#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)

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Conflict of Interest Statement: One or more authors is/are employed by an entity that manufacturers and/or distributes a material that is the subject of this presentation.

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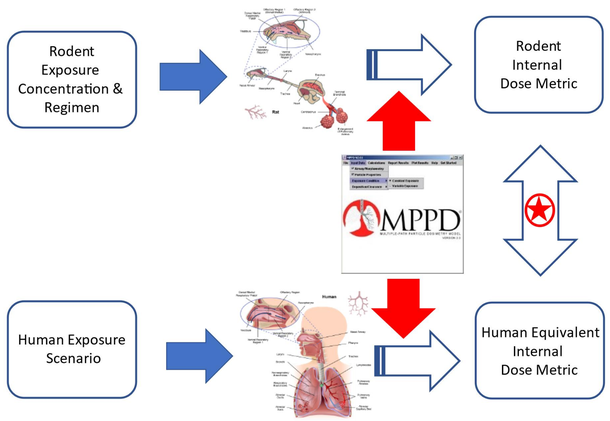
Motivation

- 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



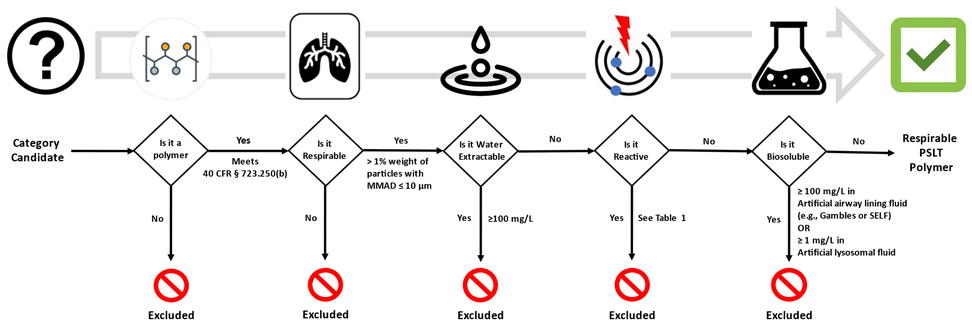


Figure 1. Decision strategy and criteria to consider critical PC properties of candidates for inclusion in the respirable PSLT polymer category

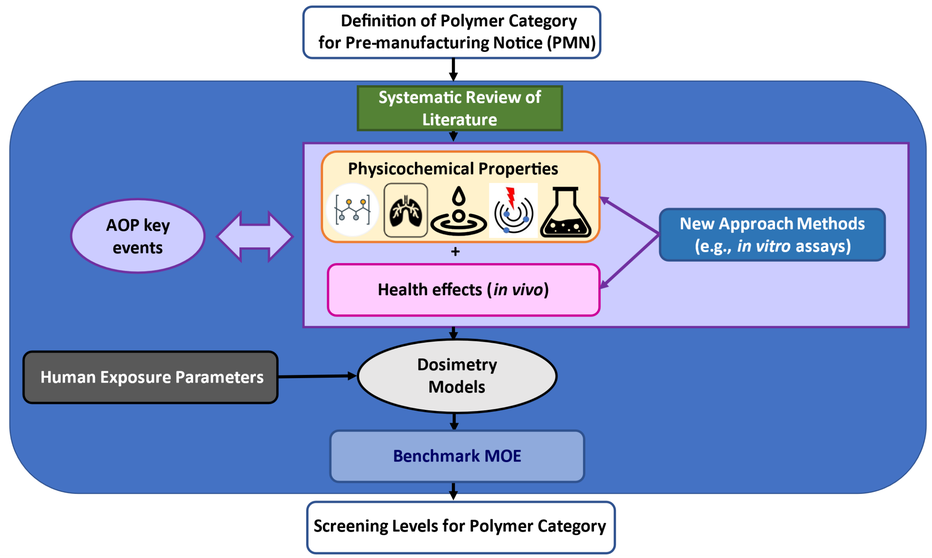


Figure 3. IATA for evidence integration and evaluating available data on respirable PSLT polymers

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.

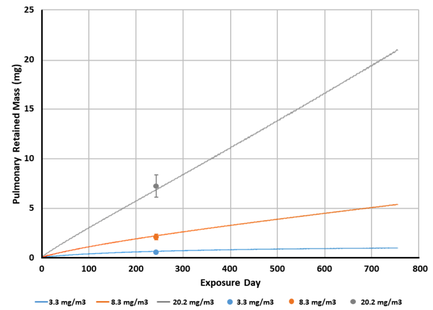


Figure 4. MPPD simulations demonstrating particle overload in PU region of rats exposed to inhaled PVC particles

Table 1. NAMs to Inform PC Properties and Evaluate Health Effects of PSLT Polymers

Assessment Questions	Inclusion criteria	Assessment Methods
Is NCS a polymer, per 40 CFR § 723.50(b)?	Number-average molecular weight (NAMW) and oligomeric content	e.g., OECD TG 118 "Determination of the Number-Average Molecular Weight and the Molecular Weight Distribution of Polymers using Gel Permeation Chromatography" and OECD TG 119 "Determination of the Low Molecular Weight Content of a Polymer using Gel Permeation Chromatography"
Is the NCS respirable under the conditions of use?	> 1 wt% of particles ≤ 10 µm	The intended conditions of use will determine the need to generate data. The use form (e.g., powder) will determine the appropriate analytical techniques (e.g., sieving, optical microscopy, or laser diffraction).
Is the NCS water extractable?	< 100 mg/L	e.g., OECD TG 120 "Solution/Extraction Behaviour of Polymers in Water"
Is the NCS reactive?	E1: 1,000 Da ≤ NAMW < 10,000; < 10 wt% below 500 Da, < 25 wt% below 1,000 Da	Low concern Functional Groups (FGs): no limit Moderate-concern FGs: Functional group equivalent weight (FGEW) ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined} \geq 5{,}000$ High-concern FGs: FGEW ≥ 5,000
	E2: NAMW ≥ 10,000 Da, < 2 wt% below 500 Da, < 5 wt% below 1,000 Da	No FG restrictions
	E3: No NAMW limit, no oligomeric limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3)
	Non-cytotoxic	e.g., ICCVAM (2006) "BALB/c3T3/A549 lung Cells Neutral Red Uptake (NRU) Cytotoxicity Test, A Test for Basal Cytotoxicity" and Wiemann et al. (2016) "An In Vitro Alveolar Macrophage Assay for Predicting the Short-Term Inhalation Toxicity of Nanomaterials"
Is the NCS biosoluble?	< 100 mg/L in artificial airway lining fluid or < 1 mg/L in artificial lysosomal fluid	Gamble's Solution (e.g., ECETOC (2013) "Poorly Soluble Particles/Lung Overload"), Simulated Epithelial Lung Fluid (SELF) (e.g., Boisa et al. (2014) "Development and Application of an Inhalation Bioaccessibility Method (IBM) for Lead in the PM10 Size Fraction of Soil"), Phagolysosomal Simulant Fluid (e.g., BAUA (2017) "Methodology for the Identification of Granular Biopersistent

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/m^3)	Density (g/cm^3) at 20 °C	MMAD (µm) GSD	HEC (mg/m^3)
PVC	6 h/d, 5 d/wk 32 weeks (Muhle et al., 1990)	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., 1990)	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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