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Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act

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Docket

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ABBREVIATIONS AND ACRONYMS

CDR	Chemical Data Reporting
COU	Conditions of Use
CRA	Cumulative risk assessment
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
HI	Hazard index
IPCS	International Programme on Chemical Safety
MIE	Molecular initiating event
MOA	Mode of action
MOE	Margin of exposure
NEI	National Emissions Inventory
NRC	National Research Council (now the National Academies of Sciences, Engineering, and Medicine)
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OLEM	Office of Land and Emergency Management
ONU	Occupational non-user
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
PESS	Potentially exposed or susceptible subpopulation(s)
(Q)SAR	(Quantitative) structure-activity relationship
RAF	Risk Assessment Forum
RPF	Relative potency factor
SACC	Science Advisory Committee on Chemicals
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
WHO	World Health Organization

1 INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act (TSCA), the Nation's primary chemicals management law, in June 2016. Through the amended statute, the U.S. Environmental Protection Agency (EPA or the Agency) is required, under TSCA section 6(b), 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 potentially exposed or susceptible subpopulation(s) (PESS) identified by EPA as relevant to the risk evaluation, under the conditions of use (COU). TSCA section 6(b)(4)(A) requires EPA to consider PESS, which are subpopulations "who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly" [15 U.S.C. § 2602(12)]. Several reports from the National Research Council (NRC)—including the 1994 report *Science and Judgment in Risk Assessment*, the 2008 report *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*, and the 2009 report *Science and Decisions: Advancing Risk Assessment*—have highlighted the importance of understanding the combined risk from multiple environmental stressors (NRC, 2009, 2008, 1994). These reports, as well as legislation such as the Food Quality Protection Act of 1996 (FQPA), have driven, in part, EPA's evolving work on cumulative risk assessment (CRA).

TSCA does not explicitly require EPA to conduct CRAs. However, TSCA does require that EPA, when conducting TSCA risk evaluations in 3 to 3.5 years [15 U.S.C. § 2605(b)(4)(G)], consider the reasonably available information, consistent with the best available science, and make decisions based on the weight of the scientific evidence [15 U.S.C. § 2625(h), (i), (k)]. EPA recognizes that for some chemical substances undergoing risk evaluation, the best available science may indicate that the development of a CRA is appropriate to ensure that any risks to human health and the environment are adequately characterized. TSCA also gives the Agency the authority to consider the combined risk from multiple chemical substances when there is an interrelated group of chemicals or mixtures [15 U.S.C. § 2625(c)]. Under TSCA section 26(c), EPA may take "any action authorized" under any provision of TSCA, in accordance with that provision with respect to a category of chemical substances or mixtures of chemical substances. Because individuals are co-exposed to many chemicals in their daily lives, some of which may have the same health effects, EPA believes that in some cases the best approach to assess risk to human health may be to look at the combined risk to health from exposure to multiple chemicals.

EPA plans to solicit comments on this draft document from the Science Advisory Committee on Chemicals (SACC) and the public, which may be used in the future as part of the development of a more detailed TSCA CRA Framework and in support of future CRAs.

2 SCOPE

EPA has developed this draft principles document providing an overview of TSCA and defining CRA within the requirements of TSCA. This draft document is not a framework nor a guidance document on the process for conducting CRAs; rather, it focuses on principles of CRA for chemical substances. There are multiple definitions of the term "cumulative risk assessment." This draft principles document primarily relies on the definition in EPA's *Framework for Cumulative Risk Assessment* that defines CRA as "an analysis, characterization, and possible quantification of the combined risks to health and/or the environment from multiple agents and/or stressors" (U.S. EPA, 2003). This could include evaluation of multiple chemical substances that jointly exert a common toxic effect. Exposures to these chemicals could result from multiple exposure pathways and through multiple routes of exposure.

Further, this draft CRA principles document does not address cumulative impacts, which refer to the total burden—positive, neutral, or negative—from chemical and non-chemical stressors and their interactions that affect the health, well-being, and quality of life of an individual, community, or population at a given point in time or over a period of time (U.S. EPA, 2022). Cumulative impacts, which may or may not include toxicologically defined risk, would be considered in other types of assessments such as a cumulative impact assessment. EPA's Office of Research and Development (ORD) is actively working to strengthen the scientific underpinning for assessing cumulative impacts. EPA's Office of Pollution Prevention and Toxics (OPPT) may consider cumulative impacts in the future and as appropriate data, methods, and guidance are available.

3 PROPOSED PRINCIPLES OF CRA UNDER TSCA

In the development of this draft principles document, EPA has relied substantially on existing CRA-related work by EPA's Risk Assessment Forum (RAF), EPA's Office of Pesticide Programs (OPP), the Organisation for Economic Co-operation and Development (OECD), the European Commission, and the World Health Organization (WHO) and International Programme on Chemical Safety (IPCS), including

- *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986)
- *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (U.S. EPA, 1999)
- *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000)
- *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001)
- *Guidance on Cumulative Risk Assessment of Pesticide Chemicals that Have a Common Mechanism of Toxicity* (U.S. EPA, 2002a)
- *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003)
- *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures, and Effects: A Resource Document* (U.S. EPA, 2007)
- *State of the Art Report on Mixture Toxicity* (European Commission, 2009)
- *Risk Assessment of Combined Exposure to Multiple Chemicals: A WHO/IPCS Framework* (Meek et al., 2011)
- *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose* (U.S. EPA, 2016)
- *Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals* (OECD, 2018)
- *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (NRC, 2008)

These documents provide the scientific foundation for the proposed TSCA CRA principles described in Sections 3.1 to 3.7.

3.1 Populations for Consideration

As required under section 6(b)(4) of TSCA, EPA issued a final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) (hereinafter "Risk Evaluation Rule"), in July 2017, which provides the procedural requirements for EPA's risk evaluations, including for chemicals designated as High-Priority Substances and chemical substances subject to a Manufacturer-Requested Risk Evaluation. Pursuant to TSCA section 6(b) and the Risk Evaluation Rule, risk evaluations must include both hazard and exposure assessments for the chemical substance in order to characterize any risk that the substance may pose under its COUs to ecological and human populations. At this time, EPA proposes to focus its CRA efforts on human health, not on ecological taxa. This is because established Agency cumulative risk guidance documents are available to support human health, but not yet ecological CRA. The Agency may, in the future, develop an approach for conducting CRA under TSCA for ecological taxa.

Under TSCA, the key human populations considered include the general population and PESS such as workers and occupational non-users (ONUs), consumers and consumer bystanders, fenceline communities, and tribal populations. TSCA section 6(b)(4)(A) requires EPA 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 to PESS [15 U.S.C. § 2605(b)(4)(A)]. As noted previously, PESS are subpopulations "who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical

substance or mixture, such as infants, children, pregnant women, workers, or the elderly" [15 U.S.C. § 2602(12)]. TSCA does not statutorily define what constitutes "greater susceptibility" or "greater exposure," thereby providing flexibility to EPA to consider both chemical and non-chemical stressors when identifying PESS. As OPPT continues to develop its approaches for CRA, OPPT will take into consideration PESS in hazard, exposure, and risk methods and results.

3.2 Stressors for Consideration

Under EPA's RAF description of cumulative risk (U.S. EPA, 2003), the term "stressors" refers to both chemical and non-chemical stressors. Non-chemical stressors may include radiological, biological, and other physical stressors; lifestyle conditions; and socioeconomic stressors. Non-chemical stressors may directly or indirectly affect health adversely, increase vulnerability to chemical stressors, or have exposure-response modifying effects on other chemical stressors (U.S. EPA, 2022, 2003). Few methods have been developed that allow for a quantitative analysis of cumulative risk from combined exposure to chemical and non-chemical stressors. However, EPA ORD is actively working to strengthen the scientific underpinning for assessing cumulative impacts, including impacts from non-chemical stressors within ORD's FY23-26 Strategic Research Action Plans (U.S. EPA, 2022). Until Agency-wide guidance and established methodologies have been developed, EPA does not expect to quantitatively evaluate non-chemical stressors when conducting CRAs under TSCA. In contrast, Agency-wide guidance and methodologies for quantitatively evaluating cumulative risk from combined exposure to multiple chemical substances and/or mixtures are available (U.S. EPA, 2000, 1986). Therefore, at this time for purposes of TSCA risk evaluations, EPA is proposing to focus its quantitative CRA efforts on the evaluation of chemical substances. However, if EPA identifies potential non-chemical stressors that may be reasonably anticipated to impact cumulative risk estimates from chemical substance exposure, then EPA may include a qualitative discussion of the non-chemical stressors and their potential impact on a case-by-case basis until such time that peer-reviewed, Agency-wide guidance for quantitative evaluation of non-chemical stressors is available.

3.3 Sources, Pathways, and Routes of Exposure Considered

If EPA determines in a TSCA section 6(b) risk evaluation that the manufacture, processing, distribution in commerce, use, or disposal of a "chemical substance," or that any combination of such activities presents an unreasonable risk of injury to health or the environment, then TSCA section 6(a) requires EPA to regulate the manufacture, processing, distribution in commerce, commercial use, or disposal of the "chemical substance" to the extent necessary so that the "chemical substance" or mixture no longer presents such risk [15 U.S.C. 2605(a)].

TSCA section 6(b)(4)(D) requires EPA to identify the hazards, exposures, conditions of use, and the PESS the Administrator expects to consider in a risk evaluation. TSCA section 3(2) excludes from the definition of "chemical substance" "any food, food additive, drug, cosmetic, or device (as such terms are defined in Section 201 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321]) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device" as well as "any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. 136 et seq.]) when manufactured, processed, or distributed in commerce for use as a pesticide." EPA may not in a risk management rule under section 6(a) directly regulate non-TSCA uses; however, incidental effects of 6(a) regulation on non-TSCA uses are not prohibited by TSCA's chemical substance definition. Additionally, as described in EPA's Risk Evaluation Rule (see Procedures for Chemical Risk Evaluation Under the Amended TSCA, 33726 Fed. Reg. 33735 (July 20, 2017), "[t]he potential risks of non-TSCA uses may help inform the Agency's risk determination for the exposures from uses that are covered under TSCA (*e.g.,* as background exposures that would be accounted for, should EPA decide to evaluate aggregate exposures)" 82 FR at 33735. For example, EPA may take into

account exposure to multiple chemical substances resulting from non-TSCA uses and/or naturally occurring sources, should the Agency decide to conduct a CRA.

Relevant pathways and routes of exposure to a person from various sources will be considered for a CRA conducted under TSCA. Potentially relevant routes of exposure include inhalation, oral, and dermal routes. Possible pathways of exposure to a chemical substance may include, but are not limited to, ingestion of contaminated groundwater, inhalation of volatile compounds emitted in an indoor environment, or dermal exposure to products during use. The determination of which exposure routes and pathways to include in a CRA requires consideration of the toxicological endpoint(s) selected on the basis of toxicologic similarity (discussed further in Section 3.4.1) and the likelihood of single or multiple routes or pathways to result in co-exposure within a relevant timeframe (discussed further in Section 3.4.2). For example, if a toxicologic effect is only observed following exposure via certain routes, then it may be appropriate to evaluate only those routes of exposure as part of the CRA. Similarly, unless various pathways of exposure result in co-exposures within a relevant timeframe, they may not be considered as part of a CRA.

3.4 Chemical Grouping Considerations

Under TSCA, the term "category of chemical substances" is broadly defined as "a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification" [15 U.S.C. § 2625(c)(2)(A)]. This broad definition provides EPA with the flexibility to group chemical substances for inclusion in a CRA based on defined criteria hereinafter referred to as a "cumulative chemical group."

Available EPA (2016, 2003, 2002a, 2000, 1986), OECD (2018), and World Health Organization/ International Programme on Chemical Safety (WHO/IPCS) (Meek et al., 2011) guidance outlines two principal considerations for grouping chemicals for inclusion in a CRA, (1) toxicologic similarity, and (2) evidence of co-exposure over a relevant timeframe. Consistent with available guidance, toxicological similarity and evidence of co-exposure will be the principal considerations when determining chemical groupings for CRA under TSCA. Consideration for determining toxicologic similarity and co-exposure over a relevant timeframe under TSCA are discussed in Sections 3.4.1 and 3.4.2, respectively. The establishment of a cumulative chemical group for purposes of CRA will be developed using a narrative that clearly characterizes the strengths and uncertainties of the evidence of toxicological similarity as well as the potential co-exposure for each chemical substance in the cumulative chemical group considered.

3.4.1 Toxicologic Similarity

As described in EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (mixtures guidance) (U.S. EPA, 2000), evidence for toxicological similarity exists along a continuum and includes, but may not be limited to (from most to least informative/restrictive with regard to data and knowledge requirements) the following:

- identical toxicodynamics (*i.e.*, same molecular initiating event [MIE], downstream key events, and apical outcome; an example of this is a group of chemical substances that have a common toxic metabolite);
- similar toxicodynamics (*e.g.*, different MIE, convergent toxicodynamic pathways leading to a common downstream effect, and same apical outcome);

- shared syndrome (*e.g.*, phthalate syndrome (NRC, 2008), T (tremor)-syndrome or CS (choreoathetosis and salivation)-syndrome elicited by Type I and II pyrethroids, respectively (U.S. EPA, 2011));
- shared apical outcome (MIE and other key events unknown);
- effect on the same target organ;
- structural similarity; and
- similarly shaped dose-response curves in comparable toxicity studies.

Empirical evidence from mixture studies may also provide support for establishing cumulative chemical groups for CRA. Generally, EPA is unlikely to conduct CRAs under TSCA when the reasonably available information is limited to an effect on the same target organ as this approach may introduce too much uncertainty to risk estimates.

A variety of toxicodynamic information can be used to inform the degree of toxicologic similarity of a cumulative chemical group. The quality, quantity, and relevance of this information must be discussed as part of the weight of evidence narrative. EPA's mixtures guidance (U.S. EPA, 2000) and other international guidance (OECD, 2018; Meek et al., 2011) describe examples of data sources that may provide evidence of toxicological similarity, including:

- ***In vivo* studies:** Evidence of toxicologic similarity may come from both animal studies (guideline and non-guideline) and human studies. Animal studies may provide evidence of the same target organ, shared apical outcome or syndrome, similar toxicokinetics (including potency of metabolites and metabolites common to multiple chemicals), and/or the same mode of action (MOA). Analyses of data from *in vivo* (as well as *ex vivo* and *in vitro*) studies may also provide evidence of similarly shaped dose-response curves (*e.g.*, linear or S-shaped), which can provide support for proportional toxicodynamics. Human studies, including controlled human exposure and epidemiologic studies, may provide additional evidence of a common target organ, shared apical effect or syndrome, as well as provide evidence of species concordance and human relevance of effects observed in animal models.
- ***Ex vivo* studies:** Organ and tissue studies may provide information about shared toxicodynamic events and pathways or evidence of the effect on the same target organ. In some cases, these studies may also provide information about shared toxicokinetics (absorption, metabolism, etc.), shared metabolites, or apical endpoint (*e.g.*, eye irritation, skin sensitization).
- ***In vitro* studies:** Cell-based bioassays and other *in vitro* high-throughput screening techniques (*e.g.*, ToxCast and Tox21 testing programs, three-dimensional tissue models, mechanistic or metabolic assays, etc.) may inform assumptions about toxicologic similarity by providing information on mechanism and/or MOA, as well as target organ effect data. In addition, *in vitro* (as well as *in vivo*) mixture studies can provide empirical evidence for toxicologic similarity when observed dose-response data are consistent with dose additive predictions.
- ***In silico* studies:** *In silico* tools may provide predictive evidence that supports toxicologic similarity. For example, structure-activity relationship and quantitative structure-activity relationship (*i.e.*, [Q]SAR) modeling can provide predictive hazard information on the target organ, apical outcome, or MOA. Similarly, molecular docking approaches can be used to predict interactions between a chemical and protein, which may inform a chemical's MOA. These tools may also help characterize structural similarity.

3.4.2 Co-exposure Considerations

In addition to toxicological similarity, inclusion and grouping of two or more chemical substances into a CRA requires consideration of whether exposure to multiple chemical substances occur at toxicologically significant concentrations and over relevant and/or overlapping timeframes (*e.g.*, during

a critical window of development). When determining relevant timeframes of exposure the duration or frequency that is relevant to effects of concern should be taken into account. Relevant timeframes may include, but may not be limited to, exposure to multiple chemicals at the same time, exposure to persistent chemicals at different times that may bioaccumulate in the body or have persistent effects from exposure to multiple chemicals at different times. Relevant timeframes of exposure can vary by factors including, but not limited to, chemicals, lifestages, or effects.

Characterizing co-exposure requires consideration of the source of chemical exposure, populations impacted by exposure, and the possible varying routes and pathways of exposure. Additionally, the magnitude, frequency, and duration of exposure to multiple chemical substances influence the potential for co-exposure to occur within a given period of time (*e.g.*, 24 hours, 1 year, or a lifetime); where the magnitude of exposure is the level of exposure dictated by the physical and chemical properties of the chemical substance and exposure scenario, frequency is the number of exposure events over a given time, and duration is the length of exposure time per event (OECD, 2018; U.S. EPA, 2001).

Because chemical substances are assessed for risk under the COUs, the magnitude of exposure is calculated through individual exposure scenarios that consider the source, pathway, route, media, frequency, and duration of an exposure and should be considered against the concentration of toxicological significance. The frequency of exposure can be given as the predicted number of days in which an exposure occurs in a year or the number of exposure events in a given timeframe such as per day, month, or year. Examples of high frequency exposure events could be daily ingestion of drinking water whereas infrequent exposure events may be a consumer painting their home. The duration of exposure is the length of time in which a person is exposed to the chemical substance of interest and can vary in length, from short-term (*e.g.*, use of bathroom cleaner) to long-term (*e.g.*, continuous emissions from home flooring). Relevant exposure patterns incorporating frequency and duration should be matched with relevant adverse effects when conducting a CRA (U.S. EPA, 2001). For example, if an adverse effect is observed in animals after a single, acute exposure, then it would be most appropriate to estimate cumulative risk based on acute or single-day exposure estimates. Alternatively, if an adverse effect is observed after sub-chronic or chronic exposure, then cumulative risk should be estimated based on corresponding relevant timeframes of exposure duration. An exception to this may be for certain developmental effects that occur after an acute or short-term exposure takes place during a window of susceptibility during pregnancy. In such cases, the acute or short-term developmental exposure may be considered more relevant than a lifetime of exposure and may be considered as part of a chronic assessment (U.S. EPA, 2002b, 1991).

Taken together, frequency and duration impact the potential for co-exposure to multiple chemical substances. Specifically, continuous long-term exposure to a chemical substance may increase the likelihood of co-exposure to another chemical substance simultaneously. In contrast, an infrequent short-term exposure to a chemical substance may not result in a co-exposure to another chemical substance where the relevant timeframe of exposure may be defined as the time in which exposure to multiple chemical substances is occurring simultaneously (OECD, 2018; U.S. EPA, 2001). Some examples of co-exposures that may occur simultaneously could include use of a product containing multiple chemical substances, simultaneous use of multiple products containing different chemical substances, or inhalation of ambient air containing multiple chemical substances. Exposures to multiple chemical substances can occur at different times, and the timeframe in which all exposures have occurred can still be considered a relevant timeframe of co-exposure depending on factors such as biological persistence of the relevant chemical substances in an organism and the relevant toxicity endpoint of interest (OECD, 2018).

For example, physical and chemical properties of a chemical substance can impact the biological persistence of the chemical substance and, therefore, the relevant timeframe of exposure. Even if exposures to multiple chemical substances do not occur simultaneously, biologically-persistent chemical substances may remain in the body during exposure to another chemical substance leading to co-exposure of both chemical substances. Short, intermittent exposures are less likely to result in co-exposure over a defined timeframe, unless there is evidence of persistence in the body. Additionally, co-occurrence may not occur for certain chemical substances that are rapidly eliminated from the body—even with frequent repeated exposure (OECD, 2018; U.S. EPA, 2001). However, it may still be appropriate to consider these chemical substances for inclusion in a CRA if frequent, albeit non-overlapping exposure, contributes to a subchronic or chronic health effect.

Some data sources that can provide evidence of co-exposures within relevant timeframes to individuals and populations considered under TSCA include the following:

- **Biomonitoring data:** Biomonitoring can be used to both identify individuals and populations exposed to chemical substances and quantify internal doses of chemical substances. Biomonitoring data sets can also indicate the presence of multiple chemical substances within persons of interest (*e.g.*, pregnant women) at the time of sampling and serve as evidence of co-exposure to multiple chemical substances of interest. However, there are limitations with using biomonitoring data in a CRA. Quantifying an intake dose from biomonitoring data can be complicated and requires many assumptions and complex modeling. Although biomonitoring data may provide evidence that co-exposure is occurring within a relevant timeframe leading to the presence of multiple chemical substances in the human body, it cannot be used to isolate the sources, routes, or timeframes of each chemical exposure. Additionally, robust biomonitoring data may not be widely available for all chemical substances undergoing TSCA risk evaluation.
- **Product formulation data:** Co-exposure to multiple chemical substances can occur through exposures from the presence of multiple chemical substances in a single product (*e.g.*, plastic products containing multiple phthalates). The presence of multiple chemical substances in a single product can be determined through process information or production formulation data provided by the manufacturer of a product or through a safety data sheet. Supporting data on multiple chemical substances in products or articles may also come from completed chemical risk assessments, including Agency for Toxic Substances and Disease Registry's Toxicological Profiles, which often present the prevalence of chemical substances in certain products available on the U.S. market and relevant usage patterns.
- **Survey of consumer behavior demonstrating co-use:** Co-exposures to two or more chemical substances from multiple COUs result from what is commonly referred to as the co-occurrence of use (or co-use) and/or co-location of exposure sources. In other words, a determination of co-exposures is dependent on evidence of co-use and/or co-location. In the context of TSCA, co-uses typically refer to scenarios from which an individual (*e.g.,* consumer) may be exposed to two or more COUs such as when a spray and powdered cleaner are used concurrently to clean a bathtub. For consumer co-exposures, which are primarily dependent on co-use data that are rare in the literature, studies that report continuous emissions of chemicals even when products are not in use (*e.g.*, formaldehyde emission from unlit candles, flame retardants that are released from upholstery via dust over time) can be used to determine which products consumers and bystanders may be co-exposed to via specific rooms or space of use and periods of time.
- **Workplace monitoring:** In industrial and commercial settings, multiple chemical substances may be manufactured, processed, or used at the same site or location leading to co-exposures of individuals to various chemical substances. It is important to consider all chemical substances used for that industry sector or site, their potential hazard, associated worker activities, and

exposure durations. When available, monitoring studies may provide evidence of exposure to multiple chemical substances via the workplace environment. Additionally, other site-specific information may provide evidence of the exposure potential for multiple chemical substances such as reviewing all the chemical substances reported to EPA programs (*e.g.*, Chemical Data Reporting [CDR], Toxics Release Inventory [TRI], National Emissions Inventory [NEI]) for a single site. For occupational co-exposures, information on a facility's chemical formulation, manufacturing, processing, and uses may be qualitatively considered to determine the potential of workers and ONUs to be co-exposed to multiple chemicals and through multiple COUs within an occupational exposure scenario.

- **Facility releases:** Emission of multiple chemical substances from a single facility or multiple facilities within a certain geographical proximity can lead to co-exposures to humans. Similar to the assessment of exposure in the workplace, site-specific information reported to EPA programs (*e.g.*, CDR, TRI, NEI) may be used to assess potential releases and resulting co-exposures near facilities. Unfortunately, location information about environmental releases is typically not available for every chemical substance.
- **Environmental monitoring:** Chemicals present in the environment rarely exist in isolation. When reasonably available, environmental monitoring data such as measurements of chemical concentrations in ambient air, indoor air and dust, surface water, drinking water, and soils can provide evidence of the presence of multiple chemical substances in various environmental media.

3.5 Additivity Considerations for Evaluating Cumulative Chemical Groups

EPA mixtures guidance documents (U.S. EPA, 2000, 1986) describe several additivity approaches to evaluate multiple chemical substances for cumulative risk, including dose addition, response addition, and integrated addition, as well as approaches to account for toxicologic interactions. EPA's default assumption when evaluating toxicologically similar chemical substances for cumulative risk is dose addition (U.S. EPA, 2000, 1986). Similarly, the WHO/IPCS and European Commission also recommend the use of dose addition as the default assumption for estimating risk from exposure to multiple chemical substances (Meek et al., 2011; European Commission, 2009). This default assumption is based on previous analyses of empirical data demonstrating that dose addition is broadly applicable and is a more conservative, health protective approach than response addition.

EPA's mixtures guidance documents also note that dose addition "provides a simple mathematical approach that attempts to estimate the outcomes of complex interactions among biological systems and combinations of chemicals from exposures in the environment" (U.S. EPA, 2000, 1986). The chemical substances in a mixture that are toxicologically similar are assumed to act as dilutions of one another. On the basis of dose addition, the response elicited by the mixture can be estimated by scaling component doses for differences in potency and summing the scaled doses; these scaled doses can be compared to a dose-response function to estimate risk or a health risk value.

The Agency has used response addition when a group of chemical substances are toxicologically dissimilar and cause a common adverse health effect through different MOAs. For example, EPA's Office of Land and Emergency Management (OLEM) regularly screens for total cancer risk at Superfund sites by summing chemical-specific cancer risks under an assumption of response addition (U.S. EPA, 1989). However, other approaches (*e.g.*, dose addition or integrated addition) may be used to estimate total cancer risk when in accordance with the best available science and supported by the weight of scientific evidence.

Neither TSCA nor EPA's Risk Evaluation Rule mandate the use of a specific additivity model or risk characterization approach to estimate cumulative hazard or risk (see p. 33,743 of 40 CFR 702).

Consistent with Agency mixtures guidance documents (U.S. EPA, 2000, 1986), EPA plans to rely upon a default assumption of dose addition when conducting CRAs for cumulative chemical groups under TSCA, unless empirical evidence supports application of another approach (*e.g.*, response addition or integrated addition, as described in (U.S. EPA, 2000)). Deciding, based on their toxicological similarity, which chemical substances to include in a cumulative chemical group that subsequently would be evaluated using dose additive models is an important element of a CRA. When available, various lines of evidence (see Section 3.4.1) can be used to evaluate the toxicological similarity and membership of a chemical substance in a cumulative chemical group.

3.6 Addressing Data Gaps

Section 4 of TSCA gives EPA the authority to issue test rules or orders, as appropriate, that require manufacturers (including importers) and processors to develop and submit information on chemical substances and mixtures to EPA [15 U.S.C. § 2603]. TSCA section 4(b) requires test rules and orders to include protocols and methodologies for the development of information for the identified chemical substance(s) or mixture(s); section 4(b)(2)(A) provides that the health and environmental effects for which such protocols and methodologies may be prescribed include "cumulative or synergistic effects." EPA may use this authority to require the development of data to inform the toxicological similarity of a group of chemical substances undergoing risk evaluation in a CRA. Additionally, the Agency may use its test order authority to obtain further information on product formulation, emissions testing, and manufacturing process information to support evidence for co-exposure.

3.7 Cumulative Risk Assessment Refinement Considerations

Not all CRAs need to be of the same depth or scope (U.S. EPA, 2016; Meek et al., 2011; U.S. EPA, 2002a). Tiered frameworks for evaluating risk from combined exposure to multiple chemicals have been developed by OPP (U.S. EPA, 2016) and the WHO/IPCS (Meek et al., 2011). The objective of those frameworks is to help assessors develop "fit for purpose" cumulative assessments. They employ hierarchical approaches in which tiered exposure and hazard assessment are conducted. With each tier, exposure and hazard assessments become more refined (*i.e.*, less conservative and less uncertain). Because refinements to exposure and hazard assessments are resource intensive and may require large amounts of exposure and toxicology data, refinements are typically made when lower tier cumulative assessments that rely on highly conservative assumptions do not demonstrate an adequate margin of exposure (MOE). When conservative lower tier assessments indicate an adequate MOE, then a resource intensive, highly refined CRA may not be warranted. The availability of data for evidence of toxicological similarity and co-exposure will dictate the level of refinement of cumulative hazard and exposure assessments, and assessments may still be possible with limited data. For example, the WHO/IPCS framework (Meek et al., 2011) outlines various tiers of assessments based on data availability ranging from a Tier 0 exposure assessment using semiquantitative estimates based on limited data and simple assumptions, to Tier 3 exposure assessments that are probabilistic in nature and incorporate representative exposure data for relevant scenarios and populations. Similarly, Tier 0 hazard assessments may group chemical substances based on a conservative assumption of dose addition with limited evidence of toxicological similarity (*e.g.*, predictive hazard tools might be used to group chemical substances based on similar target organ), while higher tier hazard assessments may incorporate more refined information on MOA or utilize physiologically-based pharmacokinetic or biologically-based dose response models that may allow for probabilistic estimates of hazard.

4 CHARACTERIZATION OF CUMULATIVE RISK UNDER TSCA

In the Risk Evaluation Rule, EPA did not codify any specific risk characterization method (see 40 CFR 702.43), thus allowing EPA the flexibility to select the most appropriate risk characterization method based on the best available science and the weight of the scientific evidence, per TSCA sections 26(h) and (i). As described in Section 3.5, when evaluating chemical substances for cumulative risk, EPA's default approach is to rely upon an assumption of dose addition for toxicologically similar chemical substances unless empirical evidence supports application of another approach. This default is based on previous analyses of empirical data that have demonstrated that dose addition is broadly applicable and a health protective assumption.

EPA regularly uses several approaches to estimate hazard or risk from exposure to multiple chemical substances that are based on an assumption of dose addition, including the hazard index (HI), relative potency factor (RPF), and margin of exposure (MOE) (U.S. EPA, 2001, 2000, 1986). For example, OLEM regularly uses the HI approach when evaluating multiple chemical substances in Superfund site risk assessments (U.S. EPA, 1989), while OPP often uses the RPF and MOE approaches to evaluate multiple pesticides when implementing the FQPA (U.S. EPA, 2002a). EPA's mixtures guidance documents (U.S. EPA, 2000, 1986) provide detailed descriptions of these risk characterization approaches. Consistent with Agency guidance and current practice, EPA will consider the applicability of these approaches when conducting CRAs under TSCA. However, the Agency may consider other applicable approaches as the science evolves or if the best available science indicates that approaches based on response addition or integrated addition are more appropriate and are similarly or more health protective.

5 SUMMARY

This draft document outlines the proposed principles of CRA as potentially conducted in support of TSCA risk evaluations and is being made available for public comment and peer review. As described in Section 1, EPA is not explicitly required to conduct CRAs under TSCA. However, TSCA does require EPA to consider reasonably available information and to use the best available science to ensure that decisions are based on the weight of the scientific evidence [15 U.S.C. § 2625(h), (i), (k)]. EPA recognizes that for some chemical substances, the best available science may indicate that the development of a CRA is appropriate to ensure that risk is adequately characterized.

At this time, EPA is proposing to focus its CRA efforts on evaluating human health (not ecological taxa) following exposure to two or more chemical substances. As described in Section 3.4, toxicological similarity and evidence of co-exposure over a relevant timeframe will be the principal considerations when determining a cumulative chemical group for CRA under TSCA. Chemical groupings for CRA will be developed using a weight of evidence approach that characterizes the strengths and uncertainties of the evidence of toxicological similarity and potential co-exposure for each chemical substance considered. Consistent with Agency mixtures guidances (U.S. EPA, 2000, 1986), EPA will evaluate toxicologically similar chemical substances under an assumption of dose additivity when conducting CRAs in support of TSCA, unless empirical evidence supports application of another approach (see Section 3.5).

EPA is soliciting comments from the SACC on charge questions and comments from the public for the SACC meeting scheduled on May 8–11, 2023.

6 REFERENCES

European Commission. (2009). State of the art report on mixture toxicity - Final report. Brussels, Belgium: European Commission. https://ec.europa.eu/environment/chemicals/effects/pdf/report_mixture_toxicity.pdf

Meek, ME; Boobis, AR; Crofton, KM; Heinemeyer, G; Raaij, MV; Vickers, C. (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol 60. http://dx.doi.org/10.1016/j.yrtph.2011.03.010

NRC. (1994). Science and judgment in risk assessment. Washington, DC: The National Academies Press. http://dx.doi.org/10.17226/2125

NRC. (2008). Phthalates and cumulative risk assessment: The task ahead. Washington, DC: National Academies Press. http://dx.doi.org/10.17226/12528

NRC. (2009). Science and decisions: Advancing risk assessment. Washington, DC: National Academies Press. http://dx.doi.org/10.17226/12209

OECD. (2018). Considerations for assessing the risks of combined exposure to multiple chemicals (No. 296). In Series on Testing and Assessment No 296. Paris, France. http://dx.doi.org/10.1787/ceca15a9-en

U.S. EPA. (1986). Guidelines for the health risk assessment of chemical mixtures. Fed Reg 51: 34014-34025.

U.S. EPA. (1989). Risk Assessment Guidance for Superfund (RAGS): Volume 1: Human health evaluation manual (part A): Interim final [EPA Report]. (EPA/540/1-89/002). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part

U.S. EPA. (1991). Guidelines for developmental toxicity risk assessment. Fed Reg 56: 63798-63826.

U.S. EPA. (1999). Guidance for identifying pesticide chemicals and other substances that have a common mechanism of toxicity. Washington, DC. https://www.epa.gov/sites/default/files/2015-07/documents/guide-2-identify-pest-chem_0.pdf

U.S. EPA. (2000). Supplementary guidance for conducting health risk assessment of chemical mixtures (pp. 1-209). (EPA/630/R-00/002). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533

U.S. EPA. (2001). General principles for performing aggregate exposure and risk assessments [EPA Report]. Washington, DC. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/general-principles-performing-aggregate-exposure

U.S. EPA. (2002a). Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity [EPA Report]. Washington, D.C.

U.S. EPA. (2002b). A review of the reference dose and reference concentration processes. (EPA630P02002F). Washington, DC. https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf

U.S. EPA. (2003). Framework for cumulative risk assessment [EPA Report]. (EPA/630/P-02/001F). Washington, DC. https://www.epa.gov/sites/production/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf

U.S. EPA. (2007). Concepts, methods, and data sources for cumulative health risk assessment of multiple chemicals, exposures, and effects: A resource document [EPA Report]. (EPA/600/R-06/013F). Cincinnati, OH. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187

U.S. EPA. (2011). Pyrethrins/pyrethroid cumulative risk assessment. Washington, DC: Office of Pesticide Programs. https://www.regulations.gov/document/EPA-HQ-OPP-2011-0746-0019

U.S. EPA. (2016). Pesticide cumulative risk assessment: Framework for screening analysis. Washington, DC: Office of Pesticide Programs. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework

U.S. EPA. (2019). Guidelines for human exposure assessment [EPA Report]. (EPA/100/B-19/001). Washington, DC: Risk Assessment Forum. https://www.epa.gov/sites/production/files/2020-01/documents/guidelines_for_human_exposure_assessment_final2019.pdf

U.S. EPA. (2022). Cumulative impacts: Recommendations for EPA's Office of Research and Development. (EPA/600/R-22/014a). Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency. https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/10555212

Appendix A GLOSSARY OF KEY TERMS

Additivity (U.S. EPA, 2007, 2000): "when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components."

Aggregate exposure (40 CFR § 702.33): "means the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways."

Best available science (40 CFR § 702.33): "means science that is reliable and unbiased. Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). Additionally, EPA will consider as applicable:

> (1) The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;
>
> (2) The extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;
>
> (3) The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;
>
> (4) The extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and
>
> (5) The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies or models."

Biomonitoring (U.S. EPA, 2019): "measures the amount of a stressor in biological matrices."

Category of chemical substances (15 U.S.C. § 2625(c)(2)(A)): "means a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of [TSCA], except that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances."

Chemical substance (15 U.S.C. § 2602(2)): "means any organic or inorganic substance of a particular molecular identity, including—(i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (ii) any element or uncombined radical. Such term does not include—(i) any mixture, (ii) any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. 136 et seq.]) when manufactured, processed, or distributed in commerce for use as a pesticide, (iii) tobacco or any tobacco product, (iv) any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 [42 U.S.C. 2011 et seq.] and regulations issued under such Act), (v) any article the sale of which is subject to the tax imposed by section 4181 of the Internal Revenue Code of 1986 [26 U.S.C. 4181] (determined without regard to any exemptions from such tax provided by section 4182 or 4221 or any other provision of such Code) and any component of such an article (limited to shot shells, cartridges, and components of shot shells and cartridges), and (vi) any food, food additive, drug, cosmetic, or device (as

such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321]) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device."

Condition of use (COU) (40 CFR § 702.33): "means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."

Consumer exposure (40 CFR § 711.3): Human exposure resulting from consumer use. This exposure includes passive exposure to consumer bystanders.

Consumer use (40 CFR § 711.3): "means the use of a chemical substance or a mixture containing a chemical substance (including as part of an article) when sold to or made available to consumers for their use."

Cumulative impacts (U.S. EPA, 2022): "are defined as the totality of exposures to combinations of chemical and non-chemical stressors and their effects on health, well-being, and quality of life outcomes."

Cumulative impacts assessment (U.S. EPA, 2022): "a process of evaluating both quantitative and qualitative data representing cumulative impacts to inform a decision."

Cumulative risk (U.S. EPA, 2003): "The combined risks from aggregate exposures to multiple agents or stressors."

Cumulative risk assessment (CRA) (U.S. EPA, 2003): "An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors."

Dose additivity (U.S. EPA, 2007, 2003, 2000): when each chemical behaves as a concentration or dilution of every other chemical. The response of the combination of chemicals is the response expected from the equivalent dose of an index chemical (the chemical selected as a basis for standardization of toxicity of components in a mixture). The equivalent dose is the sum of component doses scaled by their toxic potency relative to the index chemical."

Fenceline exposure: General population exposures occuring in communities near facilities that emit or release chemicals to air, water, or land with which they may contact.

Integrated addition: a hybrid additivity approach that incorporates both dose addition and response addition for dichotomous endpoints, thus, producing a mixture estimate that is the probabilistic risk of the adverse endpoint of concern.

Margin of exposure (MOE) (U.S. EPA, 2002a): "a numerical value that characterizes the amount of safety to a toxic chemical–a ratio of a toxicological endpoint (usually a NOAEL [no observed adverse effect level]) to exposure. The MOE is a measure of how closely the exposure comes to the NOAEL."

Mixture (15 U.S.C. § 2602(10)): "means any combination of two or more chemical substances if the combination does not occur in nature and is not, in whole or in part, the result of a chemical reaction; except that such term does include any combination which occurs, in whole or in part, as a result of a

chemical reaction if none of the chemical substances comprising the combination is a new chemical substance and if the combination could have been manufactured for commercial purposes without a chemical reaction at the time the chemical substances comprising the combination were combined."

Mode of Action (MOA) (U.S. EPA, 2000): "a series of key events and processes starting with interaction of an agent with a cell, and proceeding through operational and anatomical changes causing disease formation."

Non-chemical stressors (U.S. EPA, 2022): "Non-chemical stressors are factors found in the built, natural, and social environments including physical factors such as noise, temperature, and humidity and psychosocial factors (*e.g.*, poor diet, smoking, and illicit drug use)."

Non-TSCA exposure: exposure that can be attributed to specific activities that are excluded from the TSCA definition of "chemical substance," under TSCA Section 3(2), such as a pesticide, food, food additive, drug, cosmetic, or medical device.

Occupational non-users (ONU): Employed persons who do not directly handle the chemical substance but may be indirectly exposed to it as part of their employment due to their proximity to the substance.

Pathways (40 CFR § 702.33): "means the mode through which one is exposed to a chemical substance, including but not limited to: Food, water, soil, and air."

Point of departure (POD) (U.S. EPA, 2002a): "dose that can be considered to be in the range of observed responses, without significant extrapolation. A POD can be a data point or an estimated point that is derived from observed dose-response data. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures."

Potentially exposed or susceptible subpopulations (PESS) (15 U.S.C. § 2602(12)): "means a group of individuals within the general population identified by the Agency 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."

Reasonably available information (40 CFR § 702.33): "means information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation. Information that meets the terms of the preceding sentence is reasonably available information whether or not the information is confidential business information, that is protected from public disclosure under TSCA section 14."

Response addition (U.S. EPA, 2007, 2003, 2000): "When the toxic response (rate, incidence, risk, or probability of effects) from the combination is equal to the conditional sum of component responses as defined by the formula for the sum of independent event probabilities. For two chemical mixtures, the body's response to the first chemical is the same whether or not the second chemical is present."

Routes (40 CFR § 702.33): "means the particular manner by which a chemical substance may contact the body, including absorption via ingestion, inhalation, or dermally (integument)."

Sentinel exposure (40 CFR § 702.33): "means the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures."

Stressor (U.S. EPA, 2019): "Any chemical, physical or biological entity that induces an adverse response."

Toxicologic interactions (U.S. EPA, 2007, 2000): "Any toxic responses that are greater than or less than what is observed under an assumption of additivity."

Weight of the scientific evidence (40 CFR § 702.33): "means a systematic review method, applied in a manner suited to the nature of the evidence or decision, 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."