NATURAL RESOURCES DEFENSE COUNCIL

Comments from the Natural Resources Defense Council

Risk Evaluation Processes under Amended TSCA
Docket EPA-HQ-OPPT-2016-0400

August 24, 2016

The Natural Resources Defense Council ("NRDC") is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our 1.4 million members and online activists. NRDC does not have any financial interest in the topic of these comments.

These comments pertain to risk evaluations under the 2016 Amended TSCA, the Frank Lautenberg Chemical Safety for the 21st C. Act. (TSCA 2016)

The amended version of TSCA, at least on paper, provides EPA with a new opportunity, and obligation, to obtain data and information on chemicals, conduct risk evaluations, and impose a range of restrictions on those deemed to pose an unreasonable risk to human health or the environment. At the same time, the amended law curtails the States' previous authority to take action to restrict chemicals in important respects. Thus, it is doubly-important that EPA does the best job possible to ensure that its work meets the highest standards for evaluating chemicals and protecting the public. While states still retain considerable jurisdiction and authority for addressing the threat of chemicals, there is no question that the previously existing backstop authority of states has been partially diminished. The ostensible "trade-off" between federal and state authority compels EPA to maximize its efforts to protect the public. If the shackles on EPA's ability to take action under TSCA have truly been removed, the agency should embrace its freedom, most importantly by immediately and clearly delineating its independence from the influence of the chemical industry. To a great extent, administration of TSCA is a zero-sum game, with either the chemical industry or the public (and the environment) as the winner or loser. For too long EPA has been hindered, haggled and hounded by the chemical industry. The amended TSCA provides EPA with a golden opportunity to break free of the industry's influence and

implement the law to truly protect the public. We urge the Agency to seize this opportunity. Our comments below (and in the docket pertaining to prioritization) are intended to offer EPA advice on key steps for making the most of the amended TSCA to fulfill its purpose as well as the Agency's overall mission.

USE OF INFORMATION

The Risk Evaluation Process

TSCA section 6(b)(4) directs EPA to promulgate a final rule within 1 year of enactment to establish a process for evaluating the risk of existing chemical substances and determining whether they present an unreasonable risk of injury to health or the environment.

<u>The Risk Evaluation Rule must ensure a robust and comprehensive scoping process that aligns with EPA's mandate to protect vulnerable populations</u>
Section 6(b)(4) also states that EPA shall publish the scope of the risk evaluation to be conducted within 6 months of the initiation of a risk evaluation.

Congress did not intend the scoping process to be a "screening level' or "tiered" risk assessment
Section 6(b)(4)(D) clearly states that the scope should describe what will be considered in the full risk evaluation, and include the following:

- Hazards
- Exposures
- Conditions of use
- Potentially exposed or susceptible subpopulations

Determinations about whether or not there is an unreasonable risk can only be made after the full risk evaluation.

The scope of the risk evaluation must include all exposure pathways experienced by vulnerable populations.
In order to address the differential and increased risk of adverse outcomes experienced by populations who have higher levels of exposure and/or increased susceptibility, the rule must ensure that the scoping process addresses vulnerable populations. The scope must identify these populations, explain the basis for this determination, and describe all of the relevant exposure pathways and chemical uses that contribute to the total exposures experienced by this population. For example, EPA's recent "Initial Assessment and Problem Formulation" documents for three flame retardant clusters did not use appropriate data for fish consumption by subsistence fishers, and also failed to include higher exposures to recycling workers.[1]

In the scope, EPA should consider exposure pathways and uses that contribute to total exposure, even if it does not, or cannot, address such exposures or uses under TSCA.
Significant chemical exposures often come from sources or uses that are under the purview of other agencies or laws. For example, dietary exposure to chemicals may come from chemicals regulated as food additives by the Food and Drug Administration. Or, a chemical being evaluated may be used both

[1] Comments from Earthjustice, Natural Resources Defense Council and Washington Toxics Coalition on Problem Formulation and Initial Assessment Documents for Three Flame Retardant Clusters. (attached) Available: https://www.nrdc.org/sites/default/files/comments-epa-three-flame-retardant-clusters-20151118.pdf

as an industrial chemical and as a pesticide, with the pesticidal use not being subject to the Toxic Substances Control Act. EPA must include such exposures and sources in the scope of its risk evaluations, in order to accurately determine total exposure for the most vulnerable population and make the determination on unreasonable risk.

EPA should solicit public comment on the draft scope before finalizing

Stakeholders have valuable information on hazards, exposures, conditions of use and susceptible subpopulations that can inform EPA's scope. The risk evaluation process should include a public comment period of no less than 90 days on the draft scope.

Avoid delay - The Risk Evaluation Rule must ensure that the evaluation process can be conducted in a timely manner

In addition to the other recommended improvements to the risk evaluation process, under the Amended TSCA, EPA's risk evaluation process should be clear that the Agency will include an analysis of relevant available information available at the time – not future studies promised by regulated industries and polluters that hamstring Agency actions and create regulatory delays. The National Academy of Sciences in its report *Science and Decisions: Advancing Risk Assessment* also highlights that risk assessment processes which delay risk-based decision making can increase health risks by delaying identification and implementation of appropriate measures to eliminate or reduce risk. If EPA must consider all available information it risks being confronted with an endless litany of industry-sponsored studies in efforts to delay the completion of an assessment or to obfuscate the effort. This delay tactic is well-known and should be guarded against by Agency scientific experts and management. On the other hand, moving ahead without undue delay must not mean that EPA rushes to produce risk assessments that are inadequately health protective. Serious public health consequences might follow in the occupational, environmental, and public health communities if decision-making bodies like EPA rely on inaccurate studies or untested mechanistic hypotheses that are later shown experimentally to be incorrect.

Risk Assessment Methodology

To fulfill its mandate to protect the public, including vulnerable populations, as required by Congress under the amended TSCA, EPA's risk evaluation process must incorporate the important improvements laid out in the recommendations of the National Academies in its reports:

- Science and Decisions: Advancing Risk Assessment (NAS 2009)
- Review of EPA's Integrated Risk Information System (IRIS) Process (2014)

EPA, in light of the revisions to TSCA, needs to revisit, revise, and improve its methods for assessing chemicals. The need to amend the agency's policies, including to address the issues outlined below, can largely be done via agency guidance documents, and does not need to be done as part of the rulemaking process required under Section 6(b)(4)(B). In particular, these comments highlight the following critical improvements that EPA must adopt to bring its risk evaluations in step with current science and to support credible policies and practices that will protect human health and the environment, particularly for vulnerable populations:
We are concerned that many of the current guidelines and risk policies/procedures in use by EPA fall short of what is needed to assess and reduce the risk experienced by vulnerable populations. Without

the improvements described below, EPA will continue to underestimate risks that are increasingly shown in the scientific literature to jeopardize public health, particularly for children.

The EPA - charged with protecting our health and safety - will help its mission and improve the scientific foundation of its decisions by making these sensible recommendations part of its standard practice going forward under the Amended TSCA.

Use of systematic review

The Amended TSCA uses the term, "weight of the scientific evidence" several times, despite the National Academies 2014 report that warned against using the term because it is vague, poorly understood, and of questionable scientific relevance (NAS 2014, p. 100). Instead, the NAS recommended a systematic review process as described in the NAS 2014 report, and as being developed and successfully implemented by the National Toxicology Program's Office of Health Assessment and Translation (OHAT). The House Commerce Committee, in its report on the bill that was overwhelmingly passed by the House, stated that the 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 Committee Report stated further: "This requirement is not intended to prevent the Agency from considering academic studies, or any other category of study. The Committee expects when EPA makes a weight of evidence decision it will fully describe its use and methods." This same interpretation of the meaning of the term "weight of evidence" in the legislation was adopted by the leading Senate Democrats who were most involved in the development of the legislation, including Senators Boxer, Merkley, Udall and Markey[2]. Thus there is strong bi-partisan Congressional support for interpreting the term "weight of evidence" as used in the language of the new law to be consistent with the recommendations of the NAS in its 2014 Report.

Systematic review methods for chemical assessments have been developed and implemented through various case studies by the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT), the EPA Integrated Risk Information System (IRIS) program, the University of California San Francisco, and others (Rooney et al 2014; Thayer et al 2014; Birnbaum et al 2013; Woodruff and Sutton 2014).

Included in the systematic review is an evaluation of study risk of outcome-specific bias including selection bias, performance bias, attrition bias, detection bias, reporting bias, and funding bias. EPA's Risk Evaluations should include a comprehensive bias evaluation, reflecting the state of the science for approaches to identifying bias in a systematic and transparent manner. Such an evaluation will be critical to ensure that EPA fully and accurately assesses the multiple potential limitations of a given study. If the systematic framework were to only rely on reporting quality as a measure of study quality, it would favor/bias towards GLP-compliant (Good Laboratory Practice) studies, when, ironically, the GLP-compliant studies may actually be the most likely to be insensitive to health endpoints being measured. "Good Laboratory Practices" is a standard for animal care and data collection required for industry laboratories in response to fraudulent practices documented in the 1970s. Industry-funded studies are required by EPA and FDA to follow so-called Good Laboratory Practices (GLP) standards, which include specified approaches to recordkeeping to facilitate audits and reduce fraud (54 Fed. Reg. 34034 (August

[2] Congressional Record, June 7, 2016, p. S3518.

17, 1989). GLP requirements are not necessarily associated with higher quality research, proper study design or correct statistical analysis (Myers et al 2009). In most cases, GLP studies have not even undergone scientific peer-review and publication. GLP studies are most often designed to identify major toxic effects (apical effects) like cancer. The problem is that major (apical) endpoints will not be predictive or indicate early-warnings of potential toxicity leading to "major" adverse health outcomes. GLP studies don't necessarily use modern methods for evaluating chemicals and aren't designed to grapple with the problems of low-dose exposures, endocrine or hormonal effects, behavioral or learning effects, immunotoxicity, cardiotoxicity, or upstream effects like reduced sperm count or reduced anogenital distance which are predictors of infertility.

If there is inconsistency across studies, and it's the underpowered studies that are showing no effect (null association), than they should be excluded from consideration. However, EPA's Risk Evaluation Process should not eliminate studies that may be underpowered if they do find an effect. This is because an underpowered study that fails to find an effect cannot be interpreted, but an underpowered study that does find an effect makes it even more likely that the effect is real. As an analogy, if you reach into a haystack only a few times (an underpowered study) and don't find a needle (a null study), you cannot conclude whether or not there may be needles in the haystack, whereas if you do find a needle (an underpowered study that finds an effect), then there is at least one needle, and probably more, in the haystack (the effect is real).

Epidemiologic data provides important real-world information in humans

To generate accurate and relevant Risk Evaluations, EPA should use all available information relevant to hazard, exposure, use, manufacturing process, disposal, and other aspects of the life cycle of chemicals. In particular, occupational or environmental epidemiologic studies – cohort, case-control, ecological, and others – can provide very valuable information to inform risk evaluation because such studies capture real-world exposure conditions. As noted in the Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment:

"Specifically, these types of human information provide insight into the effects caused by actual chemical exposures in humans and thus can contribute to problem formulation and hazard/risk characterization. In addition, epidemiologic and human incident data can guide additional analyses or data generations (*e.g.*, dose and endpoint selection for use in in vitro and targeted in vivo experimental studies), identify potentially susceptible populations, identify new health effects or confirm the existing toxicological observations."[3]

For example, epidemiologic data was used quantitatively in the evaluation of risk for methylmercury and lead. Epidemiologic studies of benign or pre-neoplastic lesions are relevant for predicting potential cancer risks (IARC 2006). Epidemiologic studies using molecular biomarkers can provide important evidence of exposure, early or upstream markers of disease, and potential mechanisms of toxicity. Molecular epidemiologic studies can also help identify genetic polymorphisms and other inter-individual differences that may affect individual susceptibility or response to a toxic exposure. An observational study that does not establish controlled exposures, but does provide exposure measurements over a useful range should be considered a valuable source of information, particularly as it provides real-world human dose-response information.

[3] EPA OPP, Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Jan. 7, 2010) http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0851-0004 at pg.7

EXPOSURE ASSESSMENT AND EXPOSURE MODELS

Accurate assessment of aggregate exposures

In its 2016 Draft Guidelines for Human Exposure Assessment, EPA acknowledges the importance of evaluating aggregate exposures of contaminants of concern that may impact an individual, or community, via multiple pathways of exposure (EPA 2016). Unfortunately, the Agency's assessments often fail to accurately assess aggregate exposures. If there are insufficient data to quantify aggregate exposures, a default should be used to account for these exposures. EPA's Risk Evaluation Process needs to ensure that when exposures can occur via multiple pathways (i.e. inhalation and oral), the combined exposure is included in any risk analysis, from the start. Exposures add up, and different exposures may add up to an unsafe level—that is the fundamental premise behind an aggregate assessment. So each risk from one route individually must be considered together in context with all other exposures. All types of cancer risks must be, at least, added together. This is the reality for many children that may be exposed to formaldehyde, for example, through combustion from wood heating, cigarettes smoked in the home, emissions from plywood and particle board furniture and flooring, paints and varnishes used in homes and schools, carpets, and emissions from formaldehyde-treated permanent press fabrics including clothing and bedding (ATSDR 2015). These exposures may be in addition to formaldehyde emissions from power plants, incinerators, or refineries if the children live near any of these industrial sites (ATSDR 2015). EPA's continued failure to consider these realities results in environmental injustices.

Accounting for cumulative exposures and effects

EPA's Risk Evaluation Process should provide a clear directive to factor cumulative exposures from different chemical and non-chemical stressors into risk evaluations wherever possible. EPA acknowledges that there are additional significant health threats for individuals and communities facing: multiple sources of contaminants; multiple contaminants that together pose a larger health threat because they act through a common pathway or impact similar health endpoints; and the combined impact of contaminant exposure with social stressors. Scammell et al. (2014) describe how tools including indexes, maps, and combined approaches can provide an important first step towards evaluating background exposures and delineating the cumulative context for an assessment (Scammell et al 2014). Tools like CalEnviroScreen[4] from the California Office of Environmental Health Hazard Assessment, and US EPA's EJScreen[5] tool can provide information on existing background contamination that should be factored into chemical evaluations. Demographic analysis, including socioeconomic status, should also be considered. Recent studies document that children who experience greater early-life adversity have increased susceptibility to the toxic effects of chemicals[6]; populations with increased susceptibility must be considered under the law as vulnerable populations.

EPA should use default factors to account for the known additional risk coming from these types of exposures where they cannot be more explicitly quantified. Cumulative exposures and their associated

[4] http://oehha.ca.gov/calenviroscreen/report/calenviroscreen-version-20
[5] https://www.epa.gov/ejscreen
[6] Stein, L.J. et al., 2016. Early childhood adversity potentiates the adverse association between prenatal organophosphate pesticide exposure and child IQ: The CHAMACOS cohort. Neurotoxicology, 56, pp.180–187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27474229

health threats often fall disproportionately on disadvantaged and underserved communities where there are more sources of hazardous chemicals and psychosocial stressors.

Use of accurate exposure models

EPA recognizes the importance of the rigorous evaluation, and validation, of exposure models and algorithms (including traditional and high-throughput models and algorithms) to ensure that there is sufficient predictive capacity to meet the objectives of the risk assessment (EPA 2016). In conducting risk evaluations under amended TSCA, OCSPP must use the best-available methods and reject the use of models and algorithms that do not meet the criteria described in EPA's 2016 Draft Guidelines for Human Exposure Assessments and are found not to align with observational or experimental data.

VULNERABLE AND SUSCEPTIBLE POPULATIONS

Consideration of exposures to vulnerable populations and underserved communities

EPA must quantitatively include the burden of exposures to vulnerable and susceptible populations, and underserved communities. In a population, there are important differences and variations among individuals that affect their likelihood of developing a disease or other health problem after a chemical exposure. First, there are variations in exposure so some people are exposed to higher levels of a chemical than others, depending on where they work or live, or what they eat. Second, there is variability due to differences in the population due to factors such as age and genetic makeup, diet, socioeconomic status, or pre-existing disease. This variability results in some individuals being more susceptible to developing a health problem.

Scientific findings over the last decade clearly indicate that the prenatal period is a particular window of susceptibility to multiple adverse health outcomes in addition to cancer, including neurodevelopmental and respiratory effects (Grandjean and Landrigan, 2014; Pinkerton and Joad 2000).

All of these conditions can converge to create a terrible injustice for communities of low socio-economic status, communities of color, and particularly children from these communities. For example, the highest human levels of harmful flame retardants in the general population have been found in young children from communities of low socio-economic status and communities of color (Quirós-Alcala et al, 2011). This is believed to be primarily from exposures to dust that has been contaminated from household products containing organohalogen flame retardants.

Although updates have been made to the Exposure Factors handbook to provide additional values to account for unique exposures to children and the developing fetus, including placental transfer, breastmilk and object-to-mouth ingestion, considering these routes of exposure has not yet been incorporated into risk assessments performed by many of the EPA programs. They should be included as part of risk evaluations by OCSPP under the amended TSCA.

Another example of inadequately accounting for exposures to populations of concern is the consideration of dietary intake of bioaccumulative chemicals, which would be much higher for indigenous and some low-income communities that rely on subsistence fishing or traditional foods such as marine mammals.

This issue was elevated in the National Academies report, Science and Decisions, "small chemical exposures in the presence of existing disease processes and other endogenous and exogenous exposures can have linear dose response relationships at low doses" (NRC 2009, p. 158), suggesting that there may be no 'safe' exposure level below which negligible or no health effects will occur (a "threshold" of response).

Considerations of differences in susceptibility

EPA's Risk Evaluations must quantitatively address the fact that people may be highly variable in their susceptibility to a hazardous agent depending on genetic factors including sex, polymorphisms in the genes involved in metabolizing the agent in question, dietary factors including cross-reactivity or metabolic competition with medications, hormonal state, liver function, and immune system capacity. Age and life-stage at time of exposure can have a strong influence on individual susceptibility (discussed above).

Risk Assessors with the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA) reviewed the literature on differential susceptibility to carcinogens and non-carcinogens based on age and life stage. As a result of this review, OEHHA derived age adjustment values for carcinogens which include the prenatal period (Cal EPA 2009) and increased the default intraspecies UFs for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity (Cal EPA 2008). At a minimum, EPA should start with Cal EPA's age adjustment values and intraspecies UFs for incorporating age/early life susceptibility.

In its Science and Decisions report (NAS 2009), the committee noted that for cancer assessments differences in median versus higher-end response to carcinogens differ by a factor of 25. It would be appropriate for EPA to quantitatively address this level of variability by multiplying all cancer risk estimates by a factor of 25 in its Risk Evaluations for an early-tier assessment of most cancer-causing chemicals, unless a greater level of detail is needed. Where data are available on population variability in susceptibility, EPA can support the use of larger uncertainty factors or increase the strength of epidemiologic or other evidence of harm.

In its Risk Evaluations, EPA should clearly address and communicate the uncertainty and variability inherent in a risk assessment—including uncertainty and variability in the measurement of chemical releases into the environment, environmental fate and transport, exposure assessment, dose-response assessment, and risk characterization (NAS 2009).

EVALUATING RISKS – CANCER AND NON-CANCER

Risk estimates and linearity presumptions for both cancer and non-cancer endpoints

In its Risk Evaluations under the Amended TSCA, EPA should generate quantitative risk estimates for both cancer and non-cancer endpoints, rather than the inaccurate and unprotective 'threshold' presumption that EPA now applies to non-carcinogens. Generating risk estimates for both cancer and non-cancer endpoints will make the calculations of health benefits more accurate and more supportive of health-protective regulations.

EPA's current approach to evaluating risks for any health effects other than cancer is to assume that there is a 'safe' exposure level below which negligible or no health effects will occur (a "threshold" of

response). This is in stark contrast to the practice for carcinogens that assumes there is no threshold unless shown otherwise. The NAS (2009) recommended moving away from the MOE and RfD/RfC approaches because neither provide meaningful information about the potential risk at a given exposure – that is, they are not quantifiable risk estimates.

Newer science is finding many examples of chemicals that increase the risk of various non-cancer health effects - such as reproductive harm and neurological effects - at low doses, without any scientifically-identifiable threshold (Grandjean et al, 2008; Grandjean and Landrigan 2006, 2014). The NAS (2009) noted many differences in the population due to age, disease status, nutrition, etc, and the fact that people are exposed to multiple chemicals, make it very unlikely that a threshold exists across a diverse population, even if a threshold were to be established in an individual. This means that there may be no "safe" exposure across a diverse human population for many chemicals. For this reason, the Science and Decisions report recommended that a conceptual model be developed that is "from linear conceptual models unless data are sufficient to reject low-dose linearity; and nonlinear conceptual models otherwise" (NAS 2009, p. 144).

Extend non-threshold assumptions to all carcinogens, not just mutagens

Under Amended TSCA, EPA should treat non-mutagenic carcinogens similarly to mutagenic carcinogens, presuming for both that there is no safe level of exposure (i.e. non-threshold toxicants with dose-response linearity). In addition, increased susceptibility of in utero and early life-stages and sensitive populations should be assumed for both mutagenic and non-mutagenic carcinogenic agents, as is done by California EPA (Cal EPA 2009).

EPA must exercise extreme caution when relying on mutagenicity data to dismiss the potential for a mutagenic mechanism of cancer. Such data are notoriously unreliable. For this reason, the 2006 Preamble to the Monographs from the International Agency for Research on Cancer (IARC) states that, "Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio et al., 1992) " (IARC 2006). Such studies have questionable reliability and should not be used to move away from health-protective default assumptions or other evidence of mutagenicity.

See for example the debate between industry-sponsored scientists and the EPA and academic experts over whether or not there is a threshold of 'safety' for cancer risks from arsenic in drinking water (Heath 2014; Schmidt 2014). EPA's assessment, based on very strong evidence from National Toxicology Program rodent feeding studies, along with published scientific studies, has been challenged by industry-sponsored scientists that were ultimately able to hold up the EPA assessment, and thus stall regulatory decisions by EPA and FDA that should have tightened clean up and exposure limits and reduced harmful exposures (Heath 2014; Schmidt 2014). "Meanwhile the debate over low-dose health risks from arsenic will likely continue on two fronts: how to apply mechanistic findings from animal and in vitro research to human responses, and how to address fundamental uncertainties in the human data." (Schmidt 2014) Amended TSCA must enable EPA to move forward with health-protective Risk Evaluations, to break this industry-contrived log jam that favors polluters, leaving the rest of us to pay with our health.

PREVENTING UNCERTAINTY FROM UNDERMINING RISK EVALUATIONS

The standard of evidence should support health-protective regulations

Under the revised TSCA, EPA should be able to make health protective decisions, in a timely manner, based on strong evidence. This should include the ability to rely on data demonstrating an adverse effect – even a single study. Amended TSCA should support EPA decisions that are health-protective, avoiding false negatives (type I errors) and errors that lead to the underestimation of risk. For that reason, data demonstrating an adverse effect – even a single study in a single test species if the study is well-designed and well-conducted, or reliable read-across information – should be sufficient to support regulatory decisions and actions to protect human health. For example, EPA's minimum criteria for animal data for a reproductive or developmental hazard are data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species (U.S. EPA, 1996; U.S. EPA, 1991).

Use of science-based default uncertainty factors

EPA should make clear that health-protective assumptions are the default assumption in all cases and under all conditions; EPA should provide clear criteria for departing from defaults particularly where they lead to weakened health protections. When replacing a particular default with a particular alternative assumption for a particular chemical, EPA's Risk Evaluations should provide an explanation and quantify how using a default versus the chosen alternative assumption affects the decisions that protect the environment and public health (Janssen et al 2012). Establishing, "clear criteria for departure from defaults can provide incentives for third parties to produce research" that can reduce uncertainty and, over time, result in more accurate assessments. Importantly, by using the established defaults more often, EPA's Risk Evaluations could avoid "the delay entailed by having to re-examine generic information with every new risk assessment" (NAS 2009, p. 191).

In its Science and Decisions report, the committee recommended that the EPA and other agencies update default factors and assumptions based on the best current science, identify where unstated or implicit assumptions are used, and replace these with explicit assumptions. These recommendations push the EPA to, "continue and expand use of the best, most current science to support or revise its default assumptions," (NAS 2009, p. 207) which make the assumptions stronger, rather than reducing reliance on them. At a minimum, EPA should consider using California EPA's age adjustment values and intraspecies UFs for incorporating age/early life susceptibility, as discussed above (Cal EPA 2008, 2009).

Use of AOP information should be used to help identify chemical risks, not to dismiss them

When evaluating Adverse Outcome Pathway (AOP) information or mechanistic hypotheses, we expect regulatory agencies to require rigorous testing and validation before using incomplete data sets to downgrade the categorization of chemical carcinogens or weaken risk estimates. The use of mechanistic/AOP information should be interpreted relative to the plausibility of the health-protective default factor, and not as if the alternative to the proposed AOP were no toxicity mechanism at all.

EPA's Risk Evaluation must also address whether differences in mechanistic events among species are truly qualitative rather than quantitative in nature. For quantitative differences, the guidelines should also require information on the range of parameter variability in exposed humans so that sensitive subpopulations are not ignored in these categorizations. Animal data or other evidentiary data of hazard

potential should not be dismissed for AOP suppositions that are incompletely understood or poorly supported. Hurried and unbridled acceptance and use of mode-of-action to weaken Agency actions and reduce health protections would be contrary to the agency's obligations under revised TSCA and would fail to protect the public.

While data from high-throughput mechanistic studies present serious challenges, these data may also be used to move a chemical to a category of higher hazard. For example, these data can be used to group or cluster chemicals such that all the chemicals sharing common structure or mechanistic properties can be presumed to share common adverse outcomes, even for those chemicals lacking toxicity testing. For example, the non-polymeric organohalogen flame retardants (OFRs) include some chemicals that have clear risks for serious adverse outcomes, and others that are inadequately tested. However, when screened using standard QSAR and read-across screening tools, all were shown to be either of high concern or toxic (Eastmond et al 2015). Importantly, addressing the whole class of chemicals together will avoid regrettable substitutions.

Leaving out structurally or chemically related but untested chemicals in a regulatory decision is treating them as if they were non-toxic. The NRC (2009) identified this problem in its Science and Decisions report, "Agents that have not been examined sufficiently in epidemiologic or toxicologic studies are insufficiently included in or even excluded from risk assessments. Typically, there is no description of the risks potentially posed by these agents in the risk characterization, so their presence often carries no weight in the decision-making." (NRC 2009, p. 193) This is a problem that can be corrected by EPA going forward.

Thank you for the opportunity to present these comments. We would be happy to discuss them with you at your convenience. Please contact Daniel Rosenberg, Senior Attorney , Natural Resources Defense Council at drosenberg@nrdc.org or 202-289-6868. We look forward to working with you.

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