<EndNote><Cite><Author>Sanderson</Author><Year>2011</Year><RecNum>14814</RecNum><DisplayText>[100]</DisplayText><record><rec-number>14814</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046031">14814</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sanderson, M. J.</author></authors></contributors><auth-address>Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA 01655, USA. Michael.Sanderson@umassmed.edu</auth-address><titles><title>Exploring lung physiology in health and disease with lung slices</title><secondary-title>Pulm Pharmacol Ther</secondary-title><alt-title>Pulmonary pharmacology & therapeutics</alt-title></titles><periodical><full-title>Pulmonary pharmacology & therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></periodical><alt-periodical><full-title>Pulmonary pharmacology & therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></alt-periodical><pages>452-65</pages><volume>24</volume><number>5</number><edition>2011/05/24</edition><keywords><keyword>Animals</keyword><keyword>Cell Physiological Phenomena</keyword><keyword>Disease Models, Animal</keyword><keyword>Humans</keyword><keyword>Lung/pathology/*physiology</keyword><keyword>Lung Diseases/*pathology</keyword><keyword>Microscopy/methods</keyword><keyword>Muscle Contraction/physiology</keyword><keyword>Organ Culture Techniques</keyword></keywords><dates><year>2011</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>1094-5539 (Print)
1094-

5539</isbn><accession-num>21600999</accession-num><urls></urls><custom2>PMC3168687</custom2><custom6>NIHMS296121</custom6><electronic-resource-num>10.1016/j.pupt.2011.05.001</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. 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.

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. 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

Commented [HT41]: For the whole FRAMEWORK

ED_005294A_00000402-00124

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA], 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.

Commented [HT42]: Maybe this goes at the very end of this section?

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Commented [HT43]: ODIN: this para needs re-write; offers no edits

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 [OS44]: Tala to include some additional text – read across, etc.

Tiered-testing Strategy

Commented [HT45]: DISCUSS CATEGORY CRITERIA AS FIRST STEP

A tiered testing approach for surfactants that have been established to meet the Surfactant Criteria is discussed below. 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.

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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum><DisplayText>[105]</DisplayText><record><rec-number>14819</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596046851">14819</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, No. 39 (Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</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>], ISO 21501-1:2009 [ADDIN EN.CITE <EndNote><Cite><Author>ISO</Author><Year>2009</Year><RecNum>14820</RecNum><DisplayText>[106]</DisplayText><record><rec-number>14820</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046993">14820</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ISO</author></authors></contributors><titles><title>Determination of particle size distribution — Single particle light interaction methods — Part 1: Light scattering aerosol spectrometer</title></titles><pages>https://www.iso.org/standard/42728.html</pages><volume

>ISO 21501-
1:2009</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote
>], OECD TG 110 [ADDIN EN.CITE
<EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>14821</RecNum>
<DisplayText>[107]</DisplayText><record><rec-number>14821</rec-number><foreign-
keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
timestamp="1596047114">14821</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; Method A: Particle Size
Distribution (effective hydrodynamic radius); Method B: Fibre Length and Diameter
Distributions</title><secondary-title>OECD Guidelines for the Testing of
Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of
Chemicals</full-title></periodical><pages>13, https://www.oecd-
ilibrary.org/docserver/9789264069688-
en.pdf?expires=1596047951&id=id&accname=guest&checksum=A9C13F0DFD
CF2A5DD4DD39DAC64C47BC</pages><volume>110</volume><dates><year>1981</year><
/dates><urls></urls></record></Cite></EndNote>], and OPPTS 830.7520 [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>14822</RecNum><
DisplayText>[108]</DisplayText><record><rec-number>14822</rec-number><foreign-
keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
timestamp="1596047315">14822</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>Product Properties Test Guideline, Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection Agency</secondary-title></titles><periodical><full-title>Product Properties Test Guideline, Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection Agency</full-title></periodical><pages>13, https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPPT-2009-0151-0030&contentType=pdf</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]). 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~~μm. This cutoff is consistent with EPA's "trace amounts" threshold for the nonreportable content for nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>14823</RecNum><DisplayText>[109]</DisplayText><record><rec-number>14823</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596047488">14823</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

Commented [SM46]: Corrected to μ

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>].

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 [OS47]: 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.

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" ([REF _Ref46931271 \h * MERGEFORMAT]). 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*

Commented [HT48]: 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

vivo test systems, considering for example the surface area of the culture system or *ex vivo* tissue, loss mechanisms, *etc*.

Pulmonary surfactant interaction/loss of function

- *In vitro* lung surfactant interaction investigation ~~inhibition~~ as described by e.g. Sorli *et al.* (2017) [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Commented [SM49]: Sorli uses Rat surfactant this may be limited and we should also leave open space for alternatives and not fix this to Sorlis technique. Therefore e.g. might be important here. Further I think interaction is better than inhibition, it will alter the function sure but not really inhibit it. Therefore alteration would be also ok.

Cell interaction/penetration

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.,* OECD 492 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[88]</DisplayText><record><rec-number>14803</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</ye

ar></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like Epithelium (RhCE) Test Method; OECD 437 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecNum><DisplayText>[89]</DisplayText><record><rec-number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043719">14802</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and Permeability Test Method; OECD 438 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecNum><DisplayText>[90]</DisplayText><record><rec-number>14804</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for identifying I) chemicals inducing serious eye damage and II) chemicals not requiring classification for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test Method, *etc*.

General cytotoxicity

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.*, OECD 492 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[88]</DisplayText><record><rec-number>14803</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-

title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like Epithelium (RhCE); OECD 437 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecNum><DisplayText>[89]</DisplayText><record><rec-number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043719">14802</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and Permeability Test; OECD 438 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecNum><DisplayText>[90]</DisplayText><record><rec-number>14804</rec-

number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for identifying I) chemicals inducing serious eye damage and II) chemicals not requiring classification for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test, *etc*.

- ICCVAM (2006) [ADDIN EN.CITE <EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNum><DisplayText>[91]</DisplayText><record><rec-number>14805</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><title>In vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing</title><secondary-title>ICCVAM Test Method Evaluation Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation Report</full-title></periodical><pages>334,

https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519</volume><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] recommended protocol for the BALB/c 3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity (Appendix C1)

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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2019</Year><RecNum>14825</RecNum><DisplayText>[110]</DisplayText><record><rec-number>14825</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048386">14825</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Transmittal of Meeting Minutes and Final Report for the Federal Insecticide Fungicide and Rodenticide Act, Science Advisory Panel (FIFRA SAP) Meeting held on December 4 and 6,

2018</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>51,https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2018-0517-0030&contentType=pdf</pages><volume>EPA-HQ-OPP-2018-0517</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>] . 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.*) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. 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 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 [HT50]: SALAZAR: NOT CLEAR WHAT THE '3' ASSAYS ARE

Commented [RAB51]: 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

Commented [SM52]: Should we not better say "endpoints (surface interaction, cell interaction/penetration, cytotoxicity" than assays or tests?

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) [ADDIN EN.CITE ADDIN EN.CITE.DATA]

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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum><DisplayText>[97]</DisplayText><record><rec-number>14811</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Issue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)

</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33, https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. 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.

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_{HECS}. 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 [ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum><DisplayText>[82]</DisplayText><record><rec-number>14796</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041048">14796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title>Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2009</Year><RecNum>14827</RecNum><DisplayText>[112]</DisplayText><record><rec-number>14827</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048858">14827</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Acute Inhalation Toxicity</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>19, https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg403.pdf</pages><volume>403</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] (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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14828</RecNum><DisplayText>[113]</DisplayText><record><rec-number>14828</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596048957">14828</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>28-day (subacute) inhalation toxicity study</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>23, https://doi.org/10.1787/9789264070783-en</pages><volume>412</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>], 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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum><DisplayText>[105]</DisplayText><record><rec-number>14819</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046851">14819</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, No. 39 (Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-

title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</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. Additionally, the sensory irritant potential can be measured using ASTM E 981 to determine reflex inhibition [ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>2001</Year><RecNum>14826</RecNum><DisplayText>[114]</DisplayText><record><rec-number>14826</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048712">14826</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Alarie, Y.</author><author>Nielsen, G.D.</author><author>Schaper, M.M.</author></authors><secondary-authors><author>Spengler, B.</author><author>Samet, J. M.</author><author>McCarthy, J.F.</author></secondary-authors></contributors><titles><title>Animal Bioassays for Evaluation of Indoor Air Quality</title><secondary-title>Indoor Air Quality Handbook</secondary-title></titles><pages>23.21-23.49.</pages><dates><year>2001</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill</publisher><urls></urls></record></Cite></EndNote>].

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

CONCLUSIONS

Commented [ST53]: Needs some work

The overall objective of this investigation was to develop a chemical category for use in conducting inhalation risk assessment for new chemical surfactant substances under TSCA. This investigation provides physical-chemical properties, *i.e.*, the Surfactant Criteria, assessors can use for determining whether a new chemical substance can be considered a surfactant. Further, properties and characteristics are provided to divide the surfactant category into sub-categories for nonionic, anionic and cationic surfactants, which is important from a toxicological perspective. A systematic literature search and review were conducted to identify data to define a surfactant category and toxicological analogues from read-across could be performed. Animal toxicity studies that could be used to derive PODs for risk assessments were identified for at least one analogue for each sub-category. EPA recommended duration and dosimetric adjustment factors to these toxicity studies to derive HECs for each subcategory. Finally, a tiered-testing strategy is provided that focuses on integrating a variety of NAMs currently available. Integrating NAMs into the category testing approach not only supports EPA and TSCA goals of reducing and replacing vertebrate animal testing, but also serves to encourage development of mechanistic data to advance understanding of inhalation adverse outcome pathway and toxicity of surfactants.

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

ED_005294A_00000402-00145

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)

AUTHOR INFORMATION

Corresponding Author

*U.S. Environmental Protection Agency, EPA East Bldg., Rm. 3410B, 1200 Pennsylvania Ave., NW, Mail Code: 7401M, Washington, D.C. 20460, Tel: (202) 564-6991, E-mail: stedeford.todd@epa.gov

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.

Funding Sources

Any funds used to support the research of the manuscript should be placed here (per journal style).

Notes

ED_005294A_00000402-00146

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]

ED_005294A_00000402-00147

Message

From: Stephanie Snyder [stephanie.snyder@covestro.com]
Sent: 7/30/2020 12:53:57 PM
To: Ann Tveit [ann.tveit@basf.com]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.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: RE: draft lung overload manuscript 27 July 2020.ver.4
Attachments: Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.5.docx

Ex. 5 Deliberative Process (DP)

Thanks

From: Ann Tveit [mailto:ann.tveit@basf.com]
Sent: Wednesday, July 29, 2020 5:48 PM
To: Stephanie Snyder; Stedeford, Todd; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Irwin, William; Rick_Becker@americanchemistry.com; Henry, Tala; Owen Price; Salazar, Keith; Jarabek, Annie
Subject: RE: draft lung overload manuscript 27 July 2020.ver.4

Hi All,

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ann Tveit Ph.D., D.A.B.T.
Toxicology Manager

Phone: +1 973 245-5527, Mobile: Ex. 6 Personal Privacy (PP) - personal phone, Email: ann.tveit@basf.com
Postal Address: BASF Corporation, 2B662, 100 Park Avenue, 07932 Florham Park, USA

BASF
We create chemistry

BASF Corporation

From: Stephanie Snyder <stephanie.snyder@covestro.com>
Sent: Wednesday, July 29, 2020 1:37 PM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael <hayes.mp@pg.com>; Ladics, Greg <gregory.s.ladics@dupont.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Ann Tveit <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: RE: draft lung overload manuscript 27 July 2020.ver.4

Hi Todd,

The comments are contained in the attached version. Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

Thanks,
Stephanie

From: Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
Sent: Wednesday, July 29, 2020 5:58 AM
To: Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder; Tveit, Ann; Irwin, William; Rick_Becker@americanchemistry.com; Henry, Tala; Owen Price; Salazar, Keith; Jarabek, Annie
Subject: draft lung overload manuscript 27 July 2020.ver.4

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

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]*

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

[b] Dupont Nutrition and Biosciences, Wilmington, Delaware 19803, United States

[c] Applied Research Associates, Inc., Arlington, Virginia 22203, United States

[d] Health & Environmental Effects Assessment Division, Center for Public Health & Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, United States

[e] BASF Corporation, Florham Park, New Jersey 07932, United States

[f] Proctor & Gamble, Company, Inc., St. Bernard, Ohio 45217, United States; Temselaan 100, 1853 Strombeek-Beaver, Belgium

[g] Covestro LLC, Pittsburgh, Pennsylvania 15205, United States

ED_005294A_00000404-00001

[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

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_00000404-00002

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~~ a toxicological analogue~~s~~ 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));

ED_005294A_00000404-00003

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~~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

[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>].

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

ED_005294A_00000404-00010

		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, 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

“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 particulates 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

		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 ~~hereinin~~ 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

ED_005294A_00000404-00022

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 thereby~~to 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>].

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-

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~~ 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

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.

ED_005294A_00000404-00036

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"

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-

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].

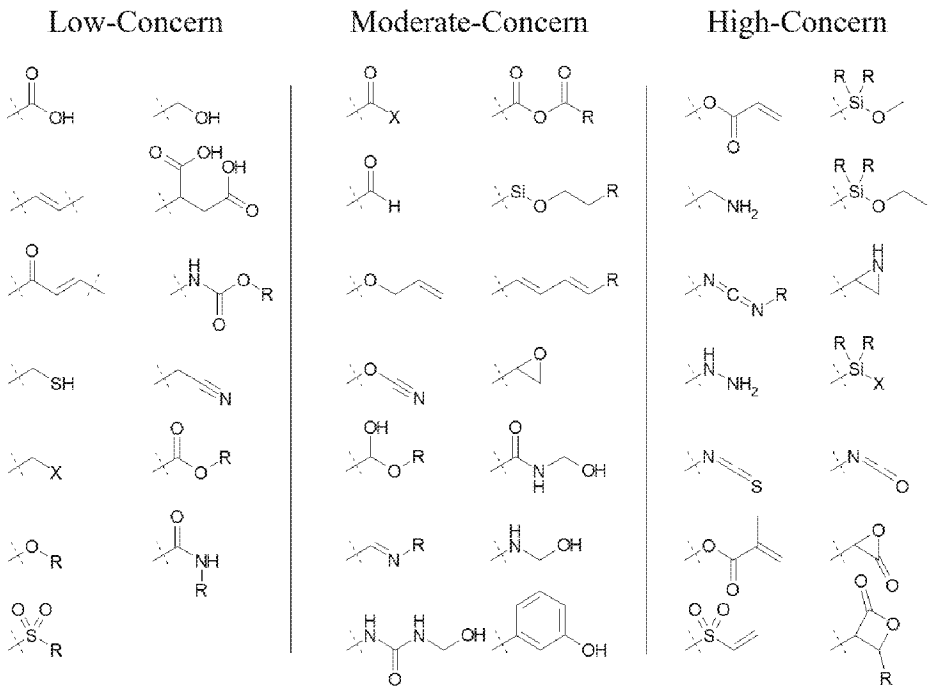


Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The 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 $\geq$ 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~~ 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}) [

ADDIN EN.CITE

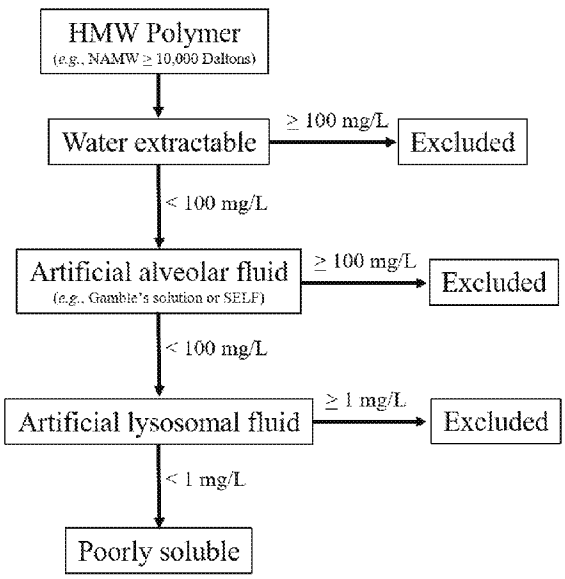
<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><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.



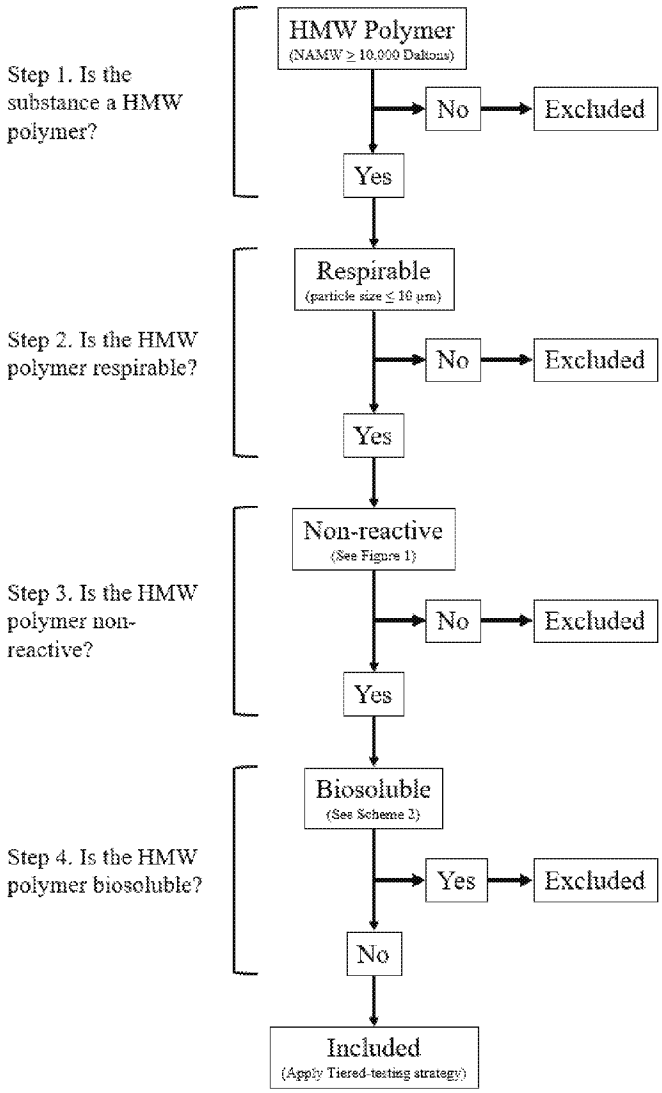
The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility 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].

[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

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-

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

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.

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
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><Di
splayText>[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)
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>].

Muhle *et al.* (1991) [ADDIN EN.CITE

Formatted: German (Germany)

<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.
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)

Formatted: German (Germany)

[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

(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><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-

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>]. No increase~~d~~ in the incidence of tumors ~~incidence~~ was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

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

medium incubated with test material ~~in cell culture medium, and~~to 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 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.

ED_005294A_00000404-00069

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><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]

ED_005294A_00000404-00073

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_00000404-00081

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-

ED_005294A_00000404-00084

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

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><tit

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 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

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

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

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>
<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><Di
splayText>[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>

ED_005294A_00000404-00095

<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.

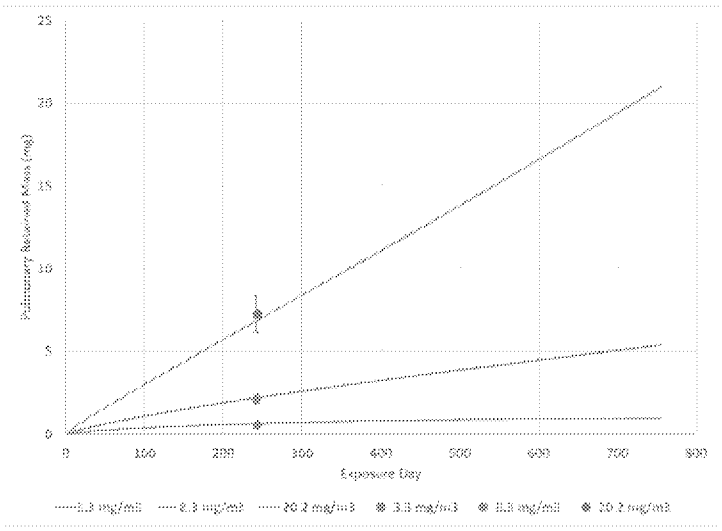


Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><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><keywo rd>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

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

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

ED_005294A_00000404-00101

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 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

ED_005294A_00000404-00102

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.

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 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

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 tomay 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</RecN

ED_005294A_00000404-00112

um><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.*, ≤ 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.*, ≤ 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

ED_005294A_00000404-00119

<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

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: respirability, reactivity, and solubility. These are the same key parameters for lung overload caused by poorly soluble particles (PSP), an extensively studied and well known phenomena. The tiered approaches proposed in this paper take advantage of the key factors identified for lung overload and apply, as applicable to HMW polymers. Two HMW polymers were identified as toxicological analogues ~~were identified~~ that may be used for "read across" when evaluating the potential of a ~~to~~ new chemical substances ~~for evaluating~~to result in lung overload. When applicable, the PODs on these analogues may be refined using MPPD to predict ~~when~~the exposure levels 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, or when a company prefers to provide data for its specific HMW polymer new chemical substance, the tiered-testing strategy

described above provides a framework that minimizes the use of vertebrate animals , takes advantage of new alternative methods and key events from PSP induced lung overload ~~with~~while providing information which may be used to determine if there is a potential for ~~informing whether~~for new HMW polymers chemical substances present a hazard for lung overload under its condition(s) of use. ~~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~~. Using these approaches, data on the respirability, reactivity and solubility of HMW polymers will be evaluated by EPA and only when needed, on a case by case basis, will animal studies be considered and discussed with the ~~new chemical substance manufacture. and may also help to~~, resulting in a reduction and refinement of ~~reduce and refine~~ the number of animals used. The tiered testing approach was developed based on the best available science currently available. It is expected that as new data ~~will be~~ is provided to EPA through new substance notifications, the tiered testing approach will be evaluated and updated as appropriate. ~~and will be evaluated as appropriate to determine if the tiered testing framework requires modification.~~ This is in line with EPA's Strategic Plan to Promote the Development and Implementation of Alternative Test Methods.

Commented [AT1]: Needs better text

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

AUTHOR INFORMATION

Corresponding Author

*U.S. Environmental Protection Agency, EPA East Bldg., Rm. 3410B, 1200 Pennsylvania Ave., NW, Mail Code: 7401M, Washington, D.C. 20460, Tel: (202) 564-6991, E-mail: stedeford.todd@epa.gov

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 a government contract to SRC (68HERH19F0197 (TO#07))~~[insert number]~~. The American Chemistry Council's TSCA Section 5 Testing Consortium sponsored an updated literature review by an independent third party.ACC ~~sponsored the supplemental literature review conducted by an independent third party.~~

Formatted: Font: Times New Roman, 12 pt

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]

ED_005294A_00000404-00125

Message

From: Stedeford, Todd [Stedeford.Todd@epa.gov]
Sent: 7/30/2020 11:26:48 AM
To: Hayes, Mike [hayes.mp@pg.com]; Kennedy, Wayne [Wayne.Kennedy@AftonChemical.com]
CC: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Henry, Tala [Henry.Tala@epa.gov]
Subject: RE: Surfactants --> THE TABLE
Attachments: draft manscript general surfactants - 29 July 2020.ver.4.docx

Ex. 5 Deliberative Process (DP)

From: Hayes, Mike <hayes.mp@pg.com>
Sent: Thursday, July 30, 2020 7:24 AM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>
Cc: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Henry, Tala <Henry.Tala@epa.gov>
Subject: RE: Surfactants --> THE TABLE

Ex. 5 Deliberative Process (DP)

From: Stedeford, Todd <Stedeford.Todd@epa.gov>
Sent: Thursday, July 30, 2020 6:43 AM
To: Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Hayes, Mike <hayes.mp@pg.com>
Cc: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Henry, Tala <Henry.Tala@epa.gov>
Subject: RE: Surfactants --> THE TABLE

Ex. 5 Deliberative Process (DP)

From: Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>
Sent: Thursday, July 30, 2020 6:41 AM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Hayes, Michael <hayes.mp@pg.com>
Cc: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Henry, Tala

<Henry.Tala@epa.gov>
Subject: RE: Surfactants --> THE TABLE

Hello Todd,

Ex. 5 Deliberative Process (DP)

Wayne

From: Stedeford, Todd <Stedeford.Todd@epa.gov>
Sent: Thursday, July 30, 2020 6:12 AM
To: Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Hayes, Michael <hayes.mp@pg.com>
Cc: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Henry, Tala <Henry.Tala@epa.gov>
Subject: RE: Surfactants --> THE TABLE

Ex. 5 Deliberative Process (DP)

From: Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>
Sent: Wednesday, July 29, 2020 4:48 PM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>
Cc: Hayes, Michael <hayes.mp@pg.com>; Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com
Subject: RE: Surfactants --> THE TABLE

Hello Tala and Todd,

Mike and I added a few last updates to the table based on our review today. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Best Regards,
Wayne

Wayne Kennedy | **Afton Chemical Corporation** | **Senior Manager – Product Stewardship and Regulatory Affairs**
500 Spring Street, Richmond, VA 23219 | (804) 788-6035 | wayne.kennedy@aftonchemical.com

The information contained in this transmission is confidential and intended only for the use of the individual or entity named above and those properly entitled to access to the information. This transmission may contain information that is privileged and/or exempt from disclosure under applicable law. If the reader of this transmission is not the intended or an authorized recipient, you are hereby notified that any unauthorized disclosure, dissemination or duplication of this transmission is prohibited. If you have received this communication in error, please notify me immediately by return email and delete the original message. This message (including attachments) is covered by the Electronic Communication Privacy Act, 18 USC sections 2510-2521, and is CONFIDENTIAL.

From: Stedeford, Todd <Stedeford.Todd@epa.gov>
Sent: Wednesday, July 29, 2020 9:49 AM
To: Sahar_Osman-Sypher@americanchemistry.com; Rick_Becker@americanchemistry.com; Hayes, Michael <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; ljovanovich@stepan.com; Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>
Subject: Surfactants --> THE TABLE

---------- EXTERNAL EMAIL ----------
This email originated from outside of your organization. Do not click links or open attachments unless you recognize the source of this email and know the content is safe. If unsure report it to IT ServiceDesk.

I don't think this one needs an explanation ☺

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

Tala R. Henry[a,‡], Keith Salazar[b,‡], Michael P. Hayes[c], Wayne Kennedy[d], Athena M. Keene[d], Annie Jarabek[e], Stefan Moors[f], Lela Jovanovich[g], Raphael Tremblay[c], Ann Tveit[f], Richard A. Becker[h], Sahar Osman-Sypher[h], Patrick D. McMullen[i], Scott D. Slattery[i], William Irwin[b], Marc Odin[j], Julie Melia[j], and Todd Stedeford[a,]*

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

[b] 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

[c] Proctor & Gamble, Company, Inc., St. Bernard, Ohio 45217, Untied States; Temselaan 100, 1853 Strombeek-Beaver, Belgium

[d] Afton Chemical Corporation, Richmond, Virginia 23219, United States

ED_005294A_00000406-00001

[e] Health & Environmental Effects Assessment Division, Center for Public Health & Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, United States

[f] BASF Personal Care and Nutrition GmbH, GBP/RD, Gebäude Z22, Henkelstrasse 67, 40589 Duesseldorf, Germany; BASF Corporation, Florham Park, New Jersey 07932, United States

[g] Stepan Company, Northfield, Illinois 60093, United States

[h] American Chemistry Council, Washington, DC 20002, United States

[i] ScitoVation, Durham, North Carolina 27713, United States

[j] SRC, North Syracuse, New York 13212, United States

KEYWORDS (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

The Toxic Substances Control Act (TSCA) requires anyone who plans to manufacture (including import) a new chemical substance for a non-exempt commercial purpose to provide EPA with a premanufacture notice (PMN) before initiating the activity. Surfactants are a class of chemicals commonly used in occupational settings, in consumer products, and in biological research and development ~~and therefore subject to PMN~~. Their use in such applications provide pathways of exposure by which potential toxicity of these compounds may occur to humans. While TSCA requires submission of any existing toxicity data, it does not require generation of toxicity data for the purpose of or prior to PMN submission. TSCA requires EPA to review the PMN to determine whether the new chemical substance presents an unreasonable risk of injury to human health or

Commented [ST1]: Recommend deleting because you list biological R&D, which is not subject to PMN

ED_005294A_00000406-00002

the environment and also mandates that EPA reduce and replace vertebrate animals in testing, to the extent practicable and scientifically justified. EPA therefore relies on a number of approaches that do not rely on *de novo* toxicity testing. Analogue read-across, in which toxicity data for a chemical of similar structure and activity is used to assess the new chemical, and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) have been used by EPA for decades to assess new chemical substances. This investigation was conducted to identify surfactant chemicals with toxicity data relevant for use in conducting quantitative human health risk assessment for new surfactant substances and define a TSCA New Chemical Category for surfactants. Category boundaries are defined, toxicological analogues suitable for conducting 'read-across' hazard assessment (*i.e.*, –hazard identification and –dose-response analysis) are identified and a tiered-testing strategy aimed at using new approach methodologies (NAMs) to reduce or replace animal testing is outlined. This surfactant category provides a pragmatic and scientifically defensible approach to facilitate EPA's review of new surfactant PMNs and a strategic testing approach that provides the data needed to conduct or refine surfactant risk assessment while also meeting the requirements of TSCA to reduce vertebrate testing.

INTRODUCTION

The Toxic Substances Control Act (TSCA) was amended in 2016 by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Pub. L. 114-182. The amended TSCA included substantial changes to EPA's authorities and responsibilities, including requirements on EPA to make a determination regarding sufficiency of information, production quantities relative to environmental releases and human exposure and unreasonable risks. The amended TSCA also included provisions

ED_005294A_00000406-00003

mandating EPA to "reduce and replace, to the extent practicable, [and] scientifically justified" the use of vertebrate animals in the testing of chemicals substances. Specifically, TSCA section 4(h) charges EPA with encouraging and facilitating –

> (1) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under TSCA;
> (2) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and
> (3) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator.

The present investigation advances each of these TSCA mandates for chemical substances characterized as surfactants.

A surfactant is a substance that reduces the surface tension of a liquid in which it is dissolved. They are surface-active, amphiphilic compounds that self-assemble to form micelles or aggregates above a critical concentration, referred to as the critical micelle concentration (CMC). These substances are commonly used in occupational settings, in consumer products (*e.g.*, household cleaning products, personal care products, *etc.*), and in biological research and development (R&D) as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. Their use in such applications provide pathways of exposure by which potential toxicity of these

ED_005294A_00000406-00004

compounds may occur to human or environmental receptors. Specifically, the inherent properties of surfactants may induce toxicity if exposures occur such that they can interfere with biological surfactants or tissues. For example, sodium dodecyl sulfate, a strong anionic surfactant, is used in R&D applications at concentrations up to 10% to disrupt cell membranes and to denature proteins, whereas octylphenoxypolyethoxyethanol, a mild nonionic surfactant, is used in R&D applications at concentrations up to 1% to disrupt cell membranes, while preserving proteins for isolation [ADDIN EN.CITE <EndNote><Cite><Author>Burden</Author><Year>2012</Year><RecNum>14727</RecNum><DisplayText>[1]</DisplayText><record><rec-number>14727</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017177">14727</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Burden, D.W.</author></authors></contributors><titles><title>Guide to the Disruption of Biological Samples - 2012, Version 1.1.</title><secondary-title>Random Primers</secondary-title></titles><periodical><full-title>Random Primers</full-title></periodical><pages>1-25</pages><number>12</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Hazard concerns for surfactants were historically focused on their observed environmental effects and potential toxicity to aquatic organisms [ADDIN EN.CITE ADDIN EN.CITE.DATA]. For example, the U.S. Environmental Protection Agency (EPA) established chemical categories for cationic (quaternary ammonium) and anionic surfactants based on environmental toxicity concerns [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017536">14729</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, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>157, 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>]. Surfactants may also be a potential hazard concern to humans, depending on the use and route of exposure, because they can disrupt the normal architecture of the lipid bilayer and reduce the surface tension, thereby solubilizing cell membranes. Mucous membranes are particularly sensitive to the surface-active effects of surfactants, which have been shown to cause irritancy and injury to the eye, based on their ability to “readily penetrate the sandwiched aqueous and lipid barriers of the cornea” [ADDIN EN.CITE <EndNote><Cite><Author>Fox</Author><Year>2008</Year><RecNum>14730</RecNum><DisplayText>[4]</DisplayText><record><rec-number>14730</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017801">14730</key></foreign-keys><ref-type name="Book

Section">5</ref-type><contributors><authors><author>Fox, D.A.</author><author>Boyes, W.K.</author></authors><secondary-authors><author>Klaassen, C.D.</author></secondary-authors></contributors><titles><title>Toxic Responses of the Ocular and Visual System</title><secondary-title>Casarett & Doull's Toxicology - The Basic Science of Poisons, Seventh Edition</secondary-title></titles><pages>665-697</pages><section>17</section><dates><year>2008</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill, Medical Publishing Division</publisher><urls></urls></record></Cite></EndNote>].

Depending on the conditions of use, inhalation exposures to workers and/or consumers may be possible that warrant consideration in quantitative risk assessments. As noted, surfactants may cause adverse effects on mucous membranes, including the respiratory tract, and have been shown to interfere with the natural pulmonary surfactants, resulting in reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, grossly visible pulmonary edema, and atelectasis [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, the chemical space for surfactants that may present inhalation hazards has not been previously defined, and the potential for inhalation toxicity ranges by orders of magnitude, such as octylphenoxypolyethoxyethanol, a nonionic surfactant 14-day lowest-observed-adverse-effect concentration [LOAEC] of 5.3 mg/m^3) [ADDIN EN.CITE ADDIN EN.CITE.DATA], versus didecyldimethyl ammonium chloride, a cationic surfactant and biocide (DDAC, CASRN 7173-51-5; 4-week lowest-observed-adverse-effect concentration [LOAEC] of 0.08 mg/m^3 for portal-of-entry effects) [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]
.

The objectives of the present investigation were to: (1) perform a systematic review of the literature with the aim of defining the chemical space for surfactants; (2) identify appropriate toxicological analogues, when available, for identifying potential inhalation hazards and when data allow, identifying quantitative point(s) of departure for use in an inhalation risk assessment; (3) describe scientifically sound new approach methodologies (NAMs) to reduce or replace animal testing, where possible; and (4) establish a tiered-testing strategy, that utilizes NAMs, as appropriate, for new chemistries in the surfactant space.

MATERIALS AND METHODS

Systematic Literature Review

Two literature searches were performed, an initial search in November 2016 and a supplemental search in April 2018. The details of these searches, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcome (PECO) criteria used for reviewing the relevance of the results are provided in the Supporting Information file at "Section 1 Systematic Literature Review". These searchers were conducted with the primary objective of identifying studies that evaluated the toxicity of surfactants in respiratory tract in exposed humans, laboratory animals, and at the cellular level in *in vitro* and *ex vivo* studies. A secondary objective of these searches was to identify potential NAMs that could inform a tiered-testing strategy for general surfactants that reduces or replaces the use of vertebrate animals in regulatory testing.

Risk Assessment Approaches under TSCA

Risk Assessment Paradigm

The current methods and approaches for assessing risks of new chemical substances under TSCA have been built upon decades of expert development, scientific peer review, refinement, and scientific knowledge. Generally, EPA conducts risk assessments following the four-step process articulated by the National Research Council, first in 1983 [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1983</Year><RecNum>14733</RecNum><DisplayText>[11]</DisplayText><record><rec-number>14733</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018654">14733</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>

Risk Assessment in the Federal Government: Managing the Process, Washington, D.C. The National Academies Press</title></titles><pages>191, DOI: https://doi.org/10.17226/366</pages><volume>ISBN: 978-0-309-03349-7</volume><dates><year>1983</year></dates><urls></urls></record></Cite></EndNote>] and reaffirmed several times since [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1994</Year><RecNum>14734</RecNum><DisplayText>[12, 13]</DisplayText><record><rec-number>14734</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018772">14734</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Science and Judgment in Risk Assessment, Washington, D.C. The National Academies Press</title></titles><pages>672, DOI: https://doi.org/10.17226/2125</pages><volume>ISBN: 978-0-309-07490-2</volume><dates><year>1994</year></dates><urls></urls></record></Cite><Cite><Author>NRC</Author><Year>2009</Year><RecNum>14737</RecNum><record><rec-number>14737</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019010">14737</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Science and Decisions: Advancing Risk Assessment, Washington, D.C. The National Academies Press</title></titles><pages>422, DOI: https://doi.org/10.17226/12209</pages><volume>ISBN: 978-0-309-12046-

ED_005294A_00000406-00010

3</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. This process includes hazard identification, dose-response analysis, exposure assessment, and risk characterization. Hazard assessment (also called effects assessment in some EPA guidance documents) identifies the types of adverse health or environmental effects or hazards that can be caused by exposure to the chemical substance. The dose-response assessment describes the relationship between the exposure or dose of a chemical and the occurrence of health or environmental effects or outcomes is assessed. The exposure assessment characterizes the extent of human or environmental exposures, including the magnitude, frequency, and duration of the exposure, to the extent necessary and practicable within the context of the assessment. Finally, the risk characterization integrates the hazard, dose-response, and exposure components to describe the nature, and when possible, the magnitude of risks to human health and the environment.

The approaches employed for these components, including, for example, the level of detail and complexity of quantitative aspects may vary across different risk assessments and typically align with specific legislative and regulatory frameworks. For example, legislative and regulatory frameworks for hazard evaluation of pesticide active ingredients, anti-microbial substances, inerts, *etc*. are described in regulations for pesticides, which include multiple and specific requirements for toxicity data. Under TSCA and its implementing regulations [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14738</RecNum><DisplayText>[14]</DisplayText><record><rec-number>14738</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596019129">14738</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA </author></authors></contributors><titles><title>40 CFR Part 720 - Premanufacture Notification</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/part-720</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], companies are required to submit a Premanufacture Notice (PMN) along with all available data on: chemical identity, production volume, byproducts, use, environmental release, disposal practices, and human exposure. These submissions are required to include all existing health and environmental data in the possession or control of the submitter, parent company, or affiliates, and a description of any existing data known to or reasonably ascertainable by the submitter. However, TSCA has never included requirements for toxicity testing or generation of hazard data for new chemical substances prior to submission for review by EPA.

Hazard Assessment

Given the lack of toxicity testing requirements under TSCA, EPA only occasionally receives human health relevant hazard data for new chemical substances. EPA conducted an analysis of toxicity tests submitted to EPA from 2004 through 2012 for new chemical substances under TSCA and found that about 15% of the PMN submissions included some type of human health relevant hazard data; mostly animal tests for acute toxicity and irritation. TSCA provides EPA with the authority to require generation and submission of additional data when the information included with the PMN, coupled with that available to EPA risk assessors from prediction

modeling, read-across, internal archives, *etc*. is insufficient to permit a reasoned evaluation of the health and environmental effects of a new chemical substance. However, prior to making a request for testing using vertebrate animals, EPA must take into consideration reasonably available existing information, including toxicity information; computational toxicology and bioinformatics; and high-throughput screening methods and the prediction models of those methods (TSCA Section 4(h)(A)(i)-(iii)).

Given the historical lack of hazard data and the new requirements to consider reasonably available existing information, EPA has, for decades, relied on a number of approaches that do not rely on *de novo* toxicity testing, including computational toxicology (*e.g.*, predictive models and expert systems), analogue read-across (wherein available toxicity data for a chemical of similar structure and activity is used to assess the new chemical substance lacking data), and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) [ADDIN EN.CITE <EndNote><Cite><Author>van Leeuwen</Author><Year>2009</Year><RecNum>14739</RecNum><DisplayText>[15]</DisplayText><record><rec-number>14739</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019290">14739</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van Leeuwen, K.</author><author>Schultz, T. W.</author><author>Henry, T.</author><author>Diderich, B.</author><author>Veith, G. D.</author></authors></contributors><auth-address>TNO Quality of Life, Utrechtseweg 48, The Netherlands.</auth-address><titles><title>Using chemical categories to fill data gaps in

hazard assessment</title><secondary-title>SAR QSAR Environ Res</secondary-title><alt-title>SAR and QSAR in environmental research</alt-title></titles><periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></periodical><alt-periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></alt-periodical><pages>207-20</pages><volume>20</volume><number>3-4</number><edition>2009/06/23</edition><keywords><keyword>Hazardous Substances/pharmacology/*toxicity</keyword><keyword>*Quantitative Structure-Activity Relationship</keyword><keyword>Safety Management/*methods</keyword></keywords><dates><year>2009</year></dates><isbn>1026-776x</isbn><accession-num>19544189</accession-num><urls></urls><electronic-resource-num>10.1080/10629360902949179</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The integration of these methods with NAMs to advance testing strategies has been recognized by EPA [ADDIN EN.CITE ADDIN EN.CITE.DATA] and is consistent with the vision articulated in the 2007 report by the National Research Council in "Toxicity Testing in the 21st Century: A Vision and Strategy [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2007</Year><RecNum>14741</RecNum><DisplayText>[17]</DisplayText><record><rec-number>14741</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019531">14741</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>NRC</author></authors></contributors><titles><title>T
oxicity Testing in the 21st Century: A Vision and a Strategy, Washington, D.C. The National
Academies Press</title></titles><pages>216, DOI:
https://doi.org/10.17226/11970</pages><volume>ISBNs: Ebook: 978-0-309-13412-5;
Paperback: 978-0-309-15173-
3</volume><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

Dose-Response Analysis

For assessing hazards to human health, EPA relies most heavily on read-across methods using an analogue or a category of analogues to identify hazards and conduct dose-response analysis to identify a point of departure (POD). While EPA has a number of existing "TSCA New Chemicals Program (NCP) Chemical Categories" [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><
DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-
keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
timestamp="1596017536">14729</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, Washington, D.C.
20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and
Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-
title></periodical><pages>157, https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201
0</year></dates><urls></urls></record></Cite></EndNote>], including for anionic, nonionic, and cationic surfactants, the existing surfactant categories were developed and defined based only on environmental toxicity considerations. Toxicity tests for analogues are used to identify a point of departure (POD) (*i.e.,* a dose or concentration that marks the beginning of a low-dose extrapolation) for assessing risks to the new chemical substance. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (*i.e.*, benchmark concentration or dose [BM(C)D], NOAE(C)L, LOAE(C)L, or human equivalent concentration or dose [HE(C)D]) for an observed incidence or change in level of response) [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>14744</RecNum><
DisplayText>[18]</DisplayText><record><rec-number>14744</rec-number><foreign-
keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
timestamp="1596019975">14744</key></foreign-keys><ref-type name="Journal
Article">17</ref-
type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B
enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.
Environmental Protection Agency, Washington, D.C. 20460</secondary-
title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection
Agency, Washington, D.C. 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>].

Once suitable analogues are identified, the strengths, limitations, and uncertainties associated with using the analogue as predictive of hazards of the new chemical substance are considered to derive a benchmark margin of exposure (MOE). The benchmark MOE is the result of multiplying all relevant uncertainty factors (UFs) to account for: (1) the variation in susceptibility among the members of the human population (*i.e.*, inter- individual or intraspecies variability); (2) the extrapolation from animal data to humans (*i.e.*, interspecies extrapolation); (3) the extrapolation from data in a study with less- than- lifetime exposure (*i.e.*, extrapolating from sub-chronic to chronic exposure); (4) the extrapolation from a LOAEL rather than from a NOAEL [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 20]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</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, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 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>2014</Year><RecNum>14742</RecNum><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. EPA prefers using existing information to develop data-derived extrapolation factors or chemical specific adjustment factors (DDEFs or CSAFs) rather than simply relying on defaults [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2014</Year><RecNum>14742</RecNum><DisplayText>[20]</DisplayText><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. This investigation includes a number of approaches to derive DDEFs to use in assessing new surfactant chemical substances.

Exposure Assessment

In assessing new chemical substances, EPA typically generates the human exposure estimates for workers using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as daily acute potential dose rates (PDRs) or lifetime average daily doses (LADDs). 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.

Commented [HT2]: Mppd guidance

Due to the surface-activity of surfactants at the point of exposure, the PDR is the appropriate dose-metric rather than the LADD which is typically used to assess cancer risks. For chemical substances used in a liquid, mist, or aerosol form, the general default PDR value is 1.875 mg/kg-

Commented [HT3]: But why? Due to long term/chronic exposure?

Commented [HT4]: Does this need more explaination? the PDR is mg/kg per day; so using repeated dose tox studies adjusted to # of days exposure. NOT using acute animal data

Tala and Marc Odin comment: explain why PDDR is appropriate

bw/day for inhalable aerosols or 0.625 mg/kg-bw/day for respirable aerosols calculated using the default values as shown in [REF _Ref46930162 \h * MERGEFORMAT] [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2015</Year><RecNum>14745</RecNum><DisplayText>[21]</DisplayText><record><rec-number>14745</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021217">14745</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, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>403, https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf</pages><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

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

Description	Equation	Description	Equation[a]	Defaults	Units
PDR (mg/kg-bw/day)	I/BW	Inhalation PDR (I)	Cm × b × h, where Cm is the mass concentration of chemical in air, b is the volumetric inhalation rate ($0 < b \leq 7.9$), and h is the exposure duration ($0 \leq h \leq 24$)	Cm = 15 mg/m^3 b = 1.25 m^3/hr h = 8 hours/day	mg/day
		Body weight (BW)	BW ($0 \leq BW$)	80 kg-bw	kg-bw

[a] Cm may also be adjusted for the mass concentration of the chemical with a PEL in air (based on OSHA PEL – TWA; default = 15 mg/m^3 inhalable; 5 mg/m^3 for respirable, the weight fraction of chemical in particulate (Ys) ($0 < Ys \leq 1$), the weight fraction of chemical or metal with a PEL in particulate (Ypel) ($0 < Ypel \leq 1$) using the following equation: Cm = KCk × Ys/Ypel

ED_005294A_00000406-00021

The PDR is calculated using a default worker values of 8 hrs/day and 5 days/week, unless chemical-specific manufacture, processing or use information are provided in the PMN. The exposure regimen used in animal studies often do not reflect occupational exposure scenarios, such that a duration adjustment and a dosimetric factor (*i.e.,* RDDR value) is applied to the POD from the animal study to derive human equivalent concentrations (HECs) exposed human population. While this adjustment would optimally be made using physiologically-based pharmacokinetic model [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</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, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]; the data required to conduct such modelling rarely exist for new chemical substances.

Therefore, occupational exposures are adjusted using particle deposition models with human exertion (work) ventilation rates and exposure durations appropriate to the particular occupational setting and chemical use scenario.

Risk Characterization

Risk characterization is an integral component of the risk assessment process for both ecological and health risks, *i.e.*, it is the final, integrative step of risk assessment. As defined in EPA's Risk Characterization Policy, the risk characterization integrates information from the hazard and exposure components of the risk assessment and synthesizes an overall conclusion about risk that is complete, informative, and useful for decision-making. A risk characterization conveys the risk assessor's judgment as to the nature and existence of (or lack of) human health or ecological risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2000</Year><RecNum>14747</RecNum><DisplayText>[23]</DisplayText><record><rec-number>14747</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021806">14747</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Risk Characterization</title><secondary-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>189,

https://nepis.epa.gov/Exe/ZyPDF.cgi/40000006.PDF?Dockey=40000006.PDF</pages><volume>EPA 100-B-00-002</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>]. As noted in EPA's Risk Characterization Handbook "Risk characterization at EPA assumes different levels of complexity depending on the nature of the risk assessment being characterized. The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written and the audience for which the characterization is intended."

Under TSCA section 5, EPA must determine whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use. EPA generally uses an MOE approach to characterize risks of new chemical substances as a starting point to estimate non-cancer risks for acute and chronic exposures. The MOE is the HEC derived from a POD for a specific health endpoint (from hazard assessment) divided by the exposure concentration for the specific scenario of concern (from exposure assessment). To determine whether the resulting MOE results in an adequate margin between human exposure estimates and the HEC derived from a POD, the MOE value is compared with a benchmark MOE. When using MOEs as risk estimates for non-cancer health effects, the benchmark MOEs are used to interpret the risk estimates. Generally, when the MOE is less than the benchmark MOE human health risks are interpreted as possible. On the other hand, negligible concerns would be expected if the MOE exceeds the benchmark MOE. The MOE approach is a widely recognized point estimate method and allows for providing a risk profile for a range of different non-cancer health effects and different exposure scenarios.

In summary, to conduct a risk evaluation for new chemical substances, as required under TSCA section 5, EPA conducts a hazard assessment, using empirical data when available, but most often using analogues, to identify a POD(s) and to develop a benchmark MOE that reflects specific uncertainties associated with data available for use in the evaluation. This hazard assessment is combined with the exposure assessment, to calculate an MOE, which is compared to the benchmark MOE to determine whether risks are identified. The risk characterization is used to inform the "unreasonable risk" determination.

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial PubMed search identified 594 articles that were subjected to title and abstract screening. Of these, 551 did not meet the PECO criteria, whereas 43 met the PECO criteria and were selected for full text review. An additional 17 references were included for full text review that met the PECO criteria and were identified through additional search strategies, screening gray literature, references for other types of chemical substances, *etc*. Of the 60 articles evaluated through full text screening, 16 were identified as relevant and carried forward in the present evaluation, whereas the remaining 44 studies were excluded because they lacked relevant information on respiratory tract effects or presented inconclusive epidemiology findings. In the supplemental literature search, 1242 studies were identified on PubMed and Embase (combined). Following title and abstract screening, 1217 of these studies were excluded because they did not meet the PECO criteria. A total of 35 studies met the PECO criteria and were selected for full text screening, which

resulted in 25 studies that were identified for review and 10 studies that were deemed irrelevant and excluded. Of the 25 studies identified for review, 15 of the studies were identified in the initial literature search.

The information identified in the systematic review was used to inform the section on Category Boundaries and subcategories with the boundaries, to summarize the health effects of surfactants under the section on Hazard Identification, and to identify potential NAMs for use in the section on Tiered-Testing Strategies.

Category Boundaries

The following structural and functional criteria (hereinafter referred to as the "Surfactant Criteria") are used to distinguish chemical substances, which include polymers and UVCB substances,[1] intended for use as surfactants from other amphiphilic compounds (*e.g.*, ethanol) [ADDIN EN.CITE ADDIN EN.CITE.DATA]:

1. A substance which has surface-active properties, and which consists of one or more hydrophilic and one or more hydrophobic groups;
2. The substance must be capable of reducing the surface tension between air and water to 45 milliNewtons/meter (mN/m) or below at a test condition of 0.5 wt% in water and a temperature of 20°C (*Cf.* Pure water has a surface tension of 72.8 mN/m at 20°C); <u>and</u>

[1] Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB Substance)

ED_005294A_00000406-00026

3. The substance self-associates in water to form micellar or vesicular aggregates at a concentration of 0.5 wt% or below.

The Surfactants Category is further defined into three general subcategories including nonionic, anionic, and cationic substances. Within these subcategories, The Surfactant Category is subcategorized for those chemical substances that initially meet the Surfactant Criteria and possess ionic or nonionic properties, as discussed below. Note, though not listed in the following subcategories, amphoteric chemical substances that meet the Surfactant Criteria would also be included within these subcategories (*i.e.*, cationic or anionic surfactants), depending on their pH. Lung lining fluids are near neutral pH, with various measurements ranging from 6.6 to 7.1 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The pKa for each component of an amphoteric surfactant should be considered within this pH range and the assessment should be conducted on the predominant components. The non-ionized fraction for acids/bases should be calculated as follows:

$$\text{Acids Fraction}_{\text{non-ionized}} = 1 / (1 + 10^{\text{pH-pKa}})$$

$$\text{Bases Fraction}_{\text{non-ionized}} = 1 / (1 + 10^{\text{pKa-pH}})$$

Where the pH represents the physiological pH in the lung (*i.e.*, 6.6 to 7.1), and the pKa represents the value for the respective component (*e.g.*, carboxylic acid or amine).

Nonionic surfactants are identified as any neutral chemical substance that meets the Surfactant Criteria. Common nonionic surfactants include alkylphenol chemical substances with one or more than one ethoxylate (EO) unit as well as linear and branched alcohol chemical substances with one or more EO units. For example, octylphenoxypolyethoxyethanol, a common nonionic octylphenol EO surfactant, and Polysorbate 80 (or Tween 80), another nonionic alkyphenol ethoxylate with increased alkyl chain length and number of EO units, are shown in [REF _Ref46930277 \h * MERGEFORMAT]. The surface tensions of octylphenoxypolyethoxyethanol and Polysorbate 80 range from 30-31 mN/m to 37.96 mN/m, respectively ([REF _Ref46930277 \h * MERGEFORMAT]) [ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025228">14758</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kothekar, S.C.</author><author>Ware, A.M.</author><author>Waghmare, J.T.</author><author>Momin, S.A.</author></authors></contributors><titles><title>Comparative Analysis of the Properties of Tween-20, Tween-60, Tween-80, Arlacel-60, and Arlacel-80</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/01932690601108045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

Commented [ST5]: CORRECT: Triton ~30.5 mN/m and Polysorbate 80 = 37.96 mN/m in Table 2.

Anionic surfactants were identified as any chemical substance with a net negative charge that meets the Surfactant Criteria (*e.g.*, alkyl sulfonates, alkylbenzene sulfonates, alkylether sulfates, alkyl silicic acids, alkyl phosphates, alkyl carboxylic acids, or combinations of these anionic groups). The surface tension of SDS is reported to be 35 mN/m ([REF _Ref46930277 \h * MERGEFORMAT]).

Commented [ST7]: CORRECT: SDS is 35 mN/m in Table 2.

Cationic surfactants are identified as any chemical substance with a net positive charge that meets the Surfactant Criteria (*e.g.*, alkylammonium chlorides and benzalkonium chlorides). DDAC is a a representative member of this subcategory, although as noted previously, it also possesses biocidal properties. The surface tension of DDAC is reported to be ~~27.61~~25.82 mN/m ([REF _Ref46930277 \h * MERGEFORMAT]).

Commented [ST8]: [redacted]

Table [SEQ Table * ARABIC]. Example Chemicals that Meet "Surfactant Criteria" and Nonionic, Anionic and Cationic Subcategorization.

Nonionic Surfactants					
Chemical Name in Text	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**
		Hydrophobic group(s)	**Hydrophilic group(s)**	**Surface Tension**	**Critical Micel Concentration (CMC)**
Octoxynol 9 Octylphenoxypoly-ethoxyethanol CASRN: 9002-93-1	Triton X-100 Octylphenol ethoxylate CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-[4-1,1,3,3-tetramethylbutyl)phenyl]-.omega.-hydroxy	octylphenol group	polyoxyethylene (9) unit	~30.5 mN/m at 5 g/L (0.5 wt%) and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sch	0.17 g/L or 0.01 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal

Commented [HT9]: Temp is provided only for some…is this acritical issue? Not part of the criteria…include of not?

Commented [HT10R9]: Footnote to address

Commented [HT11]: Add footnote regarding units reported in sources

Commented [HT12]: Have to go back through MS and harmonize this column

Commented [ST13]: I added this here because it is the name used in the text.

				ott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface	Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of

				science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-	colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isb

				num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]	n>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]
Tyloxapol Defomaire Alevaire CASRN: 25301-02-4	CAS Name: -Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)-phenol	multiple octyl phenol groups	multiple polyoxyethylene (9) units	~37 mN/m at 5 g/L (0.5 wt%) and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-	0.038 g/L or 0.0038 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-

				id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid	keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton

				Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn	X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-

				>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]	502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]
Polyoxyethylene-10-oleyl ether	$C_{18:1}E_{10}$ Oleyl ethoxylate	oleyl group	polyoxyethylene (10) unit	35.17 mN/m at 4×10^{-5} M (0.028%) and 25°C* [ADDIN EN.CITE	4×10^{-5} M or 0.028 wt % at 25°C [ADDIN EN.CITE <EndNote><Cite><

CASRN: 9004-98-2	CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-(9Z)-9-octadecen-1-yl-.omega.-hydroxy			<EndNote><Cite><Author>Liu</Author><Year>2006</Year><RecNum>14761</RecNum><DisplayText>[32]</DisplayText><record><rec-number>14761</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582">14761</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, F.</author><author>Wang, Z.</author><author>Sun, D.</author><author>Wei, X.</author><author>Zhou, W.</author><author>Li, G.</author><author>Zhang,	Author>Liu</Author><Year>2006</Year><RecNum>14761</RecNum><DisplayText>[32]</DisplayText><record><rec-number>14761</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582">14761</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, F.</author><author>Wang, Z.</author><author>Sun, D.</author><author>Wei, X.</author><author>Zhou, W.</author><autho

				G.</author></authors></contributors><titles><title>Adsorption Kinetics of Brij 97 at the Air/Solution Interface</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>657-663, https://www.tandfonline.com/doi/abs/10.1080/01932690600660624</pages><volume>27</volume><number>5</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>]	r>Li, G.</author><author>Zhang, G.</author></authors></contributors><titles><title>Adsorption Kinetics of Brij 97 at the Air/Solution Interface</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>657-663, https://www.tandfonline.com/doi/abs/10.1080/01932690600660624</pages><volume>27</volume><number>5</number><dates><year>2006</year></dates><urls></urls></

					record></Cite></EndNote>]
Polyoxyethylene-10-dodecyl ether CASRN: 9002-92-0	$C_{12}E_{10}$ Polyoxyethylene (10) lauryl ether CAS Name: Poly(oxy-1,2-ethanediyl),-.alpha.-dodecyl-.omega.-	dodecyl group	polyoxyethylene (10) unit	C12E9: 36 mN/m (concentration not reported) at 23°C* C12E12: 32 mN/m (concentration not reported) at 23°C* [ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Rosen, M.J.</author></autho	12.7×10^{-6} M or 0.0008 wt% at 30°C [ADDIN EN.CITE <EndNote><Cite><Author>Sulthana</Author><Year>2000</Year><RecNum>14762</RecNum><DisplayText>[34]</DisplayText><record><rec-number>14762</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025808">14762</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sulthana, S.B.</author><author>Rao,

				rs></contributors><titles><title>Surfactants and interfacial phenomena</title></titles><pages>431, </pages><dates><year>1989</year></dates><pub-location>New York</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]	P.V.C.</author><author>Bhat, S.G.T.</author><author>Sugihara, N.G.</author><author>Rakshit, A.K.</author></authors></contributors><titles><title>Solution Properties of Nonionic Surfactants and Their Mixtures: Polyoxyethylene (10) Alkyl Ether [CnE10] and MEGA-10</title><secondary-title>Langmuir</secondary-title></titles><periodical><full-title>Langmuir : the ACS journal of surfaces and colloids</full-title><abbr-1>Langmuir</abbr-1></periodical><pages>980-987, https://doi.org/10.1021/la990730o</pa

					ges><volume>16</volume><number>3</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>] Also, C12E9 at 1×10^{-6} M at 23°C and C12E12 at 1.4×10^{-6} M at 23°C [ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0errr5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited

					Book">28</ref-type><contributors><authors><author>Rosen, M.J.</author></authors></contributors><titles><title>Surfactants and interfacial phenomena</title></titles><pages>431,</pages><dates><year>1989</year></dates><pub-location>New York</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]
Polysorbate 20 or Tween 20 CASRN: 9005-64-5	Polyoxyethylene (20) sorbitan monolaurate CAS Name: Sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl) derivs.	dodecanoyl group	sorbitan polyoxyethylene (20) unit	38 mN/m at 8.04×10^{-5} M (0.001%) and 21°C* [ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>14756</RecNum><DisplayTex	8.04×10^{-5} M or 0.001 wt% at 21°C [ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>14756</RecNum><DisplayText>[35]</Dis

				t>[35]</DisplayText><record><rec-number>14756</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024348">14756</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, C.</author><author>Hsieh, Y.-L.</author></authors></contributors><titles><title>Wetting and absorbency of nonionic surfactant solutions on cotton fabrics</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><periodical><full-	playText><record><rec-number>14756</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024348">14756</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, C.</author><author>Hsieh, Y.-L.</author></authors></contributors><titles><title>Wetting and absorbency of nonionic surfactant solutions on cotton fabrics</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering

				title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]	Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]
Polysorbate 80 or Tween 80 CASRN: 9005-65-6	Polyoxyethylene (20) sorbitan monooleate CAS Name: Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivs.	octadecenoyl group	sorbitan polyoxyethylene (20) unit	37.96 mN/m at 5 g/L (0.5 wt %) and 30°C [ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN"	1.5×10^{-5} M or 0.002 wt% at 25°C [ADDIN EN.CITE <EndNote><Cite><Author>Mahmood</Author><Year>2013</Year><RecNum>14757</RecNum><DisplayText>[36]</DisplayText><record><rec-number>14757</rec-

				db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025228">14758</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kothekar, S.C.</author><author>Ware, A.M.</author><author>Waghmare, J.T.</author><author>Momin, S.A.</author></authors></contributors><titles><title>Comparative Analysis of the Properties of Tween-20, Tween-60, Tween-80, Arlacel-60, and Arlacel-80</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><period	number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024783">14757</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mahmood, M.E.</author><author>Al-Koofee, D.A.F.</author></authors></contributors><titles><title>Effect of Temperature Changes on Critical Micelle Concentration for Tween Series Surfactants</title><secondary-title>Global Journal of Science Frontier Research Chemistry</secondary-title></titles><perio

				ical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/01932690601108045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]	dical><full-title>Global Journal of Science Frontier Research Chemistry</full-title></periodical><pages>5, https://journalofscience.org/index.php/GJSFR/article/view/816/681</pages><volume>13(B)</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]
Poloxamer 188 CASRN: 691397-13-4	CAS Name: Oxirane, 2-methyl-, polymer with oxirane, triblock	polyoxypropylene (27) unit	two polyoxyethylene (80) units	~42-44 mN/m at ~0.5 wt% and 36°C [ADDIN EN.CITE ADDIN EN.CITE.DATA]	4.8×10^{-4} M or 0.4 wt% at 37°C [ADDIN EN.CITE ADDIN EN.CITE.DATA]
N,N-Dimethyl-dodecylamine-N-oxide*** CASRN: 1643-20-5	Lauryl dimethylamine oxide CAS Name:1-Dodecanamine, N,N-dimethyl-, N-oxide	dodecyl group	amine oxide unit	34.1 mN/~~M~~ m at 1 g/L (0.1 wt.%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14772	1.7×10^{-3} M or 0.039 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Hoffmann</Author><Year>1990</Year><RecNum>14764</RecNu

				</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14772</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596028055">14772</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Dodecyldimethylamine oxide, CASRN: 1643-20-5, EC number: 216-700-6, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European	m><DisplayText>[40]</DisplayText><record><rec-number>14764</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026736">14764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hoffmann, H.</author></authors></contributors><titles><title>Correlation between surface and interfacial tensions with micellar structures and properties of surfactant solutions</title><secondary-title>Progress in

				Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/10062/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]	Colloid & Polymer Science</secondary-title></titles><periodical><full-title>Progress in Colloid & Polymer Science</full-title></periodical><pages>16-28, https://link.springer.com/chapter/10.1007%2FBFb0116238</pages><volume>18</volume><dates><year>1990</year></dates><urls></urls></record></Cite></EndNote>] 1×10^{-5} M to 5.5×10^{-5} M or 0.0002 to 0.001 wt% at 25°C [ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><re

Formatted: Superscript

					cord><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National

					Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Anionic Surfactants					
Chemical	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**

Commented [HT14]: Temp is provided only for some…is this acritical issue? Not part of the criteria…include of not?

Commented [HT15R14]: Footnote to address

Name in Text		Hydrophobic group(s)	Hydrophilic group(s)	Surface Tension	Critical Micelle Concentration (CMC)
Sodium dodecyl sulfate CASRN: 151-21-3	SDS CAS Name: Sulfuric acid monododecyl ester sodium salt (1:1)	dodecyl group	sulfate group	35 mN/m at 0.29% (wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Hernainz</Author><Year>2002</Year><RecNum>14768</RecNum><DisplayText>[42]</DisplayText><record><rec-number>14768</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027363">14768</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hernainz, F.</author><author>Caro, A.</author></authors></contributors><titles><title>Variation	8.25×10^{-3} M or 0.24 wt% at 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels,

Commented [HT16]: Add footnote regarding units reported in sources

				of surface tension in aqueous solutions of sodium dodecyl sulfate in the flotation batch</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>19-24, https://www.sciencedirect.com/science/article/abs/pii/S0927775701005751</pages><volume>196</volume><number>1</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>]	K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.

					gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Oleoyl sarcosine CASRN: 110-25-8	CAS Name: Glycine, N-methyl-N-((9Z)-1-oxo-9-octadecen-1-y	oleyl group	carboxylic acid anion	31.91 mN/~~M~~ m at ~~(~~0.1~~%~~ wt%~~)~~ ~~at~~ and 19.9°C** [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14767</RecNum><DisplayText>[43]</DisplayText><record><rec-number>14767</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027202">14767</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration	2.6×10^{-3} wt% temperature not reported, assumed to be room temperature ~25°C [ADDIN EN.CITE <EndNote><Cite><Author>ChattemChemicals</Author><Year>2020</Year><RecNum>14769</RecNum><DisplayText>[44]</DisplayText><record><rec-number>14769</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027596">14769</key></foreign-

Commented [HT17]: Is this really right? Is this really M OR Is it 0.0026 wt%

				Dossier</author></authors></contributors><titles><title>Sodium N-methyl-N-(1-oxo-9-octadecenyl)aminoacetate, CASRN 3624-77-9, EC number: 222-829-9, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://www.echa.europa.eu/fi/web/guest/registration-dossier/-/registered-dossier/5350/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] **Note this reference is to the sodium salt.	keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ChattemChemicals</author></authors></contributors><titles><title>Oleoyl Sarcosine, CASRN 110-25-8</title><secondary-title>Product Information</secondary-title></titles><periodical><full-title>Product Information</full-title></periodical><pages>https://www.chattemchemicals.com/</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] **Note this reference is to the sodium salt.

Sodium lauroyl sarcosinate CASRN: 137-16-6	CAS Name: Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt (1:1)	lauryl group	carboxylic acid anion	40.5 mN/m at 2% w/w (▇-wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14770</RecNum><DisplayText>[45]</DisplayText><record><rec-number>14770</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027817">14770</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-lauroylsarcosinate, CASRN 137-16-6, EC number: 205-281-	8.0×10^{-2} wt% [ADDIN EN.CITE <EndNote><Cite><Author>Chattem Chemicals</Author><Year>2020</Year><RecNum>14769</RecNum><DisplayText>[44]</DisplayText><record><rec-number>14769</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027596">14769</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ChattemChemicals</author></authors></contributors><titles><title>Oleoyl Sarcosine, CASRN 110-25-	

Commented [HT19]: Really wt% or M
If wt% for consistency change to 0.08 wt%

Commented [HT18]: Assume w/w was as reported...what would be wt%?

				5, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/14123/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]	8</title><secondary-title>Product Information</secondary-title></titles><periodical><full-title>Product Information</full-title></periodical><pages>https://www.chattemchemicals.com/</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] ~~Reference? Wayne's~~
Dioctyl Sulfosuccinate Sodium Salt CASRN: 577-11-7	DOSS Dioctyl sodium sulfosuccinate CAS Name: -Butanedioic acid, 2-sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt	two 2-ethyl hexyl groups	sulfosuccinate group	<28 mN/m at 0.5 vol% and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>1957</Year><RecNum>14755</RecNum><DisplayText>[46]</DisplayText><record><rec-number>14755</rec-number><foreign-keys><key app="EN"	6.8×10^{-4} M or 0 wt% at 25°C [ADDIN EN.CIT <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-

Commented [HT21]: g/L??

Commented [HT20]: Assume vol% is what reported...what would be wt%?

				db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024180">14755</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, E.F.</author><author>Woodberry, N.T.</author><author>Dixon, J.K.</author></authors></contributors><titles><title>Purification and surface tension properties of alkyl sodium sulfosuccinates</title><secondary-title>Journal of Colloid Science</secondary-title></titles><periodical><full-title>Journal of Colloid Science</full-title></periodical><p	number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36,

				ages>452-459</pages><volume>12</volume><number>5</number><dates><year>1957</year></dates><urls></urls></record></Cite></EndNote>]	Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Cationic Surfactants					
Chemical Name in Text	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**
		Hydrophobic group(s)	**Hydrophilic group(s)**	**Surface Tension**	**Critical Micel Concentration (CMC)**

Commented [HT22]: Temp is provided only for some...is this acritical issue? Not part of the criteria...include of not?

Commented [HT23R22]: Footnote to address

Commented [HT24]: Add footnote regarding units reported in sources

Benzalkonium chloride CASRN: 8001-54-5	CAS Name: -Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides	alkyl chains are C12, C14, C16 and C18 and benzyl group	quaternary nitrogen	37 mN/m at concentrations greater than about 4×10^{-4}M and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Nandni</Author><Year>2013</Year><RecNum>14766</RecNum><DisplayText>[47]</DisplayText><record><rec-number>14766</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027033">14766</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nandni, D.</author><author>Mahajan, R.K.</author></authors></contributors><titles><title>Micellar and Interfacial	C12: reported values range from 2.3 - 8.5×10^{-3} M or 0.078 - 0.29 wt% at 25°C C14: 3.7×10^{-4} M or 0.014 wt% (temperature not stated; assumed to be room temperature, ~25°C C16: 4.2×10^{-5} M or 0.0016 wt% at 23°C C18: reported values range from 7.1 - 8.5×10^{-6} M or 0.0003 - 0.00036 wt% at 23°C [ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-

Commented [HT25]: also at 23 C?

				Behavior of Cationic Benzalkonium Chloride and Nonionic Polyoxyethylene Alkyl Ether Based Mixed Surfactant Systems</title><secondary-title>Journal of Surfactants and Detergents</secondary-title></titles><periodical><full-title>Journal of Surfactants and Detergents</full-title></periodical><pages>587-599, https://doi.org/10.1007/s11743-012-1427-z</pages><volume>16</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]	number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of

					Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Didecyldimethyl ammonium chloride CASRN: 7173-51-5	DDAC CAS Name: 1-Decanaminium, N-decyl-N,N-dimethyl-, chloride (1:1)	decyl groups	quaternary nitrogen	25.82 mN/m at 1 g/L (0.1 wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14771	0.39 g/L or 0.039 wt% at 25°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>

				</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European	14771</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals

				Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/5864/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]	Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/5864/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

*Not all of the surface tension measurement references identified are run at exactly 20°C, but they are sufficiently close (within 5°C) so as not to affect the measurement. In addition, several measurements were run at 0.1% instead of the recommended 0.5%. Increasing the concentration to 0.5% is likely to lower the surface tension.

Commented [HT26]: Any reference for this?

**Carboxylic acid compounds, such as oleoyl sarcosine, have a carboxyl group pKa value of ~5, thus at physiological pH values maintained near 7 in the lung, the carboxyl group will be 99% in the anionic form according the Henderson-Hasselbalch equation. Since sodium is the major cation in mammalian body fluids (~145 mM), the use of the sodium oleoyl sarcosine surface tension value is appropriate for its characterization.

***Zwitterionic: At pH 7, 90% expected to be nonionic; only small amount cationic.

Hazard Identification

There is concern for dysfunction of natural surfactant in the lung from inhalation of surfactants. Additionally, there is evidence that some surfactants or similar structures may also interfere with the cell membrane [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The capacity of exogenous surfactants to interfere with pulmonary surfactant and impair pulmonary function has been demonstrated in human volunteers and in laboratory animals. The pulmonary response to surfactant aerosol is likely in proportion to the exposure concentration and duration, but available data on acute and repeated-dose effect levels are limited within each subcategory, which limits establishing a correlation between chemical properties and exposure methods (*e.g.,* aerosol droplet size) and toxicity.

Nonionic Surfactants

In Vivo Studies

Several studies were identified for the nonionic siliconized superinone respiratory detergent, formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol (CASRN 25301-02-4; also known as Defomarie, Alevaire, Tyloxapol). Healthy human volunteers showed significantly decreased pulmonary compliance following acute inhalation of Defomaire beyond that produced by the distilled water control [ADDIN EN.CITE <EndNote><Cite><Author>Obenour</Author><Year>1963</Year><RecNum>13656</RecNum><DisplayText>[51]</DisplayText><record><rec-number>13656</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320595">13656</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>Obenour, R. A.</author><author>Saltzman, H. A.</author><author>Sieker, H. O.</author><author>Green, J. L.</author></authors></contributors><titles><title>Effects of surface-active aerosols and pulmonary congestion on lung compliance and resistance</title><secondary-title>Circulation</secondary-title><alt-title>Circulation</alt-title></titles><periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></periodical><alt-periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></alt-periodical><pages>888-92</pages><volume>28</volume><edition>OBENOUR, R A
SALTZMAN, H A
SIEKER, H O
GREEN, J L
1963/11/01</edition><keywords><keyword>Aerosols</keyword><keyword>Alcohols</keyword><keyword>Ethanol</keyword><keyword>Heart Failure</keyword><keyword>Humans</keyword><keyword>Infusions, Parenteral</keyword><keyword>Injections, Intravenous</keyword><keyword>Lung</keyword><keyword>Lung Compliance</keyword><keyword>Pulmonary Edema</keyword><keyword>Respiratory Function Tests</keyword><keyword>Silicones</keyword><keyword>Sodium Chloride</keyword><keyword>Surface-Active Agents</keyword></keywords><dates><year>1963</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0009-7322 (Print)
0009-7322 (Linking)</isbn><accession-num>14079193</accession-num><call-num>0 (Aerosols)
0 (Alcohols)
0 (Silicones)
0 (Surface-Active Agents)
3K9958V90M (Ethanol)
451W47IQ8X (Sodium Chloride)</call-num><urls></urls><remote-database-provider>NLM</remote-database-

provider><language>Eng</language></record></Cite></EndNote>]. Increased minimum surface tension due to detergent was demonstrated, and shown to be dose-dependent, using pulmonary surfactant extracted from dogs and mixed *in vitro* with the nonionic surfactant tyloxapol (Alevaire) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. *In vivo* exposure of dogs to Alevaire in this study (8 h aerosol exposure; vehicle and concentration not reported) produced little effect (only 1/10 dogs exposed to Alevaire showed increased minimum surface tension), which the authors concluded support the dose-dependence of the effect and indicate that small amounts of detergent can be present in the lungs without detectably altering surfactant function [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Other pulmonary effects in dogs and/or sheep exposed to nonionic surfactant, tyloxapol, included reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, and grossly visible pulmonary edema and atelectasis (*i.e.,* collapsed alveoli) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In the study by Modell *et al.* (1969) [ADDIN EN.CITE ADDIN EN.CITE.DATA], no gross pathology differences were seen in detergent-exposed vs. control lungs of dogs, although some portions of both control and exposed lungs were heavy and discolored reddish-purple, which may have been caused by fluid accumulation from the liquid aerosol exposures and/or the use of hypotonic saline in the study (0.45% NaCl). Normal appearances were observed in the remaining areas of the lungs.

In rodent models, irritation and inflammatory effects on the respiratory tract has been observed with varying degrees of severity. Acute inhalation exposure to Polysorbate 20, which is not

ED_005294A_00000406-00066

irritating to the skin or eyes [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14776</RecNum><DisplayText>[52]</DisplayText><record><rec-number>14776</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596030693">14776</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sorbitan monolaurate, ethoxylated, 1 - 6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/13525/7/4/2</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], *via* nose-only administration for 4 hours in Wistar Han rats to a concentration of 5.1 mg/L (5,100 mg/m^3, MMAD 2.2 µm, GSD 2µm) did not observed an increase in mortalities, clinical signs, or abnormalities in the gross pathology [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14777</RecNum><DisplayText>[53]</DisplayText><record><rec-number>14777</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596030813">14777</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sorbitan monolaurate, ethoxylated 1 - 6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Acute Toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-

Formatted: Font: Italic

ED_005294A_00000406-00067

title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/13525/7/3/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The total lung deposition mass was calculated to be 6.6×10^4 µg using MPPD modeling. A respiratory irritation study on a mixture containing octylphenoxypolyethoxyethanol [ADDIN EN.CITE ADDIN EN.CITE.DATA], which can be severely irritating to the skin and eyes in male Webster mice using the ASTM Method E981 where animals were exposed for 3 hours to concentrations of 12, 22, 51, 118, and 134 mg/m^3 and allowed 30-60 minutes recovery time observed signs of respiratory irritation in animals at the three highest concentrations as indicated by increased respiratory frequency without an increase in pulmonary edema or lung weight [ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>1992</Year><RecNum>14778</RecNum><DisplayText>[54]</DisplayText><record><rec-number>14778</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035219">14778</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alarie, Y.</author><author>Stock, M.F.</author></authors></contributors><titles><title>Respiratory Irritancy on a Mixture containing Polyethylene Glycol Mono(Octyl)Phenyl Eether CAS #9035-19-5</title><secondary-title>ChemView - U.S. Environmental Protection Agency</secondary-title></titles><periodical><full-title>ChemView - U.S. Environmental Protection Agency</full-title></periodical><pages>37, https://chemview.epa.gov/chemview/proxy?filename=09022526800b76c9_86960000465_09-26-2011_8D_PHCS_Original%20-

Commented [ST27]: This is an issue if we (EPA) calculated this with MPPD, but then used RDDR for the PODs

%2086960000465.pdf</pages><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>]. An acute inhalation exposure study in Syrian hamsters to 3.0 mg/L of octylphenoxypolyethoxyethanol to varying exposure durations reported that lung deposition of octylphenoxypolyethoxyethanol corresponded to mortality with an LD_{50} of 1300-2100 µg [ADDIN EN.CITE <EndNote><Cite><Author>Damon</Author><Year>1982</Year><RecNum>13323</RecNum><DisplayText>[55]</DisplayText><record><rec-number>13323</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320592">13323</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Damon, E. G.</author><author>Halliwell, W. H.</author><author>Henderson, T. R.</author><author>Mokler, B. V.</author><author>Jones, R. K.</author></authors></contributors><titles><title>Acute toxicity of polyethylene glycol p-isooctylphenol ether in syrian hamsters exposed by inhalation or bronchopulmonary lavage</title><secondary-title>Toxicology and applied pharmacology</secondary-title><alt-title>Toxicol Appl Pharmacol</alt-title></titles><periodical><full-title>Toxicology and Applied Pharmacology</full-title><abbr-1>Toxicol. Appl. Pharmacol.</abbr-1></periodical><pages>53-61</pages><volume>63</volume><number>1</number><edition>Damon, E G
Halliwell, W H
Henderson, T R
Mokler, B V
Jones, R K
1982/03/30</edition><keywords><keyword>Animals</keyword><keyword>Cricetinae</keyword><keyword>Detergents/ toxicity</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Female</keyword><keyword>Lethal Dose 50</keyword><keyword>Lung/ drug

effects/pathology</keyword><keyword>Male</keyword><keyword>Mesocricetus</keyword><keyword>Octoxynol</keyword><keyword>Polyethylene Glycols/administration & dosage/toxicity</keyword><keyword>Surface-Active Agents/toxicity</keyword><keyword>Therapeutic Irrigation</keyword></keywords><dates><year>1982</year><pub-dates><date>Mar 30</date></pub-dates></dates><isbn>0041-008X (Print)
0041-008X (Linking)</isbn><accession-num>7071873</accession-num><call-num>0 (Detergents)
0 (Surface-Active Agents)
30IQX730WE (Polyethylene Glycols)
9002-93-1 (Octoxynol)</call-num><urls></urls><remote-database-provider>NLM</remote-database-provider><language>Eng</language></record></Cite></EndNote>]. The authors concluded that the deaths in these animals were likely the result of severe laryngeal edema and ulcerative laryngitis while the lower airways and lungs in these animals were relatively free of serious pathologies. The authors hypothesized that that these observed effects were due to large tracheobronchial deposition following the aerosol exposure and the mucociliary clearance of the deposited chemical resulted in a large concentration of the chemical on the laryngeal mucosa. Finally, in the only repeated dose inhalation exposure identified for nonionic surfactants, a 2-week repeated whole-body dose inhalation study was conducted on octylphenoxypolyethoxyethanol in male and female Sprague-Dawley rats to 5.3 and 10.3 mg/m^3 (5/sex/dose; MMAD 1.8 µm, GSD 1.8µm) for 6 hours/day, 5 days/week [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Slight to minimal subacute inflammation of the alveolar walls and hyperplasia of the alveolar/bronchiolar epithelium was reported, in addition to an increase in slight discoloration of the lungs, increased lung weight, and mucoid nasal discharge; a LOAEC of 5.3 mg/m^3 was identified.

Mechanistic studies

In vitro studies of surfactant effects on cell membranes have provided evidence of possible MOAs. Warisnoicharoen *et al*. (2003) [ADDIN EN.CITE ADDIN EN.CITE.DATA] evaluated the cytotoxicity of the nonionic surfactants polyoxyethylene-10-oleyl ether ($C_{18:1}E_{10}$), polyoxyethylene-10-dodecyl ether ($C_{12}E_{10}$), and N,N-dimethyl-dodecylamine-N-oxide ($C_{12}AO$; CASRN 1643-20-5) to cultured human bronchial epithelium cells (16-HBE14o-) *in vitro*, using the MTT cell viability assay. All of the surfactants tested were cytotoxic at concentrations near or below their critical aggregation (micellular) concentrations (as determined by surface tension measurements), suggesting that surfactant toxicity was due to the disruption caused by the partitioning of monomeric surfactant into the cell membrane.

Lindenberg *et al*. (2019) [ADDIN EN.CITE <EndNote><Cite><Author>Lindenberg</Author><Year>2019</Year><RecNum>14779</RecNum><DisplayText>[57]</DisplayText><record><rec-number>14779</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035601">14779</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lindenberg, F.</author><author>Sichel, F.</author><author>Lechevrel, M.</author><author>Respaud, R.</author><author>Saint-Lorant, G.</author></authors></contributors><titles><title>Evaluation of Lung Cell Toxicity of Surfactants for Inhalation Route</title><secondary-title>Journal of Toxicology and risk assessment</secondary-title></titles><periodical><full-title>Journal of Toxicology and risk

ED_005294A_00000406-00071

assessment</full-title></periodical><pages>https://doi.org/10.23937/2572-4061.1510022</pages><volume>5</volume><number>1</number><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>] evaluated the cytotoxic activity of the three nonionic polymeric surfactants, which are commonly used in formulations of nebulized pharmaceuticals to prevent protein agglomeration, Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), and Poloxamer 188 in a BEAS-2B human bronchial epithelial cell model by using an innovative air-liquid interface (ALI) method of exposure compared to the classical liquid/liquid (L/L) model. The study measured the release of Lactate Dehydrogenase (LDH) which is an intercellular enzyme present in large amounts in the cytoplasm. Loss of membrane integrity will cause the release of LDH into the extracellular medium. Cytotoxicity of Polysorbate 20 was observed at concentrations of 1-2% (v/v) when using the more biologically relevant ALI method by measuring Lactate Dehydrogenase (LDH) activity, however, a significant increase in LDH was only observed at 4% for Polysorbate 80 and not significantly increased at concentrations of up to 10% for Poloxamer 188. These results suggest that Polysorbate 20 and to the lesser extent Polysorbate 80 induce damage to the cell membrane integrity while the linear Poloxamer 188 did not demonstrate any *in vitro* cytotoxicity.

Altogether, the available *in vitro* and *in vivo* data indicate a wide discrepancy in respiratory toxicity among nonionic surfactants. The small dataset presented in this section preclude establishing correlations between respiratory effects and chemical properties such as surface tension or CMC. Others have examined the relationship between chemical properties of nonionic surfactants and eye irritation and concluded that hydrophilic-lipophilic balance, pH, alkyl chain length, or poly [oxyethylene] chain lengths failed to predict eye irritation potential across the nonionic

subcategory [ADDIN EN.CITE <EndNote><Cite><Author>Heinze</Author><Year>1999</Year><RecNum>14780</RecNum><DisplayText>[58]</DisplayText><record><rec-number>14780</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035990">14780</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Heinze, J.E.</author><author>Casterton, P.L.</author><author>Atrash, J.</author></authors></contributors><titles><title>Relative Eye Irritation Potential of Nonionic Surfactants: Correlation to Dynamic Surface Tension</title><secondary-title>Journal of toxicology: cutaneous and ocular toxicology</secondary-title></titles><periodical><full-title>Journal of toxicology: cutaneous and ocular toxicology</full-title></periodical><pages>359-374, https://doi.org/10.3109/15569529909065552</pages><volume>18</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. However, significant correlations of eye irritation and the maximum reduction in surface tension were observed at the CMC or higher surfactant concentration when conducted under nonequilibrium conditions. Whether this chemical property similarly predicts potency of nonionic surfactants for respiratory effects requires additional data and analysis outside of the scope of this summary.

Anionic Surfactants

In vivo studies

ED_005294A_00000406-00073

Two acute inhalation toxicity studies were identified for anionic surfactants which demonstrated high toxicity via the inhalation route. Oleoyl sarcosine, which is irritating to the skin and damaging to the eye [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14781</RecNum><DisplayText>[59]</DisplayText><record><rec-number>14781</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036160">14781</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>N-methyl-N-[C18-(unsaturated)alkanoyl]glycine, CASRN: NA, EC number: 701-177-3, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/21429/7/4/2/?documentUUID=fbaef057-ecc7-4763-aa56-1fa2c88c606c</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], was evaluated in a 4-hour nose-only inhalation study in male and female Sprague-Dawley rats using concentrations of 0.3, 0.6, 2.2, and 3.7 mg/L (300, 600, 2,200, 3,700 mg/m^3). An LC_{50} of 1.37 mg/L was identified with edema of the lung at 0.6 mg/L and audible gasping at 0.3 mg/L. For sodium lauroyl sarcosinate (CASRN 137-16-6), which is irritating to the eye but not the skin, male Wistar rats were exposed to a 4-hour nose-only inhalation concentration of 0.05, 0.5, 1, and 5 mg/L (50, 500, 1,000, and 5,000 mg/m^3) (MMAD 4.4, 2.85, 3.65, 6; GSD 2.7, 3, 4.2, 2.9, respectively and 5 female rats were exposed to 1.1 or 5.5 mg/L (MMAD 3.65, 6; GSD 4.2, 2.9, respectively)[ADDIN EN.CITE

ED_005294A_00000406-00074

<EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14782</RecNum><DisplayText>[60, 61]</DisplayText><record><rec-number>14782</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036284">14782</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-lauroylsarcosinate, CASRN: 137-16-6, EC number: 205-281-5, Eye Irritation</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/14123/7/4/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14783</RecNum><record><rec-number>14783</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036540">14783</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-lauroylsarcosinate, CASRN: 137-16-6, EC number: 205-281-5, Acute Toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/14123/7/3/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. All 10 animals exposed to 5 mg/L died within 1-2 h of dosing, and 4/5 of the animals

exposed to 0.5 mg/L and the 10 animals exposed to 1 mg/ml died within 1-2 days after dosing. Animals in the 0.05 mg/L had no clinical signs or mortality at the conclusion of the study. At necropsy, red foci were noted on the lungs in animals of groups receiving concentrations of ≥ 0.5 mg/L. The LC_{50} was reported to be 0.05-0.5 mg/L. Carboxylic acid compounds, such as oleoyl sarcosine, have a carboxyl group pKa value of ~5, thus at physiological pH values maintained near 7 in the lung, the carboxyl group will be 99% in the anionic form according the Henderson-Hasselbalch equation. Since sodium is the major cation in mammalian body fluids (~145 mM), the use of the sodium oleoyl sarcosine data is appropriate for POD derivation.

Repeated-dose inhalation studies were identified for oleoyl sarcosine (CASRN 110-25-8), and dioctyl sodium sulfosuccinate (CASRN 577-11-7). Oleoyl sarcosine was evaluated in a 28-day nose-only inhalation study (6 hours/day, 5 days/week; OECD Guideline 412) in male and female Fischer rats (5/group/sex) using concentrations of 0, 0.006, 0.02, or 0.06 mg/L (6, 20, 60 mg/m^3) (MMAD 1.11, 1.15, 1.22µm, GSD 1.68-2.57µm) in 10% ethanol for 6 hours/day, 5 days/week in 10% ethanol [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14784</RecNum><DisplayText>[62]</DisplayText><record><rec-number>14784</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036869">14784</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>N-methyl-N-[C18-(unsaturated)alkanoyl]glycine, CASRN: NA, EC number: 701-177-3, Repeated dose toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-

ED_005294A_00000406-00076

title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/21429/7/6/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The mass median aerodynamic diameter (MMAD) of the aerosol particles were 1.11- 1.22 µm and the geometric standard deviation (GSD) was 1.68-2.57. Changes in the mean corpuscular volume (MCV), white blood cells (WBC), and lymphocytes in male animals of the high dose groups were observed. In female animals of the mid-dose group, reticulocyte counts were significantly reduced. Reflex bradypnea was noted in the animals of the mid and high doses which is associated with severely irritating substances. All test concentrations caused effects at several sites of the respiratory tract with indications for local irritation, such as squamous metaplasia and epithelium proliferation and submucous acute inflammation at the base of the epiglottis. In the lungs and bronchi, the most prominent finding was a focal early stage of fibrosis, but details were not provided at the dose level for this effect. Lung weights were increased at the highest dose. The LOAEC was 0.006 mg/L (6 mg/m^3) air in males and females; the basis for the effect level was local irritation.

Dioctyl ~~sodium~~ sulfosuccinate sodium salt (DOSS) was evaluated in a 13-week inhalation study in male and female Sprague-Dawley rats (12/group/sex), to an aerosol of a product containing 0.0042 mg/L (4.2 mg/m^3) DOSS, for 4 hours a day, 5 days a week [ADDIN EN.CITE <EndNote><Cite><Author>CIR</Author><Year>2013</Year><RecNum>14785</RecNum><DisplayText>[63]</DisplayText><record><rec-number>14785</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596037107">14785</key></foreign-keys><ref-type name="Journal

Commented [ST28]: Changed to match Column 1 of Table 2 "Chemical Name in Text"

Article">17</ref-type><contributors><authors><author>CIR</author></authors></contributors><titles><title>Safety Assessment of Alkyl Sulfosuccinate Salts as Used in Cosmetics, Re-Review, CIR Expert Panel Meeting, June 10-11, 2013</title><secondary-title>Cosmetic Ingredient Review (CIR), Washington, D.C.</secondary-title></titles><periodical><full-title>Cosmetic Ingredient Review (CIR), Washington, D.C.</full-title></periodical><pages>171, https://www.cir-safety.org/sites/default/files/Sulfosuccinates_RR.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. There were no statistically significant differences in dosed and control groups, for the mean body weight gain, survival, appearance and behavior, urinalysis values, and microscopic lesions. Significant differences were noted in the blood such as elevated erythrocytic values in male rats at 7 weeks and depressed mean corpuscular hemoglobin concentration values in male rats at 13 weeks. At 7 weeks, the lungs of animals necropsied were stained with Oil Red O and examined; scattered foci of neutrophils and an increase in alveolar macrophages were reported in a single dosed male rat. A LOAEC of 4.2 mg/m^3 was identified based on blood effects in male rats.

Mechanistic studies

Mechanistic studies examining the pulmonary effects of anionic surfactants have been studied in dogs and/or sheep exposed, dioctyl sulfosuccinate sodium salt~~.~~ (DOSS; CASRN 577-11-7). Increased minimum surface tension of lung extract or bronchioalveolar lavage fluid (BALF) was observed in dogs and sheep following *in vivo* aerosol exposure to ~~the anionic detergent dioctyl sodium sulfosuccinate (~~DOSS~~)~~ in 1:1 mixture of ethanol and saline for 30 – 60 minutes, at a concentration that was selected to ensure a moderate degree of edema (estimated dose of 15 mg

ED_005294A_00000406-00078

detergent/kg body weight) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Light microscopic examination of the lungs 4 hours after exposure to DOSS aerosol observed no grossly destructive effects on alveolar cells or lung architecture in exposed dogs. However, a decrease in pulmonary compliance was observed that the authors hypothesized was due to an increase in surface tension in the alveoli in the presence of detergent.

Pulmonary clearance studies using radiolabeled aerosol tracers have evaluated whether detergent effects on the surfactant layer lead to increased alveolar permeability. -For example, inhalation exposure to DOSS enhanced the pulmonary clearance of radiolabeled diethylenetriamine pentaacetic acid (DTPA), a relatively small hydrophilic molecule, reflecting increased alveolar permeability after detergent exposure [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In most studies, this effect on alveolar permeability was seen in the absence of effects on blood gas levels or pulmonary compliance that occur with higher exposure, indicating that the increase in alveolar permeability is a sensitive effect of detergent aerosol. The effect was demonstrated to be concentration-related in one study in which multiple dilutions of the liquid detergent were nebulized [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Some studies also evaluated the clearance of a radiolabeled aerosol of albumin, a much larger molecule, which was enhanced by DOSS as well, but to a lesser degree than DTPA [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Wang *et al*. (1993) [ADDIN EN.CITE ADDIN EN.CITE.DATA] observed an increase in protein flux from plasma to alveolar space after DOSS inhalation in sheep, which the authors attributed to disruption of the alveolar lining and increased microvascular permeability. The increased alveolar permeability observed in these studies has been hypothesized to result from increased alveolar surface tension, which could cause increased permeability either by opening

ED_005294A_00000406-00079

previously closed pores (through which solutes pass) in the membrane or by stretching already open pores [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, as previously mentioned, surfactants can disrupt cell membranes; thus, this mechanism may be an alternate explanation [ADDIN EN.CITE <EndNote><Cite><Author>Burden</Author><Year>2012</Year><RecNum>14727</RecNum><DisplayText>[1]</DisplayText><record><rec-number>14727</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017177">14727</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Burden, D.W.</author></authors></contributors><titles><title>Guide to the Disruption of Biological Samples - 2012, Version 1.1.</title><secondary-title>Random Primers</secondary-title></titles><periodical><full-title>Random Primers</full-title></periodical><pages>1-25</pages><number>12</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Cationic Surfactants

In vivo studies

Three acute inhalation toxicity studies were identified for DDAC, Dioctadecyldimethylammonium chloride (DODMAC), and BAC. DDAC, which is corrosive to the skin and severely damaging to the eye [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14786</RecNum><DisplayText>[71]</DisplayText><record><rec-number>14786</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

Commented [ST29]: Not listed in Table 2

ED_005294A_00000406-00080

timestamp="1596038295">14786</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/5864/7/4/2</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], was tested in rats (5/sex/dose, unspecified strain) exposed via inhalation to 0.05, 0.09, 0.13, 0.25, 1.36 mg/L, or 4.54 mg/L (50, 90, 130, 250, 1,360, 4,540 mg/m^3) for 2 hours and observed for 14 days. An LC_{50} of 0.07 mg/L was identified based on unspecified abnormalities identified in several organs including the lungs [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-

0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. A similar quaternary amine, DODMAC, which is irritating to the skin and causes serious damage to the eyes, was tested in Albino rats (10 males, strain not specified) to the test substance (1:29 distilled water) *via* inhalation at 180 mg/L (180,000 mg/m^3) for one hour and observed for 14 days [ADDIN EN.CITE <EndNote><Cite><Author>EURAR</Author><Year>2009</Year><RecNum>14787</RecNum><DisplayText>[72]</DisplayText><record><rec-number>14787</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596038841">14787</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EURAR</author></authors></contributors><titles><title>European Union Risk Assessment Report (EURAR), CAS No: 107-64-2, EINECS No: 203-508-2, dimethyldioctadecylammonium chloride (DODMAC)</title><secondary-title>European Commission, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), former Toxicology and Chemical Substances (TCS) European Chemicals Bureau (ECB)</secondary-title></titles><periodical><full-title>European Commission, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), former Toxicology and Chemical Substances (TCS) European Chemicals Bureau (ECB)</full-title></periodical><pages>123, https://echa.europa.eu/documents/10162/46f2f114-12ff-4af4-8da7-72148b6a202e</pages><volume>14</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. No mortalities were reported and observed treatment-related clinical signs included preening, excessive masticatory (chewing) movements, excessive salivation stains, lacrimation, serosanguineous stains around the nose and labored respiration. All

animals appeared normal one day after dosing. The LD_{50} (1_h) was > 180 mg/L. BAC, which is corrosive to the skin and causes severe eye damage [ADDIN EN.CITE ADDIN EN.CITE.DATA], was tested in female Wistar rats (5/group) exposed via nose-only inhalation to 37.6 and 53 mg/m^3 for 4 hours and observed for 14 days or exposed to 30.6 mg/m^3 for 6 hours and BALF was measured 18 hours post-exposure [ADDIN EN.CITE <EndNote><Cite><Author>Swiercz</Author><Year>2008</Year><RecNum>14789</RecNum><DisplayText>[74]</DisplayText><record><rec-number>14789</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596039305">14789</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Swiercz, R.</author><author>Hałatek, T.</author><author>Wasowicz, W.</author><author>Kur, B.</author><author>Grzelińska, Z.</author><author>Majcherek, W.</author></authors></contributors><auth-address>Department of Toxicology and Carcinogenesis, Nofer Institute of Occupational Medicine, Łódź, Poland. radek@imp.lodz.pl</auth-address><titles><title>Pulmonary irritation after inhalation exposure to benzalkonium chloride in rats</title><secondary-title>Int J Occup Med Environ Health</secondary-title><alt-title>International journal of occupational medicine and environmental health</alt-title></titles><periodical><full-title>International journal of occupational medicine and environmental health</full-title><abbr-1>Int J Occup Med Environ Health</abbr-1></periodical><alt-periodical><full-title>International journal of occupational medicine and environmental health</full-title><abbr-1>Int J Occup Med Environ Health</abbr-1></alt-periodical><pages>157-63</pages><volume>21</volume><number>2</number><edition>2008/08/22</edition><keywords><keyword>Animals</keyword><keyword>Benzalkonium Compounds/administration

& dosage/*toxicity</keyword><keyword>Female</keyword><keyword>Inhalation Exposure</keyword><keyword>Lung Diseases/*chemically induced/pathology</keyword><keyword>Organ Size/drug effects</keyword><keyword>Rats</keyword><keyword>Rats, Wistar</keyword></keywords><dates><year>2008</year></dates><isbn>1232-1087 (Print)
1232-1087</isbn><accession-num>18715840</accession-num><urls></urls><electronic-resource-num>10.2478/v10001-008-0020-1</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The identified LC_{50} was approximately 53 mg/m^3 and BALF analysis reported increased inflammatory markers such as TNF-a, IL-6 and an increase in indicators of lung damage such as LDH, total protein, and increased lung weight.

Three repeated dose inhalation studies of three different exposure durations were identified for DDAC: 14-day, 28-day, and 90-day.

In the 14-day study, male Sprague-Dawley rats were exposed via whole-body inhalation exposures to DDAC aerosols of 0.15 mg/m^3, 0.6 mg/m^3, and 3.6 mg/m^3 (MMAD 1.86 µm, GSD 2.75 µm) for 6 hours/day, 7 days/week [ADDIN EN.CITE <EndNote><Cite><Author>Lim</Author><Year>2014</Year><RecNum>14790</RecNum><DisplayText>[75]</DisplayText><record><rec-number>14790</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596039544">14790</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>Lim, C. H.</author><author>Chung, Y. H.</author></authors></contributors><auth-address>Toxicity Research Team, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.</auth-address><titles><title>Effects of didecyldimethylammonium chloride on sprague-dawley rats after two weeks of inhalation exposure</title><secondary-title>Toxicol Res</secondary-title><alt-title>Toxicological research</alt-title></titles><periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></periodical><alt-periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></alt-periodical><pages>205-10</pages><volume>30</volume><number>3</number><edition>2014/10/25</edition><keywords><keyword>Biocide</keyword><keyword>Didecyldimethylammonium chloride</keyword><keyword>Inhalation</keyword></keywords><dates><year>2014</year><pub-dates><date>Sep</date></pub-dates></dates><isbn>1976-8257 (Print)
1976-8257</isbn><accession-num>25343015</accession-num><urls></urls><custom2>PMC4206748</custom2><electronic-resource-num>10.5487/tr.2014.30.3.205</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Mild effects were noted in the bronchoalveolar cell differentiation counts, cell damage parameters in the BAL fluids, in addition to inflammatory cell infiltration, and interstitial pneumonia of the medium and high groups. The NOAEC was determined to be 0.15 mg/m^3.

In the intermediate exposure (4-week) study, male and female Sprague-Dawley rats (5 rats/sex/group) were exposed via dynamic nose-only inhalation for 6 hours/day, 5 days/week to concentrations of 0, 0.08, 0.5, and 1.5 mg/m^3 DDAC (MMAD 1.4-1.9 µm, GSD 1.83-1.86 µm) for 6 hours/day, 5 days/week [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] . Lung weights were increased in females in the mid- and high-concentration groups and in males in the high concentration group. The bronchoalveolar lavage fluid (BALF) analysis indicated that at the high concentration neutrophils and eosinophils increased with a concomitant decrease in macrophages. Ulceration of the nasal cavity was observed in males and females in the high concentration group. In males, there was an increase in cell count and total protein across all doses. In females, there was an increase in LDH across all concentrations, but the small sample size precluded establishing statistical significance for the effects. Minimal to mild increased

mucus of the respiratory epithelium was observed in males and females at all concentrations. A conservative LOAEC of 0.08 mg/m^3 was identified based on increased mucus of the respiratory epithelium and increased LDH; however, due to the mild effects and low number of animals/group, the effects were not statistically significant.

In the 13-week sub-chronic study, male and female Sprague-Dawley rats (10/group/sex) were exposed in whole body exposure chambers to concentrations of 0.11, 0.36, and 1.41 mg/m^3 DDAC (MMAD 0.63-1.65 µm, GSD 1.62-1.65 µm) for 6 hours/day, 5 days/week [ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2017</Year><RecNum>14736</RecNum><DisplayText>[76]</DisplayText><record><rec-number>14736</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018905">14736</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, Y. S.</author><author>Lee, S. B.</author><author>Lim, C. H.</author></authors></contributors><auth-address>Chronic Inhalation Toxicity Research Center, Chemicals Toxicity Research Bureau, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.</auth-address><titles><title>Effects of Didecyldimethylammonium Chloride (DDAC) on Sprague-Dawley Rats after 13 Weeks of Inhalation Exposure</title><secondary-title>Toxicol Res</secondary-title><alt-title>Toxicological research</alt-title></titles><periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></periodical><alt-periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></alt-periodical><pages>7-14</pages><volume>33</volume><number>1</number><edition>2017/01/31</edition><keyw

ords><keyword>Biocide</keyword><keyword>Didecyldimethylammonium chloride</keyword><keyword>Inhalation</keyword><keyword>Sub-chronic</keyword></keywords><dates><year>2017</year><pub-dates><date>Jan</date></pub-dates></dates><isbn>1976-8257 (Print)
1976-8257</isbn><accession-num>28133508</accession-num><urls></urls><custom2>PMC5266374</custom2><electronic-resource-num>10.5487/tr.2017.33.1.007</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The MMAD of the DDAC aerosol was 0.63-1.65 µm, and the GSD was 1.62-1.65 µm. Body weight was confirmed to be clearly influenced by exposure to DDAC and mean body weight was approximately 35% lower in the high (1.41 ± 0.71 mg/m^3) male group and 15% lower in the high (1.41 ± 0.71 mg/m^3) female group compared to that of the control group. Albumin and lactate dehydrogenase were unaffected in the BALF. Lung weight was increased in females in the mid- and high-concentration groups and in males in the high concentration group only, while inflammatory cell infiltration and interstitial pneumonia in the mid- and high-concentration groups. Tidal volume and minute volume were not significantly affected at any concentration. Severe histopathological symptoms such as proteinosis and/or fibrosis, were not reported. A NOAEC of 0.11 mg/m^3 was identified based on the increased lung weights in females and increase in inflammatory cells.

BAC was evaluated in a 2-week whole-body inhalation study in male and female Fischer rats (5/group/sex) to concentrations of 0.8, 4 and 20 mg/m^3 (MMAMD 1.09-1.61 µm, GSD 1.51 to 2.00 µm) for 6 hours/day, 7 days/week [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Exposure-related effects were observed in the upper airway. Nasal discharge, rale, and deep respiration were observed in the high concentration, and nasal discharge was observed in the low and mid concentrations. In the nasal cavity, ulceration with suppurative inflammation, squamous metaplasia, and erosion with necrosis were observed in the respiratory epithelium and transitional epithelium of the male and female high concentrations.

Degeneration and regeneration of terminal bronchiolar epithelium, smooth muscle hypertrophy of bronchioloalveolar junction, and cell debris in the alveolar lumens were observed in the mid and high concentration male groups and high concentration dose female group. Hypertrophy and hyperplasia of mucous cells in the bronchi or bronchiole were observed in both males and females. The authors hypothesized that BAC has greater deposition to the upper respiratory tract due to mucociliary clearance and emergency airway response caused by the irritating effects of BAC. The squamous metaplasia of the respiratory epithelium and transitional epithelium, mucinous cell hypertrophy and proliferation of the respiratory epithelium, mucinous cell metaplasia of the transitional epithelium in the nasal cavities, and mucinous cell hypertrophy and proliferation of terminal bronchiole were considered adaptive changes after tissue injury. In the BALF analysis, the concentration of ROS/RNS, IL-1β, IL-6, and MIP-2 decreased dose dependently at the end of the exposure period but did not show a concentration-dependent change at 4 weeks of recovery. In addition, the concentrations of TNF-α, IL-4, and TGF-β did not show changes associated with test substance exposure. Finally, relative lung weights were statistically significantly increased in males at the mid and high doses and in females at the high doses only. The study authors identified a LOAEC of 0.8 mg/-m^3 based on effects in the nasal cavity.

Mechanistic studies

In vitro assays have demonstrated that cytotoxic effects of cationic surfactants have significantly greater toxicity to non-polarized than polarized mammalian cells [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In this study, cell viability as measured by LDH and MTT assays in non-polarized HeLa and dendritic FSDC was more sensitive to the effects of different cationic surfactants of varying alkyl chain length and polar head groups than polarized cell lines MDCK and Caco-2. The authors concluded that cationic surfactant toxicity occurs well below their CMC, with greater toxicity associated with alkyl lengths of 10-12 than 14-16, however this association was not strictly linearly dependent. In addition, the cationic surfactants with a larger polar head group (*i.e.*, benzalkonium) were 2-5 times more toxic than cationic surfactants with a more localized charge (*i.e.*, trimethylammonium).

Formatted: Font: Italic

Formatted: Font: Italic

Formatted: Font: Italic

The effects of BAC on cell viability, inflammatory response and oxidative stress of human alveolar epithelial cells has been replicated in vitro using a dynamic culture condition to reflect the natural microenvironment of the lung [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Normal breathing levels were simulated (tidal volume 10%, 0.2Hz) through surface elongation of an elastic membrane in a dynamic culture system. This type of dynamic system provided easy control of breathing rate during lung cell culture. The system assessed toxicity using different BAC concentrations (0, 2, 5, 10, 20, and 40 µg/mL) under static and dynamic culture conditions. Following 24 hr exposure to BAC, cellular metabolic activity, interleukin-8 (IL-8) and reactive oxygen species (ROS) levels demonstrated significant differences when using either static or dynamic cell growth conditions. The dynamic culture system, which more closely mimics lung conditions, showed a higher toxic response to BAC as indicated by increased ROS levels.

ED_005294A_00000406-00090

Dose-Response Analysis: Quantitative Points of Departure (PODs)

The limited animal inhalation toxicity data identified by the literature search and PODs from the studies are summarized in [REF _Ref46931035 \h * MERGEFORMAT]. All of the identified data are from animal studies and therefore need to be extrapolated to estimate the human inhalation exposure (EPA, 1994) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</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, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Previously, the exposure duration adjustment was described. EPA has also developed guidance focused on improving the science underlying the animal-to-human uncertainty factor and provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ADDIN

ED_005294A_00000406-00091

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 22]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</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, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 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>14746</RecNum><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</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, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research

Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</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). Application of a DAF in the calculation of an HEC is considered to address the toxicokinetic aspects of ~~the animal-to-human UF~~interspecies extrapolation UF ~~(*i.e.*, to estimate from animal exposure information the human exposure scenario that would result in the same dose to a given target tissue)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</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, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 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

Commented [ST30]: Deleted and changed to match terminology in M&M section

e>]~~(EPA, 2002)~~. This procedure involves the use of species-specific physiologic and anatomic factors relevant to the form of pollutant (*e.g.*, particle or gas) and categorized with regard to elicitation of response. These factors are all employed in determining the appropriate DAF. For HECs, DAFs are applied to the "duration-adjusted" concentration to which the animals were exposed (*e.g.*, to a weekly average). The generalized DAF procedures may also employ chemical-specific parameters, such as mass transport coefficients, when available.

The Regional Deposited Dose Ratio (RDDR) was used to derive DAFs for each of the surfactants with available animal toxicity studies. The RDDR is the ratio of the deposited dose in a respiratory tract region (r) for the laboratory animal species of interest (RDD_A) to that of humans (RDD_H) and was derived according to EPA's "*Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*" ~~(EPA, 1994)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</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, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research

Formatted: Font: 12 pt

Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. EPA's RDDR software allows calculation of calculate RDDRs in various regions of the respiratory tract for animals versus humans (*i.e.*, extra-thoracic, tracheobronchial, pulmonary, thoracic, total respiratory tract and extra-respiratory regions). The RDDR calculation is based on the characteristics of the aerosol tested in the inhalation study (~~Median Mass Aerodynamic Diameter or~~ MMAD, ~~Geometric Standard Deviation or~~ GSD), animal species, animal mass, gender, etc. The RDDR selected as the DAF is informed by the effects (clinical signs, tissue effects, biochemical changes) observed in the animal toxicity study and the aerosol characteristics in the inhalation study. The summary of RDDR inputs (*e.g.*, MMAD and GSD) and results are provided in [REF _Ref46931035 \h * MERGEFORMAT] for each of the toxicity studies from which PODs could be identified.

For the nonionic surfactant, octylphenoxypolyethoxyethanol, the effects observed (increased lung weights, alveolar/bronchiolar epithelial hyperplasia and lung inflammation) are consistent with lung effects in the LRT such that the pulmonary region RDDR (0.564) was used to calculate the HEC. For the anionic surfactant, oleoylsarcosine, the effects were seen in multiple regions of the respiratory tract, including squamous metaplasia and epithelium proliferation and submucous acute inflammation at the base of the epiglottis and early stages of fibrosis in the alveoli walls. Therefore, total respiratory tract RDDR (1.504 for males and 0.970 for females) was used to calculate the HEC. In both 21- and 90-day inhalation studies with DDAC, effects observed

Commented [HT31]: SALAZAR:
I think total respiratory tract RDDR needs to be modeled not just the pulmonary region. Damon et al. demonstrated that effects occured in the laryngeal region. In addition you have effects in the TB region indicated by bronhiolar hyperplasia, and nasal effects as well.

Commented [HT32R31]: Annie – what do you think...RDDR for Total or PU or both??

(changes in BALF LDH, BALF total protein, BALF cell count (males only), increase in mucus in the respiratory epithelium, and increase in mucoid exudate, inflammatory cell infiltration and interstitial pneumonia) were indicative that the pulmonary RDDR (0.42 for 14 and 90-day exposures and 0.5 to 0.6 for 28-day exposure) is appropriate for calculating the HEC. In contrast, for the cationic surfactant, benzalkonium chloride histopathological cellular changes were observed in the nasal cavity and lungs, indicating the total respiratory tract RDDR should be used to calculate the HEC. The RDDRs applied and HECs derived from the animal study PODs are provided in [REF _Ref46931035 \h * MERGEFORMAT].

Commented [HT33]: SALAZAR:
In the 21-day study, there is an increase in mucus of the respiratory epithelium , olfactory epithelium, and larynx. The total respiratory tract RDDR needs to be calculated here as well.

Commented [HT34R33]: Annie – what do you think? Total or PU?

Table [SEQ Table * ARABIC]. Inhalation Toxicity Points of Departure and Human Equivalent Concentrations (HEC) for Surfactants

Surfactant Type	Category Analogue(s)	Inhalation Exposure Duration/Type	Study POD	Value (mg/m^3)	Reference	RDDR Model Input Parameters		RDDR[+]	HEC (mg/m^3)
						MMAD (µm)	GSD (µm)		
Nonionic	octylphenoxy polyethoxyethanol (CASRN 9002-93-1)	14-day, 6 hr/d, 5 d/wk; whole body ~~dosing~~	LOAEC	5.3 ~~mg/m^3~~	[ADDIN EN.CITE <EndNote><Cite><Author>MDEQ</Author><Year>2003</Year><RecNum>14731</RecNum><DisplayText>[8]</DisplayText><record><rec-number>14731</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0z	1.80	1.80	$RDDR_{PuMale}$ = 0.564 $RDDR_{PuFemale}$ = 0.610	male 2.989 female 3.323

Commented [ST35]: William: Did you QC these numbers?

Formatted: Centered

Formatted Table

Commented [ST36]: Still need to link table references with EndNote

Formatted: Superscript

Formatted: Centered

					re0azr5ev earxfds0e rr5sr" timestamp ="159601 8112">14 731</key ></foreig n- keys><ref -type name="Jo urnal Article"> 17</ref- type><co ntributors ><authors ><author >MDEQ< /author>< /authors> </contribu tors><title s><title> To: Memo to File for Triton X- 100 (CAS # 9002- 93-1); From:				

					Gary Butterfield; Date: November 21,2003; Subject: Screening level for Triton X-100 (CAS # 9002-93-1)</title><secondary-title>Michigan Department of Environmental Quality (MDEQ)</secondary-title></titles><periodical><full-title>Michigan Department of				

					Environmental Quality (MDEQ)</full-title></periodical><pages>2</pages><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]				
Anionic	oleoyl sarcosine (CASRN 110-25-8)~~,~~	28-day, 6 hr/d, 5 d/wk; nose-only (OECD 412)	LOAEC	6 mg/m^3 ~~(0.006 mg/L)~~	[ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14784</RecNum><DisplayText>[62]</DisplayText><recor	1.16	2.12	$RDDR_{TotMale}$ = 1.504 $RDDR_{TotFemale}$ = 0.970	male < 9 .024 female < 5.820

Formatted: Centered

					d><rec-number>14784</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5ev earxfds0err5sr" timestamp="1596036869">14784</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration				

					Dossier</author></authors></contributors><titles><title>N-methyl-N-[C18-(unsaturated)alkanoyl]glycine, CASRN: NA, EC number: 701-177-3, Repeated dose toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-				

					title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/21429/7/6/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]				
	dioctyl sodium sulfosuccinate (CASRN 577-11-7)	13-week, 4 hr/d, 5 d/wk;	LOAEC (blood effects)	4.2 ~~mg/m³~~	[ADDIN EN.CITE <EndNote><Cite><Author>C	NA	NA	NA	NA

Formatted: Centered

Formatted: Centered

					IR</Author><Year>2013</Year><RecNum>14785</RecNum><DisplayText>[63]</DisplayText><record><rec-number>14785</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5ev earxfds0err5sr" timestamp="1596037107">14785</key></foreign-keys><ref				

					-type name="Journal Article">17</ref-type><contributors><authors><author>CIR</author></authors></contributors><titles><title>Safety Assessment of Alkyl Sulfosuccinate Salts as Used in Cosmetics, Re-Review, CIR Expert Panel Meeting, June 10-11, 2013</title><secon				

ED_005294A_00000406-00105

					dary-title>Cosmetic Ingredient Review (CIR), Washington, D.C.</secondary-title></titles><periodical><full-title>Cosmetic Ingredient Review (CIR), Washington, D.C.</full-title></periodical><pages>171, https://www.cir-safety.org/sites/default/files/Sulfosuccin				

					ates_RR.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]				
Cationic	DDAC	14-day, 6 hr/d, 7 d/wk; whole body	NOAEC	0.15 ~~mg/m³~~	[ADDIN EN.CITE <EndNote><Cite><Author>Lim</Author><Year>2014</Year><RecNum>14790</RecNum><DisplayText>[75]</DisplayText><record><rec-number>14790</rec-number><foreign-	1.86	2.75	$RDDR_{PuMale}$ = 0.427 Only males tested	male 0.064

Formatted: Centered

					keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5ev earxfds0err5sr" timestamp="1596039544">14790</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lim, C. H.</author><author>Chung, Y. H.</author></authors></contr				

ED_005294A_00000406-00108

					ibutors><auth-address>Toxicity Research Team, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.</auth-address><titles><title>Effects of didecyldimethylammonium chloride on sprague-dawley rats after two weeks of inhalation exposure</title><se				

					condary-title>Toxicol Res</secondary-title><alt-title>Toxicological research</alt-title></titles><periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></periodical><alt-periodical><full-title>Toxicol Res</full-title><abbr-				

					1>Toxicological research</abbr-1></alt-periodical><pages>205-10</pages><volume>30</volume><number>3</number><edition>2014/10/25</edition><keywords><keyword>Biocide</keyword><keyword>Didecyldimethylammonium chloride</keyword><keyword>Inhalation</keyword></keywords><d				

					ates><year>2014</year><pub-dates><date>Sep</date></pub-dates></dates><isbn>1976-8257 (Print)
1976-8257</isbn><accession-num>25343015</accession-num><urls></urls><custom2>PMC4206748</custom2><electronic-resource-num>10.5487/tr.2014.30.3.205</electronic-				

					resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]				
	DDAC	4-week, 6 hr/d, 5 d/wk; nose-only	LOAEC* (lung effects)	0.08 ~~mg/m^3~~	[ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>1	1.60	1.85	$RDDR_{Pu/Male}$ = 0.539 $RDDR_{PuFemale}$ = 0.583	male 0.043 female 0.047

Formatted: Centered

					4732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5ev earxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributo				

					rs><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical				

					Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]				

	DDAC	90-day, 6 hr/d, 5 d/wk; whole-_body	NOAEC	0.11 ~~mg/m~~^{3}	[ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2017</Year><RecNum>14736</RecNum><DisplayText>[76]</DisplayText><record><rec-number>14736</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5ev earxfds0err5sr" timestamp="159601	0.86	1.63	$RDDR_{PuMale}$ = 0.421 $RDDR_{PuFemale}$ = 0.420	male 0.046 male female 0.046

Formatted: Centered

					8905">14736</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, Y. S.</author><author>Lee, S. B.</author><author>Lim, C. H.</author></authors></contributors><auth-address>Chronic Inhalation Toxicity Research Center, Chemical				

					s Toxicity Research Bureau, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.</auth-address><titles><title>Effects of Didecyldimethylammonium Chloride (DDAC) on Sprague-Dawley Rats after 13 Weeks of Inhalation Exposure</title><secondary-title>Toxi				

					col Res</secondary-title><alt-title>Toxicological research</alt-title></titles><periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></periodical><alt-periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological				

					research</abbr-1></alt-periodical><pages>7-14</pages><volume>33</volume><number>1</number><edition>2017/01/31</edition><keywords><keyword>Biocide</keyword><keyword>Didecyldimethylammonium chloride</keyword><keyword>Inhalation</keyword><keyword>Sub-chronic</keyword>				

					</keywords><dates><year>2017</year><pub-dates><date>Jan</date></pub-dates></dates><isbn>1976-8257 (Print)
1976-8257</isbn><accession-num>28133508</accession-num><urls></urls><custom2>PMC5266374</custom2><electronic-resource-num>10.5487/tr.2017.33.1.007</electro				

					nic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]				
	BAC	14-day, 6 hr/d, 7 d/wk; whole_-body	LOAEC (nasal effects)	0.8 ~~mg/m^3~~	[ADDINEN.CITE ADDINEN.CITE.DATA]	1.31	1.79	$RDDR_{TotMale}$ = 1.414 $RDDR_{TotFemale}$ = 0.991	male 1.131 female 0.793

*conservative estimate: effects were not statistically significant
+ RDDR values were calculated by RDDR.exe separately for male and female rats due to the differing body weights between genders. Further details are provided in the Supporting Information file at "Section 2 RDDR Modeling Outputs".
NA: Data not available or RDDR values could not be calculated from the available information
MMAD: Median Mass Aerodynamic Diameter of inhalation study aerosol
GSD: Geometric Standard Deviation of the inhalation study aerosol

Formatted: Centered
Formatted: Space After: 0 pt

Benchmark Margin of Exposure Analysis

The analogues shown in [REF _Ref46931035 \h * MERGEFORMAT] provide representative examples of the types of PODs that may be applied to new chemistries that meet the Surfactant Criteria. Though the initial starting point for deriving a benchmark MOE is based on a composite of the default values of 10 for each of the individual values for UF_H, UF_A, and UF_L, refinements may be warranted based on dosimetric adjustments to the applied concentrations used for establishing the experimental PODs. As shown in [REF _Ref46931035 \h * MERGEFORMAT], the data-derived uncertainty factors, RDDRs were used as DAFs to account for animal-to-human toxicokinetic difference.

In the case of surface-active substances like chemical substances meeting the Surfactant Criteria, EPA has recently adopted a generalized approach that has historically been applied on a case-by-case basis for chemical substances, in recognition that surface-active effects that lead to irritation/corrosion do not require absorption, metabolism, distribution, or elimination (ADME) (See, *e.g.*, EPA, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14794</RecNum><DisplayText>[80]</DisplayText><record><rec-number>14794</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596040494">14794</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Hazard Characterization of Isothiazolinones in Support of FIFRA Registration

Review</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>84, https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2013-0605-0051&contentType=pdf</pages><volume>EPA-HQ-OPP-2013-0605-0051</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]). In the context of this publication, irritation/corrosion include those effects in the respiratory tract that lead, for example, to inflammation, hyperplasia, and metaplasia. For chemical substances that act *via* a surface-active adverse outcome pathway (AOP), the default values for UF_H and UF_A are reduced to 3 (*i.e.*, $10^{0.5}$ or 3.162) to account for the uncertainty/variability for toxicodynamics, whereas the toxicokinetic component is reduced to 1 because ADME differences that would otherwise influence toxicokinetic differences are generally not relevant for surface-active substances. In order to apply these reductions, the following criteria must be established:

1. A description of the AOP,
2. A discussion of why the AOP is unlikely or likely to differ between humans, in the case of UF_H, or between animals, in the case of UF_A, and
3. A discussion as to why the ADME of the chemical substance is unlikely to play a role in the observed toxicity.

When the above criteria are met, application of the appropriate ~~dosimetric adjustment factor~~DAF (~~*i.e.*~~*e.g.*, RDDR) should still be applied, given that deposition is the most appropriate dosimetric

ED_005294A_00000406-00125

for assessing acute/subacute effects from surface-active agents. However, since the ~~dosimetric adjustment factor~~DAF accounts for toxicokinetic component of UF_A, ~~no additional reductions should be incorporated~~the remaining value of 3 should be retained for the toxicodynamics component of the UF_A.

Commented [HT37]: I changed this

Commented [ST38R37]: Language still needs to be cleared up based on today's call

Based on these information and criteria, the following composite values are appropriate to describe intra- and interspecies ~~uncertainty/~~variability (*i.e.*, $UF_H \times UF_A$):

UF_H = 10 or 3: The default value of 10 should be applied when the available information does not support each of the above criteria. If the available information supports all of the above criteria, then a value of 3 may be applied. The reduced value represents a reduction in the toxicokinetic component of this UF to 1, with the remaining value of 3 accounting for the toxicodynamic component.

UF_A = 10 or 3: The default value of 10 should be applied when the available information does not support the application of ~~a~~ dosimetric adjustments ~~factor to~~for quantifying an ~~human equivalence concentration (~~HEC~~)~~ or when the available information does not support each of the above criteria. If the available information allows derivation of an HEC and/or application of the above criteria, then a value of 3 may be applied, which represents a reduction in the toxicokinetic component to 1 and application of a value of 3 for toxicodynamics.

UF_L = 10 or 1: If the POD from the experimental study is based on a LOAEC, then a default value of 10 should be applied, unless there is information to support that a reduced value is

warranted. If the experimental data are amenable to benchmark dose modeling, a BMCL should be calculated and a value of 1 should be applied for this area of uncertainty.

Taken together, the above considerations and approaches support application of a benchmark MOE ranging from 10 to 1,000 and will depend on the analogue used and available data on the new chemical substance. In those instances where the data are too limited to determine when an analogue is appropriate for extrapolating the hazards to the new chemical substance, experimental testing should be performed to aid with informing the quantitative assessment, as discussed under the Tiered-Testing Strategy.

Uncertainties and Limitations

The assessment framework outlined herein includes a number of uncertainties and limitations, include those associated with extrapolating the hazards identified from the analogues shown in shown in [REF _Ref46931035 \h * MERGEFORMAT]. Uncertainties associated with using animal studies to estimate human toxicity are recognized and methods developed to reduce them [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2014</Year><RecNum>14795</RecNum><DisplayText>[81]</DisplayText><record><rec-number>14795</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596040729">14795</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Guidance on Grouping of Chemicals, Second Edition, Series on Testing &

ED_005294A_00000406-00127

Assessment</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</full-title></periodical><pages>141, http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en</pages><volume>ENV/JN/MONO(2014)4</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Exposure duration adjustment procedures for inhalation exposures and application of DAFs to derive HECs, are well-established procedures for reducing uncertainties associated with the toxicokinetic aspects of animal-to-human extrapolation factors and derivation of benchmark MOEs (*i.e.*, type and magnitude of uncertainty factors) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 22]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</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, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 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>14746</RecNum><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</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, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Likewise, EPA has recommended that BMD modeling be employed whenever possible to identify a POD and to reduce uncertainties associated with using a LOAEL from a toxicity study.

Given the small number of chemical substances that meet the Surfactant Criteria that have concentration-response inhalation toxicity data, the applicability of these analogues to new chemical substances needs to be carefully considered, particularly given the influence of additional functional groups that may increase/decrease the toxicity of the new chemical substance compared

to the analogue. Risk assessors should first consider the surface tension and CMC criteria provided in Table X, and compare them to these measurements for the new chemical substance, if available, or the influence additional functional groups present or absent from the new chemical would have on these criteria (*e.g.*, would a particular functional group increase or decrease toxicity, for example by another mechanism of action). If such structural differences are judged not to significantly influence properties and toxicity, such that the new chemical substance is expected to have comparable or lower toxicity, read-across is an appropriate approach for characterizing hazards and risk. Of course, uncertainties regarding read-across should be acknowledged in the risk characterization.

For instances where the notifier of the new chemical substance and/or EPA is unable to conclude that one of the analogues in [REF _Ref46931035 \h * MERGEFORMAT] is comparable to or represents a worse-case analogue compared to the new chemical substance, then the Tiered-Testing Strategy provided herein could be used to inform whether the new chemical substance has lower, comparable, or higher toxicity to the representative analogue in the respective subcategory. Prior to conducting such testing, the scientific basis for selecting an analogue as the comparator compound to the new chemical substance should be understood and a rationale provided as to why the analogue is anticipated to have comparable or higher toxicity than the new chemical substance.

Use of New Approach Methods (NAMs) and *In Vitro* Testing Strategies to Reduce or Replace Vertebrate Testing

The amended TSCA requires EPA to reduce reliance on animal testing using methods and strategies that "provide information of equivalent or better scientific quality and relevance for

assessing risks of injury to health or the environment" [ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum><DisplayText>[82]</DisplayText><record><rec-number>14796</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041048">14796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title>Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Additionally, in 2019, EPA was directed to prioritize efforts to use NAMs to reduce animal testing [ADDIN EN.CITE <EndNote><Cite><Author>Wheeler</Author><Year>2019</Year><RecNum>14797</RecNum><DisplayText>[83]</DisplayText><record><rec-number>14797</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041176">14797</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wheeler, A.R.</author></authors></contributors><titles><title>Directive to Prioritize Effects to Reduce Animal Testing</title><secondary-title>United States Environmental Protection Agency</secondary-title></titles><periodical><full-title>United States Environmental Protection Agency</full-title></periodical><pages>3,

https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]. Multiple NAMs exist which can be used to assess hazards and risks of new chemical substances that meet the Surfactant Criteria, including validated OECD methods for *in vitro* irritation testing, as well as other *in vitro* methods to specifically assess respiratory toxicity. Several methods are described within a tiered-testing strategy herein, ~~but~~ recognizing that these are provided as examples and the development of NAMs is advancing quickly. As such, the NAMs included here should not be considered all-inclusive or a final compilation. EPA strongly encourages the development and use of NAMs, particularly to reduce or replace the use of vertebrate animals and is open to considering and discussing additional NAMs with PMN submitters during a pre-notice consultation.[ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14829</RecNum><DisplayText>[84]</DisplayText><record><rec-number>14829</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596098792">14829</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Schedule a Pre-Submission Meeting, Reviewing New Chemicals under the Toxic Substances Control Act (TSCA)</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-

substances-control-act-tsca/forms/program-contacts-

and</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

In the interest of reducing or replacing vertebrate testing, when a surfactant is determined to be respirable, EPA encourages evaluating its potential to cause pulmonary toxicity using an Adverse Outcome Pathway (AOP) approach. The Organization for Economic Cooperation and Development (OECD) provides "An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect" and that "AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning" [ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14798</RecNum>

<DisplayText>[85]</DisplayText><record><rec-number>14798</rec-number><foreign-

keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596041285">14798</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>OECD</author></authors></contributors><titles><title

>Adverse Outcome Pathways, Molecular Screening and Toxicogenomics</title><secondary-

title>Organization for Economic Cooperation and Development (OECD)</secondary-

title></titles><periodical><full-title>Organization for Economic Cooperation and Development

(OECD)</full-title></periodical><pages>http://www.oecd.org/env/ehs/testing/adverse-outcome-

pathways-molecular-screening-and-

toxicogenomics.htm</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Representative key elements of AOPs are the molecular initiating events (MIEs), cellular level events (CLEs), organ or tissue level events (OLEs), and organism consequent events (OCEs). For surfactants, the initial key event is proposed to be the interaction of the substance with lung-surfactant (MIE) and/or the molecular interaction of the substance itself with cell membranes (MIE), resulting in the disruption of lung cells due to loss of lung cell surfactant function (CLE) and/or the loss of membrane integrity (CLE). These initial events may lead to different OLEs (*e.g.*, alveolar collapse, loss of barrier function, blood extravasation, and impaired oxygenation of blood), which may finally lead to organism consequences (OCE) (*e.g.*, pneumonia, limited lung function by chronic obstruction (COPD), fibroses, *etc.*).

In vitro systems are used to investigate specific key events in the AOP and confirm that a new chemical substance fits within the boundaries of the Surfactant Category or a sub-category and therefore may act like a surfactant (group assignment *via* similar AOP) and/or if other substance specific properties lead to a predominant type of key events within the AOP. Further, *in vitro* tests may deliver information while avoiding *in vivo* testing or providing helpful information on dose-selection for *in vivo* testing, if needed. *In vitro* tests, such as by capillary surfactometer, may be useful in preliminary screening of chemicals to be tested, but do not by themselves constitute adequate tests for acute pulmonary effects of these chemicals. This information should be taken into consideration within the design of additional ~~*in vivo*~~ tests. These assays can be used as part of

ED_005294A_00000406-00134

a weight of scientific evidence evaluation to determine whether animal testing is needed or if a point of departure (POD) can be determined for risk assessment purposes without the use of animals. These tests may also provide insight on one or more components of the AOP.

Based on the surfactant AOP framework [ADDIN EN.CITE <EndNote><Cite><Author>Sorli</Author><Year>2020</Year><RecNum>14800</RecNum><DisplayText>[87]</DisplayText><record><rec-number>14800</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041625">14800</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sorli, J. B.</author></authors></contributors><titles><title>Lung Surfactant Function Disruption Leading to Acute Inhalation Toxicity</title><secondary-title>AOPWiki</secondary-title></titles><periodical><full-title>AOPWiki</full-title></periodical><pages>https://aopwiki.org/aops/302</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], a number of different types of *in vitro* test methods, summarized in [REF _Ref46931271 \h * MERGEFORMAT], may provide potentially useful information for informing the various elements of the surfactant AOP.

ED_005294A_00000406-00135

Table [SEQ Table * ARABIC]. *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.* (2018) [ADDIN EN.CITE ADDIN EN.CITE.DATA]
	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.*, Reconstructed human Cornea-like Epithelium (RhCE) (OECD 492) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[89]</DisplayText><ref-type name="Journal Article" id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article" type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><pages>, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages>; Bovine Corneal Opacity and Permeability Test (OECD 437) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14802</key></foreign-keys><ref-type name="Journal Article" type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</pages>; Isolated Chicken Eye Test (OECD 438) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key></foreign-keys><ref-type name="Journal Article" type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for identifying chemicals not requiring classification for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><pages>, https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages>; *etc.*
Cellular Level	CLE for loss of membrane	*In Vitro/Ex Vivo*	• OECD *In vitro/Ex Vivo* eye irritation tests for cytotoxicity, *e.g.*, Reconstructed human Cornea-like Epithelium (RhCE) (OECD 492) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[89]</DisplayText><ref-type name="Journal Article" id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article"

Events (CLEs)	integrity/general cytotoxicity	Cytotoxicity Assays	type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like I irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><p https://www.oecd-ilibrary.org/docserver/9789264242548- en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7A2459C37BF048A1BDC82F2D4</page Bovine Corneal Opacity and Permeability Test (OECD 437) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043 type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Perme Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Che Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846- en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</page Isolated Chicken Eye Test (OECD 438) [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><Rec number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key>< type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method fo irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><p https://www.oecd-ilibrary.org/docserver/9789264203860- en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages> *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 (ICCVAM, 2006) [ADDIN EN. <EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNum><DisplayText>[92]</DisplayTex id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal Arti type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><title>In vitro Cytotoxicity Test Metho title>ICCVAM Test Method Evaluation Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519
Organ or Tissue Level Events (OLEs)	OLE for tissue level events	Human organotypic airway epithelial cultures	• 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells (*e.g.*, EpiAirway™, MucilAir™, SmallAir™, E
	OLE for tissue level events	Specific *Ex Vivo* Respiratory	• Precision-cut lung slice test *etc.* as described by Hess *et al.* (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA]

		Toxicity Assays	

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) [ADDIN EN.CITE ADDIN EN.CITE.DATA] 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) [ADDIN EN.CITE <EndNote><Cite><Author>Bader</Author><Year>2014</Year><RecNum>14807</RecNum><DisplayText>[94]</DisplayText><record><rec-number>14807</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044694">14807</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bader, J.E.</author><author>Norman, K.G.</author><author>Raabe, H.</author></authors></contributors><titles><title>Predicting Ocular Irritation of Surfactants Using the Bovine Corneal Opacity and Permeability Assay</title><secondary-title>Insitute for In Vitro Sciences, Inc., Gaithersburg, M.D.</secondary-title></titles><periodical><full-title>Insitute for In Vitro Sciences, Inc.,

Gaithersburg, M.D.</full-title></periodical><pages>https://iivs.org/wp-content/uploads/2018/08/iivs_poster_predicting-ocular-irritation-of-surfactants-using-the-bovine-corneal-opacity-and-permeability-assay.pdf</pages><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] 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 between cell membrane damage induced by different subcategories of surfactants provide an effective measure of cell membrane effects [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In addition, information on the potential of a substance to cause skin irritation (*e.g.*, OECD TG 439 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14808</RecNum><DisplayText>[95]</DisplayText><record><rec-number>14808</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044884">14808</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed Human Epidermis Test Method, In vitro Skin Irritation</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>26, https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1596045726&id=id&accname=guest&checksum=2580E92A5C889D0DD65599260E7866D3</pages><volume>439</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]) and/or skin corrosion (*e.g.*, OECD TG 431 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14809</RecNum><DisplayText>[96]</DisplayText><record><rec-number>14809</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044976">14809</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>29, https://www.oecd-ilibrary.org/docserver/9789264264618-en.pdf?expires=1596045820&id=id&accname=guest&checksum=E3EE55CBAAFAF0432EAD109F1B39ECF0</pages><volume>431</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]) *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 [ADDIN EN.CITE <EndNote><Cite><Author>Sigma-Aldrich</Author><Year>2020</Year><RecNum>14810</RecNum><DisplayText>[97]</DisplayText><record><rec-number>14810</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045132">14810</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sigma-Aldrich</author></authors></contributors><titles><title>Safety Data Sheet, Product name: Didecyldimethylammonium chloride, Version 8.1, Revision Date: 03/28/2020, Print Date: 05/29/2020</title></titles><pages>9, 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</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

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 [REF _Ref46931271 \h * MERGEFORMAT] 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

Formatted: Font: Italic

Alternative Methods (ICCVAM) for use ~~in before animal testing is conducted~~prior to conducting animal testing [ADDIN EN.CITE <EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNum><DisplayText>[92]</DisplayText><record><rec-number>14805</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><title>In vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing</title><secondary-title>ICCVAM Test Method Evaluation Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation Report</full-title></periodical><pages>334, https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519</volume><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] . 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, $DDAC_2$ 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

ED_005294A_00000406-00143

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 (3-D) 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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum><DisplayText>[98]</DisplayText><record><rec-number>14811</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Issue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33, https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-

epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. Unlike single cell lines, these organotypic cultures take on a pseudostratified morphology, develop tight junctions, differentiate into multiple cell types, ~~including~~ 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 determining deposition, different 3-D 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 3-D 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.

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 system that is more comparable inhalation exposures that may ~~to~~ occur during real-life scenarios ~~for inhaled aerosols. Using~~ ALI exposure systems avoid issues that occur with submerged culture systems, such as~~,~~ dilution of the test substance into medium and interaction with medium components ~~does not occur as it would in a submerged culture system~~. There is interaction of the

ED_005294A_00000406-00145

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~~surfactant AOP elements. 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 [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2007</Year><RecNum>14741</RecNum><DisplayText>[17, 99]</DisplayText><record><rec-number>14741</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019531">14741</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Toxicity Testing in the 21st Century: A Vision and a Strategy, Washington, D.C. The National Academies Press</title></titles><pages>216, DOI: https://doi.org/10.17226/11970</pages><volume>ISBNs: Ebook: 978-0-309-13412-5; Paperback: 978-0-309-15173-3</volume><dates><year>2007</year></dates><urls></urls></record></Cite><Cite><Author>NRC</Author><Year>2017</Year><RecNum>14812</RecNum><record><rec-number>14812</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045703">14812</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Using 21st Century Science to Improve Risk-Related Evaluations, Washington, D.C., The National Academies Press</title></titles><pages>200, https://doi.org/10.17226/24635</pages><volume>ISBNs: Ebook: 978-0-309-45351-6; Paperback: 978-0-309-45348-6</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>], 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 3-D human airway cell culture systems discussed above would be the test systems to be aspired.

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 [ADDIN EN.CITE <EndNote><Cite><Author>Liu</Author><Year>2019</Year><RecNum>14813</RecNum><DisplayText>[100]</DisplayText><record><rec-number>14813</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045815">14813</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, Guanghui</author><author>Betts, Catherine</author><author>Cunoosamy, Danen M.</author><author>Åberg, Per M.</author><author>Hornberg, Jorrit J.</author><author>Sivars, Kinga Balogh</author><author>Cohen, Taylor S.</author></authors></contributors><titles><title>Use of precision cut lung slices as a translational model for the study of lung biology</title><secondary-title>Respiratory Research</secondary-title></titles><periodical><full-title>Respiratory research</full-title><abbr-1>Respir Res</abbr-1></periodical><pages>162, https://doi.org/10.1186/s12931-019-1131-x</pages><volume>20</volume><number>1</number><dates><year>2019</year><pub-dates><date>2019/07/19</date></pub-dates></dates><isbn>1465-993X</isbn><urls><related-urls><url>https://doi.org/10.1186/s12931-019-1131-x</url></related-urls></urls><electronic-resource-num>10.1186/s12931-019-1131-x</electronic-resource-num></record></Cite></EndNote>]. 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 [ADDIN EN.CITE <EndNote><Cite><Author>Sanderson</Author><Year>2011</Year><RecNum>14814</RecNum><DisplayText>[101]</DisplayText><record><rec-number>14814</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046031">14814</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sanderson, M. J.</author></authors></contributors><auth-address>Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA 01655, USA. Michael.Sanderson@umassmed.edu</auth-address><titles><title>Exploring lung physiology in health and disease with lung slices</title><secondary-title>Pulm Pharmacol Ther</secondary-title><alt-title>Pulmonary pharmacology & therapeutics</alt-title></titles><periodical><full-title>Pulmonary pharmacology & therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></periodical><alt-periodical><full-title>Pulmonary pharmacology & therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></alt-periodical><pages>452-65</pages><volume>24</volume><number>5</number><edition>2011/05/24</edition><keywords><keyword>Animals</keyword><keyword>Cell Physiological Phenomena</keyword><keyword>Disease Models, Animal</keyword><keyword>Humans</keyword><keyword>Lung/pathology/*physiology</keyword><keyword>Lung Diseases/*pathology</keyword><keyword>Microscopy/methods</keyword><keyword>Muscle

Contraction/physiology</keyword><keyword>Organ Culture Techniques</keyword></keywords><dates><year>2011</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>1094-5539 (Print)
1094-5539</isbn><accession-num>21600999</accession-num><urls></urls><custom2>PMC3168687</custom2><custom6>NIHMS296121</custom6><electronic-resource-num>10.1016/j.pupt.2011.05.001</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. 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.

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. 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.

ED_005294A_00000406-00150

Uncertainties/Limitations

Commented [HT39]: For the whole FRAMEWORK

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA], 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.

Commented [HT40]: Maybe this goes at the very end of this section?

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 [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Commented [HT41]: ODIN: this para needs re-write; offers no edits

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 [OS42]: Tala to include some additional text – read across, etc.

Tiered-testing Strategy

Commented [HT43]: DISCUSS CATEGORY CRITERIA AS FIRST STEP

A tiered testing approach for surfactants that have been established to meet the Surfactant Criteria is discussed below. 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.

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.*, $\leq$ 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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum>

<DisplayText>[106]</DisplayText><record><rec-number>14819</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046851">14819</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, No. 39 (Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</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>], ISO 21501-1:2009 [ADDIN EN.CITE <EndNote><Cite><Author>ISO</Author><Year>2009</Year><RecNum>14820</RecNum><DisplayText>[107]</DisplayText><record><rec-number>14820</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046993">14820</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ISO</author></authors></contributors><titles><title>Determination of particle size distribution — Single particle light interaction methods — Part 1:

Light scattering aerosol spectrometer</title></titles><pages>https://www.iso.org/standard/42728.html</pages><volume>ISO 21501-1:2009</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>], OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>14821</RecNum><DisplayText>[108]</DisplayText><record><rec-number>14821</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596047114">14821</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; Method A: Particle Size Distribution (effective hydrodynamic radius); Method B: Fibre Length and Diameter Distributions</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>13, https://www.oecd-ilibrary.org/docserver/9789264069688-en.pdf?expires=1596047951&id=id&accname=guest&checksum=A9C13F0DFDCF2A5DD4DD39DAC64C47BC</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></record></Cite></EndNote>], and OPPTS 830.7520 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>14822</RecNum><DisplayText>[109]</DisplayText><record><rec-number>14822</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596047315">14822</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>Product Properties Test Guideline, Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection Agency</secondary-title></titles><periodical><full-title>Product Properties Test Guideline, Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection Agency</full-title></periodical><pages>13, https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPPT-2009-0151-0030&contentType=pdf</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]). 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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>14823</RecNum><DisplayText>[110]</DisplayText><record><rec-number>14823</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596047488">14823</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>].

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 [OS44]: 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.

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" ([REF _Ref46931271 \h * MERGEFORMAT]). 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 [HT45]: 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) [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Cell interaction/penetration

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.,* OECD 492 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[89]</DisplayText><record><rec-number>14803</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7

A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like Epithelium (RhCE) Test Method; OECD 437 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecNum><DisplayText>[90]</DisplayText><record><rec-number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043719">14802</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and Permeability Test Method; OECD 438 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecNum><DisplayText>[91]</DisplayText><record><rec-number>14804</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for identifying I) chemicals inducing serious eye damage and II) chemicals not requiring classification for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test Method, *etc*.

General cytotoxicity

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.*, OECD 492 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[89]</DisplayText><record><rec-number>14803</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-

title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&id=id&accname=guest&checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like Epithelium (RhCE); OECD 437 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecNum><DisplayText>[90]</DisplayText><record><rec-number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043719">14802</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&id=id&accname=guest&checksum=6B06BCD6D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and Permeability Test; OECD 438 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecN

um><DisplayText>[91]</DisplayText><record><rec-number>14804</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for identifying I) chemicals inducing serious eye damage and II) chemicals not requiring classification for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&id=id&accname=guest&checksum=37A7598040CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test, *etc*.

- ICCVAM (2006) [ADDIN EN.CITE <EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNum><DisplayText>[92]</DisplayText><record><rec-number>14805</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><title>In vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing</title><secondary-title>ICCVAM Test Method Evaluation Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation

Report</full-title></periodical><pages>334, https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519</volume><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] recommended protocol for the BALB/c 3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity (Appendix C1)

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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2019</Year><RecNum>14825</RecNum><DisplayText>[111]</DisplayText><record><rec-number>14825</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048386">14825</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Transmittal of Meeting Minutes and Final Report for the Federal Insecticide Fungicide and

Rodenticide Act, Science Advisory Panel (FIFRA SAP) Meeting held on December 4 and 6, 2018</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>51,https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2018-0517-0030&contentType=pdf</pages><volume>EPA-HQ-OPP-2018-0517</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>] . 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.*) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. 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 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 that evaluate the surfactant AOP elements (*i.e.*, MIEs and/or CLEs), 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 [HT46]: SALAZAR: NOT CLEAR WHAT THE '3' ASSAYS ARE

Commented [RAB47]: 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 comparator 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~~ comparator analogue and the data on the new chemical substance ~~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:

ED_005294A_00000406-00164

- 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) [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Based on the results of the 3D-construct and/or PCLS testing, ~~in vitro to in vivo~~IVIVE ~~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 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum><DisplayText>[98]</DisplayText><record><rec-number>14811</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Issue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)

Formatted: Font: Not Italic

Formatted: Font: Not Italic

</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33, https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. 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.

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 or~~, 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.~~

~~I~~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 modified 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 [ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum><DisplayText>[82]</DisplayText><record><rec-number>14796</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041048">14796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title>Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2009</Year><RecNum>14827</RecNum><DisplayText>[113]</DisplayText><record><rec-number>14827</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048858">14827</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Acute Inhalation Toxicity</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>19, https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg403.pdf</pages><volume>403</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] (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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14828</RecNum><DisplayText>[114]</DisplayText><record><rec-number>14828</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596048957">14828</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>28-day (subacute) inhalation toxicity study</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>23, https://doi.org/10.1787/9789264070783-en</pages><volume>412</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>], 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 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum><DisplayText>[106]</DisplayText><record><rec-number>14819</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046851">14819</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, No. 39 (Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-

ED_005294A_00000406-00169

title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</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. Additionally, the sensory irritant potential can be measured using ASTM E 981 to determine reflex inhibition [ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>2001</Year><RecNum>14826</RecNum><DisplayText>[115]</DisplayText><record><rec-number>14826</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048712">14826</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Alarie, Y.</author><author>Nielsen, G.D.</author><author>Schaper, M.M.</author></authors><secondary-authors><author>Spengler, B.</author><author>Samet, J. M.</author><author>McCarthy, J.F.</author></secondary-authors></contributors><titles><title>Animal Bioassays for Evaluation of Indoor Air Quality</title><secondary-title>Indoor Air Quality Handbook</secondary-title></titles><pages>23.21-23.49.</pages><dates><year>2001</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill</publisher><urls></urls></record></Cite></EndNote>].

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

CONCLUSIONS

Commented [ST48]: Needs some work

The overall objective of this investigation was to develop a chemical category for use in conducting inhalation risk assessment for new chemical surfactant substances under TSCA. This investigation provides physical-chemical properties, *i.e.*, the Surfactant Criteria, assessors can use for determining whether a new chemical substance can be considered a surfactant. Further, properties and characteristics are provided to divide the surfactant category into sub-categories for nonionic, anionic, and cationic surfactants, which is important from a toxicological perspective. A systematic literature search and review were conducted to identify data to define a surfactant category and toxicological analogues from which read-across could be performed. Animal toxicity studies that could be used to derive PODs for risk assessments were identified for at least one analogue for each sub-category and converted to HECs using established methods developed by ~~-~~EPA ~~recommended duration and dosimetric adjustment factors to these toxicity studies to derive HECs for each subcategory~~. Finally, a tiered-testing strategy is provided that focuses on integrating a variety of ~~NAMs~~ currently available NAMs. Though the tiered-testing strategy may be aspirational at this point for a variety of reasons (*e.g.*, jurisdictions that may still require vertebrate animal testing), the use of this strategy will aid informing the available data on surfactants and providing greater confidence in the use of non-vertebrate testing approaches for assessing the potential risks of new chemical substances. Therefore, it offers advantages to regulators, the regulated community, and consumers because ~~Integrating~~ integrating NAMs into ~~the~~ a category testing approach ~~not only~~ supports EPA and TSCA goals of reducing and replacing vertebrate animal testing and ~~, but also~~ serves to encourage development of

ED_005294A_00000406-00171

mechanistic data to advance the understanding of the potential inhalation ~~adverse outcome pathway and~~ toxicity of surfactants, which will drive the development of newer and safer chemistries.

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)~~

Supporting Information

Formatted: Font: Bold

Formatted: Normal

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. RDDR Modeling Outputs

Formatted: Font: Not Bold

Formatted: TA_Main_Text

AUTHOR INFORMATION

Corresponding Author

*U.S. Environmental Protection Agency, EPA East Bldg., Rm. 3410B, 1200 Pennsylvania Ave., NW, Mail Code: 7401M, Washington, D.C. 20460, Tel: (202) 564-6991, E-mail: stedeford.todd@epa.gov

ED_005294A_00000406-00172

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.

Funding Sources

EPA sponsored the initial literature review through a government contract to SRC (68HERH19F0197 (TO#07)). The American Chemistry Council's TSCA Section 5 Testing Consortium sponsored an updated literature review by an independent third party.~~Any funds used to support the research of the manuscript should be placed here (per journal style).~~

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]

ED_005294A_00000406-00173

Message

From: Jarabek, Annie [Jarabek.Annie@epa.gov]
Sent: 7/29/2020 10:06:37 PM
To: Ann Tveit [ann.tveit@basf.com]; Stephanie Snyder [stephanie.snyder@covestro.com]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.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]
Subject: RE: draft lung overload manuscript 27 July 2020.ver.4
Attachments: amj_Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.2.docx

Importance: High

Hello All

Thank you for including me. As I have not been privy to any of the conversations and came very late in the game, perhaps I am the only one who is unclear on these couple of points, but here they are:

Ex. 5 Deliberative Process (DP)

Cheers,

Annie

Annie M. Jarabek I Senior Science Advisor
Human and Environmental Effects Assessment Division (HEEAD)
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development (ORD) I U.S. EPA
B-243-01 Research Triangle Park, NC 27711
Mobile (*best way to reach me*): 919.637.6016 I Office: 919.541.4847

Go Green - print this email only if necessary

From: Ann Tveit <ann.tveit@basf.com>
Sent: Wednesday, July 29, 2020 5:48 PM

To: Stephanie Snyder <stephanie.snyder@covestro.com>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael <hayes.mp@pg.com>; Ladics, Greg <gregory.s.ladics@dupont.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.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: RE: draft lung overload manuscript 27 July 2020.ver.4

Hi All,

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ann Tveit Ph.D., D.A.B.T.
Toxicology Manager

Phone: +1 973 245-5527, Mobile: Ex. 6 Personal Privacy (PP) - personal phone Email: ann.tveit@basf.com
Postal Address: BASF Corporation, 2B662, 100 Park Avenue, 07932 Florham Park, USA

BASF
We create chemistry

BASF Corporation

From: Stephanie Snyder <stephanie.snyder@covestro.com>
Sent: Wednesday, July 29, 2020 1:37 PM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael <hayes.mp@pg.com>; Ladics, Greg <gregory.s.ladics@dupont.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Ann Tveit <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: RE: draft lung overload manuscript 27 July 2020.ver.4

Hi Todd,

The comments are contained in the attached version. Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

Thanks,
Stephanie

From: Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
Sent: Wednesday, July 29, 2020 5:58 AM
To: Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder; Tveit, Ann; Irwin, William; Rick_Becker@americanchemistry.com; Henry, Tala; Owen Price; Salazar, Keith; Jarabek, Annie
Subject: draft lung overload manuscript 27 July 2020.ver.4

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

Commented [JA1]: What per se is the NAM proposed? The entire category scheme? Bits and pieces are new nor novel including the MPPD simulations. Needs clarification because NAM in one place is defined as the tiered strategy per se and then later suggests alternative methods. The former makes more sense.

Todd Stedeford[a,], Gregory S. Ladics[b], Owen Price[c], Annie M. 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]*

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

[b] Dupont Nutrition and Biosciences, Wilmington, Delaware 19803, United States

[c] Applied Research Associates, Inc., Arlington, Virginia 22203, United States

[d] Health & Environmental Effects Assessment Division, Center for Public Health & Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, United States

[e] BASF Corporation, Florham Park, New Jersey 07932, United States

[f] Proctor & Gamble, Company, Inc., St. Bernard, Ohio 45217, United States; Temselaan 100, 1853 Strombeek-Beaver, Belgium

[g] Covestro LLC, Pittsburgh, Pennsylvania 15205, United States

ED_005294A_00000408-00001

[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 [ST2]: 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 2016 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_00000408-00002

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 as a first step in risk assessments on these substances. Finally, a tiered-testing strategy that maximizes the use of non-vertebrate testing (*i.e.*, a new approach method or 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.

Formatted: Highlight

Commented [JA3]: So this is the NAM? CLARIFY

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.*, the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA), 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 categorical 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

Commented [JA4]: Reference? Notably for computational approaches?

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 physicochemical ~~chemistries or physical~~ properties, the NCP Chemical Categories were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect new vertebrate testing reduction goals. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particul~~cates~~[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-

Commented [JA5]: Reference

Commented [JA6]: Particulate is an adjective. Particles is the noun. For example, particulate matter NAAQS.
THANK YOU for the footnote!! Can you CLARIFY if diameter referenced is physical or aerodynamic?

[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)[c] 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] ~~n~~No limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

Commented [JA7]: Best to have superscript here and separate out the two in header also

		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, including ~~(*i.e.*,~~ lung overload[2] ~~)~~ *via* a specific ~~the~~ mode~~(s)~~ of

[2] Overload is defined in this manuscript as when the exposure concentration is sufficiently high or the duration sufficiently long to overwhelm AM-mediated clearance.

Commented [JA8]: OTHER toxicity can still occur. SEPARATE out the SPECIFIC demonstration of overload per se. I have added a DEFINITION of overload in footnote so that everyone gets on same page.

Commented [JA9]: An important aspect of overload is that the particles are LOW toxicity, i.e., PSLT. This separates them from particles that are impairing clearance by other mechanisms and is an important aspect of the definition.

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

action (*i.e.*, impairment of alveolar-macrophage mediated clearance), as identified in rat inhalation studies, within~~to~~ chemical substances present in the NCP Chemical Categories document for respirable, poorly soluble particulates. The focus on overload has been due to the fact that poorly soluble particles appear to produce lung tumors in rats when AM mediated clearance is over-whelmed and chronic inflammation is present. 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).

Formatted: Highlight

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.

Formatted: Highlight

Formatted: Highlight

Commented [JA10]: On page 3 it is suggested that the NAM is the strategy. I think this is more likely the case as the bits and pieces in the strategy are not novel but the approach could be so construed.

MATERIALS AND METHODS

Systematic Literature Review

Commented [ST11]: 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 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~~ manifest 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 both experimental animals and humans. A secondary objective was to develop a ~~identify potential NAMs that may be incorporated into a~~ tiered-testing strategy that minimizes the use of vertebrate animals and can serve as a NAM for this chemical category.

Commented [JA12]: It is NOT "defined" differently, how it is manifest and why is different.

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 by performing benchmark dose modeling. ~~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>C

Commented [JA13]: I changed this to reflect the approach because it would be the lower limit on a concentration or BMCL. This seemed cleaner.
Would be good to include citation:

Commented [JA14]: For INHALATION?! Route-to-route is NOT RECOMMENDED for portal of entry effects. Doing this adds considerable UNCERTAINTY.

hemSTEER 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 including ~~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

Commented [JA15]: SOMEWHERE WE NEED TO CLARIFY THAT THIS TERM IS NOT NEEDED WHEN CONDUCTING RDDR OR MPPD SIMULATIONS AS IT IS ALREADY INCORPORATED IN THE CONSTRUCTION OF THE HEC.

Formatted: Highlight

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 uncertainty factor (UF)

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) applied to the adjust exposure levels of observed toxicity in the animals and perform interspecies extrapolation [ADDIN EN.CITE

Commented [JA16]: What about DURATION adjustment (i.e., subchronic to chronic, UF_S) and DATABASE uncertainty (UF_D) to account for coverage?

<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>]. As described below in the section on interspecies extrapolation and overload simulation, 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 benchmark dose lower limit value (BMDL) as described in the next section, 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.

Commented [JA17]: Benchmark dose modeling is not discussed until page 17. I am moving that section up so that the flow is more logical.

Benchmark Dose Modeling

EPA's benchmark dose modeling ~~(BMD)~~ software (BMDS) 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 available 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>].

Interspecies Extrapolation and Dosimetry Simulations Demonstrating Overload

Commented [JA18]: Needed context for why the two models were being used and to connect with the benchmark MOE section. Otherwise really hard to follow.

It has long been recognized that the external exposure concentration of particles is not the same amount that is inhaled, subsequently deposited and retained, and responsible for adverse health effects. 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. Dosimetry[3] models have been used for decades to describe the physicochemical and biological determinants of aerodynamic behavior and toxicological responses of inhaled particles. Such models are applied to account for species differences in the complex interactions among the described physicochemical, anatomical and physiological factors to determine inhaled dose metrics relevant to mode of action (MOA). Herein we explore two different available dosimetry models and conduct simulations to demonstrate factors determining overload.

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

Formatted: Font: (Default) Times New Roman, 12 pt

Commented [JA19]: ADD CITATION: Jarabek AM, Asgharian B, Miller FJ. Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). *Inhal Toxicol.* 2005;17(7-8):317-334. doi:10.1080/08958370590929394

---

[3] Dosimetry refers to measuring or predicting the amount (e.g., mass, surface area or number) of particles in a specific region of the respiratory tract at a particular point in time. Dose metrics, e.g., deposited or retained mass in a specific region of the respiratory tract normalized to its surface area for portal-of-entry effects, should be constructed to correspond to the MOA of the particle and the observed toxic effect of interest.

Regional Deposited Dose~~ose Dosimetry~~ Ratio (RDDR) Model (US EPA, 1994)

The US EPA introduced formal dosimetry modeling into its derivation procedures for risk assessment of inhaled materials with its 1994 document entitled *"Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry"* [15]. As described above, EPA may apply DAFs to PODs identified from experimental animal studies to calculate an HEC. ~~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 it is therebys reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, since the POD is dosimetrically

Formatted: Font: (Default) Times New Roman, 12 pt

Formatted: Font: (Default) Times New Roman, 12 pt

Formatted: Font: (Default) Times New Roman

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) as ~~, that is,~~ the DAF for insoluble particles [15]. 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 particulesate in the regions of the respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF), such as the respiratory tract surface area of , for the region of observed toxicity for portal-of-entry effectsf 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. Human ventilatory parameters and assumptions regarding exposure regimen (e.g., hours /day and lifetime) are analogously used in the model to predict the human deposition fraction with default values for the NF. The RDDR ismay be applied to the duration adjusted POD which describes the ; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the laboratory animal regimen, to arrive at the POD_{HEC}. 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><titl

Commented [JA20]: ADDED to clarify the NF is DIFFERENT for systemic effects

Commented [JA21]: ?? THAT IS THE DEFINITION of the POD ADJ. There is NO DIFFERENCE in approach here.

Commented [JA22]: ?? where is this version number coming from. It was 2.2 in the US EPA 1994 methods.

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) ***Model***

Commented [ST23]: 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 model that can be used to predict deposition, clearance, and retained 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>]. The MPPD model is supported by Applied Research Associates, Inc. (ARA) and is

available as freeware. An EPA version of MPPD is anticipated to undergo external peer review for application to Agency assessments in late FY20. As with the RDDR model, the MPPD model provides predictions that may be used to calculate a POD_{HEC} for inhaled deposited dose; however, unlike the RDDR model, the MPPD model additionally provides predictions of retained dose that may be more appropriate to characterize chronic effects. The MPPD model also incorporates inhalability[4], covers a wider size range of particles (0.01 – 100 μm), and has other added capabilities including the ability to construct simulations of activity patterns with different ventilation parameters within a given day.

Commented [JA24]: CAREFUL. See citation below. The nature of the dose metric is dictated by the MOA for particles. Mortality due to chronic conditions may in fact be best described by deposition.
Jarabek AM, Asgharian B, Miller FJ. Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). *Inhal Toxicol.* 2005;17(7-8):317-334. doi:10.1080/08958370590929394

To calculate clearance and thereby retained dose, ~~T~~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

[4] Inhalability can be defined as the probability that a particle of a given size will actually enter one of the respiratory tract orifices in the case of non-human primates or humans or enter the nares in the case of rodents that are obligatory nose breathers. Inhalability varies between species and is a critical adjustment for interspecies extrapolation.

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 χ^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