Children's Health Protection Advisory Committee

Chair:

Barbara Morrissey, MS
Washington State Department of Health
P.O. Box 47846
Olympia, WA 98504-7846
(360) 236-3368
barbara.morrissey@doh.wa.gov

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Administrator Scott Pruitt
United States Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460

RE: Protecting Children's Health under Amended TSCA

Dear Administrator:

The Children's Health Protection Advisory Committee (CHPAC) supports the continuing efforts by the Environmental Protection Agency (EPA) to protect children from harmful exposure to environmental chemicals. EPA has new opportunities under the 2016 Frank L. Lautenberg Chemicals Safety for the 21st Century Act (hereinafter 'amended TSCA'), which Congress passed with broad-based stakeholder and bipartisan support. The Act contains many positive changes including the requirement to use a risk-based safety standard for new and existing chemicals and greater ability for the Agency to require chemical information from manufacturers. It also requires EPA to specifically protect sensitive subpopulations including infants, children, and pregnant women in safety evaluations.

Children's unique behaviors and physiology can increase their risk of exposure to and health outcomes from chemicals in commerce. Because impacts to a child's health carry forward into adulthood, protecting this subpopulation benefits the entire population. In this letter, CHPAC responds to a request from the Agency for guidance on how risk evaluations mandated under the amended TSCA should address children as a potentially exposed and susceptible subpopulation (Attachment A). CHPAC wishes to emphasize that in addition to infants, children and pregnant women; other lifestages and subpopulations are important to consider under amended TSCA, including pre-conception, adolescence, lactating-women, and populations whose traditional diets or other indigenous practices may increase risk for toxicant exposure.

In implementing the amended TSCA, *CHPAC recommends* that the EPA give highest priority to chemical substances potentially of concern for children's health; to substances that children are likely to encounter; and to substances detected in biomonitoring studies of children, women of reproductive age, cord blood, or pregnant women.

In addition to our recommendations below, we would like to call your attention to two previous letters[1] from CHPAC that pertain to EPA's approach to children's exposures to environmental chemicals. Amended

[1] CHPAC, Evaluating existing and new chemicals for potential adverse impacts on children (July 2007) https://www.epa.gov/sites/production/files/2014-05/documents/7312007.pdf
CHPAC, Criteria for identifying chemicals of concern for children (including prenatal and preconception exposures. (March 2011). https://www.epa.gov/sites/production/files/2014-05/documents/chpac_chemicals_letter_3.pdf.

TSCA provides EPA the authority to act on several of those recommendations and CHPAC continues to support those recommendations that pertain to the amended TSCA.

Charge 1: Recommend methods and approaches for children's risk evaluation under amended TSCA

Use a Lifestage Approach

CHPAC recommends that EPA use lifestage analysis when evaluating impacts of chemicals on children under TSCA. A lifestage approach incorporates key age-related characteristics into risk assessment including children's unique and evolving anatomy, physiology, toxicokinetics, diet, environment, and behaviors. The unique characteristics of key developmental stages are important to address because these characteristics can influence exposure estimates, levels of concern, and the dose-response relationship used in a risk evaluation.

The lifestage approach includes a range of developmental stages from conception through fetal development, infancy, and adolescence. Standardized age groups corresponding to distinct lifestages have been developed for use in risk assessment at EPA and have been proposed for use globally (EPA, 2006; Cohen Hubal et al., 2014).

Children's diets differ significantly from adults. Breastmilk and infant formula reconstituted with tap water are unique sources of nutrition for the first four to six months of life and are sources of infant exposure to environmental chemicals. The transfer of contaminants from maternal blood to breastmilk has been well documented (Haraguchi, 2009; Sundström, 2011). Children also drink more water than adults. Formula fed infants have higher exposure to water contaminants (Kahn and Stralka, 2009). A preschool child's diet is much less varied, and they consume more milk, fruit, and vegetables, than most adults. These dietary differences place children at increased risk of ingesting toxic chemicals and pesticides present in these foods (American Academy of Pediatrics Council on Environmental Health, 2012; Landrigan and Etzel, 2014).

Behavioral factors can magnify a child's toxic exposure. Young children actively explore their environments by crawling on the floor engaging in oral exploration and hand-to-mouth activity. These behaviors increase their oral intake of toxic substances including those that accumulate in house dust (Johnson-Restrepo et al., 2009; Mitro et al., 2016).

Children's immature metabolic pathways typically make them more vulnerable to chemical toxicity due to their reduced ability to detoxify and excrete chemicals. For example, an infant's increased absorption and decreased excretion of manganese puts them at greater risk of manganese's neurotoxic effects compared to adults (Erikson, et al., 2007; Neal and Guilarte, 2013). Infants may also be at lower risk if their immature metabolic system is unable to convert a chemical to its toxicologically active form.

In response to Charge 1, CHPAC reviewed several chemical risk evaluation approaches and lifestage frameworks that address the unique characteristics of children from conception through adolescence. In addition, we searched for useful approaches and tools to use in children's exposure and risk evaluations. Potential frameworks, tools, and data sources are described in Attachment B.

In general, *CHPAC recommends* that EPA use the Agency's 2006 framework for lifestage assessment (EPA, 2006) along with its 2016 draft agency guidance on human exposure assessment (EPA, 2016) to guide its risk evaluations for children under amended TSCA. The World Health Organization framework (World Health Organization, 2006) is also a useful supplementary compendium of children's unique physiology, behaviors, and exposure pathways. Regarding when

to assess children's exposure in chemical evaluations, we highlight the decision tree presented at an OECD workshop in 2013 and believe is a useful starting point (OECD, 2014).

It is clear from our review that EPA has been a leader in developing state-of-the-art practices for incorporating children's unique behaviors and physiology into chemical risk assessment. We commend the Agency for this effort.

Screen for Developmental Toxicants in TSCA Risk Evaluations

Testing for developmental toxicity is critical to understanding the potential impacts on early lifestages. We encourage EPA to use its authority under amended TSCA to require chemicals to be screened for developmental toxicity especially if exposure to women of child-bearing age and children is likely. Further, the duration of observations must be sufficiently long to capture adverse outcomes across the life course. Developmental toxicity testing is critical because impacts on fetal development are not reliably predicted or characterized by toxicity studies in adult animals.

While standard *in vivo* developmental toxicity tests are invaluable tools, they are subject to limitations. The developmental toxicity methods are not comprehensive in covering all developmental toxicity outcomes and most do not contain observations for latent adverse outcomes that emerge across the life course (Makris et al., 2011). These limitations can be minimized by incorporating the methods developed by the National Toxicology Program (NTP), such as the modified one generation reproduction study design that greatly increases the power to detect post-natal developmental effects (Foster, 2014; Foster, 2017).

We encourage EPA to follow the recommendations of the National Research Council in 2007 (NRC, 2007) and the National Academies of Sciences, Engineering, and Medicine in 2017 to incorporate, where appropriate, new technologies and approaches to screening for developmental toxicity. These include *in vitro*, *in silico*, non-mammalian models such as zebrafish, and genomics and other "-omics" technologies. These could enhance traditional screening approaches such as structural alerts from modeling and "read-across" from chemical analogs. These new tools also have potential to broaden understanding about mode of action and human relevance of developmental toxicity observed in laboratory animals.

Use Biomonitoring to Inform Exposure Assessment

Biomonitoring data can be highly useful in developing estimates of chemical exposure and in understanding aggregate chemical exposure from multiple sources and pathways. CHPAC encourages EPA to use biomonitoring information from women of reproductive age and young children whenever it is available. Since children under six years of age are not regularly included in existing NHANES[2] protocols, EPA could commission or support biomonitoring studies specifically addressing chemical exposures of young children. Further, EPA should require manufacturers to submit biomonitoring data whenever available.

Charge 2: Priorities for new methods and approaches to improve children's risk evaluations under TSCA

CHPAC recognizes that there are many existing approaches that can be implemented to appropriately incorporate children's unique risks into safety evaluations. There are also many needed areas for further development. Here we highlight three critical areas for Agency focus: children's exposure information, age-appropriate safety factors, and methods for identification and characterization of developmental toxicants.

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[2] The National Health and Nutrition Examination Survey (NHANES) conducted by the CDC.

Children's Exposure Information

Greater accuracy and more detailed information in the area of actual exposures of children would improve the risk evaluation process. Four types of data would be especially helpful:

- Chemical use data including down-stream uses of chemicals in products encountered by children. *CHPAC recommends* that EPA work with industry (e.g., processors) and other stakeholders to understand the uses of chemicals in consumer and children's products.
- More current data for "Children/toddler" activity patterns. *CHPAC recommends* EPA review, for example, the European Scientific Committee on Health and Environmental Risks opinion on chemicals ingested by children from toys that included a literature review of child-specific exposures (European Commission, Scientific Committee on Health and Environmental Risks, 2016).
- Aggregate information on children's exposure to a substance under all conditions of use, including exposures that are not regulated under TSCA, such as cosmetics, food and pesticides. *CHPAC recommends* that EPA use its full authority, including its new administrative order authority, to gather any needed information about uses of these substances to fill data gaps, including information on aggregate exposures. Failure to consider aggregate exposure through all routes of exposure and products may significantly underestimate a child's total exposure and allow an unreasonable risk.
- *CHPAC recommends* that EPA research and identify biomarkers of exposure and effect in children (e.g., measures of DNA-methylation, surveillance of urine levels of toxicants or metabolites), use NHANES multi-year data for exposure and health outcomes assessment, and develop validated methods to detect and estimate the concentration of chemicals likely to appear in the bodies of children and pregnant women and in breast milk.

Age-Appropriate Safety Factors

CHPAC recommends that for risk evaluations on existing chemical substances, as well as reviews of new chemical substances and assessments of significant new uses of existing chemical substances, EPA should apply age-appropriate safety factors for children. Some frameworks to consider include:

- 10x safety factor used under the Food Quality Protection Act (FQPA).
- Age-dependent adjustment factors used to protect children in cancer risk assessment (EPA, 2005).
- Child-specific reference doses developed by the California EPA (OEHHA, 2015).

While a full ten-fold additional margin may not be needed in all cases, the specific consideration of any unique sensitivities of early lifestages should explicitly be considered. An age-specific safety factor should be the "default" approach, especially where uncertainties and data gaps in children's exposure or vulnerabilities exist. Filling these data gaps will require more research and information regarding a chemical's predicted or observed pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion data) and mechanism of action during early-lifestages (Felter et al., 2015).

Improved Methods to Identify and Characterize Developmental Toxicants

There are a variety of *in vivo* models that can be used for developmental and reproductive toxicity. While informative, these methods require high numbers of laboratory animals and may still miss important information about potential developmental harm for many substances. Many new approaches and tools have been developed (e.g., Tox21 program) that could be helpful in identifying and characterizing developmental toxicity of a new or existing chemical substance.

CHPAC recommends that EPA focus on development of a tiered approach to screening and testing for developmental toxicity. There may be the opportunity to design appropriate and cost-effective testing strategies based on sufficient understanding on the target organ and developmental period of susceptibility or based on physiologically-based pharmacokinetic modeling (Neal-Kluever et al.,

2014; Knudsen et al., 2011). Our recommendation aligns with specific language in the amended TSCA to increase reliance on testing assays that are more economical, rapid, and do not require laboratory animals.

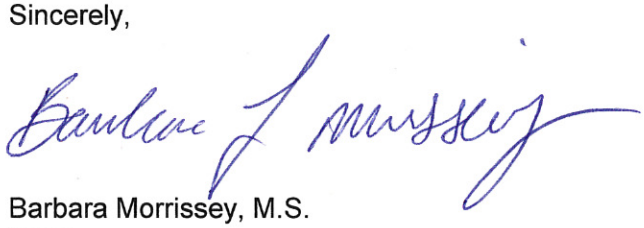
Regarding developmental toxicants with an endocrine disrupting mechanism of action, EPA should consider the principles outlined by the Endocrine Society regarding translation of endocrine findings from animal research to human health (Gore et al., 2015). If not already done, EPA should also update EPA's *in vivo* developmental toxicity assays to incorporate the changes suggested by the NTP's research program (Foster, 2014; Foster, 2017) and made to OECD 421 and 422 related to endocrine-related outcomes.

Charge 3: Identification of experts who may be consulted for further help in addressing or developing specific risk evaluation approaches or methodologies for potentially exposed or susceptible subpopulations

In response to this charge, CHPAC suggests a two-step nomination process: 1) identification of individuals with appropriate knowledge, expertise, and background based on tangible evidence, such as peer-reviewed publication; and 2) contacting potential individuals to inquire if they are willing to be nominated and to identify any potential conflicts of interests that might prevent them from providing unbiased advice to the EPA. *CHPAC recommends* that EPA consult with individuals with expertise in hazard, exposure, or risk assessment with a focus on children. Experts on other specific endpoints (e.g., developmental or reproductive toxicity, early-life carcinogenicity, respiratory development, breast milk exposures, childhood activity patterns) could be consulted for further help in development of risk evaluation approaches. In addition, CHPAC continues to be available to address specific questions from the Agency.

In summary, CHPAC supports a strong Agency effort to protect children from harmful exposure to chemicals evaluated under TSCA. We believe that the approaches outlined above will improve evaluation of new and existing chemicals for unintended impacts on sensitive early lifestages. We appreciate this opportunity to comment and we thank you for your commitment to safeguarding children's health.

Sincerely,



Barbara Morrissey, M.S.
Chair

cc: Wendy Cleland-Hamnett, Office of Chemical Safety and Pollution Prevention
Ruth Etzel, Office of Children's Health Protection
Brenda Foos, Office of Children's Health Protection
Tala Henry, Office of Pollution Prevention and Toxics
Jeff Morris, Office of Pollution Prevention and Toxics

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Attachment A

Amended Toxic Substances Control Act (TSCA) Potentially Exposed and Susceptible Subpopulations Workgroup
US EPA Children's Health Protection Advisory Committee (CHPAC)
Charge
December 13, 2016

Background

The Frank L. Lautenberg Chemicals Safety for the 21st Century Act, amends the Toxic Substance Control Act. Among other things, the new TSCA requires EPA to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulations identified as relevant to the risk evaluation under the conditions of use. The amended TSCA Definitions in Section 3(12) states: "the term "potentially exposed or susceptible subpopulation" means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers or the elderly. In the Lautenberg Act susceptible subpopulations are to be considered in the evaluation of new and existing chemicals, as well as several other provisions.

EPA has been working to gather existing Agency guidance that is useful in developing the potentially exposed or susceptible subpopulations approaches needed under the amended TSCA and will provide this information to the workgroup for consideration. The approaches will be incorporated in a publically available guidance on risk evaluation. It is anticipated that this guidance will be updated as the available science and methods continue to develop.

Charge

CHPAC's expert advice is requested on the topic of addressing children's environmental health, as it relates to potentially exposed and susceptible subpopulations, in the risk evaluations mandated under the amended TSCA. In particular recommendations regarding:

- Currently available data sources, methods, approaches, and descriptions for best considering potentially exposed or susceptible subpopulations, especially related to children,
- Identifying and prioritizing the children's health risk evaluation approaches or methodologies in need of further development, and
- Identification of experts who may be consulted for further help in addressing or developing specific risk evaluation approaches or methodologies for potentially exposed or susceptible subpopulations.

Attachment B

Potential Frameworks, Methods/Tools and Data Sources for lifestage approach for risk evaluation

Author and publication year	Strengths (or highlights)	Source
Frameworks		
EPA 2006	• Conceptual framework that provides an important overview of considerations for evaluating early-life exposures and subsequent outcomes. • Developmental lifestages considered include preconception, prenatal, infant, child and adolescent. • Incorporates timing and dosimetry concepts as unifying factors for exposure and hazard components of the analysis.	U.S. Environmental Protection Agency. (2006) A framework for assessing health risks of environmental exposures to children. National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/093F.
EPA 2016	• Draft document integrating many elements from *EPA 2006* into guidance for conducting human exposure assessment. • Section 4.4 has helpful guidance on identifying lifestages, vulnerable groups and populations of concern for exposure assessments.	EPA. Guidelines for Human Exposure Assessment, Peer review draft, January 2016.
WHO 2006	• Chapter 7 provides a similar framework as *EPA 2006*. • Other chapters supply detailed data on children as related to: biological differences, susceptibilities associated with specific developmental stages, important exposure pathways, and unique characteristics of children that affect exposure.	World Health Organization. Environmental Health Criteria 237. Principles for evaluating Health Risks in Children Associated with Exposure to Chemicals. ISSN 0250-863X.

Attachment B cont'd

Potential Frameworks, Methods/Tools and Data Sources for lifestage approach for risk evaluation

Author and publication year	Strengths (or highlights)	Source
E.A. Cohen Hubal et al., 2014	• Summarizes a WHO review of exposure-related characteristics of age groups from birth to 21 years old. • Proposes standardized age groups for use in risk assessment and to guide standardized data collection on these characteristics by governments and health researchers.	Identifying important life stages for monitoring and assessing risks from exposures to environmental contaminants: Results of a World Health Organization review. Cohen Hubal et al., 2014 (http://www.sciencedirect.com/science/article/pii/S0273230013001530)
OECD 2014	• Decision tree on when to assess children's exposure in chemical evaluations as presented at a 2013 OECD workshop (See Figure 4).	OECD. Report on OECD workshop on children's exposure to chemicals. Series on Testing and Assessment. No. 209 ENV/JM/MONO (2014) 29.
Halifax Project (2012 -2015)	• Produced key insights into biological processes involved in cancer which may help EPA use mechanistic data to refine their chemical carcinogen assessments. • This framework may help EPA screen for carcinogenic potential with Tox21 tools. • Smith et al. suggest a systematic way to identify, organize, and summarize mechanistic information as part of the carcinogen evaluation process in IARC reviews. • Participating scientists have also published on the importance of evaluating a chemical's potential to disrupt key biological defense mechanisms such as inflammation suppression, anti-growth signaling, and immune suppression of proliferating cells (*Carcinogenesis*, Suppl 1, 2015).	• Smith et al. (2016) Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis *Environ Health Perspect* 124(6):. https://ehp.niehs.nih.gov/15-09912/ • Assessing the carcinogenic potential of low dose exposures to chemical mixtures in the environment: the challenge ahead. Volume 36, Supplement 1; *Carcinogenesis*. June 2015. • More on the Halifax Project http://www.gettingtoknowcancer.org/environmental_exposures.php

Attachment B cont'd

Potential Frameworks, Methods/Tools and Data Sources for lifestage approach for risk evaluation

Author and publication year	Strengths (or highlights)	Source
Methods/Tools		
OECD 2013	• Contains an overview of methods and tools used by various entities for child-specific hazard and exposure assessments. • The compilation originates from an international (OECD) survey of governments and other groups regarding practices for assessing special risks to children from environmental contaminants.	Organization for Economic Co-operation and Development (OECD). Assessing the risks of Chemicals to Children's Health: an OECD-wide Survey. Series on Testing & Assessment No. 192. ENV/JM/MONO(2013)20
EPA 2014	• Contains important details in Sections 2.2-2.4 and 3.3 for modeling an emerging pathway of concern for young children: house dust. • Provides a helpful framework for addressing this pathway for chemicals likely to contaminate house dust or indoor air.	US EPA, Child-Specific Exposure Scenarios Examples, 600/R-14/217F, September 2014, www.epa.gov/ncea.
EPA 2005	• Guidance on using age-dependent adjustment factors to account for higher cancer risk when mutagenic chemical exposure occurs in early life. • Recognized that early life exposure to agents that affect hormone systems, impair immune function, or induce developmental abnormalities in tissues may increase cancer risk, but insufficient data were available and analyzed to support a recommendation.	EPA. (2005) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf

Attachment B cont'd

Potential Frameworks, Methods/Tools and Data Sources for lifestage approach for risk evaluation

Author and publication year	Strengths (or highlights)	Source
RIVM Netherlands	• CONSEXPO consumer exposure (computer) model. • Helps estimate indoor exposures (via inhalation, dermal or oral routes) to substances from consumer products (*e.g.,* paint, cleaning agents, and personal care products).	The Netherlands, National Institute for Public Health and the Environment. ConsExpo Web. Revised October 2016.
OEHHA California 2015	• Guidance oriented towards airborne contaminants and assessment of multiple contaminants at a given site. • Provides child-specific methods for estimating contaminant concentrations in breast milk based on modelled or empirical data of chemical in soil, air, garden vegetables/crops, or water. • Also supplies a method for estimating bioaccumulation in angler-caught fish and in breast milk based on chemical properties, metabolism and excretion. • Modifying factors for risk such as social determinants of health are discussed qualitatively. • Child-specific reference doses incorporate age-related adjustment factors for cancer.	Air Toxics Hot Spots Program Guidance Manual for the Preparation of Health Risk Assessment, March 2015.
ECHA REACH R.15 2016	• Describes tools and models used to conduct consumer exposure assessment for chemicals in consumer materials. • Appendix R.15.3 compares computer tools for estimating consumer exposure.	ECHA. Guidance on Information Requirement and Chemical Safety Assessment, Chapter R. 15: consumer exposure assessment. July 2016 https://echa.europa.eu/documents/10162/13632/information_requirements_r15_en.pdf

Attachment B cont'd

Potential Frameworks, Methods/Tools and Data Sources for lifestage approach for risk evaluation

Author and publication year	Strengths (or highlights)	Source
Data sources		
EPA 2011	• Provides data by age-group for early lifestage exposure assessments including intake of water, food, and breastmilk; ingestion of soil and dust; and frequency of hand-to-mouth and object-to-mouth activity.	Exposure Factors Handbook: 2011 Edition. EPA/600/R-09/052F.
RIVM Netherlands	• Site provides numerous factsheets with many of the default assumptions in the CONSEXPO model. • They include data sources relevant to children's exposure, *e.g.,* estimates of mouthing time for children by age in months and frequency of contact with different types of children's products.	• http://www.rivm.nl/en/Topics/C/ConsExpo/Fact_sheets • "Oral exposure of children to chemicals via hand-to-mouth contact" (2007) http://www.rivm.nl/dsresource?objectid=bac32ade-dfb8-459e-b02c-a6f589d0683e&type=org&disposition=inline • "Children's Toys Fact sheets" (2002). http://www.rivm.nl/dsresource?objectid=b6c07cb6-9bc2-4c50-ba19-cf1f7af39b5c&type=org&disposition=inline