December 19, 2020

Comments from UCSF Program on Reproductive Health and the Environment on the Draft Revised Risk Evaluation for C. I. Pigment Violet 29

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2018-0604-0091

These comments are submitted on behalf of the undersigned academics and scientists from the University of California, San Francisco's Program on Reproductive Health and the Environment. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments.

We appreciate the opportunity to provide written comments on the revised risk evaluation for Pigment Violet 29,[1] issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA"). The law requires that EPA make determinations about chemical risks based on adequate information and the best available science.[2] Unfortunately, despite EPA's assertion to the contrary,[3] the Agency's original risk evaluation, subsequent analyses, and revised risk evaluation for Pigment Violet 29 all continue to fall short of these mandates.

In January 2019 we commented that EPA does not possess adequate data to support its determination that Pigment Violet 29 does not pose an unreasonable risk.[4] In May 2019, we demonstrated more specifically how EPA's risk evaluation was insufficient because of quality deficiencies in its systematic review methodology.[5] In June 2019 we extensively commented on data gaps, which were a major problem in EPA's inhalation analysis for Pigment Violet 29, as the Agency assumed that Pigment Violet 29 was non-toxic and was not absorbed via inhalation without supplying adequate empirical data for such assumptions.[6]

In the revised draft risk evaluation for Pigment Violet 29, EPA has made some substantive changes in response to recommendations and requests from the Scientific Advisory Committee on Chemicals and public comments. For example, the Agency has incorporated a better matched analog for determine inhalation health effects (Carbon Black), although the analog of Carbon Black should be carried to other health endpoints beyond lung overload. However, EPA failed to incorporate other recommendations from the SACC and from expert comments without providing evidence-based justifications. Additionally, this revised draft risk evaluation contains issues which have been pervasive throughout the first 10 evaluations, such as assumptions of complete PPE compliance among workers, the use of a flawed

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[1] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[2] 15 USC §2601 (b)(1) and 15 USC §2625 (h)

[3] US EPA (2020). 02. PV29 Response to Peer Review+Public Comments 10.15.20 Clean Public. **"EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development."**(Pg. 91). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0092

[4] US EPA (2019). Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0014

[5] US EPA (2019). Comment submitted by Hanna Vesterinen, Research Consultant to UCSF PRHE et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0043

[6] US EPA (2019). Comment submitted by Swati Rayasam et al., Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0081

systematic review methodology, and the failure to sufficiently account for "potentially exposed and susceptible subpopulations" as required under amended TSCA.

Our comments on the revised draft risk evaluation address the following main issues:

1. **EPA should use a peer-reviewed, validated systematic review method for chemical evaluations instead of "Application of systematic review in TSCA risk evaluations."**
2. **The Pigment Violet 29 evaluation still does not use a pre-established protocol as required by EPA regulation under TSCA.**
3. **The TSCA method does not have a pre-established protocol or methods for evidence integration as required by EPA regulation under TSCA.**
4. **EPA still does not have adequate information to conclude that Pigment Violet 29 does not pose an unreasonable risk and still failed to assess all relevant health hazards.**
    a. **EPA must consider all relevant health endpoints of its analogue, Carbon Black, not just lung overload. Additionally, the data on Pigment Violet 29 and this analogue are inadequate to conclude that Pigment Violet 29 is not a carcinogen.**
    b. **EPA does not have sufficient evidence to determine that Pigment Violet 29 does not have reproductive/ developmental toxicity due to the methodological inadequacy of BASF's test protocol, the unjustified dismissal of potentially impactful findings in its study, and the lack of power of the OECD 421 screening method to determine lack of toxicity.**
    c. **Using its full authorities under TSCA sections 4 and 8, EPA must request additional test data (compliant with established standards) to fill critical health data gaps for Pigment Violet 29 .**
5. **EPA's use of a hazard test is unsuitable for use in risk assessment, and fails to account for numerous uncertainties, such as potential differences between inhalation and oral exposure routes. Further, EPA should not use MOE (Margin of Exposure) as an analysis method in the risk evaluation process.**
6. **EPA assertions that the revised risk evaluation is protective of workers, consumers, and the general population are not supported by data.**
    a. **EPA still fails to consider and pregnant workers and consumers who are at higher risk, despite listing them as a PESS**
    b. **EPA continues to make assumptions about PPE which are scientifically unsupported**
7. **EPA still assumes that Pigment Violet 29 is non-toxic and not absorbed via inhalation without providing adequate empirical data to support such assumptions and while incorrectly claiming health and safety data as confidential business information (CBI).**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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DETAILED COMMENTS:

1. **EPA should use a peer-reviewed, validated systematic review method for chemical evaluations instead of "Application of systematic review in TSCA risk evaluations."**

Our previous comments provided detailed evidence on the scientific shortcomings of the TSCA method.[7] Briefly, one of the major problems is the TSCA method's inappropriate 'scoring' scheme for rating quality of studies that assigns numerical scores to various study components and then calculates an overall "quality score." The implicit assumption in such quantitative scoring methods is that we understand how much each factor used to evaluate study quality contributes to the overall quality, and that these factors are independent of each other. This is not a scientifically supportable underlying assumption, as researchers have documented that such scoring methods have unknown validity, may contain invalid items, and that results of a quality score are not predictive of the quality of studies.[8] An examination of the application of quality scores in meta-analysis found that quality-score weighting produced biased effect estimates because quality is not a singular dimension that is additive, but may be non-additive and non-linear.[9] A relevant metaphor is the saying "the whole is greater than the sum of the parts," which captures the idea that quantitative measures cannot accurately reflect some qualities. The National Academies of Sciences (NAS) recommended against use of scoring systems, concluding that "… there is no empirical basis for weighting the different criteria in the scores…The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score."[10]

Instead of the unscientific TSCA method, we recommend that EPA adopt and implement one of the three existing empirically-based systematic review methodologies below. Having been peer-reviewed, validated, demonstrated in case studies and recommended for chemical evaluations by the NAS,[11] these are the best available science for systematic review:

- Navigation Guide: Woodruff TJ, Sutton P. *The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes*. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.
- OHAT: National Toxicology Program Office of Health Assessment and Translation. *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration*. National Institute of Environmental Health Sciences; 2015
- Integrated Risk Information System (IRIS): National Academies of Sciences, Engineering, and Medicine. 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086.

[7] US EPA (2019). Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0014

[8] National Research Council. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, D.C.; 2014.

[9] Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics*. 2001;2(4):463-471. doi:10.1093/biostatistics/2.4.463.

[10] National Research Council. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, D.C.; 2014. Pg. 69.

[11] The National Academies of Sciences. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, D.C.: National Academies Press; 2017. doi:10.17226/24758.

While the scoring system in the TSCA method is not empirically based and should not be used, we nonetheless provide analysis in our comments below of how it has been applied in the Pigment Violet 29 evaluation to demonstrate its shortcomings.

2. The Pigment Violet 29 evaluation still does not use a pre-established protocol as required by EPA regulation under TSCA.

EPA has not created a protocol for the Pigment Violet 29 systematic review. This is a critical missing piece because creating protocols for all review components *prior to conducting the review* minimizes bias and ensures transparency in decision-making, and thus is specified as best practice by all established systematic review methods.[12,13,14] Further, a "pre-established protocol" is required by EPA's regulation under TSCA. [15]

Thus, EPA's approach of conducting the Pigment Violet 29 review without a pre-established protocol is in clear violation of scientifically validated approaches to conducting systematic reviews. In its review of the EPA IRIS program's proposed systematic review methods, the NAS specified that "Completing the literature search as part of protocol development is inconsistent with current best practices for systematic review, and the IRIS program is encouraged to complete the public-comment process and finalize the protocol before initiating the systematic review."[16] In the case of the Pigment Violet 29 risk assessment, EPA not only completed the literature search without a complete protocol, it completed the entire systematic review in the absence of a protocol and complete method. It is blatantly biased to write the rules of evidence assembly and interpretation at the same time one is applying the rules, and as such, EPA's review of Pigment Violet 29 cannot be validly referred to as a science-based systematic review.

3. The TSCA method does not have a pre-established protocol or methods for evidence integration as required by EPA regulation under TSCA.

EPA's TSCA regulation governing procedures for chemical risk evaluations requires that it use a systematic review method to "integrate evidence,"[17] but EPA's TSCA method does not address this step, nor does EPA's Pigment Violet 29 risk evaluation.

The ad hoc and incomplete nature of EPA's TSCA method is incompatible with science-based methods of systematic review developed, endorsed, and/or advanced by the: National Academy of Sciences;[18] the Institute of Medicine;[19] the National Toxicology Program;[20] the Cochrane Collaboration;[21] the Grading of

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[12] National Research Council. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, D.C.; 2014.
[13] Institute of Medicine. *Finding What Works in Health Care*. Washington, D.C.: National Academies Press; 2011. doi:10.17226/13059.
[14] Higgins J, Green S. Chapter 2: Preparing a Cochrane review. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1. The Cochrane Collaboration; 2011.
[15] 40 CFR 702.33
[16] National Academies of Sciences, Engineering, and Medicine. 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086. Pg. 8
[17] 40 CFR 702.33
[18] NAS. (2017). Application of Systematic Review Methods in an Overall Stretegy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: The National Academies Press.; 2011
[19] Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Review. Washington, D.C.: The National Academies Press.; 2011
[20] National Toxicology Program Office of Health Assessment and Translation. *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration*. National Institute of Environmental Health Sciences; 2015
[21] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [Updated March 2011]: The Cochrane Collaboration. Available from http://www.cochrane-handbook.org.; 2011.

Recommendations Assessment, Development and Evaluation (GRADE) method;[22] the international scientific collaboration that developed a framework for the "systematic review and integrated assessment" (SYRINA) of endocrine disrupting chemicals;[23] the SYRCLE systematic review method for animal studies;[24] the Campbell Collaboration's methods;[25] and the Navigation Guide systematic review method developed by a collaboration of scientists led by the University of California, San Francisco.[26]

Evidence integration consists of, at minimum, qualitatively rating the confidence in the overall body of evidence for a specific outcome, translating that confidence rating into a conclusion on the level of evidence for a health effect, and then developing a hazard identification conclusion. Where available, animal and human evidence would be integrated, and mechanistic data would be used to inform the final conclusion. Examples from the OHAT method of the translation and hazard identification steps are below.

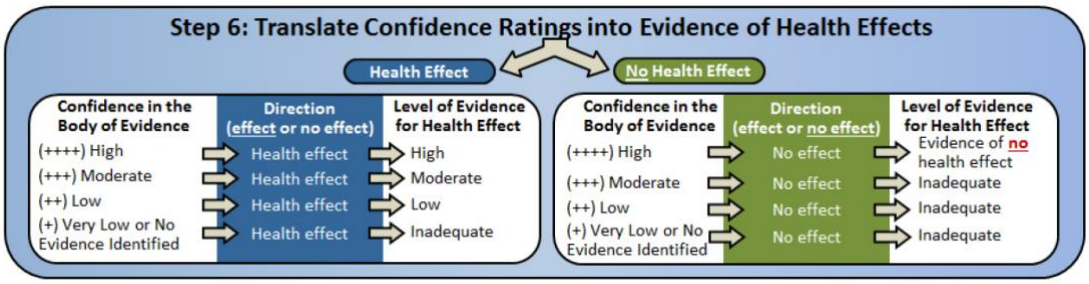

Figure 1: OHAT's process to translate confidence in the body of evidence to come to a conclusion on the level of evidence for a health effect. [27] *This step is missing from the TSCA method.*

[22] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW, Jr., Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). Journal of Clinical Epidemiology. 2011;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017

[23] Vandenberg, L. N., Ågerstrand, M., Beronius, A., Beausoleil, C., Bergman, Å., Bero, L. A., … Rudén, C. (2016). A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. *Environmental Health*, *15*(1), 74. https://doi.org/10.1186/s12940-016-0156-6

[24] Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC medical research methodology. 2014;14:43. Epub 2014/03/29. doi: 10.1186/1471-2288-14-43. PubMed PMID: 24667063.

[25] Campbell Collaboration. Better evidence for a better world. 2018 [cited 2018 July 29]The Campbell Collaboration promotes positive social and economic change through the production and use of systematic reviews and other evidence synthesis for evidence-based policy and practice.]. Available from: https://campbellcollaboration.org/research-resources/writing-a-campbell-systematic-review.html

[26] Woodruff TJ, Sutton P, The Navigation Guide Work Group. An Evidence-Based Medicine Methodology To Bridge The Gap Between Clinical And Environmental Health Sciences. Health Affairs. 2011;30(5):931-7. doi: 10.1377/hlthaff.2010.1219; PMCID: 21555477

[27] National Toxicology Program Office of Health Assessment and Translation. *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration*. National Institute of Environmental Health Sciences; 2015. Pg. 64

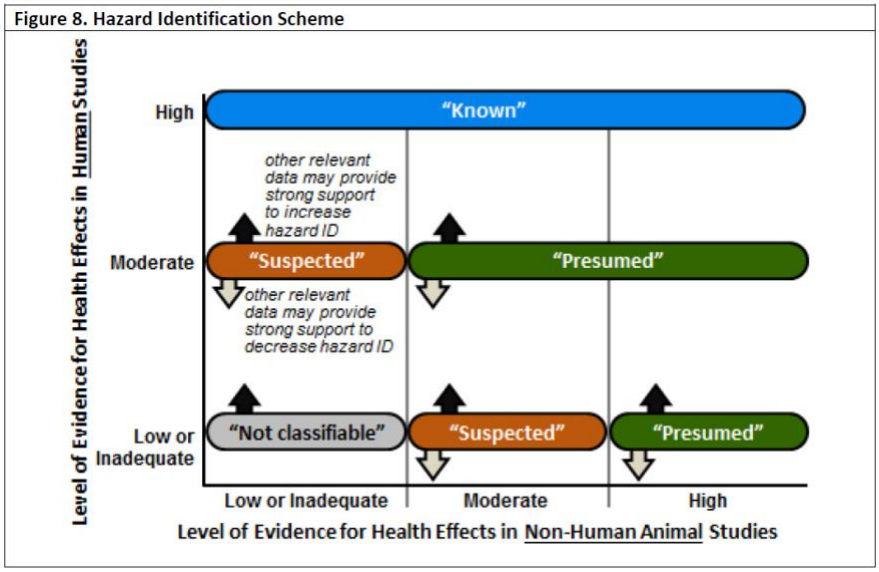

Figure 2: OHAT's process to translate the level of evidence for a health effect into a hazard identification conclusion.[28] This step is missing from the TSCA method.

EPA does not rate the confidence in the body of evidence on Pigment Violet 29, nor does it follow a proper evidence integration protocol to come to its final conclusion that Pigment Violet 29 does not pose an unreasonable risk. Therefore, it is unclear how EPA translated the available evidence into its final conclusion.

4. EPA still does not have adequate information to conclude that Pigment Violet 29 does not pose an unreasonable risk and still failed to assess all relevant health hazards.

TSCA statute[29] and regulation[30] require adequate information to inform the determination of whether a chemical poses an unreasonable risk; regulation requires the evaluation to consider "relevant" potential human and environmental hazards.[31]

Certain health hazards such as "cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects"[32] are specifically designated in TSCA statute, indicating that Congress expressly recognized these types of health effects as an unreasonable risk, and envisioned that EPA should assess them. We have commented before that the previous evaluation did not have sufficient empirical data on the carcinogenicity of Pigment Violet 29, nor on the reproductive or developmental neurotoxicity or endocrine activity, which are relevant to teratogenesis, or on behavioral disorders and birth defects. In fact, the agency only had suitable empirical data for 6 of the 14 health hazards (43%) and identified that critical data were missing for all 4 hazards named by Congress in TSCA statute.[33]

[28] Id. pg. 67
[29] 15 USC §2601 (b)(1)
[30] 40 CFR § 702.41 (b)
[31] 40 CFR § 702.41 (d)(3)
[32] 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)
[33] US EPA (2019). Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0014

a. EPA must consider all relevant health endpoints of its analogue, Carbon Black, not just lung overload. Additionally, the data on Pigment Violet 29 and this analogue are inadequate to conclude that Pigment Violet 29 is not a carcinogen.

We are pleased that EPA for revised its inhalation analogue from Barium Sulfate to Carbon Black, as the analogue is more scientifically appropriate to estimate the risks of Pigment Violet 29 both due to its physical chemistry and its use profile.[34]

One of the major revisions that EPA has made in its revised draft risk evaluation of Pigment Violet 29 is to re-evaluate the inhalation analogue based on updated particle size information obtained through Sun Chemicals; EPA's use of the 0.043um median particle size (Range 0.027-0.080um) is both health-protective and scientifically appropriate. [35] However, based on the revised evaluation, **EPA seems to only have applied its revised particle size to the hazard consideration of lung overload, despite the fact that there have been other documented health concerns around Carbon Black.**

On page 11 of the revised risk evaluation EPA states that "Structural activity relationships (SAR) considerations support EPA's conclusion that C.I. Pigment Violet 29 is **unlikely to be a carcinogen**. Based on the human health and environmental toxicity testing, EPA concludes that C.I. Pigment Violet 29 presents a low hazard to human health from oral and dermal exposure." (emphasis ours)

First, Pigment Violet 29's analogue Carbon Black, which EPA asserts shares many properties with the chemical in question, has been classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to human beings (i.e., group 2B). This is based on sufficient evidence in laboratory animals, limited primarily by inadequate epidemiological evidence for Carbon Black.[36] If Carbon Black is to be used as an inhalation analogue for Pigment Violet 29, it must not just consider how particle size impacts lung overload, but also other health outcomes, particularly outcomes which have been designated as priorities by the statute. Chronic inflammation, which can be caused by ultrafine particles such as Pigment Violet 29 and Carbon Black, is a recognized cancer risk factor by the National Cancer Institute.[37] Carbon Black has also been associated with systemic immune effects,[38] skin and lung cancer,[39,40] and cardiovascular disease.[41]

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[34] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 67. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[35] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 67. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[36] **It is important to note that three of the four epidemiological studies referenced in the IARC Monograph for Carbon Black, Titanium Dioxide, and Talc summary document (Dell et al. 2006, Wellman et al. 2006, Sorahan et al. 2001) were funded by the International Carbon Black Association (ICBA), an industry group that has Carbon Black manufacturers as member companies. We have previously commented how recent studies empirically document that industry sponsorship produces research that is favorable to the sponsor. Available: https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/NAS%20Commnets_TSCA%20SR%20Method_FINAL_0.pdf**

[37] National Cancer Institute. Chronic Inflammation. https://www.cancer.gov/about-cancer/causes-prevention/risk/chronic-inflammation.

[38] Chu C, Zhou L, Xie H, et al. Pulmonary toxicities from a 90-day chronic inhalation study with carbon black nanoparticles in rats related to the systemical immune effects. *Int J Nanomedicine*. 2019;14:2995-3013. Published 2019 Apr 30. doi:10.
2147/IJN.S198376

[39] Baan R, Straif K, Grosse Y, et al. Carcinogenicity of carbon black, titanium dioxide, and talc [published correction appears in Lancet Oncol. 2006 May;7(5):365]. *Lancet Oncol*. 2006;7(4):295-296. doi:10.1016/s1470-2045(06)70651-9

[40] Tsai PJ, Shieh HY, Lee WJ, Lai SO. Health-risk assessment for workers exposed to polycyclic aromatic hydrocarbons (PAHs) in a carbon black manufacturing industry. *Sci Total Environ*. 2001;278(1-3):137-150. doi:10.1016/s0048-9697(01)00643-x

[41] Niranjan R, Thakur AK. The Toxicological Mechanisms of Environmental Soot (Black Carbon) and Carbon Black: Focus on Oxidative Stress and Inflammatory Pathways. *Front Immunol*. 2017;8:763. Published 2017 Jun 30. doi:10.3389/fimmu.2017.00763

Second, EPA is still using genotoxicity data and SAR considerations to designate that Pigment Violet 29 is not a carcinogen, as evidenced on page 68 of the draft risk evaluation:

"The absence of a chronic carcinogenicity study for C.I. Pigment Violet 29 resulted in uncertainty regarding the carcinogenicity of C.I. Pigment Violet 29. Nonetheless, the carcinogenic potential of C.I. Pigment Violet 29 was sufficiently assessed using reasonably available data. This data included two short-term genotoxicity studies … as well as a consideration of the structural activity of the compound, which determined that C.I. Pigment Violet 29 is not likely to be carcinogenic."[42]

This conclusion is still not appropriate. As we have stated above, EPA's choice of analogue has been classified as a carcinogen by IARC, and EPA's Cancer Guidelines[43] establish that (1) negative genotoxic data and SAR considerations alone cannot show that Pigment Violet 29 is not a carcinogen, and (2) additional data is needed to establish that Pigment Violet 29 lacks carcinogenicity.

First, hazard traits are intrinsic properties of chemicals, while bioavailability relates to a chemical's exposure potential. Risk evaluations should assess hazard and exposure separately, and then integrate the information to determine risks, as described in EPA's risk evaluation rule.[44] It is not appropriate for EPA to use "expected negligible absorption and uptake" to dismiss potential carcinogenicity — carcinogenicity hazard can only be demonstrated by data, as described below.

Second, EPA incorrectly classifies Pigment Violet 29 as "**unlikely**" to be a carcinogen, as there is not sufficient available data on Pigment Violet 29 to support this conclusion. (emphasis ours) A determination of "Not Likely to Be Carcinogenic to Humans" according to EPA's Cancer Guidelines requires robust evidence as follows:

> "This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be based on data such as:
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> - animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),
> - convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans,
> - convincing evidence that carcinogenic effects are not likely by a particular exposure route (see Section 2.3), or
> - convincing evidence that carcinogenic effects are not likely below a defined dose range.
>
> A descriptor of "not likely" applies only to the circumstances supported by the data. For example, an agent may be "Not Likely to Be Carcinogenic" by one route but not necessarily by another. In those cases that have positive animal experiment(s) but the results are judged to be

[42] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 68. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[43] US EPA (2005) Guidelines for Carcinogen Risk Assessment. Pp. 84-85. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

[44] 40 CFR §702.41

not relevant to humans, the narrative discusses why the results are not relevant."[45]

Following the criteria established by the EPA, this risk evaluation would need supporting data from male and female animals of at least two species in well-designed and conducted studies to determine that Pigment Violet 29 is **not likely** to be a carcinogen.

In sum, the available data on EPA's choice of analogue (Carbon Black) indicates that Pigment Violet 29 may be carcinogenic and also may have other adverse health impacts. Additionally, the available data on Pigment Violet 29 does not meet the TSCA requirement of the best available science, adequate information, or EPA's own guidelines, to conclude that Pigment Violet 29 does not pose an unreasonable risk. Finally, EPA cannot classify Pigment Violet 29 as an unlikely carcinogen.

b. EPA does not have sufficient evidence to determine that Pigment Violet 29 does not have reproductive/ developmental toxicity due to the methodological inadequacy of BASF's test protocol, the unjustified dismissal of potentially impactful findings in its study, and the lack of power of the OECD 421 screening method to determine lack of toxicity.

In our previous comments to EPA we outlined why the Agency's choice of the OECD Guideline 421: Reproduction/Developmental Toxicity Screening Test, conducted by BASF,[46] to determine Pigment Violet 29's human health hazard was invalid. However, in the Agency's response to our comments it stated:

"EPA believes that OECD 421 is adequate to determine whether additional reproductive testing is necessary. As no significant adverse effects were observed in the study, EPA believes that this provides justification that no additional reproductive testing is necessary."[47]

While we disagree with the Agency's assertion on the adequacy of OECD 421 to determine that no additional reproductive testing is necessary, it is critical to restate that **BASF did not conduct OECD 421 properly**, so even if the screening test was sufficient (which it is not), the test, as conducted by BASF and used by EPA for this revised risk evaluation, is still insufficient.

The length of the study according to the OECD 421 Guideline Test Protocol should be as follows:

> "Duration of study, following acclimatisation and pre-dosing oestrous cycle evaluation, is dependent on the female performance and is approximately 63 days, [at least 14 days premating, (up to) 14 days mating, 22 days gestation, **13 days lactation**]."[48] (emphasis added)

But, as we stated in our previous comments, the length of the study carried out by BASF was **9 days too short** as it only covered 4 days of lactation:

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[45] US EPA (2005) Guidelines for Carcinogen Risk Assessment. Pp. 84-85. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

[46] Study summary provided as attachment 14 to US EPA, Signed PV29 SACC Transmittal Memorandum November 11, 2018 Final: Toxicity to Reproduction 2013 Available: https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPPT-2018-0604-0002&attachmentNumber=14&contentType=pdf

[47] US EPA (2020). 02. PV29 Response to Peer Review + Public Comments 10.15.20 Clean Public. **"EPA believes that OECD 421 is adequate to determine whether additional reproductive testing is necessary. As no significant adverse effects were observed in the study, EPA believes that this provides justification that no additional reproductive testing is necessary."** (Pg. 88). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0092

[48] OECD (2016) Test No. 421: Reproduction/Developmental Toxicity Screening Test. Pg. 2 Available: https://www.oecd-ilibrary.org/environment/test-no-421-reproduction-developmental-toxicity-screening-test_9789264264380-en

> "The duration of treatment covered premating period of 2 weeks and a mating period (max. of 2 weeks) in both sexes, approximately 1 week post-mating in males, and the entire gestation period as well as **4 days of lactation in females**."[49] (emphasis added)

As described below, the screening test is already too short to detect many critical post-natal effects; and BASF's further shortening of the post-natal study period is an improper deviation from the study protocol and likely resulted in potentially missing significant developmental effects. Thus, additional developmental testing is necessary before EPA can make a confident determination of no significant adverse effects.

Second, EPA concluded that the OECD 421 test did not report toxicity effects, however, the test did find toxicity, as there were major, statistically significant changes in body weight that were improperly disregarded:

> "The mean body weight gain of the F0 males in test group 2 in the entire premating phase was decreased (-37.4%). The mean body weight gain of the F0 females in test group 1 in the gestation period from study day 7 to 14 was increased (+24.2%). Because of single incidences and no dose response relationship these findings were assessed as being incidental."[50]
> (Note that test group 2 is the 300 mg/ kg bw/ d treatment condition and test group 1 is the 100 mg/ kg bw/ d treatment condition)

EPA's dismissal of the above finding as incidental is not supported by the evidence, as it is well known that males and females may exhibit sexually dimorphic responses. Further, non-monotonic dose-effect functions are common in toxicity studies, especially when endocrine pathways are involved, so the lack of traditional dose-response also cannot be used to dismiss the finding.[51,52]

Finally, the OECD 421 test protocol, EPA's own Guidelines for Developmental Toxicity Risk Assessment, and Guidelines for Reproductive Toxicity Risk Assessment clearly establish that: (1) on its own, the OECD 421 Guideline Reproduction/ Developmental Toxicity Screening test **cannot show that Pigment Violet 29 is not a reproductive or developmental toxicant** and (2) additional data is needed to establish that Pigment Violet 29 lacks reproductive/ developmental toxicity. Despite this, EPA has continued to ignore the established limitations of this test protocol and inappropriately used the data to conclude that Pigment Violet 29 does not cause reproductive or developmental toxicity.

The OECD 421 test protocol, as well as EPA's OPPTS 870.3550 guideline test protocol which the BASF study references, both contain this important note about major limitations of the protocol:

> "This test does not provide complete information on all aspects of reproduction and development. In particular, it offers only limited means of detecting post-natal manifestations of pre-natal exposure, or effects that may be induced during post-natal exposure. Due (amongst other reasons) to the relatively small numbers of animals in the dose groups, the selectivity of

[49] Study summary provided as attachment 14 to US EPA, Signed PV29 SACC Transmittal Memorandum November 11, 2018 Final: Toxicity to Reproduction 2013. Pg. 3 Available: https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPPT-2018-0604-0002&attachmentNumber=14&contentType=pdf

[50] Study summary provided as attachment 14 to US EPA, Signed PV29 SACC Transmittal Memorandum November 11, 2018 Final: Toxicity to Reproduction 2013. Pg. 6.

[51] Vandenberg LN (2013) Non-Monotonic Dose Responses in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study. Dose-Response. 12(2):259-276.

[52] Vandenberg. Birnbaum LS (2012) Environmental Chemicals: Evaluating Low-Dose Effects. Environ Health Perspectives. 120(4):a143-a144

the end points, and the short duration of the study, **this method will not provide evidence for definite claims of no effects**."[53] (emphasis added)

Developmental toxicity

EPA's Guidelines for Developmental Toxicity Risk Assessment[54] note that, in general, short-term developmental toxicity tests (such as OECD 421) are not suitable for use in risk assessment.

> "The need for short-term tests for developmental toxicity has arisen from the need to establish testing priorities for the large number of agents in or entering the environment, the interest in reducing the number of animals used for routine testing, and the expense of testing. These approaches may be useful in making preliminary evaluations of potential developmental toxicity, for evaluating structure activity relationships, and for assigning priorities for further, more extensive testing… **However, the Agency currently considers a short-term test as "insufficient" by itself to carry out a risk assessment."**[55] (Emphasis added)

Further, the Guidelines go on to state that the specific protocol used to test Pigment Violet 29 (OECD 421) is not suitable for use in risk assessment:

> "Recently, the OECD developed a screening protocol to be used for prioritizing existing chemicals for further testing (draft as of March 22, 1990). This protocol is similar to the design of the Chernoff-Kavlock test except that it involves exposure of male and female rats 2 weeks prior to mating, throughout mating and gestation, and postnatally to day 4. Male animals are exposed following mating for a period corresponding to that of the females. Adult animals are evaluated for general toxicity and effects on reproductive organs. Pups are counted, weighed, and examined for any gross physical or behavioral abnormalities at birth and on postnatal day 4. This protocol permits evaluation of reproductive and developmental toxicity following repeated dosing with an agent, **provides an indication for the need to conduct additional studies**, and provides guidance in the design of further studies. **Currently, this study design is insufficient by itself to make an estimate of human risk without further studies to confirm and extend the observations.**"[56] (Emphasis added)

The Guidelines also describe the evidence needed to make a determination on developmental toxicity:

> "The minimum evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single, appropriate, well-conducted study in a single experimental animal species. **The minimum evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory animal studies in several species (at least two) which evaluated a variety of the**

[53] OECD (2016) Test No. 421: Reproduction/Developmental Toxicity Screening Test. Pg. 2.
[54] US EPA (2000) Health Effects Test Guidelines, OPPTS 870.3550 Reproduction/ Developmental Toxicity Screening Test. Pg. 1. Available: https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/epa/epa_870_3550.pdf
[55] US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pg. 19. Available: https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf
[56] US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pg. 20-21. Available: https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult."[57] (Emphasis added)

The OECD 421 test does not meet the minimum evidence criteria for a number of reasons, including that the protocol was not followed and important manifestations of developmental toxicity, especially developmental neurotoxicity, were not assessed. This is critical as Congress was expressly concerned with "behavioral disorders" in TSCA statute. (Point 4) EPA cannot and should not be making determinations about Pigment Violet 29's developmental toxicity hazards based on the current data available.

Reproductive toxicity

EPA's Guidelines for Reproductive Toxicity Risk Assessment note that a prolonged treatment period is required to assess reproductive effects:

> "To evaluate adequately the potential effects of an agent on the reproductive systems, a prolonged treatment period is needed. For example, damage to spermatogonial stem cells will not appear in samples from the cauda epididymis or in ejaculates for 8 to 14 weeks, depending on the test species. With some chemical agents that bioaccumulate, the full impact on a given cell type could be further delayed, as could the impact on functional endpoints such as fertility. In such situations, adequacy of the dosing duration is a critical factor in the risk assessment."[58]

In OECD 421, the treatment period is approximately 4 weeks for males and 2 months for females- which is inadequate based on the criteria in the Guidelines.[59]

The Guidelines specifically note that screening tests (including OECD 421) limited to one generation are not suitable for risk assessment:

> "Several shorter-term reproductive toxicity screening tests have been developed. Among those are the Reproductive/Developmental Toxicity Screening Test, which is part of the OECD's Screening Information Data Set protocol (Scala et al., 1992; Tanaka et al., 1992; OECD, 1993a), a tripartite protocol developed by the International Conference on Harmonization (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use, 1994; Manson, 1994), and the NTP's Short-Term Reproductive and Developmental Toxicity Screen (Harris, M.W. et al., 1992). **These protocols have been developed for setting priorities for further testing and should not be considered sufficient by themselves to establish regulatory exposure levels.** Their limited exposure periods do not allow assessment of certain aspects of the reproductive process, such as developmentally induced effects on the reproductive systems of offspring, that are covered by the multigeneration reproduction protocols."[60] (Emphasis added)

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[57] US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pg. 40. Available: https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

[58] US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Pp. 7 Available: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

[59] OECD (2016) Test No. 421: Reproduction/Developmental Toxicity Screening Test.

[60] US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Pg. 12

The Guidelines describe the evidence needed to make a determination on reproductive toxicity:

> "The minimum evidence necessary to determine if a potential hazard exists would be data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species**. The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect**. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence."[61] (Emphasis added)

The OECD 421 test does not meet the minimum evidence criteria. EPA needs multiple, well-conducted studies with more than one species, with protocols including at least 2 generations and sufficiently long treatment periods. EPA cannot make a determination on Pigment Violet 29's reproductive toxicity hazards based on the current data available.

c. Using its full authorities under TSCA sections 4 and 8, EPA must request additional test data (compliant with established standards) to fill critical health data gaps for Pigment Violet 29 .

Although EPA revised its risk evaluation on Pigment Violet 29 to better address critical data gaps and qualified uncertainties[62] around critical endpoints in the revised risk evaluation,[63] it still attempts to make risk determinations without sufficient data. The Agency states on page 75 of the revised evaluation that "Because the exposure estimates and hazard assessment for inhalation exposures to C.I. Pigment Violet 29 are considered to be of high uncertainty and low confidence, the confidence in the risk estimation is considered to be low."[64] We as well agree that the evaluation has too much uncertainty, and that EPA did not go far enough in using its authority to request data to study health hazards and develop better exposure and toxicity data for Pigment Violet 29. We strongly recommend that EPA apply its analog of Carbon Black to all health endpoints (point 4a); where there continue to critical data gaps for which there is no data from either Pigment Violet 29 or Carbon Black, EPA should use its full authority under sections 4 and 8 of TSCA to request additional test data for Pigment Violet 29 to fill those gaps.

Additionally, where EPA did request and use industry-submitted data, such as with Sun Chemical's acute inhalation analogue study, the data submitted had limitations, was not collected in a manner consistent with EPA's test order study plan nor was compliant with the NIOSH 0600 test guideline.[65,66,67] This

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[61] Id. pp. 72

[62] US EPA (2020). 02. PV29 Response to Peer Review + Public Comments 10.15.20 Clean Public. **"**In EPA's comments: **"EPA obtained all reasonably available data for C.I Pigment Violet 29 and issued a TSCA Section 4(a)(2) Test Order for C.I. Pigment Violet 29 to address critical data gaps in the assessment. Other data gaps, such as environmental hazard testing with aquatic species and inhalation toxicity testing, were addressed by using analogue toxicity data or with QSAR modeling."** (Pg. 88). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0092

[63] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 70. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[64] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 75. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[65] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 53-54. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[66] Sun Chemicals. (2020). Enclosure 1 - EPA request for additional information in response to SACC peer reviewer and including public comments on the draft C.I. Pigment Violet 20 Risk Evaluation.

[67] NIOSH (1998). PARTICULATES NOT OTHERWISE REGULATED, RESPIRABLE 0600. Manual of Analytical Methods (NMAM), Fourth Edition. Available: https://www.cdc.gov/niosh/docs/2003-154/pdfs/0600.pdf

appears to have led to methodological uncertainties, in addition to the fact that as an exposure assessment it still fails to provide EPA with sufficient subchronic data around the chemical of interest, both of which may have led EPA to underestimate the risk to workers. Considering that EPA still found unreasonable risk to workers despite limitations which may have skewed the data to underestimation, it would behoove the Agency to request new data which is compliant with the above to adequately characterize Pigment Violet 29's risks to workers (an identified PESS in this evaluation) as they are required to do under TSCA.

We again recommend that EPA should request, at a minimum, additional and sufficient testing data on the Pigment Violet 29 acute inhalation toxicity (compliant with established standards), respiratory sensitization, reproductive and developmental toxicity (including developmental neurotoxicity), neurotoxicity, repeated dose toxicity, and endocrine activity to ensure it has adequate information to complete the risk evaluation.

EPA must issue orders pursuant to TSCA Section 4 and/or Section 8 to obtain these missing data based on existing standards such those described in the Developmental Toxicity, [68] Reproductive Toxicity, [69] and Cancer Guidelines. [70]

5. **EPA's use of a hazard test is unsuitable for use in risk assessment, and fails to account for numerous uncertainties, such as potential differences between inhalation and oral exposure routes. Further, EPA should not use MOE (Margin of Exposure) as an analysis method in the risk evaluation process.**

As we note in point 4 above, EPA has insufficient data to conclude that PV 29 does not present an unreasonable risk. Further, each element used in the calculation (hazard, exposure, MOE) has fundamental scientific flaws, rendering the estimate and comparison to the MOE unreliable. EPA should use health protective defaults and probabilistic risk estimates, as the current risk estimate cannot show that Pigment Violet 29 does not pose unreasonable risks nor adequately quantify the level of risk without potentially underestimating.

In the Agency's response to our comments it identified that it tried to select "uncertainty factors that are more appropriate given the limitations of the reasonably available data for PV29,"[71] however considering Pigment Violet 29's potential for carcinogenicity (see Point 4a), EPA's rationale for selecting an adjustment/uncertainty factor of 1 to account for extrapolation from a subchronic to chronic exposure duration is not scientifically supported.[72] Additionally, it is crucial to point out especially for Pigment Violet 29, that OPPT does not incorporate an adjustment factor for data deficiencies. This

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[68] US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Available: https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

[69] US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Available: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

[70] US EPA (2005) Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-03/001FMarch 2005

[71] US EPA (2020). 02. PV29 Response to Peer Review + Public Comments 10.15.20 Clean Public. **"EPA acknowledges these comments and has attempted to explain the additional assumptions used in the calculations of the MOEs used in the final Risk Evaluation. This includes selecting uncertainty factors that are more appropriate given the limitations of the reasonably available data for PV29."** (Pg. 103). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0092

[72] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 71. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

contradicts Agency guidance which recommends a factor to account for data deficiencies .[73,74] We would recommend at the minimum that this adjustment factor be set at the maximum default of 10.

Hazard

EPA used the OECD 421 reproductive/ developmental toxicity screening test to develop the POD (point of departure) for the risk estimate. First, as detailed in point 4b above, the OECD 421 test is insufficient for use in risk assessment for multiple reasons, including but not limited to: it did not assess critical developmental toxicity endpoints; the duration of exposure was too short; and the test only assessed one generation. Second, EPA considered the highest test dose (1000 mg/ kg/ day) as the NOAEL (no observed adverse effect level) for the POD, when significant adverse effects (body weight changes) were seen at the lower dose levels (100 and 300 mg/ kg/ day). Third, the OECD 421 hazard test was conducted using oral exposure, but the exposure routes assumed by EPA for the risk calculation are inhalation and dermal. EPA did not conduct route-to-route extrapolation or otherwise account for this critical issue. For these reasons, the POD EPA used is still inaccurate.

Health-protective defaults

We strongly support the use of health protective science-based defaults to incorporate factors that reflect the range of variability and susceptibility in the population to ensure risks are not underestimated. The importance of using protective science-based defaults was highlighted by the NASEM in 2009.[75] The default should be used for factors known to influence risk unless there is chemical-specific data that support increasing or decreasing such factors; when there is inadequate information to quantitatively assess inter- or intra-species differences for a specific chemical, the defaults should be used. For example, current methods do not account for *in utero* susceptibility to chemical exposures, despite ample scientific literature demonstrating increased sensitivity among developing fetuses and the potential for fetal origins of disease.[76,77,78] EPA's defaults should include:

- Intra-human variability, general;
- Intra-human susceptibility to carcinogens, adult;
- Intra-human susceptibility to carcinogens, early life (including prenatal);
- Intra-human susceptibility to non-carcinogens, early life (including prenatal);
- Animal findings as they are relevant to humans; and
- Findings from one route of exposure are considered representative unless data show otherwise

EPA has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. But newer science demonstrates that EPA's typical safety factor of 10 is insufficient to account for variability due to life stage, genetics, underlying

[73] US EPA (2002). A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-02/002F,.

[74] US EPA (2005) Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-03/001FMarch 2005

[75] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Ch 4-6

[76] Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev. 2017;75:951–70.

[77] Dzubow R, Fields C, Ginsberg G, Sandy M, Mabson M, Foos B. Comparison of carcinogenic potency across life stages: implications for the assessment of transplacental cancer risk. J Toxicol Environ Health Part A. 2019;82:769–87.

[78] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

disease status, and external stressors that may be due to poverty or other difficult life conditions. For cancer, the NASEM found that a factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses.[79]

Similarly, the science describing early-life vulnerability to carcinogens has advanced. California EPA's (Cal EPA) guidance for incorporating differential susceptibilities to carcinogens and non-carcinogens incorporates more recent science on increased susceptibility during the prenatal period and age-related susceptibility for non-mutagenic carcinogenic agents.[80] Its literature review on differential susceptibility to carcinogens and non-carcinogens based on age and life stage derived age adjustment values for carcinogens which include the prenatal period[81] and increased the default intraspecies uncertainty factors for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity.[82] The Cal EPA default factor can then be modified upwards or downwards depending on chemical specific information (*e.g.*, for benzene because of variability in metabolism and other sensitivities the non-cancer variability is 100). At a minimum, EPA should start with using Cal EPA's age adjustment values and intraspecies uncertainty factors for incorporating age/early life susceptibility. Cal EPA also developed child-specific risk values for chemicals (e.g., atrazine, lead, nickel, manganese, heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.[83] EPA should review these additional evaluations and incorporate these values as appropriate to the baseline of 30 and 100. **Furthermore, a default guidance principle should be that animal findings are relevant to humans unless there is sufficient and compelling information to support otherwise.**

Risk estimates

Thus far in the risk evaluation process, EPA has incorrectly treated the no-observed-adverse-effect-level (NOAEL) as if it is a *no/zero* effect level.[84] However, NOAELs are not zero response concentrations; they are a concentration at which there is not an observable response in the experiment. The Benchmark Dose (BMD) or its statistical lower limit (BMDL) should be used instead of a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), since NOAELs and LOAELs are limited by the dose groups tested, are not informed by the shape of the dose-response relationship, can be highly influenced by study design, and have been shown to represent levels of risk (e.g. NOAEL typically represents up to a 10% response).[85,86] The POD (*i.e.*, BMDL) is divided by a set of adjustment factors (AF) related to a) variability between humans and the experimental animals (inter-species variability), b)

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[79] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Pg. 168

[80] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

[81] California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. http://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[82] Cal EPA 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels. http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf

[83] California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds

[84] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

[85] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

[86] Despite extensive literature documenting the inadequacy of using the NOAEL/LOAEL approach in chemical risk assessment, NOAELs and LOAELs have been traditionally used and are the only values available in certain cases (*e.g.*, when lack of model fit precludes BMD estimation). Thus, NOAELs and LOAELs are commonly used in risk assessment documents.

variability among humans, including more susceptible and vulnerable humans (intra-species variability), and c) study or database limitations, including use of measured/higher doses to extrapolate to unmeasured/lower doses (*i.e.*, LOAEL-to-NOAEL); use of short-term toxicity data to inform more chronic toxicity endpoints (*i.e.*, subchronic-to-chronic); and an incomplete database (*i.e*., database uncertainty). There are multiple methodological reasons that an effect may not be observed, including low statistical power and inadequate statistical analysis. An empirical comparison of NOAELs and BMRs finds that the average NOAEL approximates the dose that represents a 1–5% Benchmark Response (BMR),[87] while some NOAELs are more similar to a 10% BMR.[88] Thus, it is more appropriate to assume that NOAELs are more similar to a 5-10% benchmark response.

EPA already recognizes the features that make BMDs superior: BMDs account for the shape of the dose–response function; are independent of study design, such as the space between dosing; and are comparable across chemicals.[89] This failure to assess a chemical's risk to the general population is of particular concern. For calculating cancer or non-cancer risks, we recommend using a point of departure (POD) of a benchmark dose (BMD) at 1%. The POD should be based on a BMD calculation, not the NOAEL/LOAEL, unless the data are insufficient to model. EPA should be calculating BMD as well as the risk-specific dose, and if it does not have sufficient data to calculate the risk levels then the Agency should state that clearly rather than relying on NOAELs, which as mentioned before are subject to study design and interpretation.

Additionally, we have previously stated our concerns with how EPA is using factors to adjust for scientific uncertainties in the risk (referred to by EPA as uncertainty factors). The first issue is that the term uncertainty factor does not reflect the variability and adjustment elements that the factor represents. This issue is discussed by the NASEM report *Science and Decisions* on page 132:

> *"Another problem posed by the current noncancer framework is that the term uncertainty factors is applied to the adjustments made to calculate the RfD to address species differences, human variability, data gaps, study duration, and other issues.* ***The term engenders misunderstanding: groups unfamiliar with the underlying logic and science of RfD derivation can take it to mean that the factors are simply added on for safety or because of a lack of knowledge or confidence in the process.*** *That may lead some to think that the true behavior of the phenomenon being described may be best reflected in the unadjusted value and that these factors create an RfD that is highly conservative. But the factors are used to adjust for differences in individual human sensitivities, for humans' generally greater sensitivity than test animals' on a milligrams-per-kilogram basis, for the fact that chemicals typically induce harm at lower doses with longer exposures, and so on. At times, the factors have been termed safety factors, which is especially problematic given that they cover variability and uncertainty and are not meant as a guarantee of safety."*[90] *(emphasis ours)*

[87] Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994. Dose–response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with no observed adverse effect levels. Fundam Appl Toxicol. 23:487–495.

[88] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, et al.2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environ Health Perspect 122(5):499–505.

[89] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

[90] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Pp 132. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

"Uncertainty factors" are generally used to make adjustments to the dose-response. Therefore, rather than uncertainty factors, these should really be thought of as "uncertainty **and** adjustment factors", as per their function within a dose-response assessment.

Second, EPA has been setting its Margin of Exposure (MOE) at 100 and calculating it as shown for example in the 1-bromopropane draft risk evaluation. We have previously detailed why MOE is not an appropriate approach for risk characterization. [91]

$(UF_S=1) \times (UF_A=10) \times (UF_H=10) \times (UF_L=1)^3 = 100$
Total UF=Benchmark MOE=100

UF_S - Subchronic to chronic "uncertainty factor"
UF_A - Interspecies "uncertainty factor"
UF_H - Intraspecies "uncertainty factor"
UF_L - LOAEL to NOAEL "uncertainty factor"

Based on the above calculation, EPA is only adjusting for animal and human variability (Inter- and Intraspecies), and by setting the UF_L and UF_s at 1, the Agency indicates that there is no need to adjust from either less chronic NOAELs to chronic NOAELs or from LOAELs to NOAELs. Reiterating the above issue, EPA is treating NOAEL as if it represents *no effect*, rather than *no observed effect,* even though Wignall et al. demonstrated that NOAEL can represent upwards of 10% of the BMR. Thus, any application of uncertainty factors to assess risks should include at least a combined value of greater than 1,000.

Third, while *Science and Decisions* acknowledged single-value "uncertainty factors" may sometimes be preferable either out of necessity or reflecting science-policy choices, a 2007 Science Advisory Board recommended that EPA "incrementally replace the current system of single-point uncertainty factors with a set of distributions, using probabilistic methods." [92] In *Science and Decisions,* NAS stated "Use of default distributions for adjustments in extrapolations, rather than default point-estimate uncertainty factors, provides an improved representation of variability and uncertainty and offers an opportunity for further refinements and incentives to gather and analyze existing information and to generate new data targeted to specific extrapolation needs." [93] In testing the feasibility and implications of replacing traditional reference doses with probabilistic estimates (as recommended by NAS), Chiu et al. found that in comparison to traditional methods, these estimates provided a more consistent, scientifically rigorous, and transparent basis for risk management decisions.[94] These methods can also be applied to a multitude of decision-making contexts such as benefit-cost analysis and life-cycle impact analysis. We recommend that EPA not use the MOE or RfD/RfC as they do not reflect risk-based values that were recommended by the NAS and have been used as described above. With so little data and so

[91] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[92] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Pp 294. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[93] Id. Pp 174.

[94] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environ Health Perspect. doi:10.1289/EHP3368.

much uncertainty for Pigment Violet 29, EPA's MOE and risk estimates cannot reliably be used and it should employ such probabilistic methods in place of these single point "uncertainty factors" and MOE.

6. EPA assertions that the revised risk evaluation is protective of workers, consumers, and the general population are not supported by data.

In EPA's response to our previous public comment, the Agency addressed our above concern by pointing to section 2.4.1. of the revised risk evaluation, where the Agency has tables that list Percentage of Employed Persons by Age, Sex, and Industry Sector.[95] While these tables describe the percentage of employed workers and occupational non-users who may be considered potentially exposed and susceptible subpopulations **within** select industry sectors relevant to EPA's Pigment Violet 29 occupational conditions of use, this still doesn't account for exposures to the susceptible general population or consumers, contrary to the Agency's statement that **"**EPA is confident that its risk determination is protective of potentially exposed or susceptible subpopulations identified in this risk evaluation." [96]

a. EPA still fails to consider and pregnant workers and consumers who are at higher risk, despite listing them as a PESS

EPA only identifies acrylic paint and watercolor as a potential consumer use for Pigment Violet 29, and despite the limited evidence base, concludes that this use does not pose an unreasonable risk despite a lack of evidence to support this claim (aside from referencing Pigment Violet 29's physical and chemical properties).

First, although the use outlined is in watercolor and acrylic artist paint, EPA's assertions about Pigment Violet 29's risk is based entirely on its properties as a neat material and not as a part of a paint product. It is entirely possible to see potential inhalation, dermal, and oral exposures to this chemical under this condition of use. Second, EPA categorized consumers as a PESS,[97] however when looking at consumer uses, the Agency failed to develop quantitative risk estimates, and determined that this use of Pigment Violet 29 posed no potential unreasonable risk, despite a key uncertainty being a lack of monitoring studies. EPA has continued this pattern of declaring unreasonable risk (a final agency action) as a default response when confronted with lack of data, which is not scientifically supported.

There is concern for Pigment Violet 29 causing reproductive/ developmental toxicity based on the OECD 421 screening test that showed effects caused by treatment, and also the listing of Pigment Violet 29 as of potential concern for reproductive toxicity on the Danish advisory list for self-classification (see Appendix B).[98] In this case, pregnant women and children would be more susceptible to toxicity, and could experience adverse impacts at exposure levels far less than the worker exposures, as early life development is highly sensitive to disruption by toxic chemicals.

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[95] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[96] US EPA (2020). 02. PV29 Response to Peer Review+Public Comments 10.15.20 Clean Public. "**EPA is confident that its risk determination is protective of potentially exposed or susceptible subpopulations identified in this risk evaluation**."(Pg. 96). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0092

[97] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 78. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[98] Data Commons Profile for Pigment Violet 29. Available: https://commons.healthymaterials.net/chemicals/2028146

EPA's revised evaluation employs the more accurate inhalation analog of Carbon Black, which is an improvement with regard to assessing occupational health concerns. Based on the data submitted to EPA by Sun Chemical, EPA considered occupational exposure to be relevant and that Pigment Violet 29 posed an unreasonable risk to workers. However, this was only based on the endpoint of lung overload, which we call into question in point 4a. Additionally, although Pigment Violet 29 is only produced at 450,000 – 600,000 pounds per year according to the CDR, [99] workers who are chronically exposed to these nanoparticles throughout a lifetime of factory shift-work are at increased risk of adverse health outcomes as these particles build up in the body over time and pose an unreasonable risk to worker health. Considering Carbon Black as the surrogate for Pigment Violet 29, EPA should assume Pigment Violet 29 poses hazards in addition to lung overload and must use its authority to request data specifically regarding repeated exposure inhalation toxicity to Pigment Violet 29 in order to assess systemic effects to workers.

Unfortunately, EPA has still failed to consider the potential susceptibility of pregnant workers. In fact, the revised risk evaluation states that "Statistics on pregnant women are not available, CPS provides data on the number of employed female workers by age group, which allows for determination of the number of employed women of reproductive age." [100] EPA cannot evaluate the impacts of Pigment Violet 29 on pregnant workers if it groups them in with all women of reproductive age. Female workers and **pregnant** female workers have very different chemical susceptibilities and grouping a susceptible subpopulation in with a subset of the general population not only runs counter to EPA's mandate under TSCA but fails to account for a subpopulation clearly delineated by the statute.[101] Not only did EPA fail to sufficiently account for pregnant workers, it failed to evaluate the exposures and risks to non-manufacturing workers, consumers, or the general population. As such, the claim that the risk assessment is protective of these populations is not reliable and EPA must use its authority to obtain further data on Pigment Violet 29 or search for parallel data on Carbon Black.

b. EPA continues to make assumptions about PPE which are scientifically unsupported

With regard to PPE, we have previously commented that EPA should always evaluate exposure scenarios **without** engineering controls and PPE in order to assess exposures and risks to the most impacted communities within the susceptible subpopulation of workers.[102] EPA continues to assume use of PPE to mitigate risks of concern to Pigment Violet 29 and make risk determinations based on scientifically unsupported assumptions, despite the fact that no OSHA standards exist for Pigment Violet 29.

On Page 14 of the risk evaluation[103], EPA states that "For manufacturing, processing, recycling, and disposal conditions of use, respirators with an APF of 10 were assumed. For one condition of use, paints and coatings for automobile (*e.g.*, Original Equipment Manufacturer (OEM) and refinishing), EPA assumed the use of a respirator with an APF of 25."

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[99] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 23. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[100] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 62. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[101] 15 USC §2605

[102] US EPA (2019). Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0014

[103] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 14. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

The Agency then goes on to find that the industrial use described above for which EPA assumed the highest level of PPE in the revised risk evaluation (Paints and coatings – Automobile (OEM and refinishing)) **does not** present unreasonable risk and thus does not necessitate further Agency action.[104] It is not surprising that the Agency found this condition of use not to present unreasonable risk, as it happens to be the condition for which the Agency assumed (without evidence) higher levels of PPE protection.

Additionally, EPA's statement that "existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE in a manner that achieves the stated assigned protection factor (APF) or protection factor (PF)"[105] is unsupported and unrealistic at best. OSHA found that for its methylene chloride standard, failure to provide PPE was one of most common violations,[106] identifying (contrary to EPA's assumption) that even when an OSHA standard exists, it is not followed.

7. EPA still assumes that Pigment Violet 29 is non-toxic and not absorbed via inhalation without providing adequate empirical data to support such assumptions and while incorrectly claiming health and safety data as confidential business information (CBI).

Although EPA expects inhalation to be a major route of exposure for workers,[107] it still relied on unsupported assumptions and failed to develop quantitative estimates, as evidenced on page 13 of the revised risk evaluation:

> "Quantitative risk estimates were not developed for non-cancer effects and cancer from acute inhalation and acute and chronic dermal occupational exposures for any conditions of use because of low hazard."[108] (Emphasis ours)

And again on page 66:

> "No information was found on the metabolism of C.I. Pigment Violet 29; hence the metabolic fate is unknown. However, C.I. Pigment Violet 29 is unlikely to be metabolized based on poor absorption."[109]

Although EPA's revised analogue better estimates the range of particle size and potential respirability of Pigment Violet 29, [110] EPA still relies on numerous assumptions that do not have any supporting empirical data, including that Pigment Violet 29 is insoluble and thus presents low hazard. The revised draft risk evaluation indicates the Agency requested an updated study on Pigment Violet 29's solubility in water and in octanol in order to evaluate risk, the Nicolaou, 2020 study,[111] which is rated high by

[104] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 15. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[105] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 15. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[106] U.S. Department of Labor, Occupational Safety and Health Administration. (2010) "Regulatory Review of 29 CFR 1910.1052: Methylene Chloride." Available: https://www.osha.gov/dea/lookback/MC-lookback-Feb-2010-final-for-publication-May-2010.pdf

[107] US EPA (2018) Draft Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline- 1,3,8,10(2H,9H)-tetrone)

[108] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 13. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[109] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 66. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[110] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 67. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[111] Nicolaou, C. (2020). Determination of the Solubility of C.I. PV29 in 1-Octanol and Water. Colors Technology Analytical Laboratory. https://beta.regulations.gov/document/EPA-HQ-OPPT-2020-0070-0008

EPA.[112] However, despite this high rating, this study is not publicly available and is claimed Confidential Business Information (CBI), EPA, 2012c[113] leads to no data on this chemical as well, thus it cannot be independently evaluated.

What is known about this study is that it utilizes an Octanol Solubility Method developed by the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD) in 2005 instead of the more appropriate OECD Guideline 105. [114] ETAD is a group representing over 30 dye and colorant manufacturers, including BASF and Sun Chemicals. For example, the summary of the octanol solubility method states:

"The octanol solubility of the test substance Pigment xxx was determined according to the method agreed upon at the "Analytical Experts Meeting" of ETAD (Basel) on January 12, 2005," [115]

There is no further explanation of how the ETAD method was developed, what kind of experts developed it (and their financial conflicts of interest), nor whether it went through the appropriate peer-review process. As we have outlined in previous comments,[116,117] recent studies empirically document that industry sponsorship produces research that is favorable to the sponsor.[118,119] The influence of financial ties on research can be traced to a variety of types of biases, and this conflict of interest needs to be distinguished from non-financial interests in the research, which can also affect research.[120] Thus, EPA must evaluate and consider the findings of the Nicolaou, 2020 study in light of its industry ties and must use its authority to make the underlying data available.

Additionally, upon investigation of the methods document, it does not seem to be supported by scientific evidence and makes numerous claims that it fails to cite. In the remarks on the method, ETAD states that "Because of the low solubility of this kind of substances in common solvents used for UV-vis spectrometry and chromatography the standard method for testing solubility (OECD guideline 105) is not applicable." [121]

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[112] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 39. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[113] U.S. EPA (U.S. Environmental Protection Agency). (2012c). Estimation Programs Interface (EPI) Suite™ for Microsoft® Windows (Version 4.11). Washington D.C.: Environmental Protection Agency. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

[114] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 20. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[115] US EPA (2020). C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone) TSCA Section 4 Test Order; TSCA Section 4(a)(2) Test Order for C.I. Pigment Violet 29 - Solubility Final Reports; Octanol Solubility Method ETAD (2005). Pg 3. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2020-0070-0008

[116] UCSF PRHE (2020). Comments from Academics, Scientists and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations. Pg 45. Available: https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/NAS%20Commnets_TSCA%20SR%20Method_FINAL_0.pdf

[117] US EPA (2020). Octamethylcyclotetra- siloxane (D4); TSCA Review. Comment submitted by Swati Rayasam et al, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0013

[118] Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017(2:MR000033.). doi: 10.1002/14651858.MR000033.pub3.; PMCID: 28207928.

[119] White J, Bero LA. Corporate manipulation of research: Strategies are similar across five industries. Stanford Law & Policy Review. 2010;21((1)):105-34.

[120] Bero L. Addressing Bias and Conflict of Interest Among Biomedical Researchers. JAMA. 2017;317(17):1723-4. doi: 10.1001/jama.2017.3854; PMCID: 28464166

[121] US EPA (2020). C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone) TSCA Section 4 Test Order; TSCA Section 4(a)(2) Test Order for C.I. Pigment Violet 29 - Solubility Final Reports; Octanol Solubility Method ETAD (2005). Pg 2. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2020-0070-0008

EPA uses the unavailable Nicolaou, 2020 study to support its claim that Pigment Violet 29 is insoluble, however the industry method which that study uses claims that substances such as Pigment Violet 29 have low solubility without presenting evidence to support that claim. Additionally, it uses this unsupported claim to declare OECD Guideline 105 inappropriate and goes on to state that "…solvents in which this substance is readily soluble are not compatible with the equipment required by the OECD guideline." [122] However, it again fails to present even a list of solvents which are incompatible with this method and in which substances such as Pigment Violet 29 are readily soluble. It is deeply concerning that EPA is basing its assessments of risk to human and environmental health on this circular and scientifically unsupported logic.

TSCA statute explicitly states that CBI protections do not apply to "any health and safety study" submitted or "any information reported to, or otherwise obtained by, the Administrator from a health and safety study."[123] Although the Agency may claim that the Nicolaou, 2020 study does not fall under the umbrella of "health and safety study" we would counter that in fact it does, as EPA uses Pigment Violet 29's insolubility as a basis to say that the chemical is poorly absorbed, not metabolized, not inherently toxic, and does not pose a risk to human health and the environment throughout the Risk Characterization section of the revised risk evaluation.

Water solubility alone is not sufficient to determine the low absorption or bioavailability; it needs to be supported with other toxicokinetic studies or repeated dose toxicity data. In our previous comments we identified that other authoritative bodies have called EPA's assumptions that Pigment Violet 29 is not bioaccumulative into question. [124] The European Chemicals Agency (ECHA) released data stating that Pigment Violet 29 presents persistence, bioaccumulation and toxicity concerns, and calling for further study. [125] ECHA's findings also counter EPA's claim regarding the insolubility of Pigment Violet 29, calling the solubility "questionable." [126] Additionally, ECHA's update document indicates toxicity concerns around Pigment Violet 29 due to its structural similarity to polycyclic aromatic hydrocarbons, of which many are carcinogenic.[127,128,129]

With regard to respirability, ECHA indicates that Pigment Violet 29 has a "high potential for bioaccumulation in air-breathers. Based on this observation [Pigment Violet 29] may accumulate in terrestrial organisms and in mammals."[130] Though EPA has revised this risk evaluation and found that Pigment Violet 29 poses risks to workers (although not the general populations), it does not find any environmental risk to terrestrial organisms.[131]

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[122] US EPA (2020). C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone) TSCA Section 4 Test Order; TSCA Section 4(a)(2) Test Order for C.I. Pigment Violet 29 - Solubility Final Reports; Octanol Solubility Method ETAD (2005). Pg 3. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2020-0070-0008

[123] 15 USC §2613 (b)(2)

[124] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 11. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091

[125] European Chemicals Agency (2019). Justification Document for the Selection of a CoRAP Substance Group Name: Diisoquinoline tetrones Available: https://echa.europa.eu/documents/10162/387374b8-62fa-c857-e60f-65e1cd9fd821

[126] Id. Page 13.

[127] European Chemicals Agency (2019). Community rolling action plan (CoRAP) update covering the years 2019, 2020 and 2021. Page 32. Available: https://echa.europa.eu/documents/10162/13628/corap_update_2019-2021_en.pdf/12451cec-ce6e-d156-5fef-7d09cb77b324

[128] WHO International Agency for Research on Cancer (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol 92: Some Non-Heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. Available: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono92.pdf

[129] ATSDR 2008. Polycyclic Aromatic Hydrocarbons (PAHs): What Health Effects Are Associated With PAH Exposure? https://www.atsdr.cdc.gov/csem/csem.asp?csem=13&po=11

[130] Id. Page 13.

[131] US EPA (2020). C.I. Pigment Violet 29; Revised Draft Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability, Letter Peer Review and Public Comment. Pg. 69. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0091