October 30, 2017

Via E-Mail

Jeffery Morris, Ph.D.
Director, Office of Pollution Prevention and Toxics
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1300 Pennsylvania Avenue, N.W.
Washington, D.C. 20004

Dear Jeff:

This letter is submitted on behalf of the New Chemicals Coalition (NCC), a group of over 20 company representatives that have come together to identify new chemical notification issues under the amended Toxic Substances Control Act (TSCA) and to work collaboratively with you and your team to address them. We wish again to thank you and your colleagues for your tireless efforts to implement amended TSCA. We appreciate all that you do.

The NCC is aware that the U.S. Environmental Protection Agency (EPA) intends soon to issue updated guidance material to assist stakeholders in developing Section 5 submissions. We further understand that the document is focused on identifying required information elements and approaches that will facilitate EPA review of such submissions. This guidance material, referred to as the "Points to Consider When Preparing TSCA New Chemicals Notification" (Points to Consider document), is expected to be available for public comment in **November 2017**.

The NCC strongly supports EPA's efforts to identify information elements that TSCA notifiers should consider in preparing their chemical notifications. The identification of this information without more explanation, however, does not provide the clarity, transparency, and understanding that affected companies need regarding EPA assessment and regulatory approaches under amended TSCA. Beyond knowing *what* to report in a submission, stakeholders need to understand *why* the information is needed by EPA assessors and *how* that information will be used by EPA and incorporated into a new chemical risk evaluation. Without this information, the lack of certainty regarding the EPA process will adversely impact investment, stifle innovation, and deny the regulated community of a clearer understanding of how EPA is actually implementing the new law as it relates to new chemical review. To achieve this objective of greater transparency, NCC strongly urges EPA either to expand the Points to Consider document to provide details on its policies, procedures, and guidance related to new chemical notifications, risk assessments, and risk management, or to agree to develop additional

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policies, procedures, and guidance material relevant to carrying out the requirements under amended Section 5. We provide specific areas of interest, and our suggested solutions, below.

Expanded Points to Consider Document Could Fulfill a Portion of Section 26 Requirements

TSCA Section 26(*l*)(1) requires that, by June 2018 (two years after enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act),

> ...the Administrator shall develop any policies, procedures, and guidance the Administrator determines are necessary to carry out the amendments of this [Act] made by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

New TSCA reflects significant amendments to Section 5, including the critically important requirement that EPA make a formal determination on notified chemicals. By expanding the Points to Consider document to include information on the policies and procedures it uses in making Section 5(a)(3) determinations, EPA could fulfill some of Congress's expectations under Section 26 as it relates to Section 5 policies, procedures, and guidance. If EPA elects not to expand the Points to Consider document, it should be prepared to explain how it intends to meet the requirements under Section 26(*l*)(1) within the mandated timeframe.

Guidance Needed on EPA Policy Interpretation and Application of TSCA Terms

In addition to enumerating specific types and categories of information that EPA needs to consider under Section 5, EPA also needs to provide each submitter and other TSCA stakeholders with a policy context within which EPA will interpret and apply key terms that are new to the TSCA lexicon and a critical part of the new chemical assessment and risk management process. The past 16 months has demonstrated that EPA's implementation of these terms has had a dramatic impact on its decisions and actions, impacts far beyond what stakeholders envisioned in reading the new law. In particular, to fulfill EPA's commitment to transparency, EPA needs to provide the submitters and other stakeholders much greater detail on its policy interpretation and application of terms, particularly as they apply to decisions related to additional testing or specific restrictions, for the following in a Section 5 review:

- Insufficient information (Section 5(a)(3)(B)(i));
- Not likely to present an unreasonable risk (Section 5(a)(3)(C));

- Reasonably foreseen (Section 3(4)); and

- To the extent necessary to protect against an unreasonable risk (Section 5(e)(1)(A)).

A lack of both clarity and context as to these pivotal terms is in no one's best interests. Providing more policy context regarding these terms will allow greater transparency, and likely diminish the time and resources EPA expends in processing notifications during the review process. If the submitter understands better how EPA will interpret and apply these terms within the submitter's particular notification, the submitter's point of reference will be more closely aligned with EPA's need for the information. This will allow notifiers to be better positioned to develop a notification that proactively addresses EPA inquiries. Otherwise, notifiers remain in limbo regarding not understanding the basis for EPA's determination. Both the notifier and EPA staff spend unnecessary time, resources, and money in back and forth communications.

Guidance Should Include Needed Updates on Chemical Categories

As further articulated in the July 26, 2017, letter to you from Bergeson & Campbell, P.C. (B&C®) (appended), it is vital that EPA develop, refine, and update the new chemicals categories and their associated documents. The Points to Consider document should, at a minimum, explain the role of these documents and how EPA uses them in its assessment processes under amended TSCA. This explanation is essential to inform more effectively how EPA decisions will be made as such on category members and in the context of the Section 26 sound science requirements under the amended TSCA and, of course, to satisfy EPA's fundamental obligations to explain decisions that compromise final agency action from a perspective of TSCA and the Administrative Procedure Act.

The chemical category documents need to be updated (many are decades old) regarding human health issues and expanded to provide submitters with further understanding on read-across and hazard characterization issues. Similarly, EPA needs to expand upon the points included under Section 4(h) concerning reduction of testing on vertebrates, and upon what stakeholders should consider in preparing their submissions. Alternatively, if EPA believes that certain new chemical categories are no longer useful or relevant, the categories and associated documents for them should be withdrawn. The Points to Consider document is an excellent opportunity for EPA to initiate this process by releasing for public comment newly revised category documents such as those concerning the four lung toxicity categories that were discussed in our July letter. We urge EPA to work toward guidance that is functionally equivalent to that developed under the Organization for Economic Cooperation and Development (OECD) category guidance to ensure consistency and predictability.

The documents also need to provide insight into EPA's category approaches on physical state and use applications. EPA should share publicly an overview as to how it assesses potential risks associated with the physical state of a new chemical substance and its listed use applications within a category context. The Points to Consider document should highlight, for example, if and when new chemical substances that are solids might be subject to inhalation testing requirements or what testing should be expected for new chemical substances that may be used in spray applications and if there is an exit ramp option for such testing depending on particle size or workplace exposure controls. If there are specific use applications that result in automatic concerns requiring additional scrutiny or automatic restrictions, EPA should include such information in the Points to Consider document. Additionally, EPA should also provide guidance as to what language should be included in a premanufacture notifications (PMN) to ensure EPA that such use applications will not occur.

We also stress the need to include in the updated chemicals categories document a robust overview of a tiered testing strategy (as required by Section 4(a)(4)) that clearly adheres to the basic principle of applying what is learned in one tier to what might eventually be needed to determine category membership and to meet a regulatory requirement. The tiering strategy needs to include "exit" decision points for each testing tier based on information requirements for the category, *i.e.*, individual test outcomes should consider the context of what we know about the toxicity and characteristics of category members, exposure considerations, and associated risk management.

Guidance Should Address Impacts to Sustainable Futures

As EPA knows well, many industry stakeholders rely on the training and tools provided under the EPA Sustainable Futures program to prepare and pre-review new chemical notifications prior to submission. Because Sustainable Futures tools allow chemical developers to use the same risk-screening models that EPA relies on for new chemicals evaluations, companies utilizing the tools, and particularly those companies that have received Sustainable Futures program training or that rely on Sustainable Futures assessments prepared by experts, should know better what the outcome of an EPA assessment will be. It is unclear to NCC members whether the EPA assessment process under amended TSCA and its use of the models and approaches included in the Sustainable Futures program have changed. Stakeholders need to be aware if there have been changes in EPA's acceptance of Sustainable Futures assessments as well as modifications in the modeling used, uncertainty factors applied within those models, or assumptions made. The Points to Consider document should include information on how EPA intends to maintain the Sustainable Futures program and highlight any altered approaches it will use in its reliance on the Sustainable Futures approaches and models provided. In particular, we remind EPA of the statement on its website that "[c]ompanies that take the training and graduate

from Sustainable Futures become eligible for an expedited EPA premanufacture review" (https://www.epa.gov/sustainable-futures).

EPA Should Provide Greater Explanation of Polymer Flags Used with Certain New Chemicals

The Points to Consider document should include an overview as to how EPA will assess and approach PMNs submitted for polymers that are intended to be manufactured in a way that meets the polymer exemption at 40 C.F.R. § 723.250. We are aware that EPA, following its review of relevant PMN cases, has previously taken the approach of using a polymer flag as a way to limit how such polymers could be made based on EPA's assessment. While the NCC supports this innovative approach and commends EPA's efforts to avoid the resort to such unnecessary regulatory actions, as a consent order and/or Significant New Use Rule (SNUR) that might otherwise have been needed to achieve the same end, we also note the need for EPA to develop and provide guidance explaining the purpose of the flag and its effect. Such flags seem to be distinctly different from other Inventory flags that merely indicate some status (*e.g.*, XU = exempt from the Chemical Data Reporting rule, S = proposed or final SNUR), but do not otherwise restrict the identity of the substance or how such a substance is manufactured. The Polymer Exemption Flag seems to operate more like a substance definition, which, in association with the substance name, make up the formal identity for TSCA purposes. Given the role and impact of these flags, it is incumbent on EPA to provide this explanation and understanding.

EPA Should Consider Alternative Naming Approaches for Polymers and UVCBs

In addition to the Polymer Exemption Flag approach noted above, EPA should consider similar approaches that provide appropriate and much needed flexibility to EPA in meeting the legal and timing requirements under Section 5(a), while speeding up commercial innovation and the introduction of other low-concern polymers that would not otherwise meet the polymer exemption criteria. For example, EPA could rely on a polymer name, perhaps with the addition of a definition, to limit the polymers that can be made based on a given name to a subcategory of the possible polymers that meets low-concern criteria or otherwise satisfies criteria EPA has developed. This approach is based on EPA's polymer guidance, which states:

> An Inventory listing for each polymer describes a category of possible chemicals that would fit that substance name, instead of just representing a single molecular structure'' and can vary within that listing in molecular weight and composition (e.g., the ratios or the order of reaction of the starting monomers; Toxics

> Substances Control Act Inventory Representation for Polymeric Substances (1995)).

Dividing the large "polymer" category into subcategories allows EPA to limit the forms of the polymer that can be manufactured under that subcategory identity, thereby providing strong protection with minimal EPA resources and without the need for a TSCA Section 5(e) order or Section 5(a)(2) SNUR.

This naming scheme could also be applied more broadly to substances with Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB). Such approaches also would speed commercial innovation via the introduction of low hazard substances, while at the same time avoiding the impacts of unnecessary regulatory impediments to the supply chain, providing strong, Section 5 protection against substances that do not meet the low-concern criteria, and reducing the burdens on EPA and manufacturers associated with developing consent orders or SNURs.

Guidance Should Explain How Mandated Consultation Process with OSHA Will Occur

Based on completed and ongoing new chemical assessments, it is evident that EPA is focused on the need to apply appropriate workplace exposure controls for new chemicals. The Points to Consider document should articulate exactly how EPA will implement the requirements in Section 5(f)(5), which states:

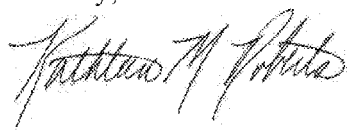
> (5) WORKPLACE EXPOSURES – To the extent practicable, the Administrator shall consult with the Assistant Secretary of Labor for Occupational Safety and Health prior to adopting any prohibition or other restriction relating to a chemical substance with respect to which the Administrator has made a determination under subsection (a)(3)(A) or (B) to address workplace exposures.

The EPA guidance should explain the steps taken by EPA to meet this requirement for ongoing consultations with the Occupational Safety and Health Administration (OSHA) and how it has satisfied the "prior to adopting any prohibition or other restrictions relating to…workplace exposures" provision. The guidance should further explain EPA's thinking as to why regulation using TSCA authority in addition to the obligations imposed by OSHA if a Safety Data Sheet specifies the necessary protections is required to maintain no unreasonable risk in the workplace.

* * * * *

We hope you find these comments helpful. We would be pleased to discuss them with you and your staff in more detail prior to the anticipated **December 2017** public workshop if that is of interest.

Sincerely,



Kathleen M. Roberts

Attachment
cc: Nancy B. Beck, Ph.D., DABT (w/attachment) (via e-mail)
Kevin W. McLean, Esquire (w/attachment) (via e-mail)
Brian P. Grant, Esquire (w/attachment) (via e-mail)

Lynn L. Bergeson
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BERGESON & CAMPBELL PC

July 26, 2017

Via E-Mail

Jeffery Morris, Ph.D.
Director, OPPT, OCSPP
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Dear Jeffery:

Thank you for sharing with us the recent new drafts of four new chemicals categories with a focus on human health: Polymer Lung Overload; Polycationic Substances (Cationic Binding); Waterproofing Agents; and General Surfactants. We appreciate the effort by the U.S. Environmental Protection Agency (EPA) to upgrade and update the category documents and encourage continued activity in this area. We offer technical comments on the documents (appended) and encourage EPA to engage in a broader effort to solicit public comments. We recognize the critical role that the new chemicals categories have played in the implementation of the New Chemicals Program over time, however, we believe there is a need to further develop and refine these documents to inform more effectively decisions in the context of the science requirements under the amended Toxic Substances Control Act (TSCA).

The new chemicals categories prior to the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg) were regarded primarily as a risk management tool to alert submitters to classes of new chemicals that were identified by EPA as being of concern. The write-ups for the most part consist of generic descriptions of potential environmental and/or human health hazards. The substance of these categories is closer to a structural alert than to a category like those developed in the Organization for Economic Cooperation and Development (OECD) program. The New Chemicals Program category documents do not provide the kind of understanding needed to inform submitters of read-across and hazard characterization issues that should be considered in submitting relevant information on a new chemical. This difference between the (traditional) new chemicals categories and categories developed under the OECD grouping programs is not always apparent to premanufacture notification (PMN) submitters. The latter categories are better models but require additional effort to design and build and the recent drafts hint at movement in this direction. Many of the new chemicals category documents are also quite dated, particularly with regard to human health issues, and are in need of update. This could be done over time and provide opportunities for public review and commenting and peer review as indicated.

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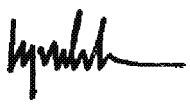
Given the changes in new TSCA, current versions of the new chemicals category documents do not provide the kind of understanding needed to inform submitters of category definitions and boundaries, read-across, and hazard/exposure/risk characterization issues and information needs that should be considered in submitting relevant information on new chemicals. The New Chemicals Program category documents also need to evolve to better align with the sound science provisions in Section 26. A goal of the New Chemicals Program could be to develop new chemical categories that are functionally equivalent to those developed under the OECD's category guidance. We note that the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) also uses categories based on the OECD guidance.

Our comments attempt to examine the category documents under the guidance of the Section 26 science standards. A topic that we feel the need to highlight is the inclusion of tiered testing strategies in these documents. The tiered testing approach illustrated in the recent categories does not conform to the basic principle of relating what is learned from each testing tier to what is eventually needed to determine category membership and to meet a regulatory requirement. The tiering strategy needs to include "exit" decision points for each testing tier based on information requirements for the category, *i.e.*, individual test outcomes need to consider the context of what we know about the toxicity and characteristics of category members, exposure considerations, and associated risk management.

We hope you find these comments helpful. We would be pleased to discuss them with your technical staff in more detail if that is of interest.

Sincerely,



Lynn L. Bergeson

Attachments
cc: Nancy B. Beck, Ph.D., DABT (w/attachments) (via e-mail)

Initial Comments on Polymer Lung Overload New Chemicals Category

Definition

This category includes a variety of poorly soluble polymers, and specifically insoluble/non-water absorbing ("non-swellable") high molecular weight materials typically formed through a free-radical polymerization process. Included are branched and linear polymers, as well as copolymers produced by random, block, graft, or other techniques. Crosslinked polymers are included in the category, but crosslinking is not necessary for inclusion.

The high molecular weight polymers included in this category are otherwise considered non-toxic and this characteristic should be included in the category boundaries discussed below. The hazard concerns for the category are limited to the effects on the lung as a result of inhaling respirable poorly soluble particles. The toxicity information that supports this category consists exclusively of inhalation studies in rodents. No epidemiological studies are cited. A title more reflective of the scope of the category should be considered as well. For example, Respirable Poorly Soluble Polymers is a better description of the category than the current title that highlights an experimental design outcome.

Section 26 Standards

(h)(1)—*The scientific information, protocols, methodologies are reasonable and consistent with the intended use of the information:* Yes, to a point. The hazard concerns require better framing that includes a pragmatic discussion of the lung overload condition and its implications in realistic human exposure scenarios.

(h)(2)—*Relevance of Information:* As above.

(h)(3)—*Clarity and Completeness:* The document makes use of available public information on these chemicals and provides a narrow rationale for the category. Lung overload is a controversial subject that should be discussed in the context of a mode of action.

(h)(4)—*Variability and Uncertainty:* Needs a better description. There are some questions about the relevance of animal inhalation data to characterize effects in humans (lung overload).

(h)(5)—*Independent Verification or Peer Review:* The information to support the category was obtained from the scientific literature. The testing strategy includes test methods that have been subjected to peer review in different forums. The category document itself has not received peer review. At a minimum, and considering the important role of category documents in guiding testing decisions by the U.S. Environmental Protection Agency (EPA) and premanufacture

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notification (PMN) submitters, a public comment period could prove valuable in increasing clarity, completeness, and better understanding of the tiered testing strategy.

Boundaries

Polymers must be respirable and poorly soluble in water. No molecular weight requirements specified. The boundaries should note that the polymers that fit the category are otherwise non-toxic.

General Testing Strategy

The purpose of a tiered strategy is to generate information to inform subsequent steps and then to determine the need to proceed to the next step or not. Tier 1, as discussed below, does not operate as a mechanism to determine the need for higher tier testing. The approach as currently framed appears to consider only moving on to the next tier, which defeats the purpose of a tiered testing strategy.

Tier 1

Physicochemical Characterization: Particle size distribution and biosolubility testing. The strategy indicates that if respirable and poorly soluble particles can be generated, proceed to Tier 2. If the studies are negative, there is still a requirement to determine if Tier 2 is needed. It is not explained why, if the chemical is not found to meet the terms of the category (respirable and poorly soluble), there is still a need to determine if higher tier testing is required. This seems to violate a basic principle of tiering where early tier results inform as to the need for higher tiers. As mentioned above, a public comment period could prove a resource to increased clarity, completeness, and understanding of the approach.

Tier 2

A series of inhalation studies in rats with durations ranging from 4 hours to 28 days.

Tier 3

90-Day Inhalation Study: Based on results of the 90-day inhalation study, a 2-year inhalation bioassay in rats may be warranted.

The *in vivo* tiering is reasonable; as discussed above, there are questions about the role and effect of the first tier. The 2-year cancer bioassay seems excessive considering there is no epidemiological or other (animal) evidence of cancer associated with exposure to these

polymers, including in occupational settings. EPA acknowledges this point in the category document but notes that poorly soluble inorganic particulates have been shown to be carcinogenic in the rat. As discussed below, this is a scientifically controversial area.

The proposed *in vivo* studies involve inhalation tests of various durations utilizing the rat. The adverse effects under consideration for the category range from pulmonary inflammation to tumor formation. The latter effect, which is associated with poorly soluble particulates, does not reflect the interspecies comparative studies that show fundamental differences in the toxicokinetics -- particle disposition, retention, and clearance -- of inhaled particles between rats and non-human primates and humans, nor does it reflect the fact that the lung tumor response is unique to the rat and not observed in other species similarly exposed. Building on the initial work that contributed to the understanding of lung overload (https://www.ncbi.nlm.nih.gov/pubmed/10715616), a scientific consensus emerged in recent years that, because of unique and substantial differences in toxicokinetics and toxicodynamics, rat lung tumor data generated under overload conditions are not considered appropriate for hazard/risk assessment of exposed human populations (http://www.sciencedirect.com/science/article/pii/S0300483X1630292X). A recent action from EPA in the diesel exhaust risk assessment (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=29060) illustrates this understanding:

> Although high-exposure chronic rat inhalation studies show a significant lung cancer response, this is not thought predictive of a human hazard at lower environmental exposures. The rat response is considered to result from an overload of particles in the lung resulting from the high exposure, and such an overload is not expected to occur in humans at environmental exposures.

The use of the rat as an inhalation model to determine lung toxicity for this category is appropriate since it represents a sensitive test species and consequently the results obtained afford an extra margin of protection. The proposed cancer bioassay, particularly with the rat model, is not a reasonable inclusion in the test strategy. The cancer question for respirable poorly soluble polymers should be evaluated on a case-by-case basis considering the weight of the scientific evidence.

Initial Comments on Polycationic Substances New Chemicals Category

The operational use of a new chemicals category is to identify hazard concerns for a particular group of chemicals and corresponding toxicity or other testing to provide information to address concerns.

Definition

Any polymer or substance with multiple functional groups bearing positive charges at physiologically relevant pH is a member of this class. Positive charges may be dissociable (*e.g.*, amine salts) or non-dissociable (*e.g.*, quaternary ammonium cations). Such structures include polyamines, polyquaternary ammonium, polyurea-amines, polyamide-amines, and polyguanidine compounds.

The definition is relatively open-ended and it is unclear what other substance(s) may be considered part of this category. The definition also lacks any indicator of minimum size or molecular weight (MW). For example, a simply alkyl polyamine such as tetraethylene pentamine (TEPA) would seemingly be included.

The toxicity information that supports the category is derived from epidemiological, animal testing and *in vitro* studies on polymeric amines/amides. A potential mode of action for these chemicals is proposed that highlights the critical role of charge density, MW, and molecular conformation in the expression of toxicity. The identified polycationic polymers that form the basis for this category have MWs around 20,000 and higher.

To the extent that lower MW polycationic chemicals (*e.g.*, MW<1,000) are considered part of this category, their inclusion would be inconsistent with the available toxicity and mode of action information. Lower MW polyamine/amides have been shown to produce predominantly irritation upon dermal and/or ocular exposure in test animals. Irritation becomes the prevalent adverse effect linked to exposure of low(er) MW polyamine/amides. The proposed mechanism of cytoxicity for high MW polycationic polymers involves the initial electrostatic interaction of the polycationinc polymer with the negatively charged cell membrane. This interaction neutralizes cell membrane charge over the area of contact. This condition weakens the membrane structure that eventually leads to leakage and a more permeable membrane. A low(er) MW polycationic substance would experience a similar but more localized interaction short of the impact associated with higher MW polycationc polymers.

A separate argument against a low MW polyamine/amide belonging to this category is the postulated mode of action for the polyamine/amides in the epidemiological studies that require certain MW, charge density, and conformation characteristics not present in the former. In addition, a lower MW would facilitate absorption of a polyamine/amide by the cell and the toxicity observed would be associated with intracellular interactions rather than the postulated membrane effects associated with the category.

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Section 26 Standards

(h)(1)—*The scientific information, protocols, methodologies are reasonable and consistent with the intended use of the information*: The scientific information and methodologies are consistent with the intended use of the information; the description of the rodent inhalation exposure protocols fall short of the standard.

(h)(2)—R*elevance of Information*: The toxicity information is relevant for making decisions about these polycationic polymers.

(h)(3)—*Clarity and Completeness*: The document makes use of available public information on these chemicals and provides a reasonable rationale for the category.

(h)(4)—*Variability and Uncertainty*: The U.S. Environmental Protection Agency (EPA) discloses the limitations of the available animal testing information. There are few adequate animal studies and some are short on experimental details. Other studies cited were conducted by intratracheal instillation, which are useful as confirmatory of the hazard concern but not very helpful for hazard and risk characterization.

(h)(5)—*Independent Verification or Peer Review*: The information to support the category was obtained from the scientific literature. The testing strategy includes test methods that have been subjected to peer review in different forums. The category document itself has not received peer review. At a minimum, and considering the important role of category documents in guiding testing decisions by EPA and premanufacture notification (PMN) submitters, a public comment period could prove valuable in increasing clarity, completeness, and understanding of the tiered testing strategy.

Boundaries

Polymers must be water soluble or water-dispersible. No MW requirements are specified. Although the Definition section includes the requirement for multiple positive charges at physiologically relevant pH, this point is not included in the discussion of boundaries.

Proposed Testing Strategy

EPA identifies a series of tests that, although not explicitly stated, partly relate to a determination whether a chemical should be included in the category.

The initial recommendations address the physicochemical characterization of the polymer. This is followed by a set of three *in vitro* tests for Cytotoxicity and Dermal Irritation. The two cytoxicity tests identify the purpose as generating data to predict the starting doses for rodent acute oral systemic toxicity assays and along the way provide a qualitative description of the cytoxicity potential of the test substance. The document does not discuss how PMN submitters and EPA should consider and use the results of the *in vitro* tests, thus it is not clear what role they play in the tiering.

The *in vitro* dermal irritation test is a standard Organization for Economic Cooperation and Development (OECD) test guideline. It is not clear what role the test plays in the polycationic substances category tiering strategy. The polymers that were the subjects of the epidemiological reports are described by the authors as not irritating. Does this suggest that evidence of irritation in this test provides a basis or a partial basis for questioning whether the category applies to a given new chemical? For polyamine/amide chemicals, irritation potential generally decreases as MW increases. This is one of the issues about potentially extending the category to low MW polycations. Low MW polycations (*e.g.*, polyamines such as TEPA) are irritants and this feature tends to drive their toxicity.

General Testing Strategy

Tier 1 -- Use physical-chemical properties to characterize lung exposure/binding potential

- Charge density in milliEquivalents/gram or functional group equivalent weight or % amine nitrogen. It would be useful to specify use of physiologically relevant pH in conducting the test.
- Particle Size Distribution or Aerosolized Droplet Size (OECD TG 110 or OPPTS 830.7520).

As discussed in the document, this tier is driven by respirability without also specifying that polycationic character at physiologically relevant pH must be shown.

Tier 2 -- Proposed *In Vivo* Studies

- Step 1: OECD Acute TG 403 featuring rats exposed for 4 hours and observed for 2 weeks (< 2000 mg/m^3, proceed to step 2).
- Step 2: Five-day study to address toxicity progression (substantial decrease in the Point of Departure (POD) over time relative to the acute study, proceed to step 3).

- Step 3: OECD TG 412 (28-day inhalation study in rats with 14-day recovery period).

EPA concludes that 28-day inhalation studies are adequate to characterize the toxicity of polycationic substances based on the appearance of lung effects in the available studies.

The purpose of a tiered strategy is to generate information to inform subsequent steps and determine the need to proceed to the next step or not. There is a need for better guidance from EPA if it intends to use the results of the initial physiochemical, *in vitro,* and *in vivo* tests. For example, what happens if a polycationic substance is not respirable or shows low cytoxicity in the identified *in vitro* assays? Similar questions can be raised about outcomes of other early toxicity tests. The process as currently framed appears to consider only moving on to the next tiered step resulting in a "tiered strategy" that then devolves into a fixed set of tests that should be implemented regardless of intermediary outcomes. A more descriptive tiered strategy should include information requirements that would inform decisions about proceeding to the next tier or exiting the process. As mentioned above, a public comment period could prove a resource to increased clarity, completeness, and understanding of the approach.

Initial Comments on Waterproofing Agents New Chemicals Category

Definition

Any compound that is applied to a solid surface (*e.g.*, carpets, clothing, fabrics, leather, wood, paper packaging, ceramic tiles, concrete, masonry, flooring) to confer or enhance repellency or resistance to water, grease, or stains is considered to be a member of this category. Of particular focus are chemicals used in consumer spray products, which may be applied without the presence of personal protective equipment.

This category includes a range of chemical functionalities with the unifying characteristic being that they bind to surfaces and confer water repellence to the coated area. The toxicity information that supports this category includes human observations, animal studies, and *in vitro* information.

Section 26 Standards

(h)(1)—*The scientific information, protocols, methodologies are reasonable and consistent with the intended use of the information*: The scientific information and methodologies are consistent with the intended use of the information.

(h)(2)—*Relevance of Information*: The toxicity information is relevant for making decisions about waterproofing agents.

(h)(3)—*Clarity and Completeness*: The document makes effective use of available public information on these chemicals and provides a reasonable rationale for the category.

(h)(4)—*Variability and Uncertainty*: Variability and uncertainty in experimental outcomes are discussed briefly.

(h)(5)—*Independent Verification or Peer Review*: The information to support the category was obtained from the scientific literature. The testing strategy includes test methods that have been subjected to peer review in different forums. The category document itself has not received peer review.

Boundaries

No boundaries are identified for this category.

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General Testing Strategy

Tier 1

Physicochemical Characterization: Particle size distribution or aerosolized droplet size; surface tension increases.

Tier 2

Similar inhalation battery to other inhalation categories that culminate with a 28-day inhalation study. The supporting data section notes that the Organization for Economic Cooperation and Development (OECD) 403 four-hour inhalation exposure with some modifications may be adequate for a comparative assessment of waterproofing agents.

The testing strategy identifies *in vitro* methods that have shown promise as tools for the hazard screening of waterproofing agents.

Initial Comments on General Surfactants New Chemicals Category

Definition

Includes anionic, cationic, and nonionic surfactants.

Anionic Surfactants: Any molecular structure with a net negative charge and having surfactant activity is a member of this category. The category includes, for example, alkyl sulfonates, alkylbenzene sulfonates, alkyl silicic acids, alkyl phosphates, alkyl carboxylic acids, or combinations of these anionic groups, *e.g.*, alkyl sulfonate with carboxylic acid substitutions.

Cationic Surfactants: Any cationic surfactant is a member of this category, for example: didecyldimethyl ammonium chloride (DDAC).

Nonionic Surfactants: Any neutral structure having surfactant activity (*e.g.*, Triton-X 100) is considered a member of this category.

This category shares several design features with the Waterproofing Agents category, including a range of different functionalities that show surfactant properties. The toxicity information that supports this category includes human observations, animal studies, and *in vitro* data from studies conducted with nonionic and anionic surfactants. An unstated assumption is that ionic character is not relevant for the expression of toxicity by surfactants.

Section 26 Standards

(h)(1)—*The scientific information, protocols, methodologies are reasonable and consistent with the intended use of the information*: The limited scientific information and methodologies are consistent with the intended use of the information.

(h)(2)—*Relevance of Information*: The toxicity information is relevant for making decisions about waterproofing agents.

(h)(3)—*Clarity and Completeness*: The document makes use of limited public information on these chemicals and provides a reasonable rationale for the category. No data included for cationic surfactants.

(h)(4)—*Variability and Uncertainty*: Variability and uncertainty in experimental outcomes are discussed briefly.

(h)(5)—*Independent Verification or Peer Review*: he information to support the category was obtained from the scientific literature. The testing strategy includes test methods that have been subjected to peer review in different forums. The category document itself has not received peer review.

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Boundaries

No boundaries are identified for this category.

General Testing Strategy

The proposed inhalation battery (Organization for Economic Cooperation and Development (OECD) 403 progressing to OECD 412) for surfactants is the same as for the other inhalation categories.

The testing strategy identifies *in vitro* methods that have shown promise as tools for the hazard screening of surfactants.