# Alliance for Telomer Chemistry Stewardship

See attachment for comments.

Alliance for Telomer Chemistry Stewardship

January 28, 2022

Ms. Irina Makarow
Washington State Department of Ecology
Hazardous Waste & Toxics Reduction Program
300 Desmond Drive SE
Lacey, WA 98503

*Submitted via*:

RE: Draft Regulatory Determinations Report to the Legislature: Safer Products for Washington Implementation Phase 3

Dear Ms. Makarow:

The Alliance for Telomer Chemistry Stewardship (ATCS[1]) appreciates this opportunity to provide comments on the Draft Regulatory Determinations Report to the Legislature: Safer Products for Washington Implementation Phase 3 (hereafter the "Report") as it relates to per- and polyfluoroalkyl substances (PFAS). ATCS is a global organization that advocates on behalf of C6 fluorotelomer-based products. Our members are leading manufacturers of fluorotelomers in North America, Europe and Japan. Our mission is to promote the responsible production, use and management of fluorotelomers, while also advocating for a sound science- and risk-based approach to regulation.

We understand the important issues facing Washington regarding determining how to address levels of certain PFAS compounds in the State. Further, we appreciate the significant efforts the Departments of Ecology and Health have put into implementing the Safer Products for Washington program (SPW) and developing this draft Report. However, to ensure the success and viability of SPW, it is crucial that the Departments pursue a science- and fact-based approach to implementation. For products containing PFAS, this requires a thorough understanding of the broad family of PFAS compounds, assigning correct definitions, including their potential hazards and other characteristics as compared to available alternatives.

As drafted, however, the Report presents an inaccurate picture of the potential hazards associated with the PFAS-containing priority products addressed in the Report and it makes unsupported assumptions regarding the availability of suitable alternatives to replace those priority products. Because of this flawed analysis and inaccurate definitions, the recommendations in the draft Report are inappropriate and should be revised. Specifically, as discussed in more detail in the attached comments, the Report should be revised based on the science to recommend the restriction of long-chain PFAS, coupled with a notification requirement for the use of PFAS other than long chains in the Priority Products.

[1] AGC Chemicals Americas, Daikin American Incorporated, Dynax Corporation and Johnson Controls (JCI)

Outlined in the accompanying attachment are ATCS' specific comments on the draft Report. We would welcome the opportunity to discuss these comments with you further.

Thank you for your consideration, and please let me know if we can provide any additional information or answer any questions regarding our comments.

Sincerely,

Shawn Swearingen
Director, Alliance for Telomer Chemistry Stewardship

**ATCS Comments on PFAS-Related Aspects of the Draft Regulatory Determinations Report to the Legislature: Safer Products for Washington Implementation Phase 3.**

Per- and polyfluoroalkyl substances (PFAS), is a catch-all term that is used as a shorthand to refer to a widely diverse universe of chemistries, many of which are critical to making the products that power our lives – from cellphones and tablets, to alternative energy sources, to life-saving medical devices. However, all PFAS are not the same. Individual PFAS chemistries (and groups of similar PFAS chemistries) have their own unique properties and uses, as well as disparate environmental, health and safety profiles.

According to the U.S. Environmental Protection Agency, "approximately 600 PFAS are manufactured (including imported) and/or used in the United States." Among these 600 are substances in the solid (e.g., fluoropolymers), liquid (e.g., fluorotelomer alcohols) and gaseous (e.g., hydrofluorocarbon refrigerants) forms. Some of these substances are soluble in water and may be mobile in the environment, while others are not. Some are very large, stable molecules that are too large to be bioavailable, while others are comprised of relatively small molecules. These very distinct physical and chemical properties illustrate how varied PFAS substances are and why it is not appropriate to regulate all members of the category as if they were the same -- without examining the specific characteristics of the particular PFAS compounds (or categories of PFAS compounds) that are used in the priority product undergoing evaluation.

A scientific consensus is emerging that it is not appropriate or even possible to group all PFAS chemistries together for the purpose of regulation. Indeed, state and federal entities that have explored the possibilities of a class-based approach have recognized the significant challenges. For instance:

- ECOS, the Environmental Council of the States. which represents state and territorial environmental agency leaders, has acknowledged that, "Many regulators and subject-matter experts advise against grouping PFAS as an entire class."[2]

- The Vermont Department of Environmental Conservation[3], which was specifically charged by the legislature to develop a class regulation or to explain why such a regulation wasn't possible said, "The Review Team spent over a year deliberating, researching, and discussing the potential to regulate PFAS as a Class. After reviewing the current peer-reviewed literature, as well as the available toxicology data for PFAS, the Review Team determined that at the current time it is not feasible to regulate PFAS as a Class."

- Federal scientists participating in a workshop convened last fall by the National Academies of Science, Engineering and Medicine (NASEM) to review the federal PFAS research program acknowledged the broad diversity of properties within this group of substances, concluding that[4] "PFAS substances thus present unique challenges for grouping into classes for risk assessment." US EPA's Roadmap also recognizes this distinction within the broad class of PFAS and reflects

[2] ECOS. Processes & Considerations for Setting State PFAS Standards (February 2020).
[3] https://dec.vermont.gov/sites/dec/files/PFAS/20180814-PFAS-as-a-Class.pdf
[4] NASEM. Workshop on Federal Government Human Health PFAS Research, October 26-27. Board on Environmental Studies and Toxicology (2020). https://www.nap.edu/read/26054/chapter/1

EPA's intent to regulate PFAS based on sub-categories of PFAS chemistries that share certain fundamental properties[5].

**The Draft Report Should Focus on the Specific PFAS Compounds Used in the Priority Products Under Consideration**

While the underlying statute identifies PFAS as a chemical class and defines PFAS broadly, Ecology should focus its Phase 3 implementation efforts on the specific PFAS substances or subcategories that are actually used in the priority products being evaluated. Indeed, the statute itself recognizes that when a priority chemical is a "chemical class" rather than a single chemical substance, it is appropriate to examine individual ***members*** of the class when determining whether restriction is appropriate for a priority product. Thus, for example, RCW 70A § 1454(3) provides in relevant part that the "department may restrict or prohibit a priority chemical or ***members of a class*** of priority chemicals" if certain conditions are met (emphasis added). Accordingly, in evaluating whether restriction or some other regulatory determination is warranted for PFAS-containing priority products, the Department should focus its analysis on the specific PFAS chemicals or subcategories – i.e., the "members of the class" of PFAS chemicals -- that are actually used in those priority products.

With respect to textile and leather furnishings, the vast majority of PFAS treatments fall into a single sub-subcategory of PFAS chemicals, referred to as "side-chain" fluorinated polymers.[6] In general, side-chain fluorinated polymers are characterized as being either "short chain" polymers or "long chain" polymers, depending on the number of carbon atoms in their side chains. In developing regulatory determinations for these priority products, Ecology should have examined the specific hazards associated with side-chain fluorinated polymers to assess whether the alternatives under consideration are, in fact, "safer" than side-chain fluorinated polymers. Similarly, the Department should have compared the efficacy of side chain polymers to the performance of potential alternatives to assess whether those alternatives perform suitably for their intended uses. Ecology's failure to analyze hazard and performance in this manner is a serious shortcoming that must be remedied in the final Report.

**The Draft Report Reflects a Flawed and Overly Simplistic Approach to Assessing Hazards**

In evaluating the hazards of PFAS compounds compared to potential alternatives, Ecology relied almost exclusively on two tools: (i) pre-existing, available GreenScreen® assessments and (ii) third party lists of "safer" chemicals. Crucially, Ecology made no effort to ascertain what types of PFAS substances are used in the priority products being considered; nor did Ecology examine the available hazard data for the PFAS substances used in those priority products or comparable data on the proposed alternatives. As a consequence, Ecology's assessment does not accurately reflect the best available science nor does it present an accurate picture of the PFAS compounds that may be found in the priority products.

As discussed above, the PFAS compounds used in the manufacture of textile or leather furnishings belong to the category of side-chain fluorinated polymers. In the United States, Japan and Europe, all of the leading manufacturers of this category of compounds have transitioned to produce only ***short-chain***

[5] Goodrum PE et al. Application of a framework for grouping and mixtures toxicity assessment of PFAS: a closer examination of dose additivity approaches. Toxicol Sci: 1-19 (2020). https://doi.org/10.1093/toxsci/kfaa123

[6] We understand that PFAS compounds are no longer used to treat carpets and rugs manufactured in the US. (Personal communication with the Carpet and Rug Institute.) Accordingly, our comments focus primarily on leather and textile furniture and furnishings.

polymers (also referred to as "C6" polymers). Therefore, to the extent that PFAS chemicals are utilized in the manufacture of leather or textile furnishings in these regions of the world, the PFAS chemicals that are utilized are almost certainly "short chain" or "C6" side-chain polymer products.[7] Products that fall within this category have been thoroughly reviewed by regulators prior to introduction into commerce, are subject to ongoing review and are supported by a robust body of rigorous scientific health and safety data.

Because side-chain polymers themselves are not bioavailable, health and safety assessments of these compounds have included review of hypothetical breakdown (degradation) products. As reflected in the published scientific literature, studies have found that one of the primary potential breakdown products of C6 side-chain polymers, perfluorohexanoic acid (PFHxA or C6 acid), does not cause cancer (NTP 2018; Klaunig et al. 2015; Loveless et al. 2009); does not disrupt endocrine activity (Borghoff et al. 2018); does not cause reproductive or developmental harm (Loveless et al. 2009; Iwai et al. 2019, Iwai and Hoberman 2014); does not build up in the human body and does not become concentrated in the bodies of living organisms (Chengelis et al. 2009b; Iwai and Hoberman 2014; Russell et al. 2013, 2015; Nilsson et al. 2010, 2013; Fujii et al. 2015; Guruge et al. 2016; Gannon et al. 2011, 2016). However, to our knowledge, these data were not reviewed by Ecology or addressed in the draft Report; nor did Ecology review comparable data on the proposed alternatives.[8]

In addition to the robust body of data on PFHxA summarized above, a certified GreenScreen® assessment conducted by an independent Licensed GreenScreen® Profiler, is available for a representative short chain side-chain fluorinated polymer. The GreenScreen® assessment assigned a benchmark score of "2" to this short-chain polymer product.[9] A copy of that GreenScreen® report is included with these comments as "Attachment A." Under the rubric utilized by Ecology for the SPW program, products with a GreenScreen® benchmark score of "2" satisfy the minimum criteria for being considered "safer." Thus, the subcategory of PFAS compounds *actually used* in treated textile and leather furnishings in the US (i.e., C6 side-chain polymers) satisfy the minimum criteria to be considered "safer" for purposes of the SPW program.[10] This determination refutes the draft Report's conclusion that PFAS, as a class, do not meet the minimum criteria for safer.

As the foregoing discussion demonstrates, side-chain polymers are the subcategory of PFAS compounds that are used in the treatment of textile and leather furnishings. C6 side-chain polymers, in particular, are data rich; and those data support the conclusion that C6 side-chain polymer products used in leather and textile furnishings meet the minimum criteria to be considered "safer" for purposes of the SPW program.

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[7] By contrast, priority products that originate from other regions of the world might incorporate "long chain" fluorinated polymers, including polymers that may degrade to perfluorooctanoic acid (PFOA) or perfluorooctanesulfonic acid (PFOS).

[8] By comparison, the hazard data for long-chain breakdown products, such as PFOA, are less favorable. For example, studies indicate that PFOA bioaccumulates and there is "suggestive evidence of carcinogenic potential." *See,* USEPA, Health Effects Support Document for Perfluorooctanoic Acid (PFOA) (May 2016).

[9] Although the specific short-chain product evaluated in the GreenScreen assessment is not intended for use in treating textile or leather furnishings, the compound that was evaluated is typical of C6 side-chain compounds, including those that are used as leather or textile treatments.

[10] *See* Draft Report at 237.

**The Draft Report's Assessment of the "Feasibility" of Alternatives is Incomplete and Unreliable**

The draft report focuses almost entirely on the ease of cleaning and associated aesthetic value of the water and oil repellency imparted by "PFAS" (i.e., C6 side-chain) leather and textile treatments, but it ignores other benefits that are equally if not more important. These include: resistance to contamination by biological fluids, including those that may be vectors of disease, and increased durability – resulting in the generation of less waste and the consumption of fewer resources. In addition, Ecology failed to adequately address how different degrees of performance may be necessary, depending on specific conditions of use (e.g., heavily trafficked public spaces versus private indoor spaces).

The report fails to assess, in an objective and measurable way, whether the proposed alternatives provide the same benefits and the same level of performance as C6 short-chain products under all relevant conditions of use. Instead, Ecology largely relies on advertising and promotional materials, and other subjective measures, to conclude that alternatives are "feasible and available."

However, empirical data indicate that at least for some applications (e.g., outdoor furnishings) available alternatives do not provide an adequate level of performance, as compared to C6 side chain polymers. For example, in comments recently submitted to the European Chemicals Agency (ECHA), the European Apparel and Textile Industry Confederation (EURATEX) reported on the results of testing conducted on potential alternatives to fluorinated treatment products. One research program being carried out by a consortium of textile and related organizations, called MIDWOR-LIFE, found that "alternative products achieved a water repellence matching the performance of conventional fluorinated products; however [their] performance against oil did not reach an acceptable level."[11] As noted by EURATEX, pollution is one of several factors that contribute to the degradation of outdoor furnishings, and oil resistance is essential to providing protection against pollution.[12]

EURATEX also reports on testing of potential alternatives to C6 side-chain polymers conducted by a French manufacturer of upholstery fabric for outdoor use.[13] Testing of ten alternative formulations (from an initial suite of 22 potential alternatives) showed that while performance, other than oil resistance, was acceptable initially, overall performance rapidly declined to unacceptable levels following weathering.[14] According to EURATEX, because of these unacceptable results, the manufacturer is currently investigating new formulations for testing.

As this example illustrates, assessing whether an alternative is "feasible" for a product requires more than an examination of the claims that are made for a commercial product or the successful marketing of a product that touts some of the broad benefits imparted by C6 side chain polymers. To ensure that a potential alternative is actually "feasible" – and that products with important functionalities are not removed from the market without a suitable alternative -- it is essential for

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[11] *See* EURATEX contribution to the SEAC public consultation: Comments on SEAC Draft Opinion on the proposed restriction for PFHxA, its salts and related substances (September 2021) at page 8, accessible through the following url: https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18323a25d under the heading "ORCOM part 2."

[12] *Id.*

[13] *Id.* at p 9.

[14] *Id.*

Ecology to fully examine both the specific contexts within which treated-furnishings are used (e.g., heavily trafficked spaces; indoor spaces, such as nursing homes, with special health-related considerations; outdoor spaces vulnerable to air pollution, etc.) as well as the particular functionality provided by the C6 short chain product in each specific context. Then, as a second step, Ecology must examine objective data to assess whether, for each relevant use scenario, the potential alternative provides equivalent functionality as compared to the C6 side chain product. To the extent that Ecology does not currently possess all of the information needed to perform this analysis, the Department should utilize the authority provided in RCW 70A.350.040 to collect such information from manufacturers.

**The Draft Report's Recommendations Should be Revised**

In light of the deficiencies discussed above, the Recommendations in the draft Report are inappropriate and should be revised. In particular, the proposed restrictions are inappropriate for C6 side chain polymer products, since (i) those products satisfy the SPW minimum criteria for being "safer" and (ii) Ecology has failed to adequately assess whether, for leather and textile furnishings, alternative products or processes are suitable for all relevant use scenarios. Instead, for leather and textile furnishings, Ecology should consider the following recommendations:

- Utilizing the authority provided in RCW 70A.350.040 to collect the information needed to conduct a thorough assessment of the feasibility of alternatives to C6 side-chain polymer products.
- Adopting a notification requirement for leather and textile furnishings manufactured using C6 side-chain polymers, so that purchasers can chose alternative products if they do not require the functionality provided by C6 side-chain polymer products.
- Imposing restrictions on leather and textile furnishings manufactured using long-chain PFAS compounds, which have not been shown to meet the SPW minimum criteria for safer.

# AG-E060
# Certified GreenScreen® Assessment

Prepared for

The Alliance for Telomer Chemistry Stewardship

September 23, 2020

GRADIENT

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# GreenScreen® Assessment for AG-E060

**Method Version:** GreenScreen® for Safer Chemicals v1.4[1]

## Assessment Details

| GreenScreen Assessment Prepared By: | GreenScreen Assessment Quality Control Performed By: |
|---|---|
| **Name:** Kim Reid | **Name:** Tom Lewandowski |
| **Title:** Principal Scientist | **Title:** Principal/Toxicologist |
| **Organization:** Gradient | **Organization:** Gradient |
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| **Name:** Megan Arnold | **Name:** Matt Lewis |
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| **Organization:** Gradient | **Organization:** Gradient |
| | |
| **Name:** Tatiana Manidis | |
| **Title:** Environmental Scientist | |
| **Organization:** Gradient | |
| | |
| **Assessment Type:**[2] | Certified |
| **Assessment Completed:** | September 23, 2020 |
| **Assessment Expiration Date:** | September 23, 2025 |
| **Assessor Type (Licensed GreenScreen Profiler, Authorized GreenScreen Practitioner, or Unaccredited):** | Licensed GreenScreen Profiler |

**Confirm Application of the Disclosure and Assessment Rules and Best Practice:**[3] NA

**Polymer Substance Trade Name:** AG-E060

AG-E060 is a 20% dispersion of the neat polymer (NPD-14), acetic acid, and water.[4] This GreenScreen is for the polymer substance AG-E060.

NPD-14 is described as a "[c]opolymer of perfluorohexylethyl methacrylate, 2-N,N-diethylaminoethyl methacrylate, 2-hydroxyethyl methacrylate, and 2,2'-ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 863408-20-2)" (ATCS, 2020).

[1] GreenScreen® for Safer Chemicals v1.4 (CPA, 2018).
[2] GreenScreen assessments are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen Practitioner), "CERTIFIED" (by Licensed GreenScreen Profiler or equivalent), or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen Verification Program).
[3] See GreenScreen Guidance v1.4 (CPA, 2018).
[4] AG-E060 is the subject of two effective Food Contact Notifications (FCNs): FCN 599 and FCN 604. For purposes of those FCNs, the substance is identified as a copolymer of perfluorohexylethyl methacrylate, 2-N,N-diethylaminoethyl methacrylate, 2-hydroxyethyl methacrylate, and 2,2'-ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 863408-20-2) or malic acid salt (CAS No. 1225273-44-8).

## Similar Polymer Substances

The following similar polymers were used to apply Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Bridging Principles.

- Manufacturer & Tradename: NPD-14
  - Number average molecular weight: Confidential
  - Molecular Structure(s): Confidential

Rationale for similarity: NPD-14 is the copolymer present in the AG-E060 20% dispersion.

### Notes:

AG-E060 is a fluoropolymer aqueous dispersion containing 20% of a neat polymer, NPD-14 (copolymer of perfluorohexylethyl methacrylate, 2-N,N-diethylaminoethyl methacrylate, 2-hydroxyethyl methacrylate, and 2,2'-ethylenedioxydiethyl dimethacrylate, acetic acid salt [CAS No. 863408-20-2] or malic acid salt, [CAS No. 1225273-44-8]). According to GreenScreen Guidance v1.4, "Polymer [species] comprise the following: (a) a simple weight majority (*i.e.*, 50%) of molecules containing at least three monomer units which are covalent bound to at least one other monomer unit or other reactant; or (b) less than a simple weight majority of molecules of the same molecular weight" (CPA, 2018). AG-E060 was assessed as a polymer substance per Section 2 of GreenScreen Guidance v1.4 (CPA, 2018), and any additional constituents were reported as impurities in Table 2. These impurities originated from the NPD-14 copolymer (present in the dispersion at 20%) and, based on information supplied by the manufacturer, were expected to be at concentrations below 100 ppm in AG-E060, and therefore were not individually assessed per the GreenScreen guidance.

Regarding nomenclature of the aqueous dispersion and the neat polymer, AG-E060 is a 20% aqueous dispersion of a neat polymer (NPD-14). In the associated studies reviewed during this assessment, the aqueous dispersion is generally referred to as "AG E060," and the neat polymer is generally referred to as "NPD-14." However, "AG-Paper" has also been used occasionally and has been used interchangeably to refer to both the polymer and the dispersion, which can present some confusion. Thus, careful attention was paid to how each test substance was described in the studies and literature to determine if the name of the test substance is indeed the substance actually being tested. In cases where there are discrepancies between the substance nomenclature and described physical/chemical properties of the test substance, we have included further clarification in footnotes throughout this report.

### GreenScreen Benchmark Score and Hazard Summary Table[5,6,7]

AG-E060 is assigned a benchmark score of 2 based on a Very High (vH) score for persistence, a Moderate (M) score for endocrine activity, and Low (L) scores for the majority of the remaining endpoints with the exception of data gaps for respiratory sensitization and chronic aquatic toxicity. Although data gaps exist for these endpoints, the minimum data requirements were met for Benchmark 2 classification.

[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen Guidance v1.4 Section 12 (Exceptions for Persistence) (CPA, 2018).
[7] Lacking single exposure data, including for aspiration hazards, does not result in a Data Gap when repeated exposure data are available. In these cases, enter the repeated exposure hazard classification in the GreenScreen Hazard Summary Table and shade out the single exposure sub-endpoint cell. See GreenScreen Guidance v1.4 (CPA, 2018).

For Group I Human Health Effects endpoints that lacked data for both the aqueous dispersion and the neat polymer (NPD-14), experimental data and authoritative/screening list searches were conducted for the four primary individual monomer units in an approach similar to evaluating qualifying constituents for polymer substances. If experimental data were available for evaluating the monomer units, a hazard score was assigned based on the most conservative individual hazard score.

If we consider the worst-case benchmarking scenario based on the reported data gap, respiratory sensitization (Group II* human health category) would be designated a High Hazard (H). Under the worst-case scenario where respiratory sensitization would be designated a High Hazard (H), AG-E060 would remain at Benchmark 2.

**Table 1 GreenScreen (v1.4) Polymer Hazard Summary Table – AG-E060**

| | Group I Human | | | | | Group II and II* Human | | | | | | | | | Ecotox | | Fate | | Phys. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | M | R | D | E | AT | ST | | N | | SnS* | SnR* | IrS | IrE | AA | CA | P | B | Rx | F | |
| | | | | | | | sgl | rpt* | sgl | rpt* | | | | | | | | | | | BM |
| **AG-E060 (Polymer Substance)** | *L* | **L** | *L* | *L* | *M* | **L** | **L** | **L** | | **L** | **L** | DG | **L** | **L** | **M** | DG | **vH** | ***vL*** | *L* | *L* | 2 |
| **Acetic Acid (Processing Aid)[a]** | **L** | **L** | DG | **L** | DG | | | | | | | | | | | | | | | | |
| **Malic Acid (Alternate Processing Aid)[b]** | *L* | **L** | DG | **L** | DG | | | | | | | | | | | | | | | | |

Notes:
BM = Benchmark
Hazard levels (Very High [vH], High [H], Moderate [M], Low [L], Very Low [vL]) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogs, and lower confidence.
Hazard levels in **bold** font indicate good-quality data, authoritative A lists, or strong analogs.
Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (*i.e.*, vH, H, M, and L) instead of three (*i.e.*, H, M, and L) and are based on single exposures instead of repeated exposures.
All acronym definitions are listed in Appendix A.
(a) GreenScreen obtained from the Clean Production Action GreenScreen Store (https://store.greenscreenchemicals.org/gs-assessments).
(b) Group I Human Health Endpoints for malic acid (CAS No. 6915-15-7). Relevant data summarized in Appendix C.

**Table 2 Inventory of Polymer Substance Constituents**

| Constituent | Chemical Name | CAS No. | Weight Percent (Wt %) in Polymer Substance | Additional Information (synonyms, *etc.*) |
|---|---|---|---|---|
| **Polymer Substance:** | | | | |
| (a) Polymer species > 0 ppm (0%) | NPD-14 | 863408-20-2 or 1225273-44-8 | 20% | |
| (b) Residual monomer(s) ≥ 100 ppm (0.01%) | None | NA | NA | |
| (c) Oligomer(s) with a molecular weight (MW) below 500 Dalton | None | NA | NA | |
| (d) Oligomer(s) with a molecular weight (MW) below 1,000 Dalton | None | NA | NA | |
| (e) Stabilizer(s) ≥ 100 ppm (0.01%) | None | NA | NA | |
| (f) Substance impurities ≥ 100 ppm (0.01%): | | | | |
| (i) Catalyst | None | NA | NA | |
| (ii) Other (processing aid) | Acetic Acid[a] or Malic Acid[b] | 64-19-7 6915-15-7 | 1% | |
| | Water | | 79% | |

Notes:
CAS No. = Chemistry Abstracts Service Number; NA = Not Available.
(a) Processing aid used in CAS No. 863408-20-2; acetic acid salt of the copolymer.
(b) Processing aid used in CAS No. 1225273-44-8; malic acid salt of the copolymer.

## Special Case Impurities

Table 3 lists four monomer units identified as impurities in the neat polymer (NPD-14; confidential CAS No.) (Communication from W. Lehrenbaum, 8/11/2020). These monomer units are present at concentrations below 100 ppm in the 20% aqueous dispersion of AG-E060; therefore, they have not been fully assessed as part of this GreenScreen assessment as they are not expected to influence the final benchmark score for the polymer substance AG-E060.

Although the monomers in Table 2 are not present above 100 ppm in AG-E060, they have been evaluated for some endpoints where data are lacking for AG-E060 or NPD-14.

**Table 3 Special Case Impurities Present at < 100 ppm in AG-E060**

| Chemical | Function | CAS No. | ppm | Pharos GreenScreen List Translator (GSLT) Result or Benchmark |
|---|---|---|---|---|
| Perfluorohexylethyl methacrylate | Monomer | 2144-53-8 | < 100 | LT-UNK |
| 2-N,N-Diethylaminoethyl methacrylate | Monomer | 105-16-8 | < 100 | LT-P1 |
| 2-Hydroxyethyl methacrylate (HEMA) | Monomer | 868-77-9 | < 100 | LT-UNK |
| 2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt | Monomer | 109-16-0 | < 100 | LT-UNK |

Notes:
CAS No. = Chemical Abstracts Service Number; LT-P1 = List Translator Possible Benchmark 1; LT-UNK = List Translator Benchmark Unknown.

## Environmental Transformation Products and Ratings[8]

Table 4 indicates the possible biotransformation products for AG-E060.

**Table 4 Biotransformation Products and Ratings**

| Functional Use | Life Cycle Stage | Transformation Pathway(s) | Environmental Transformation Products[a] | CAS No. | Feasible and Relevant? | Pharos GreenScreen List Translator (GSLT) or Benchmark Score |
|---|---|---|---|---|---|---|
| None | EOL | Hydrolysis, Biodegradation, Photolysis | 6:2 FTOH | 647-42-07 | N | LT-P1 |
| None | EOL | Biodegradation, Photolysis | PFHxA | 307-24-4 | N | LT-P1 |
| None | EOL | Biodegradation, Photolysis | 6:2 FTCA | 53826-12-3 | N | No GS |
| None | EOL | Biodegradation, Photolysis | 6:2 FTUCA | 70887-88-6 | N | No GS |
| None | EOL | Biodegradation | 5:3 FTCA | 914637-49-3 | N | No GS |
| None | EOL | Biodegradation | 5:2 sFTOH | 914637-05-1 | N | No GS |

Notes:
CAS No. = Chemical Abstracts Service Number; EOL = End of Life; GS = GreenScreen; LT-P1 = List Translator Possible Benchmark 1; N = No.
(a) The listed potential transformation products were evaluated during biodegradation and photolysis studies of AG-E060 (ATCS, 2020).

## Summary

- Potential feasible and relevant transformation products were evaluated based on anticipated reactivity of the polymer in AG-E060, confidential studies provided to Gradient (three biodegradation studies and a photolysis study; see Persistence section for study details), a literature review of environmental transformations of certain compounds, and professional judgment.
  - Several potential biological and environmental transformation products (listed in Table 4) were evaluated and measured during biodegradation and photolysis studies of AG-E060 (ATCS, 2020). The conclusion of the aerobic and anaerobic biodegradation studies was that the test substance did not display any clear pattern of transformation (ATCS, 2020), while the photolysis study indicated the test substance is "photo inert." These studies demonstrate that the product undergoes extremely limited degradation *via* these routes. Additionally, based on a review of the reported data for these potential transformation products, while potentially feasible, these products are likely not relevant based on the trace concentrations; for example, some of the concentrations were considered uncertain based on values reported below the calibration range, and the data also indicate that some of the transformation products are potentially transient. Additionally, a study of a similar fluorinated acrylate compound (Russell *et al.*, 2008) indicated that the half-life of the study compound was on the order of 1,200-1,700 years, indicating the parent compound is highly persistent and unlikely to undergo significant biodegradation.
  - With regard to nonbiological chemical transformation, although polymers are generally "persistent" by regulatory standards, the polymer in AG-E060 may theoretically be susceptible to hydrolysis of the ester groups on its side chains, which could occur at various points in the life cycle of the

[8] See GreenScreen Guidance v1.4, Section 11.4 (CPA, 2018).

product (*e.g.*, before use, in the slightly acidic aqueous solution of AG-E060, or after disposal). For example, it is possible that hydrolysis of the molecule could yield 6:2 FTOH, diethylethanolamine, ethylene glycol, and triethylene glycol. We note a hydrolysis study provided by the manufacturer indicates that the aqueous dispersion of the polymer substance is not susceptible to hydrolytic degradation at the studied pHs (4, 7, and 9), and therefore it is hydrolytically stable (ATCS, 2020). Moreover, the fact that the intended use of the polymer as a food contact substance is described as "an oil, grease, and *water resistant* treatment for paper and paper board employed either prior to the sheet forming operation or at the size press" (ATCS, 2020) indicates that hydrolysis may not occur to a significant extent.

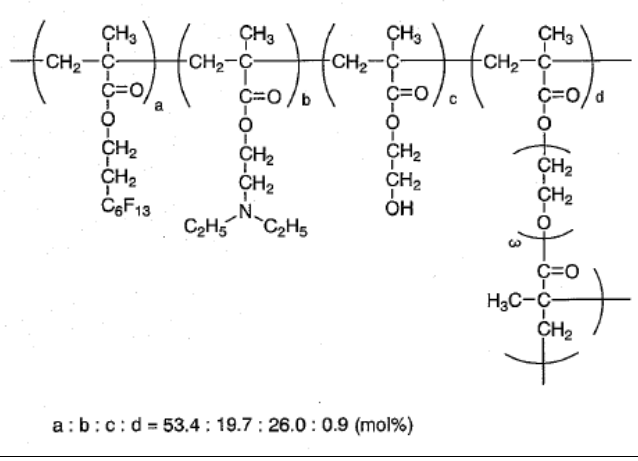
Therefore, based on our review of the available information, using professional judgment, the potential transformation products were not assessed and would not be expected to affect the benchmark score.

# Introduction

AG-E060 is a fluoropolymer substance used in food packaging. Table 5 summarizes the polymer properties obtained for AG-E060.

## Polymer Properties and Constituents

**Table 5 Structural Reporting Requirements and Properties for the Polymer Substance AG-E060**

| Property | Value | Reference |
|---|---|---|
| Molecular Formula | NA – polymer substance | Various studies as cited in ATCS (2020); AGC (2018) |
| Structure (include whether monomers are blocked and the pattern) |  a : b : c : d = 53.4 : 19.7 : 26.0 : 0.9 (mol%) | |
| General Polymer Class | Fluoropolymer dispersion | |
| Number average molecular weight (Mn) | 36,000 | |
| Weighted-average molecular weight (Mw) | 85,000 | |
| Physical State | Pale yellow to brown liquid | |
| Appearance | Liquid | |
| Boiling Point | > 100 °C (212 °F) | |
| Melting Point | NA | |
| Vapor Pressure | NA | |
| Water Solubility | Dispersible | |
| Dissociation Constant | NA | |
| Density/Specific Gravity | 1.04-1.12 (20% dispersion) | |
| Partition Coefficient, Log $P_{ow}$ | NA | |

Notes:
Log $P_{ow}$ = Octanol-Water Partition Coefficient.

# Hazard Classification Summary

Hazard classifications for all GreenScreen endpoints evaluated are provided below.

## Group I Human Health Effects (Group I Human)

### Carcinogenicity (C)

**Score (H, M, or L):** *L*

AG-E060 is assigned a score of Low (*L*) for carcinogenicity, with low confidence. No data were identified for the aqueous dispersion AG-E060 or the neat polymer (NPD-14; CAS No. 863408-20-2 or 1225273-44-8). Therefore, the Oncologic™ v.8.0 model (US EPA, 2019) was used to predict carcinogenicity for the neat polymer (NPD-14). No structural activity alerts were identified using this model and "the final level of carcinogenicity concern for [the neat polymer] is low." The neat polymer (NPD-14) does not appear on any authoritative or screening lists for carcinogenicity. In addition, the four individual monomer units of the neat polymer are not listed on any authoritative or screening lists for carcinogenicity. 2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0) was the only monomer for which experimental carcinogenicity data were available; no evidence of carcinogenic effects was observed in a 78-week dermal carcinogenicity study in mice. Additionally, no structural alerts were associated with *S. typhimurium* mutagenicity for any of the monomer units using the Toxtree predictive modeling program (Ideaconsult, 2018). The score is assigned with low confidence due to the lack of an actual carcinogenicity bioassay for AG-E060 or NPD-14.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- None.

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- None.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***

- None.

***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **ECHA (2020a)**
  - Researchers exposed C3H/HeNHsd mice (n = 70/males/dose) to 2,2'-ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0) *via* dermal exposure in an acetone vehicle for 78 weeks. Animals were exposed to doses of either 0, 100, 500, or 1,000 mg/kg-day. Treatment with 2,2'-ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0) did not result in any treatment-related changes in hematology, clinical chemistry, body weights, or weight gain. There was a significant increase in mortality in the 1,000 mg/kg-day dose group as well as observed kidney effects (increased kidney weight accompanied by histopathological changes). Epidermal basal cell proliferation at doses greater than or equal to 500 mg/kg-day was consistently increased compared to both control groups at each measurement. The authors determined "[t]here was no relationship between chronic inflammation of the skin and cell proliferation and the induction of skin tumors in normal mouse skin after 78 weeks of treatment although there was evidence of irritation and cell proliferation throughout the treatment period." The No Observed Adverse Effect Level (NOAEL) for carcinogenicity was determined to be 1,000 mg/kg-day.

**Modeled Data**

***NPD-14 (neat polymer ; CAS No. 863408-20-2)***

- **Oncologic™ v.8.0:** The final level of carcinogenicity concern for this polymer is low (US EPA, 2019).

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Toxtree:** No Toxtree structural alerts were identified for *S. typhimurium* mutagenicity (Ideaconsult, 2018).

## Mutagenicity/Genotoxicity (M)

### Score (H, M, or L): L

AG-E060 is assigned a score of Low (**L**) for mutagenicity, with high confidence. This score is based on negative results for the aqueous dispersion in an *in vitro* Ames assay and an *in vivo* mammalian micronucleus test, as well as negative results in an *in vitro* mammalian chromosome aberration test with the neat polymer (NPD-14). The score is assigned with high confidence as it is based on experimental data from multiple well-conducted studies for both the aqueous dispersion and the neat polymer (NPD-14).

Since data were available specific to the polymer substance AG-E060 and the main ingredient NPD-14, data were not evaluated for the associated monomer units.

### Authoritative and Screening Lists

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

### Studies

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **ATCS (2020)**
  - NPD-14 did not induce chromosomal aberrations in a confidential *in vitro* mammalian chromosome aberration test conducted in accordance with Japanese regulatory standard: "III Mutagenicity Test: Chromosomal Aberration Test Using Cultured Mammalian Cells" (2005; K = unknown). Chinese hamster lung fibroblasts (CHL/IU cells) were exposed to NPD-14 at concentrations of 0, 1,250, 2,500, or 5,000 μg/mL with and without S9 metabolic activation.

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - AG-E060[9] was not mutagenic in a confidential *in vitro* bacterial reverse mutation assay (2004; OECD 471; K = unknown), with and without metabolic activation, using *S. typhimurium* strains

[9] The report referred to the test substance as NPD-14, although the authors indicated that it was an aqueous dispersion of the copolymer.

TA 1535, 1537, 98, and 100 and *E. coli* strain WP2uvrA at doses ranging from 50 to 5,000 µg/plate. The substance was tested at concentrations ranging from 100 to 5,000 µg/plate both in the presence and absence of S9 mix. AG-E060 did not induce an increase in revertants at any dose level.

- In a confidential *in vivo* mammalian micronucleus test (2007; OECD 474; K = unknown), AG-E060[10] was not mutagenic. Researchers exposed male CD-1 mice (5/dose) to the test substance twice *via* oral gavage in a phosphate buffered solution vehicle at concentrations of either 0 or 2,000 mg/kg-day approximately 24 hours apart. Bone marrow cells were sampled 24 hours after the final dose administration. The test substance was cytotoxic to the bone marrow cells of mice, but no significant increases in the incidence of micronuclei were observed.

## Reproductive Toxicity (R)

**Score (H, M, or L):** *L*

No experimental reproductive toxicity data are available for AG-E060 or the neat polymer (NPD-14), but high-quality studies of reproductive toxicity were identified for each of the monomer units of the neat polymer (NPD-14). Monomer data are summarized in Appendix B.

AG-E060 is assigned a score of Low (*L*) for reproductive toxicity, with low confidence. Because no data were available for the aqueous dispersion (AG-E060) or the neat polymer (NPD-14), we evaluated reproductive toxicity data for each monomer component, even though they are present below 100 ppm in the product. In combination, these surrogates possess functional groups that may be present on the polymer substance (some may react to form the copolymer and so may not be present) and so can be informative about potential toxicity. The score is based on no observed effects on reproductive parameters in studies for all four monomers (see Appendix B). Although 2-N,N-diethylaminoethyl methacrylate (CAS No. 105-16-8) is present on a screening list for reproductive/developmental toxicity, experimental data for 2-N,N-diethylaminoethyl methacrylate (CAS No. 105-16-8) demonstrates a lack of reproductive/developmental toxicity. The score is assigned with low confidence as it is based on experimental data for all of the monomers from well-conducted studies following Organization for Economic Co-operation and Development (OECD) guidelines with high reliability scores. Additionally, neither AG-E060 nor the neat polymer (NPD-14) is listed as a reproductive toxicant on authoritative or screening lists.

### Authoritative and Screening Lists

***NPD-14 (neat polymer; CAS No. 863408-20-2)***
***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

[10] Referred to as AG-Paper [salt] in the report, although the test substance is described as an aqueous dispersion.

***2-N,N-diethylaminoethyl methacrylate (CAS No. 105-16-8)***

- **Authoritative:** Not listed.
- **Screening:** Japan GHS: Toxic to reproduction – Category 1B: H360 May damage fertility or the unborn child; Korea GHS: Toxic to reproduction – Category 1B: H360 May damage fertility or the unborn child.

**Studies**

***AG-E060 (aqueous dispersion)***
***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- None.

***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***

- **OECD (2001)**
  - A combined repeated dose and reproductive/developmental toxicity screening test (OECD 422) was conducted with Sprague Dawley (Crj:CD) rats (n = 12/sex/dose). Parental animals were administered 0, 30, 100, 300, or 1,000 mg/kg-day of HEMA (CAS No. 868-77-9) *via* oral gavage from 14 days prior to mating for 49 days (males) or until lactational day 3 (females). Six of the twelve females in the 1,000 mg/kg-day group died. No adverse effects of HEMA (CAS No. 868-77-9) were observed on estrus frequency, copulation index, number of conceiving days, fertility index, length of gestation, number of corpora lutea, or gestation index.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Appendix B**
  - See Appendix B for a summary of the reproductive and developmental toxicity studies identified for all four monomers.

## Developmental Toxicity Including Developmental Neurotoxicity (D)

**Score (H, M, or L):** *L*

No experimental or modeled reproductive toxicity data are available for AG-E060 or the neat polymer (NPD-14), but five high-quality studies of reproductive toxicity were identified for the four monomers. Monomer data are summarized in Appendix B.

AG-E060 is assigned a score of Low (*L*) for developmental toxicity, with low confidence because it is based on experimental data with specific monomers in five well-conducted studies following OECD guidelines with high reliability scores. This score is based upon a lack of adverse developmental effects observed across all five studies. Although 2-N,N-diethylaminoethyl methacrylate (CAS No. 105-16-8) is listed on a

screening list, experimental data for the monomer demonstrates a lack of developmental/reproductive toxicity (see Appendix B).

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***
***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***

- **Authoritative:** Not listed.
- **Screening:** Japan GHS: Toxic to reproduction – Category 1B: H360 May damage fertility or the unborn child; Korea GHS: Toxic to reproduction – Category 1B: H360 May damage fertility or the unborn child.

**Studies**

***AG-E060 (aqueous dispersion)***
***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- None.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***

- **ECHA (2020b)**
  - In a prenatal developmental study (2017; K = 1; OECD 414), Wistar rats (n = 22-24 sperm positive females/dose) were exposed to perfluorohexylethyl methacrylate (CAS No. 2144-53-8) *via* oral gavage from gestational day 5 to 19 in an olive oil vehicle. The animals were exposed to concentrations of the test substance of either 0, 100, 320, or 1,000 mg/kg-day. No effects on dam survival were reported, decreased body weight, food intake, and absolute placental weight were observed in high dose animals and a maternal toxicity NOAEL was determined to be 320 mg/kg-day. Decreased relative placental weights were observed at 100 mg/kg-day but not at higher doses, and thus this effect was not attributed to the test substance. Increased pre- and post-implantation loss as well as early/late resorptions were increased at the lowest dose, but due to a lack of a dose-response as well as increased implantations and higher fetal survival than controls in the 1,000 mg/kg-day dose group, these effects cannot be attributed to perfluorohexylethyl methacrylate (CAS No. 2144-53-8). Some fetal effects (decreased body weights and skeletal malformations) were observed in pups from the 1,000 mg/kg-day dose group. However, due to significant maternal toxicity at this dose, these effects cannot be reliably attributed to perfluorohexylethyl methacrylate (CAS No. 2144-53-8).

***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***

- **OECD (2001)**
  - A combined repeated dose and reproductive/developmental toxicity screening test (OECD 422) was conducted with Sprague Dawley (Crj:CD) rats (n = 12/sex/dose). Parental animals were administered 0, 30, 100, 300, or 1,000 mg/kg-day of HEMA (CAS No. 868-77-9) *via* oral gavage from 14 days prior to mating for 49 days (males) or until lactational day 3 (females). Six of the twelve females in the 1,000 mg/kg-day group died. No adverse effects of HEMA (CAS No. 868-77-9) were observed on live pups born, birth index, number of dead pups, number of pups born, delivery index, live birth index, sex ratio, viability index, external anomalies, body weight, necropsy findings, or external anomalies. The NOAEL for developmental toxicity was ≥ 1,000 mg/kg-day.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Appendix B**
  - See Appendix B for reproductive and developmental toxicity studies identified for all four monomers.

## Endocrine Activity (E)

**Score (H, M, or L):** *M*

AG-E060 is assigned a score of Moderate (*M*) for endocrine activity, with low confidence. This endpoint is conservatively assigned a Moderate (*M*) score because only a single endocrine pathway (adrenal) was assessed and one of the monomer units has an EU REACH listing as a potential endocrine disruptor. Although no adverse effects were reported and the neat polymer (NPD-14) does not appear on any authoritative or screening lists for endocrine activity, one monomer unit (perfluorohexylethyl methacrylate [CAS No. 2144-53-8]) is currently under evaluation for "potential endocrine disrupting effects with respect to the environment" (ECHA, 2019). The monomer unit in question appears on the EU REACH Public Activities Coordination Tool (PACT) – Endocrine Disruptor Assessment List of Substances: Under development under substance evaluation (Authority: Germany) and the EU REACH Community Rolling Action Plan (CoRAP)List of Substances as a potential endocrine disruptor. Presence on these lists do not indicate that the substance is endocrine active, just that it is prioritized for investigation. We note that neither of these lists are considered authoritative or screening under GreenScreen guidance. The score is assigned with a low level of confidence because only a single study was identified and one monomer unit is present on EU REACH lists as a potential endocrine disruptor.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***
***2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8)***
***2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9)***
***2,2'-Ethylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

***Perfluorohexylethyl methacrylate (CAS No. 2144-53-8)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.
- **Other:** EU REACH PACT – Endocrine Disruptor Assessment List of Substances: Under development under SEV (Authority: Germany) and EU REACH CoRAP List of Substances: Assigned to Member State Germany (Initial Grounds for Concern: Potential endocrine disruptor).

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - A short-term (28-day) repeated dose oral toxicity study (OECD 407) was conducted with Sprague Dawley (Crj:CD) rats (n = 5/sex/dose). Animals were administered 0, 50, 250, or 1,000 mg/kg-day for 28 days *via* oral gavage in an olive oil vehicle. No adverse effects were reported on adrenal weights at any dose tested.

## Group II and II* Human Health Effects (Group II and II* Human)

*Note*: *Group II and Group II* endpoints are distinguished in the v1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. When classifying hazard for Systemic Toxicity/Organ Effects and Neurotoxicity endpoints, repeated exposure data are required and preferred. Lacking repeated exposure data results in a data gap. Lacking single exposure data does not result in a data gap when repeated exposure data are present (shade out the cell in the hazard table and make a note). If data are available for both single and repeated exposures, then the more conservative value is used.*

### Acute Mammalian Toxicity (AT) Group II – Single

**Score (vH, H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for acute mammalian toxicity, single exposure, with high confidence. This score is based on a well-conducted acute oral toxicity study in rats using the test substance in which median lethal doses ($LD_{50}$) greater than 2,000 mg/kg-bw were reported (greater than would

warrant classification per GHS guidelines). Confidence in this score is high because it is based on reliable experimental data for the test substance.

Since data were available specific to the polymer substance AG-E060, data were not evaluated for the neat polymer (NPD-14) or the associated monomer units.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a confidential acute oral toxicity study (2004; OECD 423), female Sprague Dawley rats (n = 6) were administered a single dose of 2,000 mg/kg-bw of AG-E060[11] *via* oral gavage. No mortality or signs of toxicity were observed during the 14-day observation period. The $LD_{50}$ was determined to be greater than 2,000 mg/kg-bw.

## Systemic Toxicity/Organ Effects Including Immunotoxicity (ST)

### ST Group II – Single

**Score (vH, H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for single exposure systemic toxicity/organ effects including immunotoxicity, with high confidence. This score is based on an acute oral toxicity study conducted in rats in which no adverse effects were reported at values greater than would warrant classification per GHS guidelines. Confidence in this score is high because it is based on reliable experimental data for the test substance.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

[11] Referred to in the report as NPD-14, although it is described in the report as an "extremely pale yellow liquid" which is consistent with how the aqueous dispersion is described in other literature.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In an acute oral toxicity study (2004; OECD 423), female Sprague Dawley rats (n = 6) were administered a single dose of 2,000 mg/kg-bw of AG-E060[12] *via* oral gavage. No mortality or signs of toxicity were observed during the 14-day observation period. Body weight gains were as expected throughout the course of the study, and no abnormalities were noted at necropsy. The NOAEL was determined to be greater than 2,000 mg/kg-bw.

## ST Group II* – Repeated

**Score (H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for repeated exposure systemic toxicity/organ effects including immunotoxicity, with high confidence. This score is based on a NOAEL of greater than 1,000 mg/kg-day in a 28-day repeat oral toxicity study. Because only a 28-day study was available, the GHS guidance values to assist in classification are increased by a factor of 3 to adjust for a shorter duration study. This results in a Category 2 Lowest Observed Adverse Effect Level (LOAEL) threshold of less than or equal to 300 mg/kg-day (United Nations, 2019). The 28-day study did not identify a LOAEL, and the NOAEL is well above 300 mg/kg-day; thus, AG-E060 is not classified under GHS. This score is assigned with a high level of confidence because it is based on reliable experimental data for the test substance.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - A confidential short-term (28-day) repeated dose oral toxicity study (OECD 407, 2005) was conducted with Sprague Dawley (Crj:CD) rats (n = 5/sex/dose). Animals were administered 0, 50, 250, or 1,000 mg/kg-day of AG-E060 for 28 days *via* oral gavage in an olive oil vehicle. No mortality or adverse clinical, histopathological, biochemical, hematological, neurobehavioral, or body/organ weight effects were noted over the duration of the study. The NOAEL was determined to be 1,000 mg/kg-day.

[12] Referred to in the report as NPD-14, although it is described in the report as an "extremely pale yellow liquid," which is consistent with how the aqueous dispersion is described in other literature.

## Neurotoxicity (N)

### Neurotoxicity (N) Group II – Single

**Score (vH, H, M, or L):** NA

AG-E060 is not assigned a score for single exposure neurotoxicity. A lack of single exposure data is not a Data Gap (DG) when repeated exposure data are available.[13]

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- None.

### Neurotoxicity (N) Group II* – Repeated

**Score (H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for repeated exposure neurotoxicity, with high confidence. This score is based on a lack of central nervous system or neurotoxic effects observed across a 28-day repeated dose oral toxicity study conducted in Sprague Dawley rats with the test substance. The NOAEL was determined to be 1,000 mg/kg-day based on no adverse effects for any neurological endpoint, at any dose tested. Because only a 28-day study was available, the GHS guidance values to assist in classification are increased by a factor of 3 to adjust for a shorter duration study. This results in a Category 2 LOAEL threshold of less than or equal to 300 mg/kg-day (United Nations, 2019). The 28-day study did not identify a LOAEL, and the NOAEL is well above 300 mg/kg-day; thus, AG-E060 is not classified under GHS. This score is assigned with a high level of confidence because it is based on reliable experimental data for the test substance.

Since data were available specific to the polymer substance AG-E060, data were not evaluated for the neat polymer (NPD-14) or the associated monomer units.

[13] In that case, the score for repeated exposure hazard classification is entered in the GreenScreen Hazard Summary Table, and the single exposure sub-endpoint cell is shaded out. See GreenScreen Guidance v1.4 (CPA, 2018).

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - A confidential short-term (28-day) repeated dose oral toxicity study (OECD 407, 2005) was conducted with Sprague Dawley (Crj:CD) rats (n = 5/sex/dose). Animals were administered 0, 50, 250, or 1,000 mg/kg-day of AG-E060 for 28 days *via* oral gavage in an olive oil vehicle. During the final week of exposure, animals were assessed for sensorimotor function including reflexes (approach contact/touch response, pinna response, pain response, pupillary reflex, air righting reflex), grip strength, and locomotor activity. No adverse effects for any neurological endpoint, at any dose tested, were reported.

## Skin Sensitization (SnS) Group II* – Repeated

**Score (H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for skin sensitization, with high confidence. This score is based on a lack of effects observed in a mouse local lymph node assay. The score is assigned with a high level of confidence because it is based on reliable experimental data for the test substance. Since data were available specific to the polymer substance AG-E060, data were not evaluated for the neat polymer (NPD-14) or the associated monomer units.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a confidential LLNA skin sensitization study (2006; OECD 429) conducted in CBA/Ca mice (n = 4 females/dose), researchers applied 25 µL of 5, 10, or 30% w/v of AG-E060[14] in acetone

[14] Referred to in the report as AG-Paper.

to the dorsal ear surface for three consecutive days. None of the doses resulted in an increase in isotope incorporation (stimulation indices were reported to be 0.8, 1.0, and 2.1 respectively). The test substance was classified as unlikely to be a skin sensitizer.

## Respiratory Sensitization (SnR) Group II* – Repeated

**Score (H, M, or L):** DG

No experimental data are available for the aqueous dispersion (AG-E060) or the neat polymer (NPD-14) for respiratory sensitization. Therefore, this endpoint was assigned a Data Gap (DG) score.

### Authoritative and Screening Lists

***NPD-14 (neat polymer)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

### Studies

***AG-E060 (aqueous dispersion)***

- None.

## Skin Irritation/Corrosivity (IrS) Group II – Single

**Score (vH, H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for skin irritation/corrosivity, with high confidence. This score is based on a lack of effects in a skin irritation study conducted in rabbits using the test substance. The score is assigned with a high level of confidence because the study upon which it was based was conducted following OECD guidelines.

### Authoritative and Screening Lists

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a skin irritation study (2005; OECD 404) conducted in New Zealand White rabbits (n = 3 unspecified sex/dose), researchers applied AG-E060[15] to a shaved area under semi-occlusive conditions for three minutes and one hour. All scores were zero, and the test substance was classified as a non-irritant.

## Eye Irritation/Corrosivity (IrE) Group II – Single

**Score (vH, H, M, or L): L**

AG-E060 is assigned a score of Low (**L**) for eye irritation/corrosivity, with high confidence. This score is based on a lack of effects in an eye irritation study conducted in rabbits. The score is assigned with a high level of confidence because the study upon which it was based was conducted following OECD guidelines and was of good quality.

Since data were available specific to the polymer substance AG-E060, data were not evaluated for the neat polymer (NPD-14) or the associated monomer units.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a confidential eye irritation study (2005; OECD 405) conducted in white New Zealand rabbits (n = 3) of unspecified sex, a single application of AG-E060[16] was instilled into one eye of each animal and not washed. The rabbits were observed for 72 hours. The test material produced mean skin irritation scores of less than 1 for all measures of ocular irritation. All signs of irritation were fully reversible by 72 hours in all animals. The test substance was determined to be non-irritating to the eye.

[15] Referred to in the report as NPD-14, but described as a "pale yellow liquid," which is consistent with descriptions of the aqueous dispersion in other literature.
[16] Referred to in the report as NPD-14, but described as a "pale yellow liquid," which is consistent with how the aqueous dispersion is described in other literature.

# Ecotoxicity (Ecotox)

## Acute Aquatic Toxicity (AA)

### Score (vH, H, M, or L): M

AG-E060 is assigned a score of Moderate (**M**) for acute aquatic toxicity based on experimental acute algae, invertebrate, and fish toxicity data for the polymer substance. Experimentally derived Median Lethal/Effect Concentration ($LC/EC_{50}$) values were greater than 10 and less than 100 mg/L for all trophic levels. Studies for all three trophic levels were conducted in accordance with Good Laboratory Practice (GLP) and OECD guidelines, and therefore, high confidence is assigned.

Since data were available specific to the polymer substance AG-E060, data were not evaluated for the neat polymer (NPD-14) or the associated monomer units. However, NPD-14 was not listed as an acute aquatic toxicant on any authoritative or screening lists.

#### Authoritative and Screening Lists

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

#### Studies

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a confidential 2006 GLP-compliant algal growth inhibition study (OECD 201; K = not reported), algae (*Pseudokirchneriella subcapitata*) were exposed to a control and measured test concentrations of 0.116, 0.824, 4.26, 24.2, and 107 mg/L in freshwater for 72 hours (three replicates per test level). The test solution was prepared by dilution with eluent tetrahydrofuran (5 mmol/L sodium trifluoroacetic acid)/trifluoroacetic acid 1,000/1 (v/v). A 72-hour $EC_{50}$ of 43.3 mg/L was determined based on reproduction.
  - In a confidential 2005 GLP-compliant acute toxicity study (OECD 202; K = not reported), water fleas (*Daphnia magna*) were exposed to a control and measured (geometric mean) test concentrations of 4.86, 12.6, 26.7, 47.2, and 89.1 mg/L for 48 hours in a semi-static closed system (four replicates per test level; twenty daphnids per test level). A 48-hour $EC_{50}$ of > 89.1 mg/L was determined based on mobility.
  - In a confidential 2005 GLP-compliant acute toxicity study (OECD 203; K = not reported), fish (*Oryzias latipes*) were exposed to a control and measured (geometric mean) test concentrations of 2.69, 7.51, 24.1, 34.3, and 51.2 mg/L for 96 hours in a semi-static closed system (seven fish per test level). A 96-hour $LC_{50}$ of 44.6 mg/L (95% Confidence Interval: 36.5 to 63.5 mg/L) was determined.

**Table 6 Acute Ecotoxicity Data**

| Trophic Level | Test Species | Endpoint (Basis for Effect) | Measured Concentration | Method | Year |
|---|---|---|---|---|---|
| Algae | *Pseudokirchneriella subcapitata* | 72-hour $EC_{50}$ (reproduction) | 43.3 mg/L | OECD 201 | 2006 |
| Invertebrate | *Daphnia magna* | 48-hour $EC_{50}$ (mobility) | > 89.1 mg/L | OECD 202 | 2005 |
| Fish | *Oryzias latipes* | 96-hour $LC_{50}$ | 44.6 mg/L (95% CI: 36.5 to 63.5 mg/L) | OECD 203 | 2005 |

Notes:
95% CI = 95% Confidence Interval; $EC_{50}$ = Median Effect Concentration; JIS = Japanese Industrial Standard; $LC_{50}$ = Median Lethal Concentration; OECD = Organisation for Economic Co-operation and Development Test Guideline.

### Chronic Aquatic Toxicity (CA)

**Score (vH, M, or L):** DG

No experimental or modeled chronic aquatic toxicity data are available for AG-E060 or the neat polymer (NPD-14). Additionally, NPD-14 was not listed as a chronic aquatic toxicant on authoritative or screening lists. Due to the lack of chronic aquatic toxicity data, this endpoint was assigned a Data Gap (DG) score.

#### Authoritative and Screening Lists

- **Authoritative:** Not listed.
- **Screening:** Not listed.

#### Studies

***AG-E060 (aqueous dispersion)***

- None.

***NPD-14 (neat polymer)***

- None.

## Environmental Fate (Fate)

### Persistence (P)

**Score (vH, H, M, or L): vH**

AG-E060 is assigned a score of Very High (**vH**) based on an OECD 316 study that determined the half-life of AG-E060 in water to be 850 days and an OECD 301 C ready biodegradability study for NPD-14, the neat copolymer present in the product at 20% solution, which observed an average of 3% degradation by biochemical oxygen demand (BOD) after 28 days. NPD-14 was not listed as a persistent toxicant on authoritative or screening lists.

**Authoritative and Screening Lists**

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

***AG-E060 (aqueous dispersion)***

- **ATCS (2020)**
  - In a 2015 18-day photolysis study (OECD 316; EPA OPPTS 835.5270; K = not report), the indirect photolysis of NPD-14 in synthetic natural water by artificial sunlight was evaluated. This study was conducted in compliance with GLP with the exception of the "characterization and stability of the test and reference substances under the conditions of storage at the test facility" (ATCS, 2020). A nominal concentration of 2.52 mg/L NPD-14 was exposed to the "average summer solar sunlight" of latitude 30 °N to 50 °N in synthetic humic water. The humic water was prepared with 1.001 g humic acid, 0.1 M $H_2SO_4$, and HPLC-grade water, and then diluted with "sterile 0.01 M phosphate pH 7.0 buffer" (ATCS, 2020). The half-life of NPD-14 in water was determined as 850 days at a pH of 7 and 25 °C.

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

- **ATCS (2020)**
  - In a 2004 GLP-compliant ready biodegradability study (OECD 301 C; K = not reported), degradation of NPD-14 was measured in activated sludge at 25±1 °C. Three vessels of activated sludge were prepared using sludge from four sewage plants and using surface water and surface soil collected from three rivers, one lake, and two bays. After 28 days, the degradation of the initial concentration of 100 mg/L test substance by BOD was measured as 2%, 4%, and 2% in the three vessels, respectively. Therefore, the study concluded that NPD-14 is not readily biodegradable with an average of 3% degradation by BOD after 28 days.

## Bioaccumulation (B)

**Score (vH, H, M, or L): vL**

Data were not available for the polymer substance AG-E060. Thus, data were evaluated for NPD-14, the neat copolymer present in AG-E060 at 20% dispersion. NPD-14 is assigned a score of Very Low (**vL**) for bioaccumulative potential based on experimental bioconcentration data for NPD-14. Reported experimentally derived bioconcentration factors (BCFs) for carp (*Cyprinus carpio)* exposed to two levels of NPD-14 were both less than 100. This study was conducted in accordance with GLP and OECD Guideline 305, and therefore, high confidence is assigned. Additionally, NPD-14 was not listed as a bioaccumulative toxicant on authoritative or screening lists.

***NPD-14 (neat polymer; CAS No. 863408-20-2)***

**Authoritative and Screening Lists**

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

- **ATCS (2020)**
  - In a confidential 28-day, GLP-compliant bioconcentration study (OECD 305; K = not reported) conducted in 2005, carp (*Cyprinus carpio)* were exposed to a control and two exposure levels of NPD-14 (0.01 mg/L and 0.1 mg/L) in a continuous flow system. A 500 mg/L stock solution was prepared with crystallized sugar, 300 mg/L of dispersant Megafac F-142D, and ion-exchanged water. This stock solution was further diluted with ion-exchanged water to prepare 4 mg/L stock solution for the 0.01 mg/L exposure level and to prepare 40 mg/L stock solution for the 0.1 mg/L exposure level. Twenty-nine fish were used in the exposure groups, and twelve fish were used in the control group. Using gas chromatography-mass spectrometry, the BCF for the 0.01 mg/L and 0.1 mg/L exposure groups were determined as 9.1 and $\leq$ 38, respectively.

## Physical Hazards (Physical)

### Reactivity (Rx)

**Score (vH, H, M, or L):** *L*

AG-E060 is assigned a score of Low (*L*) for reactivity, with low confidence. This score is based on the Safety Data Sheet (SDS) for the 20% dispersion, which indicates a National Fire Protection Association (NFPA) instability rating of 1 (unstable if heated). This equates to a GreenScreen score of Low. The score is assigned with low confidence as it is based on an SDS and not experimental data.

**Authoritative and Screening Lists**

- **Authoritative:** Not listed.
- **Screening:** Not listed.

**Studies**

- None. The SDS indicates an NFPA instability of 1 (unstable if heated) (AGC, 2018).

## Flammability (F)

### Score (vH, H, M, or L): *L*

AG-E060 is assigned a score of Low (*L*) for flammability. This score is based on the product SDS, which indicates that the 20% dispersion was assigned an NFPA flammability code of 1 (flashpoint was found to be greater than 220 °C). This equates to a GreenScreen score of Low. The score is assigned with low confidence as it is based on an SDS and not experimental data.

### Authoritative and Screening Lists

- **Authoritative:** Not listed.
- **Screening:** Not listed.

### Studies

- **SDS**
  - According to the SDS for the 20% dispersion, the product was assigned a flammability code of 1, which means that the flashpoint was found to be greater than 220 °C (AGC, 2018).

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# Appendix A

## Hazard Benchmark Acronyms

# *Hazard Benchmark Acronyms*

| | |
|---|---|
| AA | Acute Aquatic Toxicity |
| AT | Acute Mammalian Toxicity |
| B | Bioaccumulation |
| C | Carcinogenicity |
| CA | Chronic Aquatic Toxicity |
| D | Developmental Toxicity |
| DG | Data Gap |
| E | Endocrine Activity |
| F | Flammability |
| IrE | Eye Irritation/Corrosivity |
| IrS | Skin Irritation/Corrosivity |
| M | Mutagenicity and Genotoxicity |
| N | Neurotoxicity |
| P | Persistence |
| R | Reproductive Toxicity |
| rpt | Repeated Dose Exposure |
| Rx | Reactivity |
| sgl | Single Dose Exposure |
| SnS | Sensitization – Skin |
| SnR | Sensitization – Respiratory |
| ST | Systemic/Organ Toxicity |

# Appendix B

## AG-E060 Monomer Unit DART Studies

| Monomers | Reliability/ Test/ Strain/ Species | Dose/ Duration | Reported Results | | Source |
|---|---|---|---|---|---|
| | | | P0 | F1 | |
| Perfluorohexylethyl methacrylate (CAS No. 2144-53-8) | K = 1/ Prenatal Developmental Study/ Han Wistar Rat | 100, 320, 1,000 mg/kg-day *via* oral gavage from GD 5 to 19 | NOAEL = 1,000 mg/kg-day (reproductive) NOAEL = 320 mg/kg-day (maternal body weight and food intake) (maternal) | NOAEL = 320 mg/kg-day (body weight and placental weight) | Development (2017) in ECHA (2020b) |
| 2-N,N-Diethylaminoethyl methacrylate (CAS No. 105-16-8) | K = 1/ Reproductive and Developmental Screening/ Wistar Rat (M/F) | 50, 150, 500 mg/kg-day *via* oral gavage for 54 days (F) and 49 days (M) | NOAEL (F) ≥ 500 mg/kg-day (no effects) NOEL (M) = 500 mg/kg-day (unspecified reproductive performance) | NOAEL = (M/F) ≥ 500 mg/kg-day (no effects) | Repro (1996) in ECHA (2020c) |
| 2-Hydroxyethyl methacrylate (HEMA) (CAS No. 868-77-9) | K = 1/ OECD 422/ Crj:CD(SD) Rat | 30, 100, 300, or 1,000 mg/kg-day *via* oral gavage from 14 days prior to mating through lactation day 4; males for 49 days | NOAEL ≥ 1,000 mg/kg-day (F) (reproductive endpoints). Clinical signs present | NOAEL ≥ 1,000 g/kg-day teratogenicity | Development (1997) in ECHA (2020d) |
| | K = 1/ Reproductive and Developmental Screening/ Crj:CD(SD) Rat | 0, 30, 100, 300, 1,000 mg/kg-day *via* oral gavage 14 days prior to exposure until lactation day 4 (F) or 50 days (M) | NOAEL ≥ 1,000 mg/kg-day | NOAEL ≥ 1,000 mg/kg-day | Repro (1997) in ECHA (2020d) |
| 2,2'-thylenedioxydiethyl dimethacrylate, acetic acid salt (CAS No. 109-16-0) | K = 1/ Reproductive and Developmental Screening/ SD Rat | 100, 300, 1,000 mg/kg-day *via* oral gavage from 14 days prior to mating and 3 weeks after mating (M/F) | NOAEL ≥ 1,000 mg/kg-day | NOAEL ≥ 1,000 mg/kg-day | Repro (2013) in ECHA (2020a) |

Notes:
GD = Gestational Day; NOAEL = No Observed Adverse Effect Level; NOEL = No Observed Effect Level; OECD = Organisation for Economic Co-operation and Development Test Guideline; SD = Sprague Dawley.

# Appendix C

## Malic Acid (CAS No. 6915-15-7) Group I Human Health Effects

| Endpoint | Data | Source |
|---|---|---|
| **Carcinogenicity** | Low (*L*): Malic acid is assigned a score of low for carcinogenicity with low confidence based on no reported lesions in two 104-week feeding studies with limited details on the study results and supported by negative OncoLogic™ modeling results. The score is assigned with low confidence as the feeding studies did not report detailed results on lesions. | |
| **104-week Feeding Studies** | Beagle dogs (n=4/sex/dose) were provided diets supplemented with 0, 500, 5,000, or 50,000 ppm DL-malic acid. No significant lesions were detected upon macro- or microscopic examination, and no dose-dependent changes in absolute or relative organ weights were observed. | TRW/Hazleton Labs (1971), as cited in Fiume (2001) |
| | Charles River rats were fed 0, 500, 5,000, or 50,000 ppm malic acid for 104 weeks. "Significant lesions were not found at gross and microscopic examination." | TRW/Hazleton Labs (1971), as cited in Fiume (2001) |
| **OncoLogic™ Results** | "Low potential to be a significant carcinogen." | US EPA (2019) |
| **Mutagenicity** | Low (**L**): Malic acid is assigned a score of low for mutagenicity with high confidence based on four negative Ames assays and one negative chromosomal aberration study. The score is assigned with high confidence as it is based on multiple well-conducted studies for the chemical of interest. | |
| ***In Vitro*** | Negative in an Ames assay with and without metabolic activation at doses up to 0.001% using *S. typhimurium*. | Litton Bionetics (1974), as cited in Fiume (2001) |
| | Negative in an Ames assay at doses up to 10.0 mg/plate with metabolic activation. | Ishidate *et al*. (1984), as cited in Fiume (2001) |
| | Negative in an Ames assay at doses up to 2,000 µg/plate with and without metabolic activation using *S. typhimurium*. | Al-Ani and Al-Lami (1988), as cited in Fiume (2001) |
| | Negative in an Ames assay at doses up to 0.001% using *S. typhimurium* or at doses up to 0.1% using *S. cerevisiae* with and without metabolic activation. | Litton Bionetics (1974), as cited in Fiume (2001) |
| | Negative in a chromosomal aberration test without metabolic activation using a Chinese hamster fibroblast cell line at doses up to 1.0 mg/mL. | Ishidate *et al*. (1984), as cited in Fiume (2001) |
| **Reproductive Toxicity** | Data Gap (DG): No data were identified. | |
| **Developmental Toxicity** | Low (**L**): Malic acid is assigned a score of low for developmental toxicity with high confidence based on no reported developmental/teratogenic effects at the highest doses tested across three species. The score is assigned with high confidence as it is based on well-conducted studies. | |
| **Teratological Evaluations** | In a US Food and Drug Administration evaluation of malic acid in three animal species (mice, rats, and rabbits) no teratogenic/developmental effects were noted at the highest doses tested in each respective study.<br><br>NOAEL ≥ 266 mg/kg-day in mice<br>NOAEL ≥ 350 mg/kg-day in rats<br>NOAEL ≥ 300 mg/kg-day in rabbits | Food and Drug Research Laboratories, Inc (1974) |
| **Endocrine Activity** | Data Gap (DG): No data were identified. | |