important that all evidence streams be evaluated by the same principles for study quality and strength of evidence. Systematic review methods have been developed and applied to human and nonhuman animal evidence streams. While they have not been applied to other evidence streams such as *in vitro* or modeling data, the same methodological concepts can be applied to these evidence streams, and agencies such as the NTP are currently working on drafting these guidelines. Although these have not yet been developed and validated, EPA will be incorporating these data into its hazard assessment and in doing so making decisions as to what it thinks are high and low quality data. The NAS report also encourages EPA to advance methods in this nascent field, stating:

> "Although additional methodologic work might be needed to establish empirically supported criteria for animal or mechanistic studies, an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by EPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream" [6](Chapter 8, page 131).

Given the import of mechanistic studies in the evidence integration phase, we strongly recommend that the criteria EPA will use to judge the quality of mechanistic studies be explicitly stated beforehand in the form of a risk of bias assessment for this evidence stream.

We have also found that this is important for assessing the quality of evidence for proposed hypotheses, models, and mechanisms. For example, during the course of our systematic review of the relationship between PFOA and fetal growth an alternate "reverse causality" hypothesis was proposed—a potential alternate explanation for observational studies demonstrating an inverse association between prenatal exposure to chemicals with renal clearance and fetal growth. We therefore additionally conducted a systematic review for the evidence of an association between fetal growth and glomerular filtration rate (GFR) to assess the strength of the evidence. Through the use of pre-specified evaluation factors of the quality and strength of the evidence, we concluded that there was "inadequate" evidence overall from an evaluation of observational human, non-human, and experimental non-human studies [18]. This demonstrates how proposed hypotheses, models, and mechanisms can be explored through

a systematic evaluation of the evidence to evaluate whether they are sufficiently supported by the existing scientific literature.

Overall, we recommend that EPA incorporate a systematic and transparent method to evaluate the quality of evidence for each evidence stream it considers in its review in order to transparently carry these ratings into the evidence integration step of the review.

Recommendation 4. Clarify that determination of "unreasonable risk" can be based on qualitative findings, i.e., any chemical with the documented potential to produce harm (i.e., hazard data) and for which there is also potential for exposure.

EPA guidance should reflect that risk, by definition, is the **possibility** of harm, not the **certainty** of harm. EPA's guidance should reflect that "unreasonable risk" is related to whether the chemical is a potential hazard and whether there is a potential for exposure, to the entire population or a sub-population. Numerical risk estimates should not be required for determining whether a chemical poses an "unreasonable risk." Rather, numerical estimates of the risk should be addressed in the risk management phase of assessment. Moreover, numerical estimates of risk in the risk management phase should present quantitative estimates of risk for both the general population as well as all relevant susceptible populations.

Recommendation 5. Match the evidence needed to the decision to be made.

Once a chemical has been designated high priority, meaning EPA has concluded that it "MAY present an unreasonable risk," EPA should require strong, affirmative data in the risk evaluation phase to conclude that a chemical does NOT pose an "unreasonable" risk. This is because the health and associated economic consequences of being wrong (i.e., thinking a chemical does NOT pose a risk when in fact it does) are very high. In contrast, there should be a lower burden of proof for determining that a chemical MAY pose an unreasonable risk. As described in recommendation #4, chemicals that do not yet have enough evidence to conclude "known" toxicity (i.e., the evidence of toxicity is "suggestive" or "probable") should NOT be designated as NOT posing an unreasonable risk. This differing level of evidence for different decisions is consistent with modern science based decision-making in clinical sciences, where decisions reflect the extent to which we can be confident that desirable effects of an intervention outweigh its undesirable effects. This approach is also informed by more than a half century of lessons in the regulation of toxic chemicals, including that exposure to toxic chemicals expands over time, for example, from workers to consumers to future generations; the nature of harm expands over time, from one adverse endpoint to many, and that "safe" limits get lower over time, not higher [2, 3]. Lastly, as stated above in Recommendation 1, when chemicals lack data to evaluate toxicity, this cannot be interpreted as an indication of lack of toxicity. This conclusion can be made only when strong scientific data demonstrate lack of toxicity.

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