OPPT's Progress Implementing the Near-term Activities (2018-2021) in the Strategic Plan under Section 4(h)(2)(A) of TSCA

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Impact of Biden-Harris Executive Order on Protecting Public Health and the Environment

- As the Biden-Harris Administration works to advance EPA's mission of protecting human health and the environment, the agency is committed to ensuring the safety of chemicals used by all Americans.
- To that end, EPA will follow the science and law, and review the agency's actions issued under the previous Administration and take any needed steps to ensure that they protect human health and the environment.
- This review is being done in accordance with the Administration's Executive Orders and other directives, including those on environmental justice, scientific integrity, and regulatory review.
- The agency will keep stakeholders updated as decisions are made, and next steps are determined.

Topics Covered

- 2016 Amendments to the Toxic Substances Control Act (TSCA)
- TSCA Section 4 (h) – Reduction of Testing on Vertebrates
- June 2018 Strategic Plan
- Progress Implementing the Strategic Plan
- Other Related Activities

Amended TSCA

On June 22, 2016, the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg Chemical Safety Act) was signed into law. The Lautenberg Chemical Safety Act amends the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law.

President Obama signs TSCA reform into law. Photo courtesy of the White House via YouTube.

Statutory Mandate: TSCA Section 4(h)(1)

- Prior to requesting testing using vertebrates:
  - Consider *reasonably available existing information*, and
  - Encourage and facilitate (Section 4(h)(1)(B)(I, ii and iii):
    - "Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while providing information *of equivalent or better scientific quality and relevance* that will support regulatory decisions;
    - The grouping of 2 or more chemical substances into scientifically appropriate categories…; and
    - The formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests…"

Statutory Mandate: TSCA Section 4(h)2 – The Strategic Plan

4(h)(2) - ***Implementation of Alternative Testing Methods*** - To promote the development and timely incorporation of new scientifically valid test methods and strategies that are not based on vertebrate animals, the Administrator ***shall*** **-** 4(h)(2)**(A)** develop a strategic plan to ***promote the development and implementation of alternative test methods and strategies*** to reduce, refine, or replace vertebrate animal testing ***and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment***…"

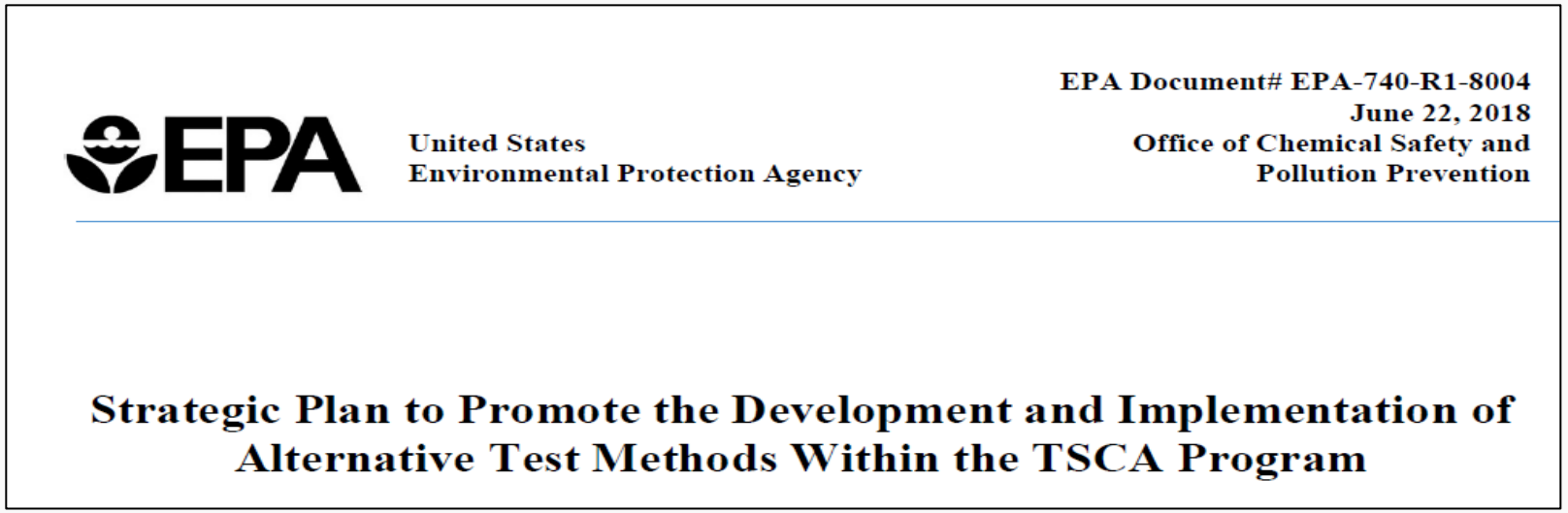
Overview of Strategic Plan

Three core components:

(1) identifying, developing and integrating NAMs for TSCA decisions;

(2) building confidence that the NAMs are scientifically reliable and relevant for TSCA decisions; and

(3) implementing the reliable and relevant NAMs for TSCA decisions.



EPA

United States
Environmental Protection Agency

EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and
Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

Implementing the TSCA Strategic Plan:

- Eight Near-Term Activities (2018-2021)

- Other Activities:
  - Lung effect project categories

TSCA Implementation: Activities (2018-2021)

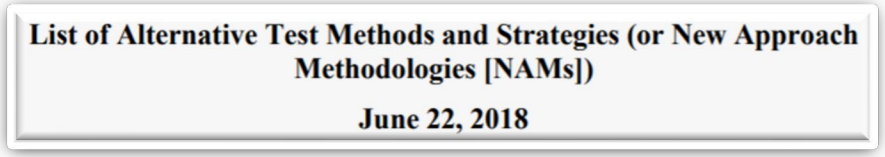
1. Continue to Implement NAMs to Evaluate Hazard, Exposure and Environmental Fate for New and Existing Chemicals

- Draft policy to reduce animal testing for skin sensitization (April 2018) (Link)
- Integrated Indoor Outdoor Air Calculator (March 2019) (Link)
- Final rule revoking a significant new use rule (SNUR) based on NAM data (biosolubility testing) (April 2020) (Link)
- Species Sensitivity Distribution (SSD) Toolbox (November 2020) (Link)
- OncoLogic™ (version 9.0) (January 2021) (Link)
- External peer review of Multiple-Path Particle Dosimetry (MPPD) Model Software (MPPD EPA 2021 v.1.01) announced (March 2021) (Link)

TSCA Implementation: Activities (2018-2021)

2. Maintain and Regularly Update a List of NAMs per Section 4(h)(2)(C)

- Initial list of NAMs published on June 22, 2018 (Link)
- First update to the initial list published on December 5, 2019 (Link)
- Second update to the initial list published on February 4, 2021 (Link)



TSCA Implementation: Activities (2018-2021)

3. Identify and Maintain a List of Most Requested/Needed Studies for New and Existing Chemicals Under TSCA

A retrospective Analysis of TSCA Available, Expected, and Potentially Useful Information (ATAEPI) to identify and evaluate studies the Agency has requested or received for new and existing chemical substances

Table 1. Summary of studies identified by EPA as part of its ATAEPI project.

Available[a]				Expected[b]				Potentially Useful[c]			
Test	N	Test	N	Test	N	Test	N	Test	N	Test	N
Acute eye irritation / corrosion	2852	Fish, acute toxicity test	4886	Subchronic inhalation toxicity: 90-day study	413	Freshwater alga and cyanobacteria, growth inhibition test	1029	Repeated dose 28-day oral toxicity study	252	Freshwater alga and cyanobacteria, growth inhibition test	77
Acute dermal irritation / corrosion	2169	Daphnia sp. acute immobilization test	4287	Prenatal developmental toxicity study	309	Fish, acute toxicity test	794	Prenatal developmental toxicity study	233	Fish, acute toxicity test	61
Skin sensitization	1640	Freshwater alga and cyanobacteria, growth inhibition test	2990	Repeated dose 28-day oral toxicity study	243	Daphnia sp. acute immobilization test	773	Subchronic inhalation toxicity: 90-day study	94	Daphnia sp. acute immobilization test	56
Repeated dose 28-day oral toxicity study	1301	Microbial toxicity test (*e.g.*, sewage and soil)	503	Carcinogenicity study	226	Fish, early-life stage (FELS) toxicity test	472	Combined repeated dose toxicity study with the reproductive / developmental toxicity screening test	62	Fish, early-life stage (FELS) toxicity test	43
Acute dermal toxicity	1211	Fish, prolonged toxicity test: 14-day study	286	Combined repeated dose toxicity study with the reproductive / developmental toxicity screening test	153	Daphnia magna reproduction test	467	Mammalian erythrocyte micronucleus test	47	Daphnia magna reproduction test	36

[a] Examples of Available information include: information housed in the TSCA CBI discipline databases (*e.g.*, hazard and fate) and Substantial Risk Information databases (*i.e.*, notifications under Section 8(e) of TSCA).
[b] Examples of Expected information include: information EPA expects to receive as part of Pended testing under Section 5 of TSCA and Focus Letters.
[c] Examples of Potentially Useful information include: information EPA may receive as part of Consent Orders and SNURs under Section 5 of TSCA.

TSCA Implementation: Activities (2018-2021)

4. Identify and Curate Available Existing TSCA Information on NAMs (And Traditional Test Data)

- Cataloging and analyzing NAMs information received from industry submissions under TSCA. This work represents an extension of EPA's ATAEPI project discussed under near-term activity #3.
- The results of this TSCA in-house inventory of NAMs information will be made publicly available as part of EPA's intermediate-term objectives (2022-2025), to the extent possible with information claimed as CBI, to advance the development and implementation of NAMs.

5. Use of NAMs to Identify Candidates for Prioritizing Existing Chemicals for TSCA Risk Evaluation

- Issued a conceptual approach titled "A Working Approach for Identifying Potential Candidate Chemicals for Prioritization" on September 27, 2018 (Link); updated based on public comments and peer-review; publication expected in 2021.
- Used NAM information in identifying the 20 low-priority chemical substances (Link)

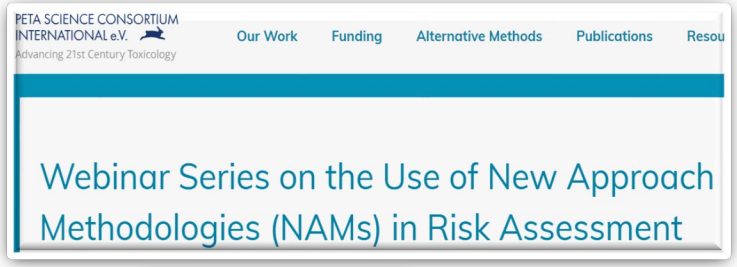
TSCA Implementation: Activities (2018-2021)

6. Begin Development of Scientific Information Technology Platforms

- Deploying the International Uniform Chemical Information Database (IUCLID) for managing data on chemical substances, including the data identified under near-term activities #3 and #4
- Collaborating with the European Chemicals Agency and Health Canada to exchange public chemical substance data via the IUCLID cloud platform

7. Collaborate with Partners and Stakeholders to Identify NAMs for Further Development

- Partnered with PETA Science Consortium International e.V. and the Physicians Committee for Responsible Medicine (PCRM) to host public webinars (Link)
- Advancing the science of NAMs through its Chemical Safety for Sustainability Strategic Research Action Plan 2019-2022 (CSS StRAP) (Link)



TSCA Implementation: Activities (2018-2021)

8. Launch TSCA NAM Website (Link)

Other Activities: Lung Effect Project Categories (Link)

#2583 | Surfactants Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods (NAMs) for Assessing Inhalation Risks under the Toxic Substances Control Act (TSCA)

T.R. Henry[1], K.D. Salazar[1], M.P. Hayes[2], W. Kennedy[3], A.M. Keene[5], A.M. Jarabek[4], O.T. Price[6], S. Moors[6], L. Jovanovich[7], J.L. Rose[8], A. Tveit[9], R.T.Tremblay[10], R.A. Becker[11], S. Osman-Sypher[11], P.D. McMullen[12], S.D. Slattery[12], W. Irwin[1], M. Odin[13], J. Melia[13], M. Sharma[14], A.O. Stucki[14], A.J. Clippinger[14], and T. Stedeford[1]. [1]US EPA, Washington, DC; [2]Procter & Gamble, St. Bernard, OH; [3]Afton Chemical Corporation, Richmond, VA; [4]US EPA, Research Triangle Park, NC; [5]Applied Research Associates, Inc., Arlington, VA; [6]BASF Corporation, Duesseldorf, Germany; [7]Stepan Company, Northfield, IL; [8]Procter & Gamble, Mason, OH; [9]BASF Corporation, Florham Park, NJ; [10]Procter & Gamble, Strombeek-Beaver, Belgium; [11]American Chemistry Council, Washington, DC; [12]ScitoVation, Durham, NC; [13]SRC Inc., North Syracuse, NY; and [14]PETA Science Consortium International e.V., Stuttgart, Germany

Motivation

- Section 5 of TSCA including pre-manufacturing notification (PMN) does not require testing for new chemical substances (NCS); only extant health or environmental effects data need to be submitted.
- EPA uses various methods to assess risks of NCS with limited data, including chemical categories and "read across" based on analogs. Chemical categories have specific chemical definitions, categorical boundaries, representative analogs, and testing recommendations to aid submitters in understanding potential hazard concerns and to facilitate EPA's review and evaluation of NCS.
- Surfactants may pose a potential inhalation hazard to humans, depending on their conditions of use, chemistry, or size characteristics, because they can disrupt the epithelial lining or perturb cell membranes.
- EPA has authority to require testing on NCS, but also must consider TSCA's mandate to reduce or replace the use of vertebrate animal testing. We present an IATA that supports consideration of physicochemical (PC) properties of the category and facilitates use of NAMs to screen for potential key events and adverse outcomes associated with inhaled surfactants.

Methods

- Inhalable surfactants were defined as those NCS that have the PC properties and meet the functional criteria for inclusion/exclusion shown in Figure 1. Subcategories considered are amphoteric, nonionic, cationic, and anionic surfactants.
- Systematic review methods were applied using population/exposure/comparator/outcome (PECO) statements that considered PC properties and key events (KEs) of potential adverse outcome pathways (AOPs) to identify relevant toxicity data and NAMs.
- The multi-path particle dosimetry (MPPD) model was used to translate observed effect levels from rodent studies to human equivalent concentrations (HECs) as depicted in Figure 2.
  - Due to potential direct interaction with epithelial lining and cells of the entire respiratory tract, the dose metric chosen was the daily deposited mass in each respiratory region normalized to its surface area.
  - The MPPD model may also be deployed to simulate target human exposure scenarios.
- Potential NAMs to inform screening were identified based on KEs and AOP that characterize KE of epithelial lining disruption or cell membrane perturbation.
- Figure 3 depicts the IATA as the resultant strategy for evidence integration and evaluation of inhaled surfactants.

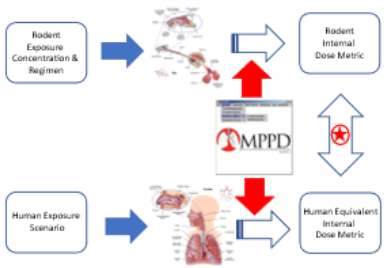


Figure 2. Schematic of MPPD model deployed to extrapolate a rodent exposure regimen to an HEC. Default exposure assumptions or parameters specific to the target human exposure such as: particle size distribution, ventilation rate or pattern, and duration can be used to tailor simulations

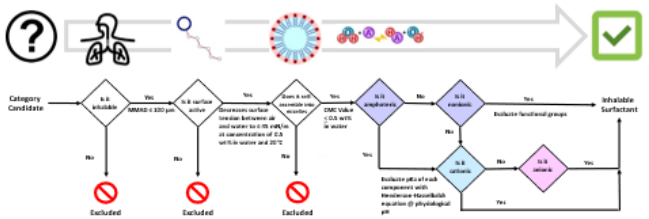


Figure 1. Decision strategy and criteria to consider critical PC properties of candidates for inhalable surfactants category

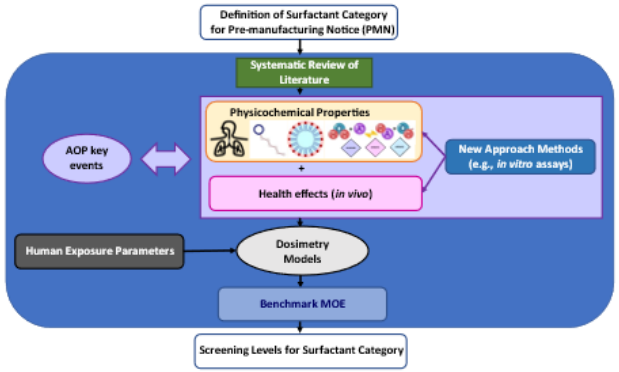
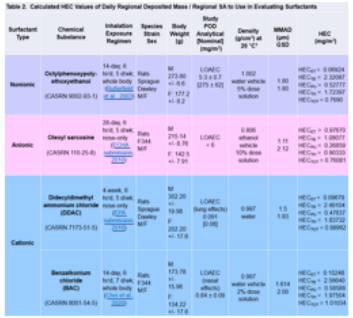


Figure 3. IATA for evidence integration and evaluation of available data on inhalable surfactants

Results

- Table 1 lists identified NAMs relevant to inhalable surfactants.
- Table 2 provides the HEC values to use in assessing risks of surfactants that meet the category definition.



Impact

- IATA represents a strategy to evidence integration and evaluation to aid assessment of surfactants with minimal available test data.
- Consideration of PC properties and NAMs aimed at KEs of AOPs creates context for evaluation of the need and strategy for higher-tiered testing based on mechanistic responses, dosimetry, and exposure information.
- Emphasis on development of mechanistic data will advance understanding of the potential inhalation toxicity of surfactants to drive the development of newer and safer chemistries.

References

- Available in the Notes pane.

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Other Activities: Lung Effect Project Categories (Link)

#2593 | Poorly Soluble, Low Toxicity (PSLT) Polymer Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods (NAMs) under the Toxic Substances Control Act (TSCA)

A.M. Jarabek[1], T. Stedeford[2], G.S. Ladics[3], O.T. Price[4], A. Tveit[5], M.P. Hayes[6], R.T. Tremblay[7], S.A. Snyder[8], K.D. Salazar[2], S. Osman-Sypher[9], W.Irwin[2], M. Odin[10], J. Melia[10], H. Carlson-Lynch[10], M. Sharma[11], A.O. Stucki[11], A.J. Clippinger[11], S. Anderson[2], and T.R. Henry[2]. [1]US EPA, Research Triangle Park, NC; [2]US EPA, Washington, DC; [3]IFF, Wilmington, DE; [4]Applied Research Associates Inc., Arlington, VA; [5]BASF Corporation, Florham Park, NJ; [6]Procter & Gamble, Mason, OH; [7]Procter & Gamble, Strombeek-Beaver, Belgium; [8]Covestro LLC, Pittsburgh, PA; [9]American Chemistry Council, Washington, DC; [10] SRC Inc., North Syracuse, NY; and [11]PETA Science Consortium International e.V., Stuttgart, Germany.

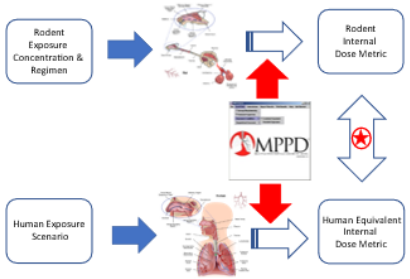
Motivation

- Section 5 of TSCA including pre-manufacturing notification (PMN) does not require testing for new chemical substances (NCS); only extant health or environmental effects data need to be submitted.
- EPA uses various methods to assess risks of NCS with limited data, including chemical categories and "read across" based on analogs. Chemical categories have specific chemical definitions, categorical boundaries, representative analogs, and testing recommendations to aid submitters in understanding potential hazard concerns and to facilitate EPA's review and evaluation of NCS.
- PSLT may pose a potential inhalation hazard to humans, depending on their conditions of use, chemistry, or size characteristics, because they can disrupt the epithelium or accumulate in tissues of the pulmonary (PU) region.
- EPA has authority to require testing on NCS, but also must consider TSCA's mandate to reduce or replace the use of vertebrate animal testing. We present an IATA that supports consideration of physicochemical (PC) properties of the category and facilitates use of NAMs to screen for potential key events and adverse outcomes associated with inhaled PSLT polymers.

Methods

- PSLT polymers were defined as those NCS that have the PC properties and meet the functional criteria for inclusion/exclusion shown in Figure 1. Some may require evaluation for other hazard concerns (e.g., adverse effects resulting from direct translocation of ultrafine particles to the brain).
- Systematic review methods were applied using population/exposure/comparator/outcome (PECO) statements that considered PC properties and key events (KE) of potential adverse outcome pathways (AOPs) to identify relevant toxicity data and NAMs.
- The multi-path particle dosimetry (MPPD) model was used to translate observed effect levels from rodent studies to human equivalent concentrations (HECs) as depicted in Figure 2.
  - Due to the potential of PSLT polymer particles to accumulate, the dose metric chosen was the retained mass in the PU region normalized to its surface area.
  - The MPPD model was deployed to demonstrate if particle overload, a kinetic phenomenon, may have occurred in experimental studies to create context for interpretation of results.
  - The MPPD model may also be deployed to simulate target human exposure scenarios.
- Potential NAMs to inform screening were identified based on KE and AOP that characterize KE of epithelial disruption or PU retention.
- Figure 3 depicts the IATA as the resultant strategy for evidence integration and evaluation for screening inhaled PSLT polymers.

Figure 2. Schematic of MPPD model deployed to extrapolate a rodent exposure regimen to an HEC. Default exposure assumptions or parameters specific to the target human exposure scenario such as: particle size distribution, ventilation rate or pattern, and duration can be used to tailor simulations



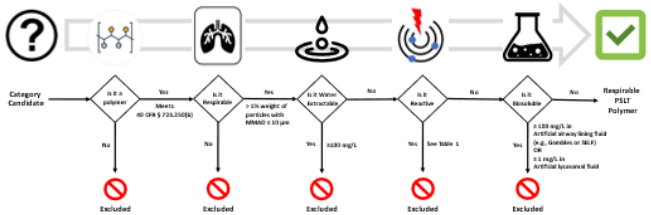


Figure 1. Decision strategy and criteria to consider critical PC properties of candidates for inclusion in the respirable PSLT polymer category

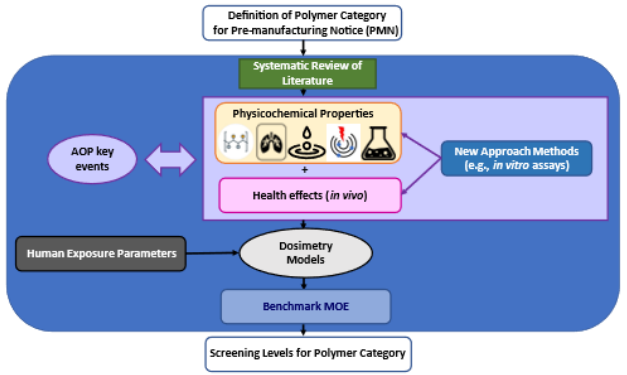


Figure 3. IATA for evidence integration and evaluating available data on respirable PSLT polymers

Results

- Figure 4 shows MPPD simulations to characterize particle overload of an inhalation study in F344 rats exposed to polyvinyl chloride (PVC) particles (Muhle et al., 1991). The exposure was 5 h/d and 5 d/w for 22.5 weeks with an MMAD of 1.3 µm, a GSD of 2.07, and a density of 1.3 g/cm^3. Overload did not occur at the lowest exposure level under the experimental conditions of the study. Tumors in rats that may result from such kinetics may not be relevant to human risk assessment.
- Table 1 lists identified NAMs relevant to inhalable PSLT polymers.
- Table 2 provides the HEC values to serve as basis for deriving boundaries of category.

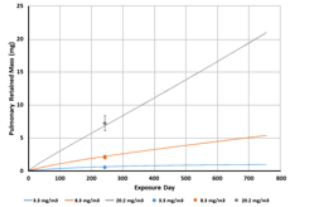


Figure 4. MPPD simulations demonstrating particle overload in PU region of rats exposed to inhaled PVC particles

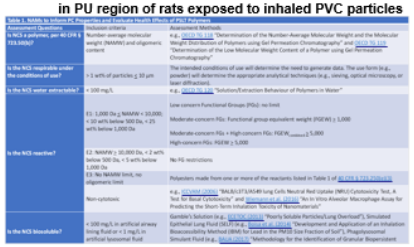


Table 2. Calculated HEC Values of PU Retained Mass / PU SA to Evaluate PSLT Polymers

PSLT Polymer	Inhalation Exposure Regimen	Species Strain Sex	Body Weight (g)	Study POD Analytical [Nominal] (mg/m³)	Density (g/cm³) at 20 °C	MMAD (µm) GSD	HEC (mg/m³)
PVC	6 h/d, 5 d/wk 32 weeks (Muhle et al., 1991)	Rat F344 Female	229	NOAEC	1.30	1.3 2.07	HEC_{PU} = 0.19
Toner	6 h/d, 5 d/wk 24 weeks (Muhle et al., 1991)	Rat F344 Female	229	LOAEC	1.15	4 1.5	HEC_{PU} = 0.092

Impact

- IATA represents a strategy to evidence integration and evaluation to aid assessment of PSLT polymers with minimal available test data.
- Consideration of PC properties and NAMs aimed at KEs of AOPs creates context for evaluation of the need and strategy for higher-tiered testing based on mechanistic responses, dosimetry, and exposure information.
- Emphasis on development of mechanistic data will advance understanding of the potential inhalation toxicity of PSLT polymers to drive the development of newer and safer chemistries.

References

- Available in the Notes pane.

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THANK YOU!

QUESTIONS?