Table XX. *In Vitro* Test Methods and New Approach Methods That May Be Useful for Evaluating Chemicals for Inclusion in Surfactant AOP and Category.

Surfactant AOP	*Information on AOP*	*In Vitro* Assay	Test System
Molecular Initiating Events (MIEs)	MIE for interaction with pulmonary surfactant/loss of function	*In Vitro* Respiratory Toxicity Assays	• *In vitro* lung surfactant inhibition as described by Sorli et al., (2017)
	MIE for interaction/penetration through cell membrane	*In Vitro/Ex Vivo* Irritation Assays	• OECD *In vitro/Ex Vivo* eye irritation tests for penetrance, *e.g.*: (OECD 492) Reconstructed human Cornea-like Epithelium (RhCE), (OECD 437) Bovine Corneal Opacity and Permeability Test, (OECD 438) Isolated Chicken Eye Test, *etc*.
Cellular Level Events (CLEs)	CLE for loss of membrane integrity/general cytotoxicity	*In Vitro/Ex Vivo* Cytotoxicity Assays	• OECD *In vitro/Ex Vivo* eye irritation tests for cytotoxicity, *e.g.*: (OECD 492) Reconstructed human Cornea-like Epithelium (RhCE), (OECD 437) Bovine Corneal Opacity and Permeability Test, (OECD 438) Isolated Chicken Eye Test, *etc*.
			• Cell membrane integrity test (LDH-lactate dehydrogenase cytotoxicity assay), MTT assay or lysosomal membrane integrity test. • BALB/c3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity [HYPERLINK "https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf"]
Organ or Tissue Level Events (OLEs)	OLE for tissue level events	Human organotypic airway epithelial cultures	• EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells • MucilAir EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells
	OLE for tissue level events	Specific *Ex Vivo* Respiratory Toxicity Assays	• Precision-cut lung slice test *etc*. as described by Hess et al (2016)

MIEs

The surfactant AOP is hypothesized to consist of two MIEs that may be informed by *in vitro* assays to determine whether a particular chemistry causes adverse effects on the pulmonary surfactant system (MIE #1), pulmonary cell membranes (MIE #2), or both. For MIE #1, Sorli et al., (2017) developed an *in vitro* lung surfactant inhibition assay that specifically measures whether the substance interferes with lung surfactant function. The assay was initially benchmarked for predicting the effect of waterproofing agents that were shown to be acutely toxic to mice. The authors noted that it may be overly conservative for some substances. Nevertheless, this assay investigated a basic principle (MIE #1) which may also be relevant for some types of surfactants. For MIE #2, *in vitro* eye irritation assays represent appropriate screening approaches for determining the ability of surfactants to interact with cellular membranes and penetrate the corneal layer of the eye. For example, Bader et al., (2013) showed that the Bovine Corneal Opacity and Permeability (BCOP) assay was effective at demonstrating that nonionic (*i.e.*, octylphenoxypolyethoxyethanol), anionic (*i.e.*, SDS), and cationic (*i.e.*, BAC) substances cause irritation to the eye; however, the authors also noted that the endpoints evaluated in this assay should be carefully assessed independently. For octylphenoxypolyethoxyethanol and SDS, the permeability score was more predictive of eye irritation than the ocular opacity score, whereas for BAC, the opacity score was more predictive of eye irritation than the permeability score. Therefore, a systematic investigation of opacity and permeability measures with surfactants using this approach may be helpful with elucidating MIE #2 of the AOP. Combining this assay with another *in vitro* test, such as LDH or MTT assay in confluent nonpolarized cells such as HeLa, which has demonstrated sensitivity for differentiating

Commented [HT32]: Why? Does this make sense with the chemistry, BAC being cationic, causes more X than Y???

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between cell membrane damage induced by different subcategories of surfactants provide an effective measure of cell membrane effects (Inacio et al., 2011). In addition, information on the potential of a substance to cause skin irritation (e.g. OECD TG439) and/or skin corrosion (OECD TG 431) *in vitro*, can provide evidence of the potential for a substance to cause similar irritant or corrosive effects in respiratory tract cells. Corrosion effects mediated by pH extremes should be distinguished from necrosis effects *via* membrane disruption, for example DDAC causes tissue effects in inhalation studies despite having a neutral pH value of 6.8-6.9 ([HYPERLINK "https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=34466&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F34466%3Flang%3Den"]).

Commented [SK33]: Ina´cio A^ S, Mesquita KA, Baptista M, Ramalho-Santos J, Vaz WLC, et al. (2011) In Vitro Surfactant Structure-Toxicity Relationships: Implications for Surfactant Use in Sexually Transmitted Infection Prophylaxis and Contraception. PLoS ONE 6(5): e19850. doi:10.1371/journal.pone.0019850

CLEs

Several *in vitro/ex vivo* assays are available that may indicate whether a new chemical substance is acting via the surfactant AOP and can be assessed within the Surfactant Category. For general cytotoxicity, the ocular irritation/corrosion studies cited in Table XX provide one set of options using cell types that are known to be sensitive to the effects of surfactants. The BALB/c 3T3 NRU cytotoxicity test has been reviewed and recommended by the reviewed by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for use in before animal testing is conducted.(ICCVAM Test Method Evaluation Report, 2006). For each assay, the surfactants with identified inhalation toxicity data that would serve as an analogue for assessing the new chemical substance (*e.g.,* octylphenoxypolyethoxyethanol, oleoyl sarcosine,

DDAC or BAC) should be tested along with the new chemical substance to benchmark the results, whereas nonirritating surfactants with low acute inhalation toxicity such as Polysorbate 20 may serve as negative controls, thereby providing reliable results for estimating the potential for surfactants to cause irritation and cytotoxicity.

OLEs

Commented [ST34]: See ACC edits to this section s

Based on the results of the testing on the CLEs, it may be necessary to perform more robust testing, given the limitations of these assays. For example, the discussed assays measure single cell types, whereas human and animal airway epithelia are composed of multiple cell types that each have specialized functions. Several human airway models have been developed that allow for the assessment of multiple endpoints in three-dimensional culture systems. Two commonly employed systems include EpiAirway™ and MucilAir™ developed by MatTek Life Sciences and Epithelix, respectively.

Organotypic airway epithelial cultures, such as EpiAirway™ and MucilAir™, provide a more realistic physiological *in vitro* model system than *in vitro* cell lines (EPA, 2018). Unlike single cell lines, these organotypic cultures take on a pseudostratified morphology, develop tight junctions, differentiate into multiple cell types, including: basal cells, ciliated cells, and goblet cells; generate mucus, exhibit ciliary beating, have xenobiotic metabolizing capacity, and maintain cultural homeostasis for months. Because of these characteristics, these human airway models are expected to better represent the response of *in vivo* tissue to surfactant exposure than cell line cultures of a single cell type. Depending on the level in the respiratory system where the site of contact / exposure is predicted to occur, using for example RDDR or MPPD modeling for

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determining deposition, different 3D cell culture systems are available that are composed of the different cell types that occur at different anatomical sites in the respiratory tract. For example, MucilAir™ provides 3D co-culture models of cells from nasal, tracheal or bronchial sites, as well as a co-culture of cells from small airways (SmallAir™). EpiAirway™ is composed of a co-culture of normal human tracheal/bronchial epithelial cells and EpiAlveolar™ is a 3D co-culture model of the air-blood barrier produced from primary human alveolar epithelial cells, pulmonary endothelial cells and fibroblasts.

Commented [HT36]: This could be re-written more succintly

Commented [HT37]: Change Table to be 'generic' resp tract regional co-culture models

Exposure to aerosols at the ALI using a Vitrocell® exposure system is a lower throughput approach to *in vitro* two-dimensional exposure systems; however, it provides an exposure more comparable exposure to real-life scenarios for inhaled aerosols. Using ALI exposure, dilution into medium and interaction with medium components does not occur as it would in a submerged culture system. There is interaction of the aerosol with a mucus or surfactant layer if organotypic cultures are used, as there would be *in vivo*, thus more physiologically relevant.

Exposures of these organotypic cultures at the ALI can be combined with a number of assays for assessing cell function and viability which inform the MIEs. Measurement of transepithelial electrical resistance (TEER), LDH-release, and viability assays such as MTT or ATP assays have all been reported for use with these cultures. Further, multiple assays can be performed on the same cultures. TEER measures epithelial integrity, including functionality of intercellular tight junctions. LDH-release measures loss of plasma membrane integrity, which is indicative of cytotoxicity, and MTT and ATP assays measure cell viability. MatTek Life Sciences

recommends the MTT assay for use with their EpiAirway™ cultures and recommends the surfactant octylphenoxypolyethoxyethanol at 0.2% concentration as a positive control for cytotoxicity. These assays can also be used to determine an HEC, which may be used for quantitative risk assessment.

While significant progress has been made toward achieving the objectives to use of high-throughput *in vitro* assays and computational models based on human biology to evaluate potential adverse effects of chemical exposures (NAS 2007, NAS 2017), the investigation of effects using *in vitro* models of higher levels of biological organization remains challenging. All other things being equal, for relevancy to humans and for animal welfare considerations, the 3D human airway cell culture systems discussed above would be the test systems to be aspired.

Commented [RAB38]: NAS 2007 Toxicity Testing in the 21st Century [HYPERLINK "https://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a"]

NAS 2017 Using 21st Century Science to Improve Risk-Related Evaluations [HYPERLINK "https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations"]

Commented [HT39]: Removed BEST. says who?; need a citation from a Workshop or ICCVAM or something like that. Also, next up is PCLS, which is even more realistic, so is this meant to say best of the in vitro cell culture systems?

Precision-cut lung slices (PCLS) is one way to gather OLE data. The PCLS measures multiple endpoints, such as LDH for cytotoxicity and IL-1α for pro-inflammatory cytokine release in *ex vivo* cultures of rodent lung slices, to determine whether a chemical is likely to be toxic to the respiratory tract by inhalation exposure (Liu et al., 2019). PCLS contain intact alveoli, rather than monolayers of one or two cells types (co-cultures). Crucially, in contrast to organoids, cell types are present in the same ratios and with the same cell–cell and cell–matrix interactions as *in vivo*. PCLS are often used in toxicological and anatomical studies regarding contractility in relation to asthma and other respiratory illnesses, such as emphysema (Sanderson et. al. 2011). Therefore, physiological responses, other than cytotoxicity, that may be evoked by the surfactant may be monitored. One further advantage of PCLS is that the PCLS assay can be performed on multiple species to determine inter-species variability in susceptibility.

Commented [RAB40]: Liu et al. 2019 [HYPERLINK "https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-019-1131-x"]

Commented [SM41]: Michael J. Sanderson, Ph.D. Exploring lung physiology in health and disease with lung slices
Pulm Pharmacol Ther. 2011 October ; 24(5): 452–465.

The PCLS test system has been pre-validated in multiple, independent laboratories, and the results showed good correlation when translated from *in vivo* LC_{50} values (Hess et al., 2016). While considered an alternative test, this assay still requires use of laboratory animals, albeit that, compared to *in vivo* inhalation tests, this assay reduces the number of animals that would be needed to conduct dose response studies. From a rat lung (1 g), about > 200 slices can be prepared. In general, for 1 concentration, 2 slices are used, resulting in 100 different concentrations or repeats that can be tested with one sacrificed rat. Additionally, PCLS cultures are stable for up to 4 weeks and allows for exposures via media or air with additional adaptations. As such, the PCLS system meets the goal of reducing animal testing. The rationale for selection of the PCLS assay, as with any inhalation toxicity assay, should be scientifically justified in advance of initiating testing.

Uncertainties/Limitations

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A number of *in vitro* assays have been discussed as to their potential utility within the context of surfactant AOP elements (*i.e.*, MIEs, CLEs, and OLEs). Uncertainties and limitations associated with these assays are discussed for each of the above testing systems, as well as others (Clippinger et al., 2018), it is important to consider that these assays were not systematically tested using surfactants or benchmarked against *in vivo* inhalation toxicity data on surfactants. Nonetheless, these assays, alone or in combination should be considered from the point of view of providing information to determine whether a new chemical meets the Surfactant Category criteria and/or to understand whether the new chemical may be more or less bioactive or toxic than the sub-category analogue(s) currently available. In other words, absent any refining

information, EPA will generally use the framework and analogue toxicity data identified in this investigation to assess potential risks from surfactants.

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In this regard, approaches to evaluate the scientific confidence of test methods for hazard assessment and risk assessment have, and continue to, evolve. A fit for purpose framework, employing specific criteria to establish relevancy, reliability, variability, sensitivity, domain of applicability, *etc*., for evaluating and documenting the scientific confidence of a new method for use for informing specific decision context has emerged from the regulatory science community to address the challenges posed for validation of NAMs that provide scientific rigor, but that are also flexible and adaptable (Parish et al., 2020; Patlewicz et al., 2015, EPA 2020).

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[HYPERLINK "https://www.sciencedirect.com/science/article/pii/S0273230015000392"]
[HYPERLINK "https://www.epa.gov/sites/production/files/2020-06/documents/epa_nam_work_plan.pdf"]

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Once such fit for purpose scientific confidence evaluations are documented, there are several ways that these assays can be used to avoid excessive animal testing. First, testing can be performed on the surfactant AOP to evaluate the potency of new surfactants versus a comparator surfactant (analogue) within the relevant subcategory that has repeated concentration inhalation toxicity data. Second, depositional data using models such as RDDR or MPPD for determining the depositional fraction of the new surfactant may be used for test concentration estimation and for estimating a potency ratio. Finally, *in vitro* to *in vivo* extrapolations (IVIVEs) may be used to determine a HEC for quantitative risk assessment.

Commented [OS46]: Tala to include some additional text – read across, etc.

Tiered-testing Strategy

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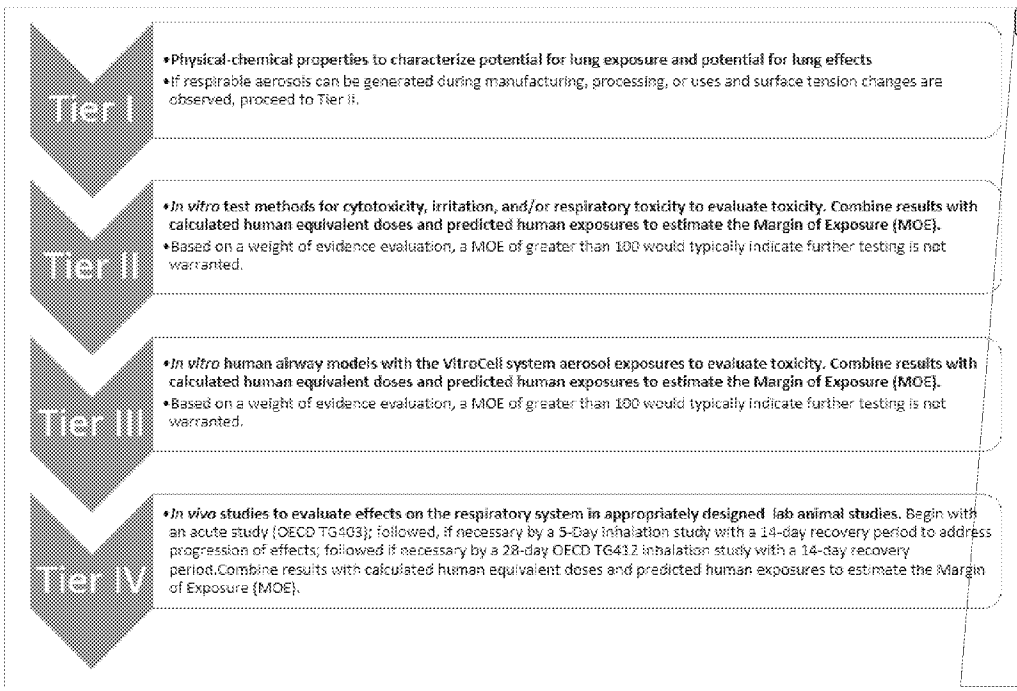
A tiered testing approach for surfactants that have been established to meet the Surfactant Criteria is presented in Figure 1. It commences with the least complex, most efficient testing methods, and the complexity of the test system increases, commensurate with the AOP, to more effectively emulate the biology and physiology of the *in vivo* respiratory tract system.

Draft Figure 1.



Commented [OS48]: Additional changes coming

Tier I—Physical-chemical properties

Surfactants are proposed to cause a specific sequence of biological events in the pulmonary region if they are respired. Manufacture, processing or use of a surfactant in a respirable form, (*i.e.*, ≤ 10 µm) is therefore, an initial consideration of the potential for a surfactant to cause pulmonary toxicity. Particle size is an established method for determining respirability of particles/droplets. Several validated test methods exist for determining potential respirability, i.e., particle size, of a new chemical substance (*e.g.*, OECD GD 39, ISO 21501-1:2009, OECD TG 110 and OPPTS 830.7520). As a practical matter, a particle size cutoff of > 1% respirable particles/droplets by weight (wt%), determined in a well conducted study using a valid measurement method will generally be considered as triggering a quantitative assessment of inhalation toxicity on a new chemical substance meeting the Surfactant Criteria. In other words, EPA will generally assess the potential inhalation toxicity for a new surfactant chemical substance when the manufacture, processing or use results in greater than 1% (by weight) of the surfactant particles/droplets having a particle size of less than 10 um. This cutoff is consistent with EPA's "trace amounts" threshold for the nonreportable content for nanoscale materials (EPA, 2017).

If respirable particles/droplets can be generated at greater than 1 wt% during manufacturing, processing, or any of the uses for the new chemical substance, proceed to Tier II.

Commented [OS49]: Raphael: As per polymer overload, having a mg/m3 metric in addition to the 1% respirable would be helpful in certain situation e.g. very low particle/droplet emission during use so measuring 1% respirable is technically challenging or not feasible.

Commented [ST50R49]: I need to discuss this with Tala. The mg/m3 approach for this category is a bit more complicated than for the PLO category.

Commented [HT51R49]: We cannot figure out how this could be done without going to Tier II to see if AOP is invoked.
One could always explain in the PMN the use conditions that would keep EXPOSURE very low, i.e., below 1%.

Tier II—*In vitro/Ex vivo* studies

The following *in vitro/ex vivo* test methods may provide potentially useful information indicating whether or not a new chemical substance invokes MIEs and CLEs. In order to determine the best approach for *in vitro/ex vivo* testing, a pre-notice consultation with EPA is highly encouraged,

given that none of the following studies are validated to determine lung toxicity induced by surfactants. In general, the testing approach should include a combination of assays, such as one on "Pulmonary surfactant interaction/loss of function", one on "Cell interaction/penetration", and one on "General cytotoxicity" (see Table Z). The *in vitro*/*ex vivo* eye irritation studies may satisfy the latter two endpoints. If equivocal findings are obtained on the "Cell interaction/penetration" or "General cytotoxicity" assays, then the NRU cytotoxicity test should be performed. For each assay, the representative analogue to the new chemical substance for the respective subcategory of surfactants should be tested under identical conditions for comparison . Further, dosimetry models such as RDDR or MPPD may be applied to the new chemical substance to aid with identifying the appropriate test concentrations for the *in vitro*/*ex vivo* test systems, considering for example the surface area of the culture system or *ex vivo* tissue, loss mechanisms, *etc*.

Commented [HT52]: Needs more explanation; EPA would normally do this in assessing...if PRIMARILY for identifying app test, say that and then add in that any RDDR or MPPD modeling should be discussed at pre-submission consultation AND sent in with PMNcc

Pulmonary surfactant interaction/loss of function

- *In vitro* lung surfactant inhibition as described by Sorli et al., (2017)

Cell interaction/penetration

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.,* OECD 492: Reconstructed human Cornea-like Epithelium (RhCE) Test Method; OECD 437: Bovine Corneal Opacity and Permeability Test Method; OECD 438: Isolated Chicken Eye Test Method, *etc*.

General cytotoxicity

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.*: (OECD 492) Reconstructed human Cornea-like Epithelium (RhCE), (OECD 437) Bovine Corneal Opacity and Permeability Test, (OECD 438) Isolated Chicken Eye Test, *etc*.
- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recommended protocol for the BALB/c 3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity (Appendix C1, [HYPERLINK "https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf"])

Each of the assays may be used to determine a starting point to calculate a modified POD_{HEC} using *in vitro* to *in vivo* extrapolation (IVIVE) for the purpose of evaluating the relative potency of the new chemical substance versus the comparator analogue. The most sensitive of the biologically relevant endpoints identified from the assays should be used to calculate a POD using BMD modeling, when possible, with the $BMCL_{1SD}$ metric. This metric is based on the benchmark response (BMR) of one standard deviation suggested for *in vitro* assays (a ~15%, 13% and 5% change from the control group values relative to the data range for the TEER, resazurin and lactate dehydrogenase assays, respectively), per the 2018 FIFRA Inhalation Scientific Advisory Panel meeting ([HYPERLINK "https://www.regulations.gov/docket?D=EPA-HQ-OPP-2018-0517"]). However, alternative metrics may be considered. For example, the pharmaceutical industry has used fixed adverse response thresholds that are appropriate for the specific biological assay (*i.e.*, EC_{15}, EC_{30}, *etc*; O'Brien 2006). Regardless of the metric used, a justification for its selection should be provided. In those situations where data are not amenable to BMD modeling, the *in vitro* concentration tested should be determined based on the expected HEC for the appropriate subcategory (taking

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into account the necessary MOE) to ensure that the *in vitro* data are generated in a concentration range relevant to the expected HEC.

Based on the results of the above testing combinations, the following outcomes are possible, noting that a positive result in one of the 3 assays, will drive the determination of "greater" or "comparable" toxicity, whereas negative results in all 3 assays will drive the determination of "lower" toxicity, as described below.

Commented [HT54]: SALAZAR: NOT CLEAR WHAT THE '3' ASSAYS ARE

Commented [RAB55]: Its not clear how MOE fits into these decision criteria. I inserted draft text below – highlighted -- as a suggestion – please review and revise as needed

If the new chemical substance exhibits greater toxicity versus the comparator analogue, per the study method criteria, in any one of the evaluated assays, proceed to Tier III.

If the new chemical substance exhibits comparable toxicity to the comparator analogue, per the study method criteria, in any of the evaluated assays, then stop at Tier II. The analogue POD is suitable for conducting the risk assessment.

If the new chemical substance exhibits lower toxicity or negative findings relative to the comparator analogue, per the study method criteria, in all the evaluated assays, then determine if a modified POD_{HEC} can be calculated from the representative analogue in the respective subcategory of surfactants. If a modified POD_{HEC} can be calculated, then recalculate the MOE using the modified POD_{HEC}. If risks are still identified with the modified POD_{HEC}, then stop at Tier II. Evaluate whether to use the analogue POD and/or modified POD_{HEC} for conducting the risk assessment.

If it is not possible to calculate a modified POD_{HEC}, then use the comparator analogue for risk assessment or proceed to Tier III.

Tier III – Human Airway Models/PCLS Assay

Several testing options are available for evaluating OLEs in the surfactant AOP. The test system employed should focus on evaluating effects in the respiratory tract at the predicted sites of deposition (*e.g.*, TB and/or PU regions) using RDDR or MPPD modeling, as discussed previously. A justification for using a particular system(s) versus another should be provided and may be discussed with EPA as part of a pre-notice consultation. Available test systems include, but are not limited to, the following:

- EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells
- MucilAir EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells
- SmallAir™ 3-D constructs of primary human small airway epithelia reconstituted *in vitro*.
- Precision-cut lung slice test *etc*. as described by Hess et al (2016)

Based on the results of the 3D-construct and/or PCLS testing, *in vitro* to *in vivo* extrapolation may be possible for developing a POD_{HEC} for use with characterizing potential risks using the MOE approach. Though the occupational/consumer exposure estimates may be the same between Tiers II and III, the Tier III test results may offer the opportunity for refining the risk

estimates. For example, the BMR used for calculating the POD_{HEC} may be refined because the ALI-based exposure is more consistent with inhalation exposure in a human than the submerged culture exposures employed in Tier II (EPA, 2018). Further, application of uncertainty factors for calculating the benchmark MOE may also be refined, if for example, human cultures are used, which may preclude the need for applying a UF_A.

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August 30, 2018

If the Tier III test data are amenable for developing a POD_{HEC}, then the risk estimates should be reassessed. If no risks are identified under the conditions of use, then stop at Tier III. If risks are still identified under the conditions of use, then consider engineering controls and/or appropriate PPE requirements for worker risks and/or reformulation of the new chemical substance at a lower wt% in products for consumer risks.

If the Tier III test data are not amenable for developing a POD_{HEC}, then proceed to Tier IV.

Tier IV—*In vivo* studies

Strategic *in vivo* testing may be needed to inform the hazard and risk assessment of new chemical substances, particularly in those instances where a new chemical substance has unique properties that preclude a determination that one of the subcategory analogues is appropriate for read across, as well as in instances where the test data generated under Tiers II and III are not amenable for deriving POD_{HEC}s. If *in vivo* testing is needed, a pre-notice consultation meeting with EPA is strongly encouraged prior to initiating any vertebrate animal testing. This point is especially

important because TSCA section 4(h)(3) indicates that any person developing information for submission under TSCA section 5 on a voluntary basis shall first attempt to develop the information by means of an alternative test method or strategy identified by EPA before conducting new vertebrate animal testing U.S.C. 2603 (h)(3)(A).

The potential for surfactants to cause adverse effects on the respiratory tract are based on acute toxicity concerns, that is, interfering with pulmonary surfactant and/or disrupting cellular membranes. Since these effects may be captured using appropriate exposure concentrations in short-term inhalation studies, the following *in vivo* tests should be considered:

- Step 1: OECD Acute TG 403 (modified)** featuring rats exposed for 4 hours and observed for 2 weeks using aerosol exposure.

- Step 2: 5-Day inhalation study with a 14-day recovery period** to address progression of effects (use OECD TG 412, but conduct exposure duration for at least 5 days).

**Modifications to all of the above studies should (if measurable) include pulmonary function testing, analysis of BALF, LDH release, blood oxygen (pO_2) content, and satellite reversibility. OECD TG 412 and OECD GD 39 should be consulted. Additionally, the sensory irritant potential can be measured using ASTM E 981 to determine reflex inhibition (Alarie et al., 2001).

Commented [KA571]: Alarie, Y., G.B. Nielsen, and M.M. Sch
bioassays for evaluation of indoor air quality. *Quality Handbook*. Spengler, J.D., J.M. J.F. McCarthy (eds.). New York: McGra pp 23.31–23.49.

The results of the *in vivo* testing should be used for reassessing and recharacterizing the risks estimated using a surfactant analogue chemical.

CONCLUSIONS

[To be added once text is finalized]

ASSOCIATED CONTENT

(Word Style "TE_Supporting_Information"). **Supporting Information**. A listing of the contents of each file supplied as Supporting Information should be included. For instructions on what should be included in the Supporting Information as well as how to prepare this material for publications, refer to the journal's Instructions for Authors.

The following files are available free of charge.

brief description (file type, i.e., PDF)

brief description (file type, i.e., PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

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Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

[ADDIN EN.REFLIST]

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Message

From: Stedeford, Todd [Stedeford.Todd@epa.gov]
Sent: 7/29/2020 9:57:47 AM
To: Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Snyder, Stephanie [stephanie.snyder@covestro.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Rick_Becker@americanchemistry.com; Henry, Tala [Henry.Tala@epa.gov]; Owen Price [oprice@ara.com]; Salazar, Keith [Salazar.Keith@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]
Subject: draft lung overload manuscript 27 July 2020.ver.4
Attachments: Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.4.docx

All,

Here is the latest draft with comments/edits I received yesterday from Stephanie and from EPA. I kept the edits in track changes. Note, I also added some conclusions, which need review/editing. We can review this draft during our call today at 1 pm. If any of you have additional edits/comments, please keep them coming. I will continue to update as I receive them.

Thanks,

Todd

Polymer Lung Overload Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

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KEYWORDS: Inhalation, Lung Overload, New Approach Methods, Particle Toxicity, Risk Assessment~~, (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval~~.

ABSTRACT

Poorly soluble and non-reactive high-molecular weight (HMW) polymers (≥10,000 Daltons) represent a generic category of substances that are extensively used in industrial and consumer applications (*e.g.*, plastics). Under the amended Toxic Substances Control Act (TSCA), HMW polymers may qualify for an exemption from the pre-notification requirements that exist for polymeric, new chemical substances. However, for HMW polymers that do not meet the exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload. In the present evaluation, a systematic review of the literature was performed to identify studies that would aid with defining key properties for determining whether respirable HMW polymers may present an unreasonable risk to human health. These properties included: respirability, reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a

chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for ~~several~~ a toxicological analogues that ~~can~~ may be used in risk assessments on these substances. Finally, a tiered-testing strategy that maximizes the use of non-vertebrate testing (*i.e.*, NAMs) was developed that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));
2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

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3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));
4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or
5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, Federal Insecticide, Fungicide, and Rodenticide Act), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><DisplayText>[1]</DisplayText><record><rec-number>31</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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EPA has historically used various approaches to evaluate the potential hazards of new chemical substances including ~~the use of~~ computational toxicology models and ~~analogue and~~ category approaches to "read-across" from existing data to new chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program (NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on specific ~~chemical~~ definitions and boundaries that summarize the hazard concerns (*e.g.*, human health or environmental toxicity) and recommend testing ~~that may be conducted~~ prior to submitting a new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T

SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical propertiesto the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties, the NCP Chemical Categories were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect vertebrate testing reduction goals. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particulates[1] includes vertebrate animal testing, such as a 90-day subchronic inhalation toxicity study in rats with a 60-day recovery period [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key

[1] EPA identified particles as "respirable" to humans "if there are any particles ≤10 μ[m] in diameter in the material being handled by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical Categories cover ~~the~~ defined boundaries ~~defined therein~~and therefore may not ~~reflect development of~~include alternative chemistries that are intended to replace a chemical in the ~~do not fit within the~~ current NCP Chemical Categories~~, even for chemicals that the alternative chemistries are intended to replace~~ (*e.g.*, the use of polymeric alternatives to replace monomeric forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has ~~also~~ developed exemption criteria for specific types of polymeric substances, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption"~~, for specific types of polymeric substances~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria are exempt from the new chemical substance notification requirements, although there are still ~~some requirements, including~~ annual reporting and recordkeeping requirements [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

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EPA~~'s polymer exemption~~ established three polymer exemption types, designated as E1, E2, and E3. The general criteria for new ~~chemical~~ polymer substances meeting these exemption types ~~for polymers~~ are shown in [REF _Ref46665925 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

Exemption Type	*Number-average molecular weight (NAMW)*	*Oligomeric Material Criteria*	*Functional Groups (FGs) and Functional Group Equivalent Weight (FGEW) Content*
E1	1,000 ≤ NAMW < 10,000	< 10 wt% below 500 Daltons < 25 wt% below	Low concern FGs:[c] no limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

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		1,000 Daltons	
E2	NAM W ≥ 10,000	< 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons	No FG restrictions
E3	No limit	No limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

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[a] See 40 CFR § 723.250(b) Polymers. "Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units." [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Water absorbing polymers with NAMW ≥ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[c] "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

~~As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption"~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]~~; however, t~~There are instances, however, where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc.*, in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather ~~are based~~ on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW $\geq$ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, $\leq$ 10 μm) represent a ~~general~~ class of chemical substances (hereinafter referred to as "HMW polymers") that may cause an~~potential~~ inhalation ~~toxicity~~ hazard (*i.e.*, lung overload) *via* the mode(s) of action (*i.e.*, impairment of alveolar-macrophage mediated clearance), as identified in rat inhalation studies, to chemical substances ~~present~~ in the respirable, poorly soluble particulates ~~in the~~ NCP Chemical Categor~~ies document for respirable, poorly soluble particulates~~y. ~~However,~~

~~the chemical substances that are provided as~~ The analogues for the respirable, poorly soluble particulates ~~within the boundaries for the~~ NCP Chemical Category ~~on respirable, poorly soluble particulates~~ are ~~limited to~~ discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for ~~those~~ polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as representative toxicological analogues with points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. ~~An additional aim was to introduce~~In addition, new approach methodologies (NAMs) were introduced as part of the tiered-testing strategy ~~to~~ that meet the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

MATERIALS AND METHODS

Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at

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"Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies that evaluated potential "lung overload" toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, "lung overload" refers to the "type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance" [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[6]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-57</pages><volume>12</volume><number>1-2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals,

Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><keyword>Risk Assessment</keyword><keyword>Species Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-Feb</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>10715617</accession-num><urls></urls><electronic-resource-num>10.1080/089583700196536</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is defined differently in experimental animals versus humans [ADDIN EN.CITE ADDIN EN.CITE.DATA], the literature searches used search strings that were intended to be overly inclusive to identify studies that evaluated "overload" in experimental animals and humans. A secondary objective was to identify potential NAMs that may be incorporated into a tiered-testing strategy that minimizes the use of vertebrate animals.

Risk Assessment Approaches Under TSCA

EPA generally uses ~~the~~ a margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments ~~performed~~ on new chemical substances ~~under TSCA~~. The MOE ~~approach~~ is calculated based on a point(s) of departure (POD) divided by ~~a~~ the human exposure estimate(s). The POD is ~~typically identified~~developed from an effect level ~~from a study(ies) in experimental animals~~ (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or benchmark dose [BMD]) typically

identified from animal studies. An ~~duration~~ adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*, workers = 8 hours/day, 5 days/week) versus the exposure conditions ~~employed~~ in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated ~~for new chemical substances~~ using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) in mg/day or lifetime average daily doses (LADDs) in mg/kg-bw/day. Given that most new chemical substances ~~will~~ usually do not have occupational exposure monitoring data, ~~except for possible monitoring data on analogues,~~ the PDR is ~~typically~~ used as an initial conservative exposure estimate when calculating the MOE. For chemical substances ~~used~~ in a powder or particulate form, the ~~general~~ default PDR values for respirable ~~or~~ and total partic~~ulate~~s are 50 mg/day (*i.e.*, 5 mg/m^3) ~~or~~ and 150 mg/day (*i.e.*, 15 mg/m^3), respectively [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><DisplayText>[12]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595776956">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></reco

rd></Cite></EndNote>]. However, for chronic effects like lung overload, the LADD represents the more appropriate exposure metric for quantifying potential risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><DisplayText>[13]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595778575">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Interpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>20, https://www.epa.gov/sites/production/files/2015-05/documents/05-iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. A summary of the default values used ~~for~~ in calculating PDRs and LADDs for new chemical substances in powder or particulate form is provided in [REF _Ref46666189 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	Cm × b × h	Mass concentration of chemical in air (Cm)	5	mg/m^3

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		Volumetric inhalation rate (b) ($0 < b \leq 7.9$)	1.25	m^3/hr
		Exposure duration (h) ($0 \leq h \leq 24$)	8	hrs/day
LADD (mg/kg-bw/day)	(I × ED × EY) / (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) ($0 \leq$ ED (integer) ≤ 365)	250	days/site-yr
		Years of occupational exposure (EY) ($0 \leq$ EY)	40	years
		Body weight (BW) ($0 \leq$ ATc)	80	kg
		Averaging time over a lifetime (chronic) ($0 \leq$ ATc)	70	years

For each of the MOEs calculated ~~herein~~in this article, both the PDR and LADD have been provided ~~are provided~~ for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE is higher than the benchmark MOE, the ~~risks are not considered a concern under TSCA~~chemical substance is considered as not posing a potential risk.

Benchmark MOE Derivation

The benchmark MOE ~~is derived to~~ accounts for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><Dis

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playText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or UF_H), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or UF_A), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or UF_L). The default values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance ~~focused on improving~~to improve the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Application of DAFs to the animal airborne exposure values yields estimates of the

concentration ~~that would result in the same concentration to~~in humans, ~~that is,~~ the Human Equivalent Concentration (HEC). For studies ~~reporting~~ with only a LOAEC, EPA recommends benchmark dose modeling be performed~~, if the experimental data are amenable,~~ to identify a BMDL ~~, and therebyto~~ reduce the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with their potential applicability to the available studies that evaluated lung overload from HMW polymers.

Regional Dose Dosimetry Ratio (RDDR)

EPA may apply DAFs to PODs ~~identified~~ from experimental animal studies based on the methods described in ~~its~~ EPA's 1994 guidance document ~~titled~~ "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. ~~When applied~~In this method, the default DAF accounts for the toxicokinetic component of the UF_A and is reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, ~~since~~ the POD is dosimetrically adjusted to a POD_{HEC}, ~~whereas~~and the ~~remaining~~ UF_A value of approximately 3 accounts for the toxicodynamic component of the UF_A. EPA's 1994 guidance document recommends the use of ~~Dosimetry~~ dosimetry or physiologically-based pharmacokinetic models ~~are preferred to the~~over default models when they are available [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

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To derive a DAF for particle exposures, EPA developed a software program for calculating the regional deposited dose ratio (RDDR), ~~that is,~~ the DAF for particles. The RDDR is an empirical model of deposition, ~~that is~~ applicable to particles in the size range of 0.5-30 μm and calculates an RDDR ~~value~~ as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute volume (V_E; mL/min), depositional fraction (Fr) ~~of the particulate~~ in the different regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF) for the region of interest, such as respiratory tract surface area~~, for the region of interest~~. The RDDR ~~user~~ inputs include mass median aerodynamic diameter (MMAD), geometric standard deviation (σ) ~~for the particle of interest~~, and the average bodyweight of the animal ~~used in the study~~ from which default V_E and surface areas of the respiratory tract regions ~~for the animal~~ are calculated. The RDDR may be applied to the ~~duration~~ duration-adjusted POD; however, risk assessments performed under TSCA apply the RDDR to the POD obtained ~~under~~ in the laboratory animal regimen~~. Thereafter~~, and the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ADDIN EN.CITE <EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[16]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>DOSBox</author></authors></contributors><titles><titl e>DOSBox "Way more FPA than Counterstrike !"</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></ dates><urls></urls></record></Cite></EndNote>].

Multiple-Path Particle Dosimetry (MPPD)

Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum>< DisplayText>[17]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian,

B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy & histology/physiology</keyword><keyword>Lung/*anatomy & histology/physiology</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal Volume/physiology</keyword><keyword>Trachea/anatomy & histology/physiology</keyword></keywords><dates><year>1995</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590</isbn><accession-num>8566482</accession-num><urls></urls><electronic-resource-num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.* (2016) [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>[18]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author><author>Asgharian, B.</author><author>Schroeter, J.D.</author><author>Price, O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>14-26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] is a mechanistic, multipath model that was modified and used to predict deposition, clearance, and lung burden over the course of a long-term exposure , as described by Ladics *et al.* (2020) [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In

preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. As with the RDDR outputs, the MPPD outputs provide values that may be used to calculate a POD_{HEC}; however, unlike the RDDR model, MPPD provides outputs that may be used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via* retained dose.

The MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-

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Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. These rates are considered representative of insoluble particles. More recently, the ICRP model and clearance rates have been updated based on improved lung burden data [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Refinements may be imparted by chemical-specific dissolution data and exploration of these new model values. Hygroscopic growth is currently not addressed in either the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers. In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-week rat exposures. In humans, MPPD implements the ICRP clearance model localized for individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human model. Additional uncertainty in

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the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach~~, as discussed in EPA (2012)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not ~~identified~~ available in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1. ~~, because t~~The statistical lower confidence limit on the concentration at the BMD (*i.e.*, the BMDL) is a dose level corresponding to specific

response levels near the low end of the observable range ~~of the data and~~that incorporates and conveys more information than the NOAEC or the LOAEC [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, ~~and~~ model fit ~~was~~ evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit ~~as displayed graphically~~. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

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app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract screening, 28 articles were selected for full text review, and 23 articles were identified using additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review, only 24 articles contained relevant information that satisfied the PECO criteria for lung overload from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in 46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review; seven of the13 articles were also identified in the initial literature search. Complete details on the

systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries, to develop the health effects summaries in the section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The ~~category~~ boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed ~~further~~ below.

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It should be noted, although ~~that even if~~ a HMW polymer satisfies the ~~category~~ boundary criteria for the category, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

Respirable particles are those chemical substances with a particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its "Air Quality Criteria for Particulate Matter", represents "particles collected by a sampler with an upper 50% cut point of 10 μm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, depending on the sampling method and size fraction collected, the sample may

contain particles between 10 and 30 μm diameter that are excluded from the 10 μm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size ~~cuts~~ of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm D_a particles as an upper limit for particles ~~with this size~~ entering the alveolar region [ADDIN EN.CITE <EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><DisplayText>[24]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Further, consideration must ~~also~~ be given to the particle settling ~~that may occur~~rate. ~~For example,~~ ~~i~~In still air, 10 μm spherical particles with a density of 1 g/cm^3 can remain airborne for approximately 8 minutes [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-

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title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]~~. However~~, and as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 μm particles to settle in still air) [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[24, 25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-

title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. ~~Though~~ Although occupational monitoring data provide ~~the most direct~~ assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and ~~the reality~~ that ~~nearly all~~ solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion. For the purposes of this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc*., in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 μm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, ~~a practical cutoff of~~ >particles that are greater than or equal to 1% respirable particles by weight (wt%) based on particle size distribution data for the material is the practical ~~as the~~ cutoff for assessing respirable particles and ~~this percentage would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt%~~ is the same cutoff EPA applies to the nonreportable content of

nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[26]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ~~This~~ The same cutoff would apply to the particle/droplet size distribution ~~in the case of~~for aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

EPA's Functional Group (FG) and Functional Group Equivalent Weight (FGEW) criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive and included or reactive and ~~included or~~ excluded from the category~~, respectively~~. As shown in [REF _Ref46665925 \h * MERGEFORMAT], the E1 polymer exemption criteria include low-concern, moderate-concern, or high-concern FGs. ~~A summary of r~~Representative FGs meeting each of these hazard concern levels is shown in [REF _Ref46674358 \h * MERGEFORMAT].

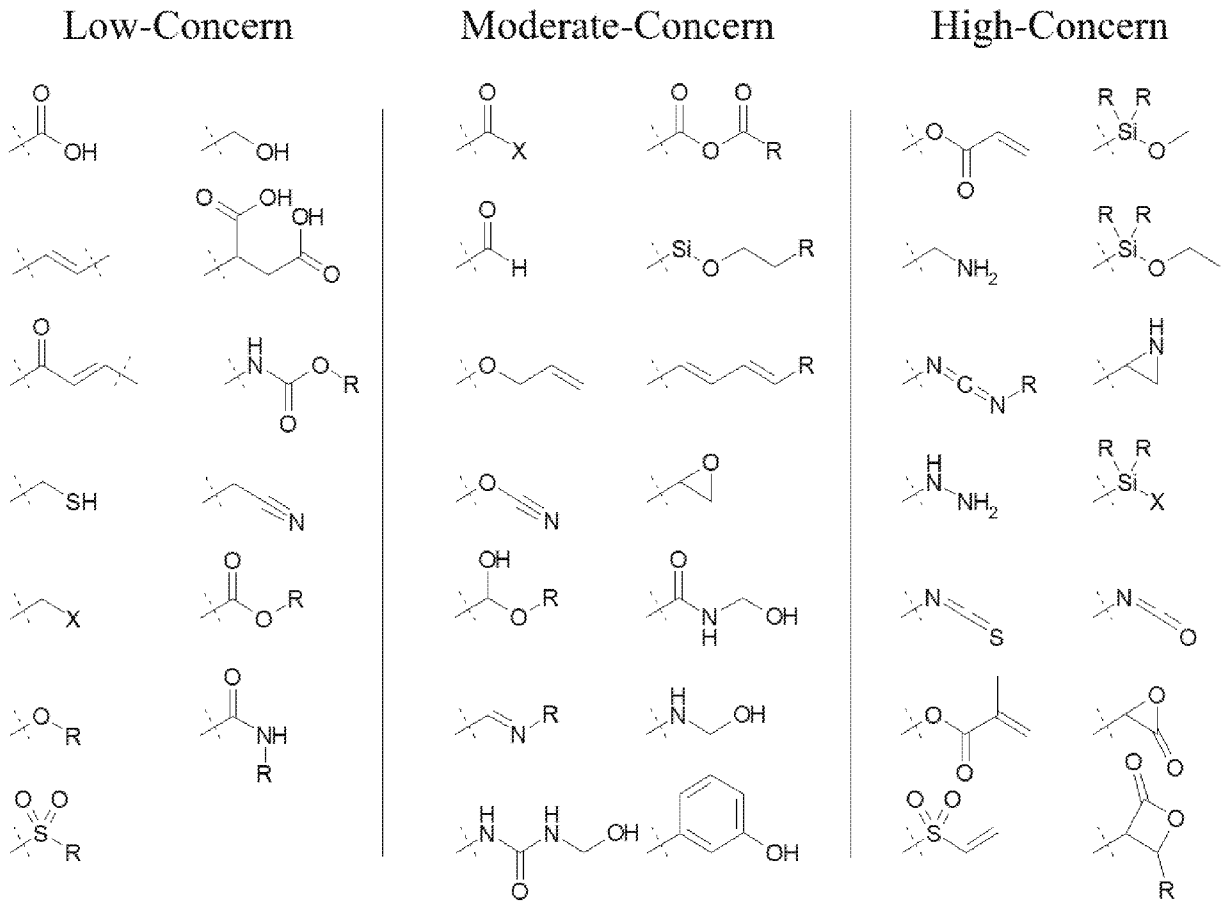

Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The following cutoffs are proposed as the category boundaries for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-concern FGs (FGEW ≥ 1,000), or high-concern FGs (FGEW ≥ 5,000). "R" represents an undefined structure; "X" represents a halide. See: EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A ~~generally recognized~~ property of respirable, low reactive (*i.e.*, low toxicity) particles that ~~can~~ may cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><DisplayText>[27]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792442">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Section 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM,

Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>22, https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-748-B12-001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. These values were not established for evaluating the solubility of particles for lung overload; however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><DisplayText>[28]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792078">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW

polymers. ECETOC (2013) [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial biosolubility screening approach that provided qualitative determinants (*i.e.*, "soluble", "insoluble", "Low dissolution rate", or "Very high dissolution rate") for assessing biosolubility; however, no quantitative thresholds were provided. In comparison, the International Commission on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and Health (FIOSH) provided quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day^{-1}), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day^{-1}), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day^{-1}) [

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<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-

urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of ≤ 1 mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed previously, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are ≤ 10 μm and ≥ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [REF _Ref46673847 \h * MERGEFORMAT], which consider water extractability/biosolubility and the legally binding

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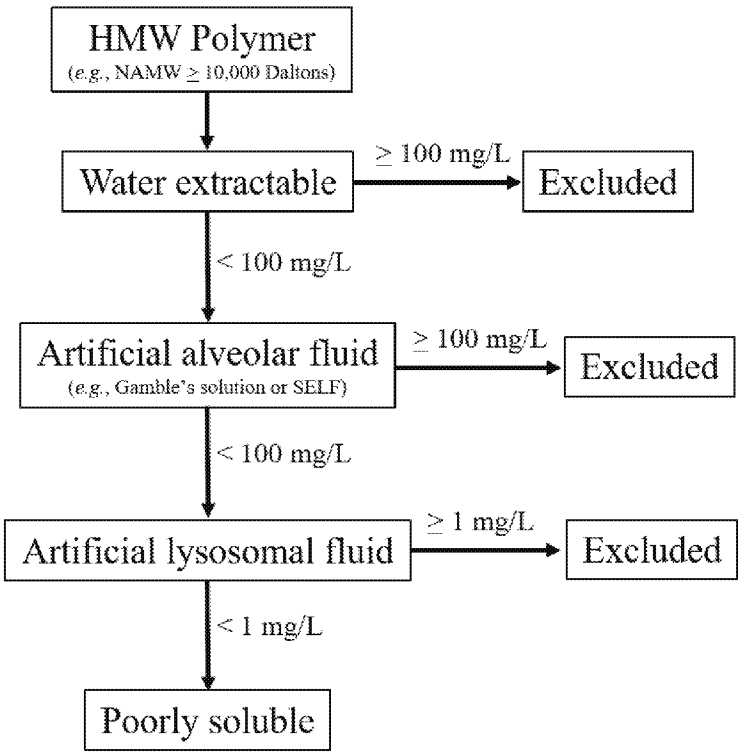
permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health Administration (OSHA) for respirable particulates not otherwise regulated or PNOR (*i.e.*, 5 mg/m^3).

Scheme [SEQ Scheme * ARABIC]. Screening criteria for determining water extractability and biosolubility.



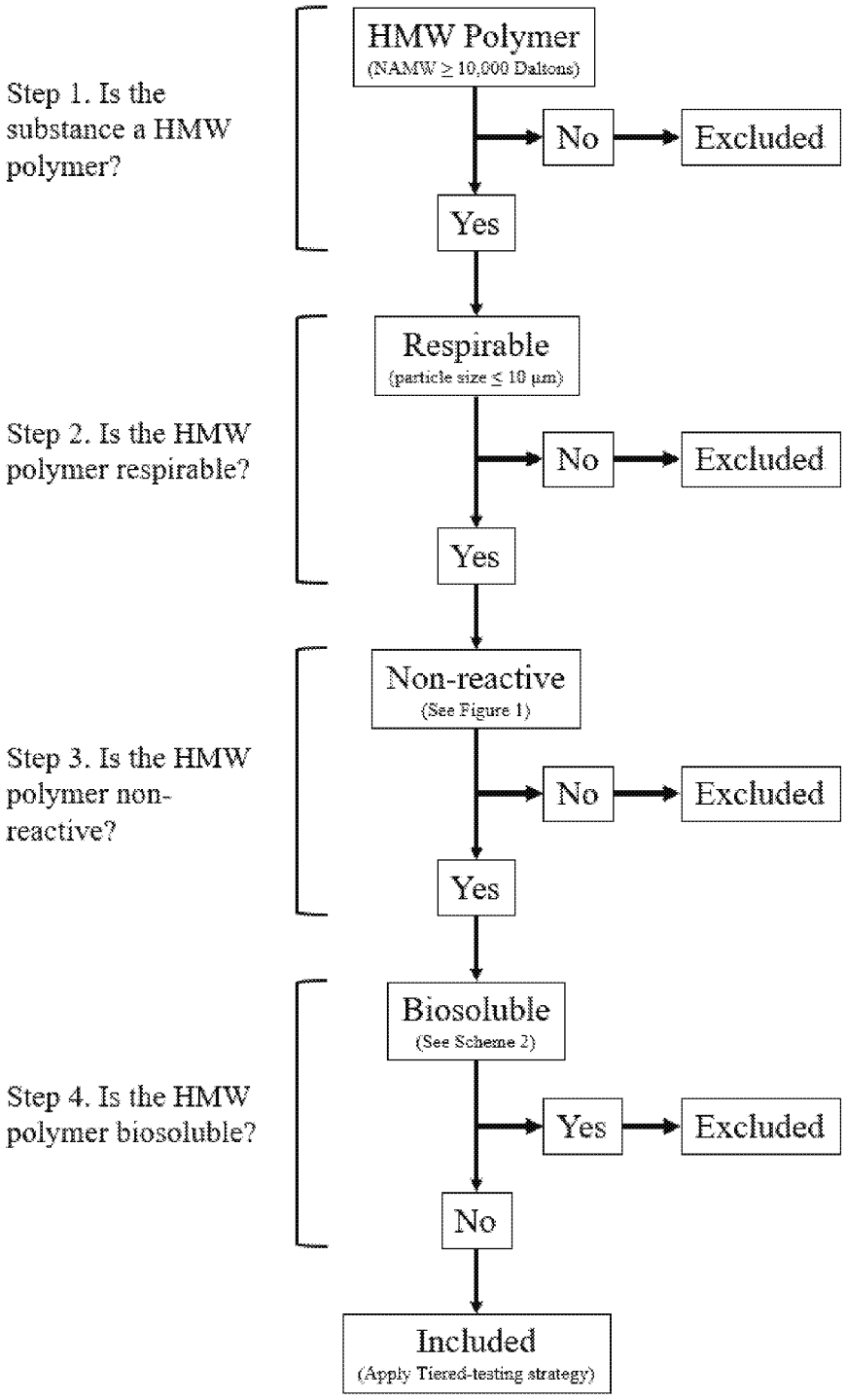
The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been ~~established to correlate~~correlated with

biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected~~ rather than the low water solubility cutoff~~, since it ~~represents a transition from slight to moderate water solubility and~~ is ~~therefore~~ expected to be conservatively inclusive ~~in the first step because water extractability is generally expected~~and to overestimate the insolubility of polymers in biological fluids. In the second ~~screen~~step, ~~two~~ biosolubility cutoffs ~~may be used,~~are either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m^3 (*i.e.*, 50 mg/day; 5 mg/m^3 × 10 m^3/day) for the respirable fraction. The ~~first value is based on EPA (2020)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>75</RecNum><DisplayText>[31]</DisplayText><record><rec-number>75</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595843741">75</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Revocation of Significant New Use Rule for a Certain Chemical Substance (P-16-581), Proposed rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>18179-18181</pages><volume>85</volume><number>63</number><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]~~, where the Agency applied a~~ biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid~~. This value would~~ equates to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ADDIN EN.CITE

<EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum><DisplayText>[32]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons) materials, which meet the ~~above-stated~~ criteria for these parameters. HMW polymers ~~meeting these criteria are those which~~ are typically formed through various polymerization processes~~.~~ ~~Chemical substances~~, included ~~are~~ branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

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[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A, on the left, is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B, on the right, is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C, on the bottom, is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

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systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of "overload" for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[35]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: "This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies ~~that were identified~~ are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload ~~of some~~for new chemical substances.

Human Data

The hazard concerns discussed ~~herein~~ are limited to chronic effects in the lower respiratory tract of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies ~~have shown that~~with rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-

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135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the ~~available studies that evaluated~~ evaluation ~~potential hazards from~~of exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good

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laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

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title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al*. (1992) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

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effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance ~~used by~~as Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.

/author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
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Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[42]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies ~~and~~ under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed similar effects ~~similar~~ to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining ~~time~~test period. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters

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(increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week)

to PVC powder at concentrations ≥ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, respectively, supporting that lung overload occurred at concentrations ≥ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

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Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for predicting biologically active ~~toxicity~~ from passive (*i.e.*, overload condition) toxicity. The assay ~~uses~~ used rat NR8383 alveolar macrophages in cell culture

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medium incubated with test material ~~in cell culture medium, and~~to assess~~es~~ toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours)~~ in the cell culture supernatant~~. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay used a particle surface area-based threshold of <6000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL) to determine the biological relevance of the lowest observed significant *in vitro* effects ~~threshold for active toxicity was a surface-area/volume concentration of 6,000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL)~~ in at least two of the four measured parameters~~ measured in supernatant~~. The results for the nanomaterials ~~tested~~ showed good ~~correspondence~~ correlation between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure frequency, and aerodynamic particle size (MMAD and GSD).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

~~For the polyacrylates and methacrylates subcategory, s~~Several subchronic studies , for the polyacrylates and methacrylates subcategory that met the initial POD selection criteria, are included in [REF _Ref46678612 \h * MERGEFORMAT]~~ that met the initial POD selection criteria~~; however, BMD modeling was not performed on these studies because chronic studies were available and ~~deemed~~ more relevant for the hazard assessment. Two chronic studies met the

POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed ~~for the data in~~on the rat study performed by Muhle *et al.* (1991) [ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.
<author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address>
<titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords

><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]_~~, as~~because it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study_~~, whereas, in t~~The hamster study~~,~~ modified the exposure concentrations ~~were modified~~ after the first five months. ~~Among t~~The endpoints affected at the LOAEC in ~~that~~ the rat study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the incidence of fibrosis ~~incidence~~ could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

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9000 Toner (styrene/butylmethacrylate random copolymer)	Syrian Golden Han:AURA Hamster, male and female, (50/group); 18 months (6 hr/d, 5 d/wk); 3-5 mo. recovery	0, 1.5, 6, or 24 (months 1-5); 0, 4, 16, or 64 (months 6-18)	ND	1.5-4	Not derived; variable exposure regimen	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation particle-laden macrophages in lungs; interstitial inflammatory cell infiltration in lungs (males); lymphatic hyperplasia in LALN (males); and particle deposits in LALN	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[49]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title>An investigation of the biological effects of a toner fraction. Final Report of a subchronic inhalation study in Syrian Golden hamsters. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-2</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							><urls></urls></record></Cite></EndNote>]

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Toner A (styrene/butylmethacrylate random copolymer)	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6 mo. recovery	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[43]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title>An investigation of the biological effects of a toner fraction in a subchronic inhalation study in rats (Toner A). Final Report. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-7</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher><urls></urls></record

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							></Cite></ EndNote>]

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9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rat, female (≥18/group); 3 months (6 hr/d, 5 d/wk), 15 months recovery	0, 10, or 40	ND	10	Not derived	Significantly decreased alveolar clearance	[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellman

							n, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles

							><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keywor

							d><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><d

							ates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							</EndNote>]

ED_005294A_00000421-00085

9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rat, male and female (56-74/sex/group); 3 months (6 hr/d, 5 d/wk), 3 months recovery	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased relative lung weight in males; histopathology showed a few particles in alveolar walls and a slight degree of thickening of the alveolar structure due to hypertrophy and hyperplasia of Type II cells and accumulation of a few interstitial cells; slightly enlarged LALN; decreased alveolar clearance	[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

							H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title>

							<secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]

Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo. recovery	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[50]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title>An investigation of the biological effects of a toner fraction in a subchronic inhalation study in rats (Toner B). Final Report. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-7</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher><urls></urls></record

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							></Cite></EndNote>]
Polyvinyls Sub-Category							

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Polyvinyl chloride Powder	Rat, female (strain not reported); group sizes not reported; 8 months (25 hr/wk); up to 100 d recovery	0, 3.3, 8.3 or 20.2	ND	3.3	Not derived; missing SD/SE	Significantly decreased alveolar clearance	[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

							H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodica

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							l><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of inorganic PSPs (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al.*, 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[52]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

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type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data ~~as reviewed herein~~ suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages, thereby leading to tumor formation in humans. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study ~~on this sub-category of materials~~ and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

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title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have ~~comparable or greater~~a potential for ~~causing~~ lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance~~ compared to the PVC powder~~. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among

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mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). ~~For example, h~~Humans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than

rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al*. (2001) [ADDIN EN.CITE

<EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[54]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Vehicle Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765</isbn><accession-num>11335177</accession-num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-num>10.1289/ehp.01109311</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] showed that "the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats." In rats, accumulation of particulate matter in the intraluminal space leads to adverse "alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses" [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m^3 for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable ~~between the new chemical substance and the PVC powder~~. The polyvinyls sub-category POD is then subject to the established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [REF _Ref519678474 \h * MERGEFORMAT], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) ~~up~~ to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU RDDR was used for deriving a POD_{HEC}, as follows:

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3\ mg/m^3 \times 0.5 = 1.65\ mg/m^3$$

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Table [SEQ Table * ARABIC]. Depositional fractions and RDDRs for rats and humans.[a]

SPECIES	Extrathoracic (ET)		Tracheobronchial (TB)		Pulmonary (PU)		Thoracic (TB + PU)		Total Respiratory Tract (RT)	
	Surface Area (cm^2)	Depositional Fraction	Surface Area (cm^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction
Rat	15	0.33	22.5	0.068	0.34	0.061	0.342	0.129	0.344	0.459
Human	200	0.24	3200	0.059	54	0.267	54.32	0.125	54.34	0.566
RDD	0.075	1.373	0.007	1.15	0.006	0.229	0.006	1.028	0.006	0.811
RDDR	0.252		2.248		0.501		0.863		1.763	

[a] Inputted values included: MMAD = 1.30; GSD = 2.07.

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD software internally scales ventilation parameters and respiratory volumes based on BW, so this resulted in tidal volume (V_T) of 1.54, a breathing frequency of 166 bpm, functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of 0.34 mL. The 229 g rat PU surface area is predicted to be 1997 cm^2. The particle MMAD, GSD of the particle size distribution, and its density were: 1.3 μm, 2.07, and 1.3 g/cm^3, respectively. The regimen and duration of the nose-only exposure in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

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overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8 months and was used in the simulation. We note that there were discrepancies in the reported duration of exposure of 7 months versus 8 months in Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al.*

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(1986) [ADDIN EN.CITE

<EndNote><Cite><Author>Bellmann</Author><Year>1986</Year><RecNum>77</RecNum><DisplayText>[55]</DisplayText><record><rec-number>77</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595887108">77</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The Effect of a "Nuisance" Dust Inhalation of Lung Clearance</title><secondary-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</full-title></periodical><pages>209-211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>]

abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344 rats, shown in [REF _Ref46766078 \h * MERGEFORMAT], demonstrated the goodness of fit of the MPPD model to the experimental data reported by Muhle *et al.* (1990) [ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. For example, Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] reported a retained PU mass of 0.56 mg in rats exposed to 3.3 mg/m^3; the MPPD model predicted a retained PU mass of 0.63 mg at this exposure concentration. Additional simulations were conducted using the same three exposure concentration as Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file.

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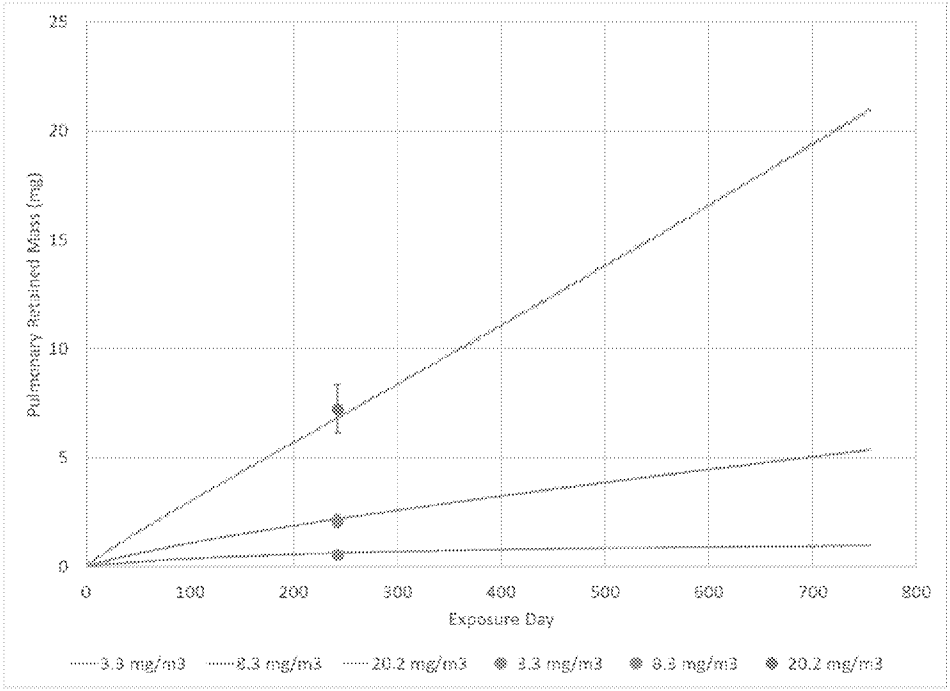

Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-

title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-

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3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) found in [REF _Ref46666189 \h * MERGEFORMAT] of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><Dis

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playText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. As shown in [REF _Ref46767442 \h * MERGEFORMAT], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [REF _Ref46766078 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of [REF _Ref46767442 \h * MERGEFORMAT] demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity. The HEC values represent PODs that may be used with the LADD in quantitative risk assessments where the hazard concern is based on lung overload.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for Muhle *et al.* (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	**3.3**	**8.3**	**20.2**
Experimental Rat Retained PU Mass (mg)	0.56±0.16	2.09±0.29	7.24±1.10
Predicted Rat Retained PU Mass (mg)	0.63	2.21	6.88
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	2.8	10.5	36.3
Light Activity 40-Year HEC (mg/m^3)	0.33	1.23	4.25
Heavy Activity 40-Year HEC (mg/m^3)	0.14	0.53	1.84

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HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Category benchmark margin of exposure (MOE)

EPA currently applies a composite UF of 1,000 as the benchmark MOE for the PVC powder POD of 3.3 mg/m^3. The composite UF consists of default values of 10 for UF_H, UF_A, and UF_L. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. ~~However, s~~Several refinements to these values may be made~~, including reducing~~. ~~the~~ The TK and TD components of the UF_A value and reducing the UF_L. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD_{HEC}, thereby reducing the TK component of the UF_A to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose, the RDDR model is not necessarily the most appropriate for deriving a POD_{HEC}, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the ~~other approaches versus the~~ respective benchmark MOE, given that the RDDR approach is recommended in EPA guidance for quantifying POD_{HECs} for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: "For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active inflammation in the rat appears to be a more sensitive response than in other species, including humans" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The UF_L may

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be reduced from 10 to 1 for the PVC powder analogue POD because this dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung. This approach is consistent with EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], which states that the UF_L “may be altered, depending on the magnitude and nature of the response at the LOAEL”. Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

UF_H = 10: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA's guidance for reducing the default UF_H [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

UF_A = 3 or 1: A reduced value of 1 should be applied for the TD component based on the proposal documented by Olin (2000). In addition, if the data are amenable for deriving a POD_{HEC}, the dosimetric adjustment for the TK component further supports reducing this UF [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

UF_L = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when ~~for example,~~ the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the UF_L based on other key events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

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The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. For example, the default POD of 3.3 mg/m^3 and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require engineering controls and/or a respirator with an applied protection factor (APF) of 1,000. In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the $POD_{HEC\text{-}light\ activity}$ of 0.33 mg/m^3 and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.

Uncertainties and Limitations

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[57]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>High Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-

substances-control-act-tsca/high-molecular-weight-polymers-new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. In addition, the following uncertainties and study limitations were noted, that if known, may serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle size, distribution, density, and hygroscopicity) and biopersistence and bioreactivity (*e.g.*, solubility, surface chemistry, and composition). However, the available studies of test materials in this category are generally missing information on these properties, with the exception of particle size.
- Information on molecular weight was not reported for test materials used in the studies of the PVC powder [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-

title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] included colorant materials (predominantly carbon black) at up to 10%, and the influence of these colorants on the observed effects is unknown.
- The PODs summarized in [REF _Ref46678612 \h * MERGEFORMAT] for the HMW polymers were reported on a mass/volume basis. However, there is evidence that number of particles, particle volume, and/or volume of particles retained in the lung can influence the threshold at which lung overload conditions occur [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Thus, particle density may be an important consideration in identifying a POD; however, the appropriate density metric and how density should be incorporated remain uncertain [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-

Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertain~~ty~~ ~~associated~~ association ~~with~~ of the human relevance of lung tumors observed in rats exposed to PSPs. The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (*e.g.*, coal miners). The rat also appears to be unique among species with regard to carcinogenesis due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [ADDIN

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<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload because it is a sensitive model for inflammatory response to PSPs, and ~~because~~ protecting against inflammation and proliferation may also protect against tumor formation [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Tiered-testing Strategy

The POD and benchmark MOE derived herein provide an analogue/read-across approach for assessing new chemical substances that fit within the chemical category boundaries for HMW

polymers~~, also defined herein~~. As with any analogue read-across, assessors must carefully consider the comparability of the new chemical substance to the analogue or another acceptable toxicological analogue.~~;~~ ~~this~~ This framework provides specific criteria for evaluating whether a new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive, insoluble in water, not expected to be directly cytotoxic, not expected to release toxic degradates). ~~When~~ If information is not available to evaluate whether the new chemical substance fits within the category boundaries and the analogue is appropriate for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that ~~are anticipated to~~may present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle size distribution, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

Tier I

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- Particle Size Distribution or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[59]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804668">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Particle Size Distribution/Fibre Length and Diameter Distributions</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>13, https://www.oecd-ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-distributions_9789264069688-en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></record></Cite></EndNote>], OPPTS 830.7520 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>65</RecNum><DisplayText>[60]</DisplayText><record><rec-number>65</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804850">65</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles>

<title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></End Note>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

  - If the % of respirable particles (*i.e.*, $\leq$ 10 μm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.
  - If the % of respirable particles (*i.e.*, $\leq$ 10 μm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- Reactivity
  - If the HMW polymer is a potential concern for reactivity, based on ~~function or~~ other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a pre-notice consultation meeting and prior to study initiation. The assay developed

by Wiemann *et al*. (2013) [ADDIN EN.CITE ADDIN EN.CITE.DATA] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.

- If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- Biosolubility Testing
  - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]), simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al*. 2014 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and/or phagolysosomal simulant fluid (*e.g.*, BAUA, 2017 [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-

title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>])

- Employ a simple exponential decay model to predict the dissolution half-life: $P(t)=P0e^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

- If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
- If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II

- Perform computational modeling (*e.g.*, MPPD) including the effect of dissolution to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al.*, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]).
- If the clearance t½ is less than 60 days, stop at Tier II.

If the clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-

keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>], consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III

- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis. When performed, the testing should include:
    - Exposure at concentrations high enough to demonstrate impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al.*, 2015 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and
    - Special attention to pulmonary function tests; blood oxygen (pO_2); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of marker enzyme activities, total protein content, and cell counts; lung retention and

clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[64]</DisplayText><record><rec-number>71</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838832">71</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>90-Day (Subchronic) Inhalation Toxicity Study</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>23, https://www.oecd-ilibrary.org/environment/test-no-413-subchronic-inhalation-toxicity-90-day-study_9789264070806-en</pages><volume>413</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] and OECD GD 39 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>72</RecNum><DisplayText>[65]</DisplayText><record><rec-number>72</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839002">72</key></foreign-keys><ref-type name="Journal

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><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on
Testing and Assessment (Second Edition)</title><secondary-title>Environment
Directorate Joint Meeting of the Chemicals Committee and the Working Party on
Chemicals, Pesticides and Biotechnology</secondary-
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the Chemicals Committee and the Working Party on Chemicals, Pesticides and
Biotechnology</full-title></periodical><pages>106,
https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm
/mono(2009)28/rev1&doclanguage=en</pages><volume>ENV/JM/MONO(
2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></rec
ord></Cite></EndNote>] should be consulted, given that the 90-day subchronic inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is sufficient for identifying lung overload for PSPs in this species [ADDIN
EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</
RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-
number><foreign-keys><key app="EN" db-
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Article">17</ref-
type><contributors><authors><author>EPA</author></authors></contributors>

<titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

CONCLUSIONS

In summary, the available toxicological studies on HMW polymers support that the key parameters for determining whether a HMW polymer may present a hazard for lung overload are: repirability, reactivity, and solubility. Two toxicological analogues were identified that may be used for "read across" to new chemical substances for evaluating lung overload. When applicable, the PODs on these analogues may be refined using MPPD to predict when overload might occur in the experimental species ~~The MPPD software provides for a straightforward approach to predict when overload might occur in the experimental species~~, to perform interspecies extrapolation to HEC estimates, and to inform inferences for human health risk ~~evaluation~~assessment. For new chemical substances that are not suitable for read across from these toxicological analogues, the tiered-testing strategy provides a framework that minimizes the use of vertebrate animals with informing whether new chemical substances present a hazard for lung overload. ~~Concentrations at which overload was not achieved in the rat are relevant to~~

~~human assessment, as are other endpoints other than tumors at overload.~~ Collectively, the read across approach, ~~Simulations~~ the MPPD model simulations, and the tiered-testing strategy represent approaches that will aid with evaluating new chemical substances to ensure that they do not present an unreasonable risk to human health ~~would also be most useful to design of experiments before costly investments in inhalation studies are made~~ and may also help to reduce and refine the number of animals used.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Outputs

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ~~‡These authors contributed equally. (match statement to author names with a symbol)~~

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Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

~~**ACKNOWLEDGMENT**~~

~~Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).~~

REFERENCES

[ADDIN EN.REFLIST]

Message

From: Stephanie Snyder [stephanie.snyder@covestro.com]
Sent: 7/28/2020 4:26:27 PM
To: Stedeford, Todd [Stedeford.Todd@epa.gov]; Owen Price ARA/AD [oprice@ara.com]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]
Subject: RE: Polymer Lung Overload Manuscript Draft - July 27, Version 2 + surfactants status update
Attachments: Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.2.docx

I had just a few comments. I am still reading thru the supplemental information and will send any comments to that this afternoon.

Thanks,
Stephanie

From: Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
Sent: Monday, July 27, 2020 8:26 PM
To: Owen Price ARA/AD; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder; Tveit, Ann; Irwin, William; Jarabek, Annie; Henry, Tala
Subject: Polymer Lung Overload Manuscript Draft - July 27, Version 2 + surfactants status update
Importance: High

All,

Please find the attached, latest draft of the lung overload manuscript. This draft includes updates based on all of the comments I received to date (200+). Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP). Please see if you agree with this presentation. Just as a reminder, our submission deadline is this Friday, so please review as quickly as you can. Also, please be mindful that I cross-referenced all tables/figures/schemes, so please do not try to re-number these. The references have also been linked up using EndNote, so please don't try to edit these either. If you spot an error on any these, just flag it with a comment. There are three items I still need to complete. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) I will aim to complete these tasks tomorrow. Otherwise, we are still working on addressing all of the comments on the surfactant manuscript, so hopefully, we can send out the update tomorrow. Sorry for the delay on this.

Thanks,

Todd

Polymer Lung Overload Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

Todd Stedeford[a,], Gregory S. Ladics[b], Owen Price[c], Annie Jarabek[d], Ann Tveit[e], Michael P. Hayes[f], Raphael Tremblay[f], Stephanie A. Snyder[g], Keith Salazar[h], Sahar Osman-Sypher[i], William Irwin[h], Marc Odin[j], Julie Melia[j], Heather Carlson-Lynch[j], and Tala R. Henry[a]*

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ED_005294A_00000423-00001

[h] Risk Assessment Division, Office of Pollution Prevention and Toxics, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, DC 20460, United States

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[j] SRC, North Syracuse, NY 13212, United States

KEYWORDS: Inhalation, Lung Overload, New Approach Methods, Particle Toxicity, Risk Assessment, (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval.

ABSTRACT

Commented [ST1]: Abstract is new

Poorly soluble and non-reactive high-molecular weight (HMW) polymers (≥10,000 Daltons) represent a generic category of substances that are extensively used in industrial and consumer applications (*e.g.*, plastics). Under the amended Toxic Substances Control Act (TSCA), HMW polymers may qualify for an exemption from the pre-notification requirements that exist for polymeric, new chemical substances. However, for HMW polymers that do not meet the exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload. In the present evaluation, a systematic review of the literature was performed to identify studies that would aid with defining key properties for determining whether respirable HMW polymers may present an unreasonable risk to human health. These properties included: respirability, reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a

ED_005294A_00000423-00002

chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for several toxicological analogues that can be used in risk assessments on these substances. Finally, a tiered-testing strategy that maximizes the use of non-vertebrate testing (*i.e.*, NAMs) was developed that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));
2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));
4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or
5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, Federal Insecticide, Fungicide, and Rodenticide Act), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><DisplayText>[1]</DisplayText><record><rec-number>31</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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EPA has historically used various approaches to evaluate the potential hazards of new chemical substances including the use of computational toxicology models and analogue and category approaches to "read-across" from existing data to new chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program (NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on specific chemical definitions and boundaries that summarize the hazard concerns (*e.g.*, human health or environmental toxicity) and recommend testing that may be conducted prior to submitting a new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T

SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties, the NCP Chemical Categories were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect vertebrate testing reduction goals. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particulates[1] includes vertebrate animal testing, such as a 90-day subchronic inhalation toxicity study in rats with a 60-day recovery period [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-

[1] EPA identified particles as "respirable" to humans "if there are any particles ≤10 μ[m] in diameter in the material being handled by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical Categories cover the boundaries defined therein may not reflect development of alternative chemistries that do not fit within the current NCP Chemical Categories, even for chemicals that the alternative chemistries are intended to replace (*e.g.*, the use of polymeric alternatives to replace monomeric forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has also developed exemption criteria, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption", for specific types of polymeric substances [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>P

remanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria are exempt from the new chemical substance notification requirements, although there are still some requirements, including annual reporting and recordkeeping [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. EPA's polymer exemption established three exemption types, designated as E1, E2, and E3. The general criteria for new chemical substances meeting these exemption types for polymers are shown in [REF _Ref46665925 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

Exemption Type	*Number-average molecular weight (NAMW)*	*Oligomeric Material Criteria*	*Functional Groups (FGs) and Functional Group Equivalent Weight (FGEW) Content*
E1	1,000 ≤ NAMW < 10,000	< 10 wt% below 500 Daltons < 25 wt% below	Low concern FGs:[c] no limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

		1,000 Daltons	
E2	NAM W ≥ 10,000	< 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons	No FG restrictions
E3	No limit	No limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[a] See 40 CFR § 723.250(b) Polymers. “Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units.” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Water absorbing polymers with NAMW $\geq$ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[c] "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]; however, there are instances where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc.*, in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather are based on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW $\geq$ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, $\leq$ 10 μm) represent a general class of chemical substances (hereinafter referred to as "HMW polymers") that may cause potential inhalation toxicity (*i.e.*, lung overload) *via* the mode(s) of action (*i.e.*, impairment of alveolar-macrophage mediated clearance), as identified in rat inhalation studies, to chemical substances present in the NCP Chemical Categories document for respirable, poorly soluble particulates. However, the chemical substances that are provided as analogues within the

boundaries for the NCP Chemical Category on respirable, poorly soluble particulates are limited to discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for those polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as representative toxicological analogues with points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. An additional aim was to introduce new approach methodologies (NAMs) into the tiered-testing strategy to meet the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

MATERIALS AND METHODS

Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at "Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies

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ED_005294A_00000423-00016

that evaluated potential “lung overload” toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, “lung overload” refers to the “type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance” [ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[6]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-57</pages><volume>12</volume><number>1-2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals, Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response

Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><keyword>Risk Assessment</keyword><keyword>Species Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-Feb</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>10715617</accession-num><urls></urls><electronic-resource-num>10.1080/089583700196536</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is defined differently in experimental animals versus humans [ADDIN EN.CITE ADDIN EN.CITE.DATA], the literature searches used search strings that were intended to be overly inclusive to identify studies that evaluated "overload" in experimental animals and humans. A secondary objective was to identify potential NAMs that may be incorporated into a tiered-testing strategy that minimizes the use of vertebrate animals.

Risk Assessment Approaches Under TSCA

EPA generally uses the margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments performed on new chemical substances under TSCA. The MOE approach is calculated based on a point(s) of departure (POD) divided by a human exposure estimate(s). The POD is typically identified from an effect level from a study(ies) in experimental animals (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or benchmark dose [BMD]). A duration adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*,

workers = 8 hours/day, 5 days/week) versus the exposure conditions employed in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated for new chemical substances using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) in mg/day or lifetime average daily doses (LADDs) in mg/kg-bw/day. Given that new chemical substances will not have occupational exposure monitoring data, except for possible monitoring data on analogues, the PDR is typically used as an initial conservative exposure estimate when calculating the MOE. For chemical substances used in a powder or particulate form, the general default PDR values for respirable or total particulates are 50 mg/day (*i.e.*, 5 mg/m^3) or 150 mg/day (*i.e.*, 15 mg/m^3), respectively [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><DisplayText>[12]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595776956">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. However, for chronic effects like lung overload, the LADD represents

the more appropriate exposure metric for quantifying potential risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><DisplayText>[13]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595778575">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Interpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>20, https://www.epa.gov/sites/production/files/2015-05/documents/05-iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. A summary of the default values used for calculating PDRs and LADDs for new chemical substances in powder or particulate form is provided in [REF _Ref46666189 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	Cm × b × h	Mass concentration of chemical in air (Cm)	5	mg/m^3
		Volumetric inhalation rate (b)	1.25	m^3/hr

		(0 < b ≤ 7.9)		
		Exposure duration (h) (0 ≤ h ≤ 24)	8	hrs/day
LADD (mg/kg-bw/day)	(I × ED × EY) / (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) (0 ≤ ED (integer) ≤ 365)	250	days/site-yr
		Years of occupational exposure (EY) (0 ≤ EY)	40	years
		Body weight (BW) (0 ≤ ATc)	80	kg
		Averaging time over a lifetime (chronic) (0 ≤ ATc)	70	years

For each of the MOEs calculated herein, both the PDR and LADD are provided for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE higher than the benchmark MOE, the risks are not considered a concern under TSCA.

Benchmark MOE Derivation

The benchmark MOE is derived to account for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or UF_H), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or UF_A), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or UF_L). The default values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance focused on improving the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A

Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Application of DAFs to the animal airborne exposure values yields estimates of the concentration that would result in the same concentration to humans, that is, the Human Equivalent Concentration (HEC). For studies reporting only a LOAEC, EPA recommends

benchmark dose modeling be performed, if the experimental data are amenable, to identify a BMDL, and thereby reduce the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with their potential applicability to the available studies that evaluated lung overload from HMW polymers.

Regional Dose Dosimetry Ratio (RDDR)

EPA may apply DAFs to PODs identified from experimental animal studies based on the methods described in its 1994 guidance document titled "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. When applied, the default DAF accounts for the toxicokinetic component of the UF_A and is

reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, since the POD is dosimetrically adjusted to a POD_{HEC}, whereas the remaining UF_A value of approximately 3 accounts for the toxicodynamic component of the UF_A. Dosimetry or physiologically-based pharmacokinetic models are preferred to the default models when they are available [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the regional deposited dose ratio (RDDR), that is, the DAF for particles. The RDDR is an empirical model of deposition that is applicable to particles in the size range of 0.5-30 μm and calculates an RDDR value as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute volume (V_E; mL/min), depositional fraction (Fr) of the particulate in the regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF), such as respiratory tract surface area, for the region of interest. The RDDR user inputs include mass median aerodynamic diameter (MMAD), geometric standard deviation (σ) for the particle of interest, and the average bodyweight of the animal used in the study from which default V_E and surface areas of the respiratory tract regions for the animal are calculated. The RDDR may be applied to the duration adjusted POD; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the laboratory animal regimen. Thereafter, the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ADDIN EN.CITE <EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[16]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox "Way more FPA than Counterstrike !"</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].

Multiple-Path Particle Dosimetry (MPPD)

Commented [ST4]: Updated based on Owen and Annie write up

Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><DisplayText>[17]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian, B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the

Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy & histology/physiology</keyword><keyword>Lung/*anatomy & histology/physiology</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal Volume/physiology</keyword><keyword>Trachea/anatomy & histology/physiology</keyword></keywords><dates><year>1995</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590</isbn><accession-num>8566482</accession-num><urls></urls><electronic-resource-num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.* (2016) [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>[18]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author><author>Asgharian, B.</author><author>Schroeter, J.D.</author><author>Price,

O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>14-26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] is a mechanistic, multipath model that was modified and used to predict deposition, clearance, and lung burden over the course of a long-term exposure , as described by Ladics *et al*. (2020) [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. As with the RDDR outputs, the MPPD outputs provide values that may be used to calculate a POD_{HEC}; however, unlike the RDDR model, MPPD provides outputs that may be

used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via* retained dose.

The MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory

System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. These rates are considered representative of insoluble particles. More recently, the ICRP model and clearance rates have been updated based on improved lung burden data [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Refinements may be imparted by chemical-specific dissolution data and exploration of these new model values. Hygroscopic growth is currently not addressed in either the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers. In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-week rat exposures. In humans, MPPD implements the ICRP clearance model localized for individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach, as discussed in EPA (2012) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not identified in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1, because the BMDL is a dose level corresponding to specific response levels near the low end of the observable range of the data and incorporates and conveys more information than the NOAEC or the LOAEC [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, and model fit was evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract screening, 28 articles were selected for full text review, and 23 articles were identified using additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review, only 24 articles contained relevant information that satisfied the PECO criteria for lung overload from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review. Complete details on the systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

Commented [HT5]: How many overlap with the 51 from first search/review?

Commented [ST6R5]: I will add this, need to double check

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries to develop the health effects summaries in the

section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The category boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed further below. It should be noted that even if a HMW polymer satisfies the category boundary criteria, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

Commented [ST7]: Modified text

Respirable particles are those chemical substances with a particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its “Air Quality Criteria for Particulate Matter”, represents “particles collected by a sampler with an upper 50% cut point of 10 μm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size cuts of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm D_a particles as an upper limit for particles with this size entering the alveolar region [ADDIN EN.CITE <EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><DisplayText>[24]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American

Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Further, consideration must also be given to particle settling that may occur. For example, in still air, 10 μm spherical particles with a density of 1 g/cm^3 can remain airborne for approximately 8 minutes [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 μm particles to settle in still air) [ADDIN EN.CITE

<EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[24, 25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-

particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. Though occupational monitoring data provide the most direct assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and the reality that nearly all solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion. For the purposes of this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc*., in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 µm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, a practical cutoff of ≥ 1% respirable particles by weight (wt%) as the cutoff for assessing respirable particles and this percentage would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt% is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[26]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting

and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. This same cutoff would apply to the particle/droplet size distribution in the case of aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

EPA's FG and FGEW criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive or reactive and included or excluded from the category, respectively. As shown in [REF _Ref46665925 \h * MERGEFORMAT], the E1 polymer exemption criteria include low-concern, moderate-concern, or high-concern FGs. A summary of representative FGs meeting each of these hazard concern levels is shown in [REF _Ref46674358 \h * MERGEFORMAT].

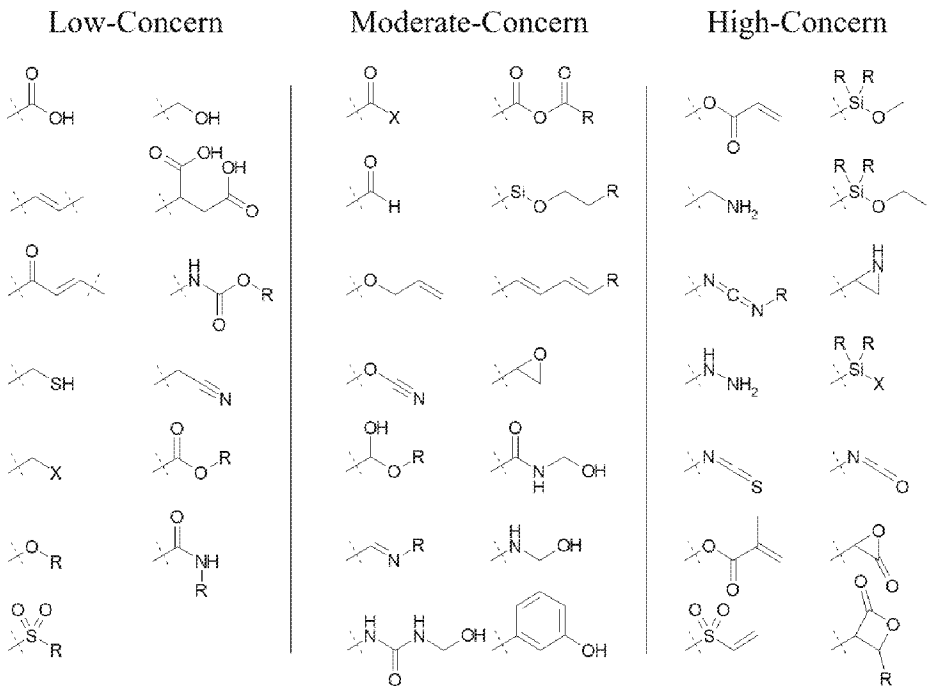


Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The following cutoffs are proposed as the category boundaries for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-concern FGs (FGEW $\geq$ 1,000), or high-concern FGs (FGEW $\geq$ 5,000). "R" represents an undefined structure; "X" represents a halide. See: EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A generally recognized property of respirable, low reactive (*i.e.*, low toxicity) particles that can cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><DisplayText>[27]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792442">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Section 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM, Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution

Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>22, https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-748-B12-001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. These values were not established for evaluating the solubility of particles for lung overload; however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><DisplayText>[28]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792078">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW polymers. ECETOC (2013) [ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial biosolubility screening approach that provided qualitative determinants (*i.e.*, “soluble”, “insoluble”, “Low dissolution rate”, or “Very high dissolution rate”) for assessing biosolubility; however, no quantitative thresholds were provided. In comparison, the International Commission on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and Health (FIOSH) provide quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day^{-1}), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day^{-1}), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day^{-1}) [ADDIN EN.CITE

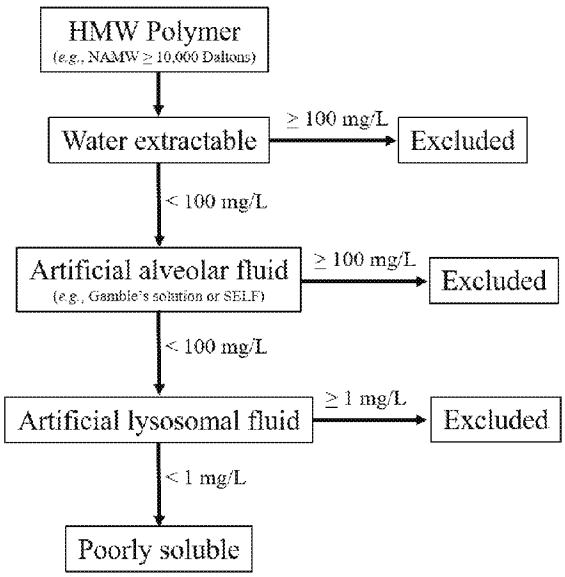
<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of ≤ 1 mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed previously, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are ≤ 10 µm and ≥ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [REF _Ref46673847 \h * MERGEFORMAT], which consider water extractability/biosolubility and the legally binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health

Administration (OSHA) for respirable particulates not otherwise regulated or PNOR (*i.e.*, 5 mg/m^3).

Scheme [SEQ Scheme * ARABIC]. Screening criteria for determining water extractability and biosolubility.



The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first screen is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been established to correlate with biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected rather than

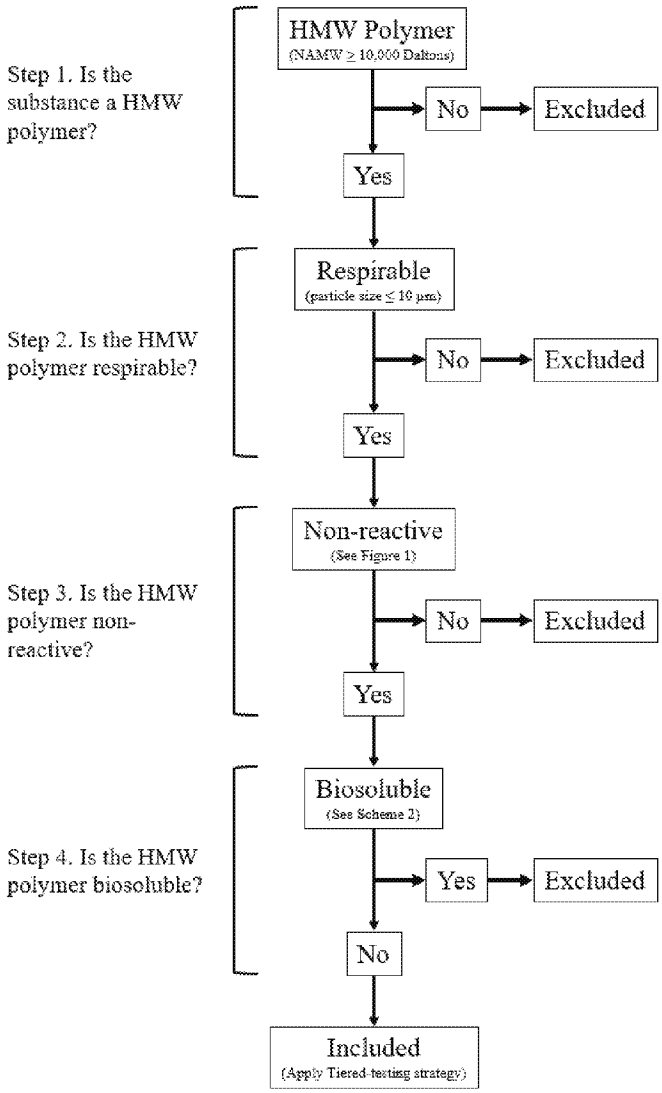
the low water solubility cutoff, since it represents a transition from slight to moderate water solubility and is therefore expected to be conservatively inclusive in the first step because water extractability is generally expected to overestimate the insolubility of polymers in biological fluids. In the second screen, two biosolubility cutoffs may be used, either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m^3 (*i.e.*, 50 mg/day; 5 mg/m^3 × 10 m^3/day) for the respirable fraction. The first value is based on EPA (2020) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>75</RecNum><DisplayText>[31]</DisplayText><record><rec-number>75</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595843741">75</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Revocation of Significant New Use Rule for a Certain Chemical Substance (P-16-581), Proposed rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>18179-18181</pages><volume>85</volume><number>63</number><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], where the Agency applied a biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid. This value would equate to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ADDIN EN.CITE <EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum><DisplayText>[32]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.

ED_005294A_00000423-00050



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons)

materials, which meet the above-stated criteria for these parameters. HMW polymers meeting these criteria are those which are typically formed through various polymerization processes. Chemical substances included are branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

ED_005294A_00000423-00052

[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of "overload" for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[35]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: "This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies that were identified are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload of some new chemical substances.

Human Data

The hazard concerns discussed herein are limited to chronic effects in the lower respiratory tract of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies have shown that rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-

135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the available studies that evaluated potential hazards from exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good

laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.

<author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al*. (1992) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

effects/enzymology</keyword><keyword>Macrophages/*drug
effects/pathology/physiology</keyword><keyword>Phagocytosis/drug
effects</keyword><keyword>Polymers/*adverse
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urls></urls><custom2>PMC1519531</custom2><electronic-resource-
num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance used by Muhle *et al*. (1990) [ADDIN EN.CITE
<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><Di
splayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key
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R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in
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title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
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Muhle *et al.* (1991) [ADDIN EN.CITE

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Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address>
<titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al*. (1991)

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0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies and under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed effects similar to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining time. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters (increased cell number,

macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week)

to PVC powder at concentrations ≥ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, supporting that lung overload occurred at concentrations ≥ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><Di splayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

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Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for biologically active toxicity from passive (*i.e.*, overload condition) toxicity. The assay uses rat NR8383 alveolar macrophages incubated with test material in cell

culture medium, and assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours) in the cell culture supernatant. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay threshold for active toxicity was a surface-area/volume concentration of 6,000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL) in at least two of the four parameters measured in supernatant. The nanomaterials tested showed good correspondence between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not

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report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure frequency, and aerodynamic particle size (MMAD and GSD).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

For the polyacrylates and methacrylates subcategory, several subchronic studies are included in [REF _Ref46678612 \h * MERGEFORMAT] that met the initial POD selection criteria; however, BMD modeling was not performed on these studies because chronic studies were available and deemed more relevant for the hazard assessment. Two chronic studies met the POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed for the data in the rat study performed by Muhle *et al.* (1991) [ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><Di
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resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-

num><language>English</language></record></Cite></EndNote>], as it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study, whereas, in the hamster study, exposure concentrations were modified after the first five months. Among the endpoints affected at the LOAEC in that study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the fibrosis incidence could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[49]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a
9000 Toner (styrene/butylmet	Syrian Golden Han:AURA Hamster, male and female,	0, 1.5, 6, or 24 (months 1-5); 0,	ND	1.5-4	Not derived; variable	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation of particle-laden macrophages in lungs; interstitial	

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner A (styrene/butylmethacrylate random	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[43]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo.	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[50]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyvinyls Sub-Category							

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

ED_005294A_00000423-00080

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of inorganic PSPs (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al*., 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[52]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data as reviewed herein suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages, thereby leading to tumor formation in humans. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study on this sub-category of materials and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have comparable or greater potential for causing lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance compared to the PVC powder. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among

mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). For example, humans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than

rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al*. (2001) [ADDIN EN.CITE

<EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[54]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle

Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred

F344</keyword><keyword>Vehicle

Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-

dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-

6765</isbn><accession-num>11335177</accession-

num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-

num>10.1289/ehp.01109311</electronic-resource-num><remote-database-

provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>] showed that “the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats.” In rats, accumulation of particulate matter in the intraluminal space leads to adverse “alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses” [ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><

DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key

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le>Poorly Soluble Particles / Lung Overload</title></titles><pages>130,

http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m^3 for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable between the new chemical substance and the PVC powder. The polyvinyls sub-category POD is then subject to established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [REF _Ref519678474 \h * MERGEFORMAT], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) up to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU RDDR was used for deriving a POD_{HEC}, as follows:

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3\ mg/m^3 \times 0.5 = 1.65\ mg/m^3$$

Table [SEQ Table * ARABIC]. Depositional fractions and RDDRs for rats and humans.[a]

SPECIES	Extrathoracic (ET)		Tracheobronchial (TB)		Pulmonary (PU)		Thoracic (TB + PU)		Total Respiratory Tract (RT)	
	Surface Area (cm^2)	Depositional Fraction	Surface Area (cm^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction
Rat	15	0.33	22.5	0.068	0.34	0.061	0.342	0.129	0.344	0.459
Human	200	0.24	3200	0.059	54	0.267	54.32	0.125	54.34	0.566
RDD	0.075	1.373	0.007	1.15	0.006	0.229	0.006	1.028	0.006	0.811
RDDR	0.252		2.248		0.501		0.863		1.763	

[a] Inputted values included: MMAD = 1.30; GSD = 2.07.

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

Commented [ST8]: Section new based on parts of the write up that Owen and Annie developed. The remaining sections of the write up are in the Supporting File.

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD software internally scales ventilation parameters and respiratory volumes based on BW, so this resulted in tidal volume (V_T) of 1.54, a breathing frequency of 166 bpm, functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of 0.34 mL. The 229 g rat PU surface area is predicted to be 1997 cm^2. The particle MMAD, GSD of the particle size distribution, and its density were: 1.3 μm, 2.07, and 1.3 g/cm^3, respectively. The regimen and duration of the nose-only exposure in the Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8 months and was used in the simulation. We note that there were discrepancies in the reported duration of exposure of 7 months versus 8 months in Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al.*

(1986) [ADDIN EN.CITE

<EndNote><Cite><Author>Bellmann</Author><Year>1986</Year><RecNum>77</RecNum>
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H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The
Effect of a "Nuisance" Dust Inhalation of Lung Clearance</title><secondary-
title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol
Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and
Reactivity, Proceedings of the Second International Aerosol Conference</full-
title></periodical><pages>209-
211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>]
abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months
was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344
rats, shown in [REF _Ref46766078 \h * MERGEFORMAT], demonstrated the fit of the
MPPD model to the experimental data reported by Muhle *et al.* (1990) [ADDIN EN.CITE

Commented [SS9]: I would include a statement about whether the simulations matched the Muhle data and demonstrated lung overload.

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><Di
splayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key
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timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. Additional simulations were conducted using the same three exposure concentration as Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file.

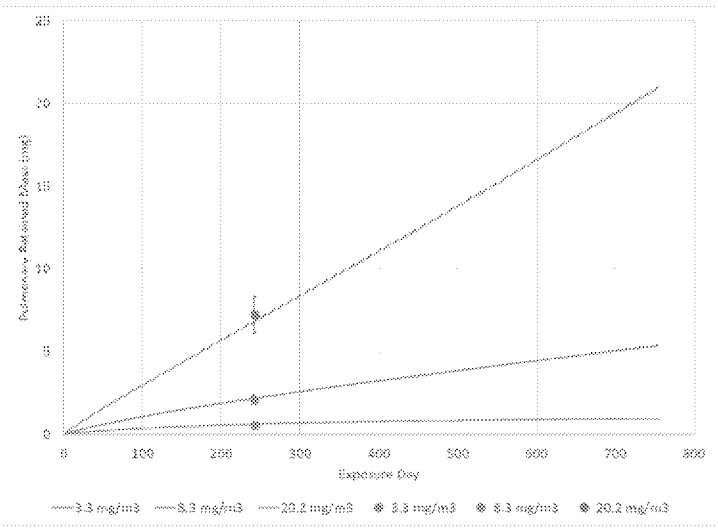

Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>

Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) found in [REF _Ref46666189 \h *

MERGEFORMAT] of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. As shown in [REF _Ref46767442 \h * MERGEFORMAT], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al.*

Commented [SS10]: I suggest adding a statement about the overall meaning of the data in the table.

ED_005294A_00000423-00098

(1990) [ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [REF _Ref46766078 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of [REF _Ref46767442 \h * MERGEFORMAT] demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for Muhle *et al*. (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	**3.3**	**8.3**	**20.2**
Experimental Rat Retained PU Mass (mg)	0.56±0.16	2.09±0.29	7.24±1.10

Predicted Rat Retained PU Mass (mg)	0.63	2.21	6.88
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	2.8	10.5	36.3
Light Activity 40-Year HEC (mg/m^3)	0.33	1.23	4.25
Heavy Activity 40-Year HEC (mg/m^3)	0.14	0.53	1.84

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Category benchmark margin of exposure (MOE)

EPA currently applies a composite UF of 1,000 as the benchmark MOE for the PVC powder POD of 3.3 mg/m^3. The composite UF consists of default values of 10 for UF_H, UF_A, and UF_L. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. However, several refinements to these values may be made, including reducing the TK and TD components of the UF_A value and reducing the UF_L. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD_{HEC}, thereby reducing the TK component of the UF_A to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose, the RDDR model is not necessarily the most appropriate for deriving a POD_{HEC}, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the other approaches versus the respective benchmark MOE, given that the RDDR approach is recommended in EPA guidance for quantifying POD_{HECs} for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: "For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that

the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active inflammation in the rat appears to be a more sensitive response than in other species, including humans" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The UF_L may be reduced from 10 to 1 for the PVC powder analogue POD because this dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung. This approach is consistent with EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], which states that the UF_L "may be altered, depending on the magnitude and nature of the response at the LOAEL". Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW

polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

UF_H = 10: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA's guidance for reducing the default UF_H [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

UF_A = 3 or 1: A reduced value of 1 should be applied for the TD component based on the proposal documented by Olin (2000). In addition, if the data are amenable for deriving a POD_{HEC}, the dosimetric adjustment for the TK component further supports reducing this UF [

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<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

UF_L = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when for example, the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the UF_L based on other key

events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. For example, the default POD of 3.3 mg/m^3 and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require engineering controls and/or a respirator with an applied protection factor (APF) of 1,000. In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the $POD_{HEC\text{-}light\ activity}$ of 0.33 mg/m^3 and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.

Uncertainties and Limitations

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[57]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>High Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/high-molecular-weight-polymers-new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. In addition, the following uncertainties and study limitations were noted, that if known, may serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle size, distribution, density, and hygroscopicity) and biopersistence and bioreactivity (*e.g.*, solubility, surface chemistry, and composition). However, the available studies of test materials in this category are generally missing information on these properties, with the exception of particle size.
- Information on molecular weight was not reported for test materials used in the studies of the PVC powder [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] included colorant materials (predominantly carbon black) at up to 10%, and the influence of these colorants on the observed effects is unknown.
- The PODs summarized in [REF _Ref46678612 \h * MERGEFORMAT] for the HMW polymers were reported on a mass/volume basis. However, there is evidence that number of particles, particle volume, and/or volume of particles retained in the lung can influence the threshold at which lung overload conditions occur [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Thus, particle density may be an important consideration in identifying a POD; however, the appropriate density metric and how density should be incorporated remain uncertain [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-

type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertainty associated with the human relevance of lung tumors observed in rats exposed to PSPs. The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (*e.g.*,

coal miners). The rat also appears to be unique among species with regard to carcinogenesis due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload because it is a sensitive model for inflammatory response to PSPs, and because protecting against inflammation and proliferation may also protect against tumor formation [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Tiered-testing Strategy

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The POD and benchmark MOE derived herein provide an analogue/read-across approach for assessing new chemical substances that fit within the chemical category boundaries for HMW polymers, also defined herein. As with any analogue read-across, assessors must carefully consider the comparability of the new chemical substance to the analogue or another acceptable toxicological analogue; this framework provides specific criteria for evaluating whether a new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive, insoluble in water, not expected to be directly cytotoxic, not expected to release toxic degradates). When information is not available to evaluate whether the new chemical substance fits within the category boundaries and the analogue is appropriate for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that are anticipated to present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle size distribution, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

Tier I

- Particle Size Distribution or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[59]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804668">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Particle Size Distribution/Fibre Length and Diameter Distributions</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>13, https://www.oecd-ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-distributions_9789264069688-en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></record></Cite></EndNote>], OPPTS 830.7520 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>65</RecNum><DisplayText>[60]</DisplayText><record><rec-number>65</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804850">65</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></End Note>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

  - If the % of respirable particles (*i.e.*, $\leq$ 10 μm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.
  - If the % of respirable particles (*i.e.*, $\leq$ 10 μm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- Reactivity
  - If the HMW polymer is a potential concern for reactivity, based on function or other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a

pre-notice consultation meeting and prior to study initiation. The assay developed by Wiemann *et al.* (2013) [ADDIN EN.CITE ADDIN EN.CITE.DATA] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.

- If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- Biosolubility Testing
  - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung

Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]), simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al.* 2014 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and/or phagolysosomal simulant fluid (*e.g.*, BAUA, 2017 [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-

title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>])

- Employ a simple exponential decay model to predict the dissolution half-life: $P(t)=P0e^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

- If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
- If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II

- Perform computational modeling (*e.g.*, MPPD) including the effect of dissolution to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al*., 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]).
- If the clearance t½ is less than 60 days, stop at Tier II.

If the clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum

><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>], consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III

- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis. When performed, the testing should include:
    - Exposure concentrations high enough to demonstrate impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al*., 2015 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and
    - Special attention to pulmonary function tests; blood oxygen (pO_2); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of

marker enzyme activities, total protein content, and cell counts; lung retention and clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[64]</DisplayText><record><rec-number>71</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838832">71</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>90-Day (Subchronic) Inhalation Toxicity Study</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>23, https://www.oecd-ilibrary.org/environment/test-no-413-subchronic-inhalation-toxicity-90-day-study_9789264070806-en</pages><volume>413</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] and OECD GD 39 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>72</RecNum><DisplayText>[65]</DisplayText><record><rec-number>72</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595839002">72</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment (Second Edition)</title><secondary-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology</secondary-title></titles><periodical><full-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology</full-title></periodical><pages>106, https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted, given that the 90-day subchronic inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is sufficient for identifying lung overload for PSPs in this species [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

CONCLUSIONS

The MPPD software provides for a straightforward approach to predict when overload might occur in the experimental species, perform interspecies extrapolation to HEC estimates, and inform inferences for human health risk evaluation. Concentrations at which overload was not achieved in the rat are relevant to human assessment, as are other endpoints other than tumors at overload. Simulations would also be most useful to design of experiments before costly investments in inhalation studies are made and may also help to reduce and refine the number of animals used.

Commented [ST11]: In process

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Outputs

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally. (match statement to author names with a symbol)

Funding Sources

EPA sponsored the initial literature review through contract [insert number]. ACC sponsored the supplemental literature review conducted by an independent third party.

Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

ACKNOWLEDGMENT

Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

REFERENCES

[ADDIN EN.REFLIST]

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Message

From: Marrapese, Martha [MMarrapese@wileyrein.com]
Sent: 9/23/2019 2:41:16 PM
To: Henry, Tala [Henry.Tala@epa.gov]
Subject: FW: Presentation
Attachments: ATT00001.txt; LexisNexis Newsdesk.pdf; SIA TSCA Presentation DRAFT_MEM.pptx

Just making sure you got this – I had a bounce-back in my mail this morning. Sincerely, Martha

Martha E. Marrapese | Attorney at Law
1776 K Street NW | Washington, DC 20006
T: 202.719.7156 | mmarrapese@wileyrein.com
wileyrein.com | LinkedIn | Twitter

From: Marrapese, Martha
Sent: Friday, September 20, 2019 11:37 AM
To: Tala R. Henry - U.S. EPA (henrytala@epa.gov) <henrytala@epa.gov>
Subject: Presentation

Dear Tala,

Hello - I am following up on our call about preparing for the SIA webinar next week. As you know, we have an organizational call on Tuesday at 11 a.m. My goal is to have a draft slide deck circulated by noon on Monday. A very rough draft is attached to help you in preparing your material. As we discussed, we hope that you can consider incorporating the following points into your presentation -

1) Explain PFAS, EPA's concerns about PFAS, and emphasize that PFAS is a program focus throughout EPA that is not going away
2) Explain how EPA regulates PFAS under TSCA (10 year or more history or regulation, so not new as a concern)
3) Explain what EPA does when it receives a new chemical submission for a PFAS chemical in terms of the use of analogs and the exposure and hazards that are likely to arise, and any efforts by EPA to encourage companies to find alternatives

Also, the first attachment is a news article, following up on my understanding that the update to the New Chemical Framework was supposed to be out this month or by October!

Sincerely, Martha

Martha E. Marrapese | Attorney at Law
Wiley Rein LLP
1776 K Street NW | Washington, DC 20006
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wileyrein.com | LinkedIn| Twitter

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ENVIRONMENTALISTS THREATEN SUIT AS EPA READIES TSCA NEW CHEMICALS PLAN

Inside EPA Weekly Report

Inside EPA Weekly Report

Publish Date: Sep 20, 2019 8:00 AM

Length: 917 words

Posted September 12, 2019

Environmental and labor groups are threatening to sue EPA over how the agency is inadequately releasing information about new chemicals under the Toxic Substances Control Act (TSCA), detailing concerns that they will likely urge the agency to address as it prepares to release a new framework for its new chemicals review process.

Earthjustice's Sept. 3 notice, explains that the groups intend to sue EPA using the citizen suit provisions of TSCA section 20(a) "for EPA's repeated and ongoing failures to comply with TSCA's nondiscretionary mandates to disclose to the public information about new chemical substances reviewed by EPA."

The environmentalist law firm is representing Center for Environmental Health, Environmental Defense Fund, Environmental Health Strategy Center, Natural Resources Defense Council (NRDC), Sierra Club and the United Steelworkers union, according to the notice posted to EPA's website Sept. 11.

The groups' notice follows EPA toxics chief Alex Dunn's statement during a webinar last July that the agency is updating its framework for reviewing applications for new chemicals to enter the commercial market and will release it before hosting a public meeting probably in October.

An earlier version of the new chemicals framework, released in November 2017, was not implemented after NRDC sued the agency over it. NRDC later dropped the suit after EPA officials stipulated the framework had not been placed into use.

At issue is EPA's new chemicals program, which accepts applications from manufacturers for new chemicals they are proposing to release on the commercial market, or new uses of existing chemicals.

New chemicals -- those not on the market when the original TSCA took effect in 1976 -- cannot legally enter the commercial market until EPA reviews and green lights them. Program staff has been challenged by significant changes Congress made to the new chemicals program in its 2016 reform of TSCA, requiring the agency to review all applications and issue written determinations upon each, most notably. These changes were implemented with no phase-in period, resulting in an immediate backlog of reviews when the standards changed overnight.

The backlog has led to a clash of stakeholders. Industry groups have charged that the process has become overly cumbersome and EPA routinely fails to meet the statutory deadline of 90-180 days for pre-manufacture notice (PMN) review, while environmentalists argue that EPA's efforts to speed the process give short shrift to health and safety concerns. Implementing Regulations

Now, Earthjustice points to TSCA section 5(d)(2), as well as "EPA's implementing regulations mandate that EPA disclose certain information regarding the submission and review of new chemical applications under the PMN and [test marketing exemption (TME)] provisions. For PMNs, EPA must quickly notify the public of its receipt of the PMN (i.e., within five business days of receipt) by publishing a notice in the Federal Register, and then must make the PMN and supporting documentation submitted with the PMN available for examination by interested members of the public."

For a subset of new chemicals applications, TMEs, TSCA requires that EPA immediately notify the public of their receipt to allow for public comment.

But the groups argue that "[d]espite the unambiguous language of the statutory provisions and EPA 's implementing regulations, EPA routinely fails to disclose the information as mandated by TSCA. Accordingly, EPA has violated and is in ongoing violation of its statutory and regulatory disclosure obligations, and this suit would seek to restrain those violations under the citizen suit provision of TSCA . . . and compel EPA to comply with its nondiscretionary duties to disclose such information."

They also cite EPA's 1983 Federal Register notice outlining TSCA's PMN notice requirements and review process, describing the notification requirements as indication that "Congress intended informed citizen involvement in review of new chemical substances ... Public participation cannot be effective unless meaningful information is made available to interested persons."

The notice cites a host of related issues beyond its concerns over timely notice, including "substantively incomplete" notices; failure "to make the PMNs publicly available for examination by interested persons," including health and safety data; failure "to make [confidential business information] substantiation documents available for examination by interested persons" and "unlawfully allow[ing] confidentiality claims without the required substantiation documents" among other related issues.

EPA explains of its first concern that statute and regulation state the agency must, when it announces receipt of new PMN applications, describe the toxicity information submitted with the PMN and a list of the tests performed. It argues that "when EPA belatedly publishes notice of receipt of a PMN in the Federal Register, EPA does not publish a list or descriptions of the test data submitted with the PMN, despite the fact that the PMN must include such test data to the extent it exists."

The notice is accompanied by pages of charts of PMNs received, some as far back as 2014, and the dates associated with EPA's receipt of the PMNs and publication of that notice in the Federal Register or on

EPA's website that Earthjustice says are examples of EPA's failures to follow TSCA and regulatory requirements. -- Maria Hegstad

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Harvest Date: Sep 19, 2019 8:44 AM

Industry: Toxic & Hazardous Substances (90%), Factory Workers (75%), Chemicals Regulation & Policy (74%), Chemicals Safety Regulation (74%), Hazardous Materials Regulation (74%), New Chemicals (74%), Manufacturing (73%), Lawyers (71%), Teleconferencing (63%)
Subject: Environment & Natural Resources (90%), Environmental & Wildlife Organizations (90%), Environmental Departments (90%), Environmental Law (90%), Toxic & Hazardous Substances (90%), US Environmental Law (78%), Business & Professional Associations (75%), Factory Workers (75%), Chemicals Safety Regulation (74%), Hazardous Materials Regulation (74%), New Chemicals (74%), Public Hearings (74%), Lawyers (71%), Environmentalism (70%), Suits & Claims (68%), Law & Legal System (66%), Talks & Meetings (65%)

Message

From: Stedeford, Todd [Stedeford.Todd@epa.gov]
Sent: 7/28/2020 12:26:04 AM
To: Owen Price ARA/AD [oprice@ara.com]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Snyder, Stephanie [stephanie.snyder@covestro.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]
Subject: Polymer Lung Overload Manuscript Draft - July 27, Version 2 + surfactants status update
Attachments: Supporting Information File - 27 July 2020.ver.1.docx; Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.2.docx

Importance: High

All,

Please find the attached, latest draft of the lung overload manuscript. This draft includes updates based on all of the comments I received to date (200+). Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) Please see if you agree with this presentation. Just as a reminder, our submission deadline is this Friday, so please review as quickly as you can. Also, please be mindful that I cross-referenced all tables/figures/schemes, so please do not try to re-number these. The references have also been linked up using EndNote, so please don't try to edit these either. If you spot an error on any these, just flag it with a comment. There are three items I still need to complete. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) I will aim to complete these tasks tomorrow. Otherwise, we are still working on addressing all of the comments on the surfactant manuscript, so hopefully, we can send out the update tomorrow. Sorry for the delay on this.

Thanks,

Todd

Polymer Lung Overload Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

Todd Stedeford[a,], Gregory S. Ladics[b], Owen Price[c], Annie Jarabek[d], Ann Tveit[e], Michael P. Hayes[f], Raphael Tremblay[f], Stephanie A. Snyder[g], Keith Salazar[h], Sahar Osman-Sypher[i], William Irwin[h], Marc Odin[j], Julie Melia[j], Heather Carlson-Lynch[j], and Tala R. Henry[a]*

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ED_005294A_00000429-00001

[h] Risk Assessment Division, Office of Pollution Prevention and Toxics, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, DC 20460, United States

[i] American Chemistry Council, Chemical Products and Technology Division, Washington, DC 20002, United States

[j] SRC, North Syracuse, NY 13212, United States

KEYWORDS: Inhalation, Lung Overload, New Approach Methods, Particle Toxicity, Risk Assessment, (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval.

ABSTRACT

Commented [ST1]: Abstract is new

Poorly soluble and non-reactive high-molecular weight (HMW) polymers (≥10,000 Daltons) represent a generic category of substances that are extensively used in industrial and consumer applications (*e.g.*, plastics). Under the amended Toxic Substances Control Act (TSCA), HMW polymers may qualify for an exemption from the pre-notification requirements that exist for polymeric, new chemical substances. However, for HMW polymers that do not meet the exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload. In the present evaluation, a systematic review of the literature was performed to identify studies that would aid with defining key properties for determining whether respirable HMW polymers may present an unreasonable risk to human health. These properties included: respirability, reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a

ED_005294A_00000429-00002

chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for several toxicological analogues that can be used in risk assessments on these substances. Finally, a tiered-testing strategy that maximizes the use of non-vertebrate testing (*i.e.*, NAMs) was developed that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));
2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

ED_005294A_00000429-00003

3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));
4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or
5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, Federal Insecticide, Fungicide, and Rodenticide Act), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><DisplayText>[1]</DisplayText><record><rec-number>31</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595768685">31</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 720.50 - Submission of test data and other data concerning the health and environmental effects of a substance</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><dates><year>2020</year></dates><pub-location>U.S.</pub-location><urls><related-urls><url>https://www.law.cornell.edu/cfr/text/40/720.50</url></related-urls></urls></record></Cite></EndNote>].

EPA has historically used various approaches to evaluate the potential hazards of new chemical substances including the use of computational toxicology models and analogue and category approaches to "read-across" from existing data to new chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program (NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on specific chemical definitions and boundaries that summarize the hazard concerns (*e.g.*, human health or environmental toxicity) and recommend testing that may be conducted prior to submitting a new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T

SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties, the NCP Chemical Categories were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect vertebrate testing reduction goals. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particulates[1] includes vertebrate animal testing, such as a 90-day subchronic inhalation toxicity study in rats with a 60-day recovery period [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-

[1] EPA identified particles as "respirable" to humans "if there are any particles ≤10 μ[m] in diameter in the material being handled by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical Categories cover the boundaries defined therein may not reflect development of alternative chemistries that do not fit within the current NCP Chemical Categories, even for chemicals that the alternative chemistries are intended to replace (*e.g.*, the use of polymeric alternatives to replace monomeric forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has also developed exemption criteria, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption", for specific types of polymeric substances [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>P

remanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria are exempt from the new chemical substance notification requirements, although there are still some requirements, including annual reporting and recordkeeping [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. EPA's polymer exemption established three exemption types, designated as E1, E2, and E3. The general criteria for new chemical substances meeting these exemption types for polymers are shown in [REF _Ref46665925 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

Exemption Type	*Number-average molecular weight (NAMW)*	*Oligomeric Material Criteria*	*Functional Groups (FGs) and Functional Group Equivalent Weight (FGEW) Content*
E1	1,000 ≤ NAMW < 10,000	< 10 wt% below 500 Daltons < 25 wt% below	Low concern FGs:[c] no limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

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		1,000 Daltons	
E2	NAM W ≥ 10,000	< 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons	No FG restrictions
E3	No limit	No limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[a] See 40 CFR § 723.250(b) Polymers. “Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units.” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Water absorbing polymers with NAMW ≥ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[c] "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]; however, there are instances where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc.*, in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather are based on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW $\geq$ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, $\leq$ 10 μm) represent a general class of chemical substances (hereinafter referred to as "HMW polymers") that may cause potential inhalation toxicity (*i.e.*, lung overload) *via* the mode(s) of action (*i.e.*, impairment of alveolar-macrophage mediated clearance), as identified in rat inhalation studies, to chemical substances present in the NCP Chemical Categories document for respirable, poorly soluble particulates. However, the chemical substances that are provided as analogues within the

boundaries for the NCP Chemical Category on respirable, poorly soluble particulates are limited to discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for those polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as representative toxicological analogues with points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. An additional aim was to introduce new approach methodologies (NAMs) into the tiered-testing strategy to meet the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

MATERIALS AND METHODS

Systematic Literature Review

Commented [ST2]: New text, the original SR text was placed in the Supporting Information file, since it only included our initial search, rather than a combo of the initial and supplemental search

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at "Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies

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that evaluated potential “lung overload” toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, “lung overload” refers to the “type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance” [ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[6]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-57</pages><volume>12</volume><number>1-2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals, Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response

Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><keyword>Risk Assessment</keyword><keyword>Species Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-Feb</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>10715617</accession-num><urls></urls><electronic-resource-num>10.1080/089583700196536</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is defined differently in experimental animals versus humans [ADDIN EN.CITE ADDIN EN.CITE.DATA], the literature searches used search strings that were intended to be overly inclusive to identify studies that evaluated "overload" in experimental animals and humans. A secondary objective was to identify potential NAMs that may be incorporated into a tiered-testing strategy that minimizes the use of vertebrate animals.

Risk Assessment Approaches Under TSCA

EPA generally uses the margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments performed on new chemical substances under TSCA. The MOE approach is calculated based on a point(s) of departure (POD) divided by a human exposure estimate(s). The POD is typically identified from an effect level from a study(ies) in experimental animals (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or benchmark dose [BMD]). A duration adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*,

workers = 8 hours/day, 5 days/week) versus the exposure conditions employed in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated for new chemical substances using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) in mg/day or lifetime average daily doses (LADDs) in mg/kg-bw/day. Given that new chemical substances will not have occupational exposure monitoring data, except for possible monitoring data on analogues, the PDR is typically used as an initial conservative exposure estimate when calculating the MOE. For chemical substances used in a powder or particulate form, the general default PDR values for respirable or total particulates are 50 mg/day (*i.e.*, 5 mg/m^3) or 150 mg/day (*i.e.*, 15 mg/m^3), respectively [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><DisplayText>[12]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595776956">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. However, for chronic effects like lung overload, the LADD represents

the more appropriate exposure metric for quantifying potential risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><DisplayText>[13]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595778575">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Interpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>20, https://www.epa.gov/sites/production/files/2015-05/documents/05-iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. A summary of the default values used for calculating PDRs and LADDs for new chemical substances in powder or particulate form is provided in [REF _Ref46666189 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	Cm × b × h	Mass concentration of chemical in air (Cm)	5	mg/m^3

		Volumetric inhalation rate (b) ($0 < b \leq 7.9$)	1.25	m^3/hr
		Exposure duration (h) ($0 \leq h \leq 24$)	8	hrs/day
LADD (mg/kg-bw/day)	(I × ED × EY) / (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) ($0 \leq$ ED (integer) ≤ 365)	250	days/site-yr
		Years of occupational exposure (EY) ($0 \leq$ EY)	40	years
		Body weight (BW) ($0 \leq$ ATc)	80	kg
		Averaging time over a lifetime (chronic) ($0 \leq$ ATc)	70	years

For each of the MOEs calculated herein, both the PDR and LADD are provided for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE higher than the benchmark MOE, the risks are not considered a concern under TSCA.

Benchmark MOE Derivation

The benchmark MOE is derived to account for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><Dis playText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or UF_H), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or UF_A), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or UF_L). The default values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance focused on improving the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Application of DAFs to the animal airborne exposure values yields estimates of the concentration that would result in the same concentration to humans, that is, the Human

Equivalent Concentration (HEC). For studies reporting only a LOAEC, EPA recommends benchmark dose modeling be performed, if the experimental data are amenable, to identify a BMDL, and thereby reduce the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with their potential applicability to the available studies that evaluated lung overload from HMW polymers.

Regional Dose Dosimetry Ratio (RDDR)

EPA may apply DAFs to PODs identified from experimental animal studies based on the methods described in its 1994 guidance document titled "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>]. When applied, the default DAF accounts for the toxicokinetic component of the UF_A and is reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, since the POD is dosimetrically adjusted to a POD_{HEC}, whereas the remaining UF_A value of approximately 3 accounts for the toxicodynamic component of the UF_A. Dosimetry or physiologically-based pharmacokinetic models are preferred to the default models when they are available [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the regional deposited dose ratio (RDDR), that is, the DAF for particles. The RDDR is an empirical

model of deposition that is applicable to particles in the size range of 0.5-30 µm and calculates an RDDR value as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute volume (V_E; mL/min), depositional fraction (Fr) of the particulate in the regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF), such as respiratory tract surface area, for the region of interest. The RDDR user inputs include mass median aerodynamic diameter (MMAD), geometric standard deviation (σ) for the particle of interest, and the average bodyweight of the animal used in the study from which default V_E and surface areas of the respiratory tract regions for the animal are calculated. The RDDR may be applied to the duration adjusted POD; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the laboratory animal regimen. Thereafter, the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ADDIN EN.CITE <EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[16]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox "Way more FPA than Counterstrike

!"</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].

Multiple-Path Particle Dosimetry (MPPD)

Commented [ST3]: Updated based on Owen and Annie write up

Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><DisplayText>[17]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian, B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-

path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy & histology/physiology</keyword><keyword>Lung/*anatomy & histology/physiology</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal Volume/physiology</keyword><keyword>Trachea/anatomy & histology/physiology</keyword></keywords><dates><year>1995</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590</isbn><accession-num>8566482</accession-num><urls></urls><electronic-resource-num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.* (2016) [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>[18]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Miller, F. J.</author><author>Asgharian, B.</author><author>Schroeter, J.D.</author><author>Price, O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>14-26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record><</Cite></EndNote>] is a mechanistic, multipath model that was modified and used to predict deposition, clearance, and lung burden over the course of a long-term exposure , as described by Ladics *et al*. (2020) [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. As with the RDDR outputs, the MPPD outputs provide values that may be used to

calculate a POD_{HEC}; however, unlike the RDDR model, MPPD provides outputs that may be used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via* retained dose.

The MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation

Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. These rates are considered representative of insoluble particles. More recently, the ICRP model and clearance rates have been updated based on improved lung burden data [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Refinements may be imparted by chemical-specific dissolution data and exploration of these new model values. Hygroscopic growth is currently not addressed in either the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers. In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-week rat exposures. In humans, MPPD implements the ICRP clearance model localized for individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach, as discussed in EPA (2012) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not identified in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1, because the BMDL is a dose level corresponding to specific response levels near the low end of the observable range of the data and incorporates and conveys more information than the NOAEC or the LOAEC [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, and model fit was evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract screening, 28 articles were selected for full text review, and 23 articles were identified using additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review, only 24 articles contained relevant information that satisfied the PECO criteria for lung overload from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review. Complete details on the systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

Commented [HT4]: How many overlap with the 51 from first search/review?

Commented [ST5R4]: I will add this, need to double check

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries develop the health effects summaries in the section on Hazard Identification and identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The category boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed further below. It should be noted that even if a HMW polymer satisfies the category boundary criteria, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

Commented [ST6]: Modified text

Respirable particles are those chemical substances with a particle size of less than or equal to 10 µm. The cutoff of 10 µm, as defined by EPA in its "Air Quality Criteria for Particulate Matter",

represents “particles collected by a sampler with an upper 50% cut point of 10 μm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A