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BERGESON & CAMPBELL PC

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Via E-Mail

Jeffery Morris, Ph.D.
Director, OPPT, OCSPP
Office of Pollution Prevention and Toxics
Ronald Reagan Bldg. and International Trade Center
Room 71184
1300 Pennsylvania Avenue, NW
Washington, DC 20004

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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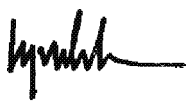
Given the changes in new TSCA, current versions of the new chemicals category documents do not provide the kind of understanding needed to inform submitters of category definitions and boundaries, read-across, and hazard/exposure/risk characterization issues and information needs that should be considered 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,



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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.