UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Supplemental Comments of Safer Chemicals Healthy Families, Earthjustice, Environmental Health Strategy Center, Natural Resources Defense Council and the Undersigned Groups on EPA's Draft Risk Evaluation for C.I. Pigment Violet 29 under the Amended Toxic Substances Control Act

Submitted via Regulations.gov (May 17, 2019)

Docket ID EPA-HQ-OPPT-2018-0604

INTRODUCTION AND SUMMARY

Safer Chemicals Healthy Families (SCHF), Earthjustice, Environmental Health Strategy Center, Natural Resources Defense Council, and the undersigned groups submit these supplemental comments on the Environmental Protection Agency (EPA) draft risk evaluation for C.I. Pigment Violet 29 (PV29) under section 6(b) of the Toxic Substances Control Act (TSCA).[1]

Our organizations are committed to assuring the safety of chemicals used in our homes, schools and workplaces and in the many products to which our families and children are exposed each day. During the legislative process to amend TSCA, we worked hard to maximize public health protection and to assure that EPA has the necessary authority to evaluate and eliminate the risks of unsafe chemicals. We strongly support a proactive approach to implementing the new law that uses the improved tools that Congress gave EPA to deliver significant health and environmental benefits to the American public.

On April 17, 2019,[2] EPA reopened the comment period on the PV29 evaluation for 30 days in order to receive feedback on supplemental materials it had added to the PV29 docket. These materials include portions of 24 studies on PV29 that the Agency had initially withheld as Confidential Business Information (CBI), as well as updated systematic review files and backup scoring sheets.

The PV29 evaluation is the first effort by EPA to carry out the mandate in the 2016 TSCA amendments to evaluate the risks of existing chemicals of concern and determine whether they are safe. These requirements establish a rigorous process for examining the hazard and exposure profile of chemicals and assessing whether they present an unreasonable risk of injury to health and the environment. Congress required these determinations to be based on the "best available science" and all "reasonably available" information.

As our initial January 14 comments demonstrate,[3] the PV29 evaluation falls far short of meeting these obligations. Its determination that PV29 does not present an unreasonable risk is based on limited and incomplete information that is insufficient, under the Agency's own risk assessment guidelines, to

[1] Throughout these comments, the draft evaluation is referenced as the "PV29 evaluation."
[2] 84 Federal Register 16011.
[3] Comments of Safer Chemicals Healthy Families, Earthjustice, Environmental Health Strategy Center, Natural Resources Defense Council, and the undersigned groups on EPA's Draft Risk Evaluation for C.I. Pigment Violet 29 under the Amended Toxic Substances Control Act, Docket ID EPA-HQ-OPPT-2018-0604, January 14, 2019 (Initial Comments).

establish the absence of risk. Its analysis of hazard and exposure is flawed in approach, poorly documented and explained, and contrary to the scientific evidence on which it relies. EPA itself recognizes the large uncertainty in its risk determinations as a result of the absence of critical information. Importantly, the Agency had ample opportunity to use TSCA authorities to obtain additional hazard and exposure data that could have supported a defensible risk evaluation – as Congress intended – yet refused to do so, instead reaching categorical conclusions about the absence of risk that simply cannot be supported by the inadequate data in the record.

EPA has still not disclosed full reports of all the 24 industry studies relied on in the draft risk evaluation. Thus, the public's ability to comment on the evaluation remains impaired, contrary to the law's requirements. However, the new information that has now been made available further demonstrates the poor quality and limited scope of the data in the draft evaluation and underscores the lack of evidence to support a finding that PV29 does not present an unreasonable risk of injury. Thus, there is an even more compelling basis than before for withdrawing the PV29 evaluation because of the lack of adequate data; EPA should instead use TSCA authorities to obtain sufficient information on PV29's hazards and exposures so the Agency can determine its risks with an acceptable level of confidence.

As we show in the body of these comments:

- EPA's continued unlawful withholding of health and safety data on PV29 is a serious flaw in its process and will compromise the transparency that is a necessary precondition to the credibility of EPA's risk evaluations for this substance and others that will be assessed under TSCA in the future;

- Based on the partial disclosure of reports of the 24 PV29 studies, the limitations and deficiencies of these studies in assessing PV29's acute and chronic health effects have been further demonstrated, providing more evidence that EPA's lacks any justification for its conclusion that PV29 "presents a low hazard to human health across all routes of exposure";

- The scoring sheets now available for PV29 illustrate why the TSCA systematic review protocol is deeply flawed and should not be used to conduct TSCA risk evaluations. The initial scoring results for PV29 are inconsistent and arbitrary and provide a skewed and unreliable basis for evaluating study quality. The scoring system has not been validated, peer reviewed and empirically justified, and is inconsistent with accepted best practices for systematic review. In conducting the PV29 and other 9 ongoing risk evaluations, EPA should replace the TSCA scoring system with a peer reviewed systematic review methodology;

- The PV29 review by the EU REACH Program calls into question EPA's draft risk evaluation and demonstrates a significantly greater level of concern about PV's potential for harm and the adequacy of available data than the Agency has recognized; and

- In response to FOIA requests and our initial comments, EPA has failed to provide any supporting data or other justification for the critical workplace air concentration on which its MOE calculation is based, further weakening its assertion that workers and other exposed populations are not at risk of harm.

I. EPA's Continued Withholding of Health and Safety Data on PV29 Violates TSCA and Impedes Meaningful Public Comment on the Draft Risk Evaluation

In our January 14 comments,[4] our groups expressed deep concern about EPA's failure to disclose the 24 industry studies on which it based the draft PV29 evaluation. We emphasized that TSCA requires all "health and safety studies" submitted to EPA to be disclosed to the public and that timely access to the PV29 studies was necessary for a meaningful opportunity to comment on the draft evaluation.

On March 22, EPA announced a partial release of the 24 studies but continued to withhold substantial portions of these studies,[5] even though Assistant Administrator Dunn's April 16 blog stressed that the Agency is "committed to being transparent about chemical information as we work to develop risk evaluations under TSCA."[6] This continued lack of access to the full studies is blocking informed review and comment on critical data underpinning the draft evaluation.

Most troubling is the withholding of all but about 100 pages of the 430-page report for the BASF reproductive/developmental toxicity screening study on PV29.[7] The redacted portions of the report include the detailed animal-by-animal observations of reproductive performance and the results of pathology examinations. These data are essential to independently evaluating the study findings regarding the effects of PV29 exposure on the test animals.

Importantly, this screening study plays a central role in the draft risk evaluation: its results form the basis for the Margin of Exposure (MOE) analysis that purports to show that PV29 is without harmful effects to workers, a finding that EPA then uses to determine the absence of risk to other exposed subpopulations. In our initial comments, we demonstrated, based on the European Chemicals Agency (ECHA) "robust summary" of the test results, that the study used biased and faulty statistics, disregarded statistically significant body weight changes in males and females, and dismissed gross lesions (abnormal tissue that may indicate cancer) in the treatment groups.[8] Access to the individual animal data and pathology findings would shed further light on these concerns.

For example, the robust summary does not address whether there was a dose-related trend in the pathology observations, the type or size of the lesions, the location of the lesions, the biological systems or organs affected by the lesions, whether or not they were malignant, or any other relevant details. Without these and other details, an independent statistical analysis of the possible significance of the lesions cannot be conducted. Because individual animal data were not provided, it is impossible to verify the justification for disregarding gross lesions or single observations.

Plainly, then, the continued withholding of all the underlying data not only limits the public's ability to file complete comments with EPA but makes it impossible to provide fully informed feedback to the Science Advisory Committee on Chemicals (SACC) during its upcoming peer review of the PV29 risk evaluation. In short, EPA's lack of transparency is a serious impediment to full public scrutiny of the

---

[4] Initial Comments at 5-8.

[5] https://www.epa.gov/sites/production/files/2019-03/documents/memo_transmitting_studies_for_pv29_and_attachment_a.pdf ("March 21 Transmittal Memo")

[6] https://blog.epa.gov/2019/04/16/epa-seeks-additional-comment-on-pv29-draft-risk-evaluation/

[7] This study is #17 in the EPA table listing the 24 studies attached to the transmittal memo. The redacted version of the study can be found at https://www.epa.gov/sites/production/files/2019-03/documents/study_17_repro-dev_toxicity_non-confidential.pdf.

[8] Initial Comments, at 18-20.

central study in its risk evaluation and the validity of the Agency's reliance on that study to demonstrate an absence of unreasonable risk.

In our initial comments and letters to EPA dated December 6, 2018 and April 19, 2019, we emphasized that EPA's withholding of critical health and safety data on PV29 is directly contrary to TSCA. A number of our groups have requested the withheld data under the Freedom of Information Act (FOIA), but EPA has denied this request.[9] EPA claims that the redacted data constitutes "confidential" information that was voluntarily provided to EPA by a foreign chemical manufacturer. However, as our letters and comments have underscored, TSCA section 14(b)(2)(A) expressly prohibits EPA from withholding "health and safety studies submitted under this Act" as confidential, affirming the public's right to know the health and safety effects of the chemicals that it is exposed to.

Here, EPA requested the PV29 studies for the express purpose of conducting its risk evaluation under TSCA, the studies were shared with EPA with the explicit understanding that they would be used to carry out the Agency's TSCA responsibilities, and EPA relies on the studies throughout its draft risk evaluation. Accordingly, they are, under any definition of the term, "health and safety studies submitted under" TSCA. As House Energy and Commerce Committee Chair Frank Pallone and Subcommittee Chair Paul Tonko emphasized in their March 21 letter to EPA Administrator Wheeler, to create an exemption from disclosure for such information despite the clear language of the statute is "to skirt the balanced system of CBI protection established by the Lautenberg Act" and "to mask health and safety information used under TSCA."[10]

TSCA section 14(b)(2)(B) independently requires the disclosure of "any information reported to, or otherwise obtained by, the Administrator from a health and safety study" on a chemical offered for distribution in commerce. EPA does not, and cannot, deny that the data withheld from the PV29 studies constitutes information obtained by EPA from a health and safety study of a commercially available chemical and is required to be disclosed.

In sum, EPA's continued unlawful withholding of health and safety data on PV29 despite the plain language of section 14(b)(2) is a serious flaw in the risk evaluation process. Such withholding will compromise the transparency that is vital to the credibility of EPA's risk evaluations for this substance and others that will be assessed under TSCA in the future.

II. The New Information EPA Has Released Following the Original Comment Period Confirms that the PV29 Data are of Poor Quality and Insufficient in Scope to Support the Risk Evaluation

A. Studies on PV29 Fall Short of the Minimum Level of Data Required for Chemical Safety Determinations under EPA's Risk Guidelines and Policies

As we showed in our initial comments, the weak and incomplete database on PV29 falls far short of the minimum level of evidence that longstanding EPA guidance and policy demand for determining that a chemical is without risk of harm. EPA should have required testing under section 4 of TSCA to fill these

[9] Letter to Jonathan Katz, Earthjustice from Pamela Myrick, EPA, re Freedom of Information Act Request No. EPA-HO-201853, April 18, 2019.

[10] https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/E%26C%20Follow%20Up%20Letter%20PV29.pdf

data gaps in order to meet its obligation under TSCA section 26(k) to obtain all "reasonably available information." Instead, however, it chose to reach overbroad and unsupported conclusions about the absence of health risk on the basis of inadequate evidence.

Our initial comments compared the data available on PV29 with the studies EPA considers necessary for a chemical to qualify for its Safer Choice Green Circle label. In the EPA Safer Choice Program, "[e]very chemical, regardless of percentage, . . . is evaluated through EPA's rigorous scientific process and only the safest ingredients are allowed."[11] To receive the label, a chemical must be "verified to be of low concern based on experimental and modeled data."[12] EPA looks to several endpoints in applying this standard, including carcinogenicity, reproductive and developmental effects, systemic or internal organ toxicity, mutagenicity, acute toxicity, sensitization, neurotoxicity and endocrine effects.[13] For each endpoint, EPA's Safer Choice Program Master Criteria for Safer Ingredients prescribes recommended test methods that "should be used to develop data for conducting chemical reviews based on the [low concern] criteria."[14]

The table below compares the available data on PV29 with the criteria and test methods for a determination of chemical safety in the Safer Choice program:[15]

Health hazards important to assess for chemical safety compared to the available Pigment Violet 29 data.

Health Hazards	**Suitable Empirical Data Available for Pigment Violet 29?[16]**
Acute mammalian toxicity	
Oral	Deficient and poor-quality experimental studies. Inadequate
Dermal	
Inhalation	No.
	Experimental studies unreliable and deficient. Inadequate.
Respiratory sensitization	No.
Skin sensitization	In vivo experimental study
Eye irritation/ corrosivity	In vivo experimental study

[11] https://www.epa.gov/saferchoice/frequently-asked-questions-safer-choice
[12] https://www.epa.gov/saferchoice/safer-ingredients#greencircle
[13] https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf
[14] Id**.**
[15] Similar criteria are recommended by the Clean Production Action (2018) GreenScreen for Safer Chemicals. Available: www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf
[16] Information from: US EPA (2018) Draft Risk Evaluation for C.I. Pigment Violet 29.
European Chemicals Agency (ECHA). (2017). Perylene-3, 4; 9, 10-tetracarboxydiimide. Helsinki, Finland. Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/10330

Skin irritation/ corrosivity	In vivo experimental study
Carcinogenicity	No.
Mutagenicity/ genotoxicity	Two in vitro experimental studies. No in vivo experimental studies.
Reproductive and developmental toxicity	Experimental screening study inadequate.
Developmental neurotoxicity	No.
Neurotoxicity	No.
Repeated dose toxicity	No.
Endocrine activity	No.

For PV29, EPA has identified suitable experimental data for only 4 of the 15 critical endpoints in Safer Choice (see Table above). A determination under TSCA that a substance does not present an unreasonable risk of injury should be based on equivalent (if not greater) evidence of safety than Safer Choice has recommended. Clearly, then, adequate information is not available for a comprehensive and scientifically credible risk evaluation under TSCA.

B. Unredacted Portions of the 24 Studies and Systematic Review Scoring Sheets Demonstrate that EPA Lacks Reliable Acute Toxicity Data for All Routes of Exposure

The insufficiency of the available data to evaluate PV29's risks to health is further demonstrated by the additional information on the 24 PV29 studies that the Agency released on March 22 and the updated systematic review scoring sheets it added to the docket on April 4. These new materials make clear that all of the 5 acute animal toxicity studies used in the draft evaluation lack basic indicia of reliability and data quality and cannot be used to conclude that PV29 is not toxic." This conclusion has significant implications for the overall risk evaluation: whereas it initially seemed that sufficient data was only lacking for longer-term health effects, it now appears that the data on PV29's acute toxicity are inadequate as well.

The EPA evaluation (p.25) "concludes that C.I. Pigment Violet 29 presents a low hazard to human health across all routes of exposure." This conclusion is based on acute toxicity studies that, according to EPA, found "that no adverse effects were observed for all routes of exposure (oral, dermal, inhalation)." Several of the acute toxicity studies on which EPA relies (# 1,2, 5-10, 12 and 13) are described in a single 10-page memo prepared by BASF.[17] This memo is dated January 31, 2018 and is characterized by BASF as a "summary" of study reports issued in 1975 and 1978. (The first page of and EPA's own filename assigned to this document likewise use the word "summary" and "summaries," respectively, to describe its contents.[18]) They do not provide individual animal data or the details of pathological examinations

[17] https://www.epa.gov/sites/production/files/2019-03/documents/study_s_1_2_5-10_12_13_toxicological_investigation_summaries_non-confidential.pdf.

[18] EPA earlier suggested that it had "full study reports" for these studies but was withholding them for CBI reasons. It is troubling that no such reports have been provided. It is possible that EPA's earlier representation was in error

and lack basic information about study methods and execution. Given this lack of essential documentation and underlying data, EPA is not justified in using the 10 studies to conclude that PV29 lacks acute toxicity.

When the 10 studies are examined more closely, their inadequacy for risk evaluation purposes becomes even more apparent.[19]

Acute Inhalation Toxicity Studies. Among the 10 studies are two described as "Non-Guideline Acute Toxicity: Acute Inhalation Toxicity with Rats" from 1976 and 1978 (#5-6 in Attachment A of March 21, transmittal memo). The ECHA "robust summaries" labeled these studies as "not reliable" due to use of an "unsuitable test system." Although the robust summaries advised that these studies should be "disregarded due to major methodological deficiencies," EPA staff unaccountably ranked them as of "medium confidence" in its initial systematic review scoring exercise.[20] However, according to the April 4 memo of Mary Fehrenbacher transmitting EPA's scoring sheets to the docket, this ranking "erroneously omitted" "the technical concerns" flagged in the BASF robust summary. Because public comments on the draft evaluation took issue with the "medium confidence" ranking based on the robust summaries, EPA reexamined this ranking and, after additional scoring, "determined that the two acute inhalation studies (HERO ID 4731525 and 4731526) were *Unacceptable* primarily due to deficiencies in the exposure inhalation methods."[21]

While the Fehrenbacher memo asserts that "EPA's risk determination did not rely on the two acute inhalation toxicity studies," this is plainly incorrect since EPA's draft evaluation concluded that PV29 lacks adverse effects "for all routes of exposure (oral, dermal, inhalation)." Moreover, since PV29 is known to be inhaled during spray application of paints in the auto industry and perhaps other use scenarios, the absence of reliable data on inhalation toxicity is a significant shortcoming of the risk evaluation.

1975 and 1978 Acute Oral Toxicity Studies. In its second round of systematic review scoring, the remaining 8 studies in the group of 10 were ranked as "moderate," "low" or "high" confidence, meaning EPA believed they could be considered in evaluating PV29's toxicity. However, a closer examination of

---

and it has never in fact possessed full reports of the studies. It's also possible that EPA does have the full study reports and is still not making them publicly available. Whatever the explanation, the full study reports were used by BASF to prepare the January 31, 2018 summary memo but either do not exist any longer or are being withheld by EPA or BASF. As a consequence, the public lacks access to the reports, compromising its ability to review and comment on the 10 studies.

[19] While the following discussion draws on observations in the EPA scoring sheets, this is to help illustrate the quality concerns for the studies under review. As noted later in these comments and in previous submissions, we question the scientific validity of the TSCA scoring system and oppose reliance on the metrics it uses to determine whether study quality is acceptable for inclusion in TSCA risk evaluations.

[20] The surprising finding of "medium quality" during EPA's initial systematic review of the two studies notwithstanding the manufacturer's conclusion that they are unreliable raises troubling questions about the rigor and objectivity of EPA's application of its systematic review criteria and the expertise of the EPA reviewers. These issues are explored more fully later in these comments.

[21] Mary C. Fehrenbacher, Transmission of Background Materials on Systematic Review for the Peer Review Meeting of the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29)", April 4, 2019 ("Fehrenbacher Transmittal Memo").

the scoring sheets for the two PV29 acute oral toxicity studies in the group of 10 reveals serious inadequacies and information gaps that should have been disqualifying.

The EPA reviewer ranked the BASF 1975 rat acute oral toxicity study (#9 in Attachment A of March 21 transmittal memo) as "medium" in confidence.[22] However, the scoring sheet includes a disclaimer that "[although] the study indicated that this study was conducted according to an internal protocol comparable to OECD Guideline 401, insufficient study details are reported in the study report to verify this." The reviewer's comments also noted several problems that seem in conflict with the scores he or she assigned: "the physical nature of the test substance was not described", "no details were provided about the test substance purity", "[a] concurrent negative control group was not reported", "no details were provided on test substance preparation," the "study report did not state how animals were allocated to study groups", "details of exposure administration were not fully addressed", "the health status and age [of animals] at initiation were not reported", "it is not possible to determine whether there were confounding variables with the limited information given in the report", the "study provided minimal information on the adequacy of animal husbandry conditions", "details on how [mortality and clinical sign] observations were collected were not provided", and "the investigators did not conduct a statistical analysis."

Despite these stated deficiencies, the reviewer scored the study as "medium" for the several quality metrics, often on the basis of an "inference" that the study was conducted correctly despite no documentation to that effect. Moreover, for several of the quality attributes requiring scoring on the EPA sheet, the reviewer entered "not rated" (or NR). In these cases, no score, as opposed to a "low" score, was assigned, even though a "low" score would seem warranted in the absence of any evidence that correct testing approaches were followed. For example, NR designations were entered for "positive controls," "negative control group response" and "statistical methods." Had these quality metrics been included in the scoring process instead of being ignored, the overall score and quality ranking would have been lower. Thus, EPA's scoring process was skewed to downplay serious quality concerns that, if fully considered, would have been disqualifying.

1984 Oral Toxicity (HERO ID: 4731531). In addition to the two oral acute toxicity studies described in the BASF January 31, 2018 10-page summary, a third acute oral study (#11 in Attachment A of EPA March 21 transmittal memo) was performed in 1984 by researchers at the German chemical company Hoechst.[23] In contrast to the two earlier studies, a study report for this study was provided to EPA and is in the docket. The second EPA scoring exercise ranked the study as "high" in confidence. However, closer review reveals serious concerns with this ranking.

The study purports to follow an OECD protocol 401, but that cannot be independently verified because that protocol is no longer publicly available online. It was deleted in 2002.[24] It was replaced by other acute oral toxicity guidelines, including OECD 423 and 420.[25]

---

[22] The second acute oral study (#10 in Attachment A of March 21 transmittal memo) was conducted in 1978. The scores and reviewer comments for the study were very similar to those for the 1975 acute oral study and it suffered from the same quality concerns.

[23] Rupprich, N, Weigand, W. 1984. Testing the acute oral toxicity in the male and female Wistar rat. Hoechst, Pharma Research Toxicology. Report No. 84.0225. Report date: May 2, 1984. HERO ID: 4731531

[24] https://www.oecd-ilibrary.org/environment/test-no-401-acute-oral-toxicity_9789264040113-en

[25] https://read.oecd-ilibrary.org/environment/test-no-420-acute-oral-toxicity-fixed-dose-procedure_9789264070943-en#page1

Both the OECD 423 and 420 Test Guidelines require testing animals across a range of doses, none of which should exceed 2000 mg/kg except under exceptional circumstances (see OECD 423, para 19 and Annex 4). The HERO ID: 4731531 study tested only a single dose, 5000 mg/kg. Because the study failed to test across a range of doses, there is no way to determine how the treatment affected the animals at all, other than if they had died (they didn't), because there is no comparison group.

Both the OECD 423 and 420 Test Guidelines require collecting observational and clinical measurements daily during the observation period, so that toxicity can be assessed using sub-lethal signs and symptoms. The only data that HERO ID: 4731531 study reported is body weight (a poisoned or sickened animal will usually eat less, so will gain less weight or even lose weight compared to a control animal). Weight was only recorded once weekly (consistent with the protocol), so the study yields a total of only two actual points of data per animal during the course of the entire study. The study concludes that the dose had no effect on weight gain. However, this is impossible to determine since there is no comparison group because it was a single dose study, with no concurrent control group.

There were also serious flaws in the study that should have raised concern but were given short shrift in applying the TSCA systematic review criteria:

A concurrent negative control group was not included or reported - The HERO ID: 4731531 study did not include either a positive or negative control (metric #4). According to the TSCA Systematic Review for animal studies, this is a "serious flaw that would make animal toxicity studies unacceptable" (TSCA SR, G.5.1, p. 186). The PV29 reviewer notes that the OECD Guideline protocol for this study does not require either a positive or negative control (PV29 p. 18), a statement that cannot be verified given that the Test Guideline 401 has been cancelled and is no longer publicly available. However, the reviewer's statement is likely incorrect, given that OECD 401 pre-dated the effort to reduce the number of animals used in toxicity tests. The updated replacement tests, OECD 423 and 425, do not require a control group, but these test guidelines require multiple dose groups and extensive recording of both subjective and objective signs and symptoms of toxicity. "The most noteworthy achievement is the deletion of the much criticised Test Guideline 401 on Acute Toxicity Testing, and its replacement with Test Guidelines 420, 423 and 425, introducing reduction and refinement."[26] Thus, the HERO ID: 4731531 study should have been identified as being seriously flawed due to the failure to report on a control group, or documentation should be provided to demonstrate that it followed the described protocol as claimed.

Outcome assessment methodology was not sensitive - The HERO ID: 4731531 study also failed to report on any clinical or behavior signs or symptoms of toxicity. In contrast, both OECD 420 and 423 say animals should be observed daily, and should include, "changes in skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous systems, and somatomotor activity and behavior pattern. Attention should be directed to observations of tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma." (OECD 420 para 28, OECD 423 para 25).[27] [28] Instead of tables reporting daily on whether or not any of these signs and symptoms of toxicity occurred, the HERO ID: 4731531 study simply reports under the "clinical toxic reactions" section that:

[26] https://www.oecd.org/chemicalsafety/testing/animal-welfare.htm
[27] https://read.oecd-ilibrary.org/environment/test-no-420-acute-oral-toxicity-fixed-dose-procedure_9789264070943-en#page5
[28] https://read.oecd-ilibrary.org/environment/test-no-423-acute-oral-toxicity-acute-toxic-class-method_9789264071001-en#page4

"Neither male nor female animals showed any symptoms of being poisoned". What signs did they look for? How often did they check for signs? And, most importantly, how could they have expected to see any changes when they had no comparison group because it was a single dose study, so every animal was treated the same? It is concerning that the PV29 reviewer noted only the "lack of reporting of food/water intake and respiratory rate" (PV SR p. 19, metric #21), as if information on only those two parameters were missing, instead of the entire clinical and subjective toxicity profile. The TSCA systematic review protocol states that an outcome assessment that is not sensitive for the outcome of interest, "e.g. a systemic toxicity study that evaluated only grossly observable endpoints such as clinical signs and mortality" is considered seriously flawed and should be deemed unusable (TSCA SR, G.5.1, p. 188). In fact, this study is so flawed it even failed to measure basic clinical signs of toxicity.

Blinding of assessors - The HERO ID: 4731531 study fails to report on whether or how the study assessors were blinded to the treatment groups (metric #19, not rated). The TSCA systematic review protocol lists failure to report on whether assessors were blinded as a "serious flaw that would make animal toxicity studies unacceptable" (TSCA SR, G.5.1, p. 188). In particular, the protocol explains that, without blinding, the assessors could be biased when measuring subjective outcomes like animal appearance or behavior. The study was scored as NR by the EPA reviewer for this metric and it was thus ignored, resulting in a "high" overall ranking of the study, yet it should have been considered "unacceptable" under EPA's own systematic review scoring system.

C. Review of the Acute Toxicity Studies under the Navigation Guide Demonstrates Significant "Risk of Bias"

To provide further perspective on the reliability of the acute oral and inhalation toxicity studies on PV29, scientists at the University of California San Francisco (UCSF) reviewed these studies using the Navigation Guide "risk of bias" criteria. The Navigation Guide is a systematic review method developed by an international, interdisciplinary collaboration of clinical and environmental health scientists from academia, government and NGOs.[29] It has been applied in multiple case studies and the National Academy of Sciences has evaluated and recommended both the Navigation Guide and OHAT methods for systematic reviews, noting that:

> "The two approaches [OHAT and Navigation Guide] are very similar… and they are based on the same established methodology for the conduct of systematic review and evidence assessment (e.g., Cochrane Collaboration, AHRQ Evidence-based Practice Center Program, and GRADE). Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, protocol development, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and integrating the evidence."[30]

[29] 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

[30] 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. Pg. 119

Risk of bias means characteristics of a study that can introduce a systematic error in the magnitude or direction of the results of the study, thus 'biasing' the results away from the true result.[31] The Navigation Guide risk of bias assessment for animal toxicity studies was developed based on the Cochrane Collaboration's Tool for Assessing Risk of Bias,[32] which includes domains that have been empirically demonstrated to have a material effect on study outcomes, outlined in the table below.

Domain	**Criteria for low risk of bias rating**
Sequence generation	Study authors reported the use of a random component in the sequence generation process.
Allocation concealment	Study authors reported that study personnel could not foresee which animals were allocated to the various experimental groups.
Blinding	Study authors reported that personnel and outcome assessors were adequately prevented from knowledge of the allocated exposures during the study.
Incomplete outcome data	Study authors reported when and why participants left the study.
Selective reporting	The study's prespecified outcomes that are of interest in the review were reported in a prespecified way.
Conflict of interest	The study was free of support from a company, study author, or other entity having a financial interest in the exposures of interest in the review.
Other bias	Study appears to be free of other sources of bias.

Table: Navigation Guide tool for assessing risk of bias of animal toxicity studies contains seven domains empirically shown to affect bias. [33]

According to the UCSF comments, the "risk of bias" for the 15 PV29 health effects studies was considered "probably high" for most of these metrics, resulting in a conclusion that, based on validated criteria, "the evidence base of toxicity studies for Pigment Violet 29 is low quality." [34]

In sum, none of the three oral acute toxicity studies used in the PV29 draft evaluation meet minimum quality standards when EPA's systematic review criteria are objectively applied. The deficiencies of these studies are also evident from application of the Navigation Guide "risk of bias" criteria. Given the disqualifying flaws in the two acute inhalation studies and the absence of any acute dermal toxicity data, it is thus clear that EPA lacks reliable information to support a conclusion that PV29 is not acutely toxic by any route of exposure.[35] When coupled with the lack of acceptable data to determine its longer term

[31] Higgins JPT, Altman DJ, Sterne JAC, eds. 2011. Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (Higgins JPT, Green S, eds).

[32] Id.

[33] Koustas, E., Lam, J., Sutton, P., Johnson, P. I., Atchley, D. S., Sen, S., … Woodruff, T. J. (2014). The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth. *Environmental Health Perspectives*, *122*(10), 1015–1027. https://doi.org/10.1289/ehp.1307177

[34] Comments from Academics, Scientists and Clinicians on Materials Supporting the Colour Index (C. I.) Pigment Violet 29 Risk Evaluation, May 17, 2019.

[35] Our comments do not address the 4 eye and dermal irritation studies described in the 2018 BASF summary but, like the remaining studies described in the summary, the amount of information provided on study procedures and findings is too general and lacking in detail for these studies to be deemed acceptable in quality.

health effects, this conclusion reinforces the absence of scientific support for EPA's determination that PV29 does not present an unreasonable risk to human health.

III. The Additional Details Now Available About EPA's Application of its TSCA Systematic Review Protocol Reinforce Deep Concerns About the Protocol's Scientific Validity and Value as a Tool for Conducting TSCA Risk Evaluations

A. *The Highly Questionable Scoring Process EPA Conducted for PV29 Raises Serious Concerns about Use of the TSCA Protocol*

Our groups have previously expressed deep concerns about the study quality scoring system in the TSCA systematic review protocol.[36] Among these concerns is the absence of any external validation phase for the system and its application to ongoing TSCA risk evaluations without thorough pilot testing to assess how it performed in practice for a large universe of studies.

The consequences of this rushed and undisciplined approach are painfully evident in the newly disclosed scoring sheets for the PV29 evaluation. As EPA has acknowledged, it "re-evaluated the study reports and updated the data evaluation scoring sheets" after public comments "revealed both process and technical inconsistencies."[37] The second round of scoring produced markedly different results from the first. For the 15 animal toxicity studies alone, UCSF experts found that 124 scores (including 18 unacknowledged by EPA) were changed out of a possible total of 360 (34%). The overall quality rankings of 8 of these 15 studies were modified based on the revised scores (including the two acute inhalation studies, which were downgraded to "unacceptable" from "medium").[38]

Why such discrepancies occurred has not been explained by EPA. For example, the Agency has not described the training, qualifications and supervision of the study reviewers and the instructions they were given. In addition, it appears that different reviewers were used for the second round of scoring than the first, which would suggest that the scores depend heavily on the subjective judgment of the reviewer assigning them. Similarly, it seems that there was one reviewer for each study, although best scientific practice is to have two independent reviewers.

Further, the reviewers liberally used "not rated" (NR) scores for important quality metrics, skewing the overall study rankings. EPA has provided no justification for failing to assign scores to study attributes that EPA's protocol treats as critical elements of study quality. An example is the extensive use of NR scores for "blinding of assessors", which refers to the importance of ensuring that personnel involved in assessing the study animals did not know which animals were assigned to which group. As EPA itself has recognized,[39] this is a significant precaution for studies calling on assessors to make subjective judgments about treatment outcomes, as was the case for most of the PV29 studies. Finally, EPA reviewers made "inferences" about how studies were conducted to compensate for the absence of

[36] Comments of Safer Chemicals Healthy Families on Application of Systematic Review in Risk Evaluations under Section 6 of the Amended Toxic Substances Control Act, Docket ID EPA-HQ-OPPT-2018-0210, August 16, 2018 ("Systematic Review Comments").
[37] Fehrenbacher Transmittal Memo, at 2.
[38] Comments from Academics, Scientists and Clinicians on Materials Supporting the Colour Index (C. I.) Pigment Violet 29 Risk Evaluation, May 17, 2019.
[39] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Pg. 188

information in the study summaries. Such deviations from the EPA protocol raise red flags in the absence of clear guidance from the Agency on when the reviewer could use judgment where direct evidence was lacking on how a study was conducted. Given this lack of transparency, there is no way to judge whether the judgment exercised by the reviewers was legitimate or evidence of bias in applying the scoring system.[40]

The changes in the scores and overall rankings, coupled with the many concerns about how the scoring was conducted, greatly weaken confidence in the scientific validity of the TSCA systematic review protocol. This is an immediate concern for the PV29 evaluation because, for the reasons described above, the scoring process as applied was simply not a meaningful and objective tool for determining study quality and, in fact, masked serious study deficiencies that should have been disqualifying. More broadly, EPA's use of the scoring process for the other nine TSCA risk evaluations now underway raises the same questions as the PV29 evaluation and creates legitimate distrust in the validity of the Agency's assessment of the relative quality of the studies on which it is basing its determinations of risk and safety.

In general comments on the EPA TSCA systematic review protocol, our groups expressed concern that the TSCA scoring system arbitrarily emphasizes seemingly "objective" metrics of debatable significance while deemphasizing or ignoring indicators of study quality that are more important in weighing how a study should be used in an overall evaluation of risk.[41] We argued that EPA had failed to empirically document the link between its scoring metrics and the overall value of a study in a holistic evaluation of risk. As we explained, the "TSCA benchmarks for study quality and formula for calculating a composite score . . . will inevitably lead to a bias in study evaluation, based on pre-determined weighting strategies that fail to account for the complexity of study design, study conduct, how the study is being used, and other features." The PV29 experience graphically illustrates the potential for such bias and also demonstrates the difficulty of using the scoring system in an objective and consistent manner.

Many of these issues could have been fleshed out and carefully examined had EPA not peremptorily applied the system to all 10 draft risk evaluations. It is universally recognized that systematic review protocols need to be established in advance of individual evaluations to eliminate the potential for bias and to assure that evidence reviews are conducted using consistent, well-defined criteria. EPA failed to do this.

B. Numerical Scoring of Data Quality Attributes Is Strongly Disfavored by Systematic Review Experts

As our earlier comments point out, other systematic review methodologies do not use numerical scoring systems for assessing study quality and, in fact, expert bodies strongly recommend against numerical scoring for this purpose. As stated by the Institute of Medicine, "… systematic review teams have moved away from scoring systems to assess the quality of individual studies toward a focus on the components

[40] The Fehrenbacher Transmittal Memo for the scoring sheets (p.2) indicates that problems with the initial round of scoring led "EPA to implement procedures for further optimization" such as "improvements in our quality assurance procedures and training of reviewers." However, no detail on these improvements is provided, making it impossible to determine how EPA has changed the scoring process and whether these changes have been effective. It is significantly concerning that EPA has made on-the-fly and undocumented corrections in a scoring process that should have been extensively pilot tested before its application to ongoing risk.

[41] Systematic Review Comments, at 3-4.

of quality and risk of bias."[42] The Cochrane Collaboration, founded in 1993, is an international non-profit and independent organization that possesses the world's most authoritative expertise on systematic review methods. This organization states: "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* (emphasis added)."[43] The National Academy of Sciences (NAS) recently reviewed the systematic review method of the EPA Integrated Risk Information System (IRIS) and strongly argued against quantitative scoring, stating:

> … Cochrane discourages using a numerical scale because calculating a score involves choosing a weighting for the subcomponents, and such scaling generally is nearly impossible to justify (Juni et al. 1999). Furthermore, a study might be well designed to eliminate bias, but because the study failed to report details in the publication under review, it will receive a low score. Most scoring systems mix criteria that assess risk of bias and reporting. However, there is no empirical basis for weighting the different criteria in the scores. Reliability and validity of the scores often are not measured. Furthermore, quality scores have been shown to be invalid for assessing risk of bias in clinical research (Juni et al. 1999). *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* (Higgins and Green 2008) (Pg. 69)(emphasis added).[44]

C. The TSCA Program Lacks a Systematic Review Framework for Evidence Synthesis and Integration

In addition to adopting a numerical scoring process for data quality that systematic review experts have consistently rejected, the TSCA review protocol does **not** include other key elements of systematic review that are universally recognized as essential. EPA's July 2017 risk evaluation framework rule defines systematic review as a comprehensive, consistent and transparent process to "identify and evaluate each stream of evidence" and "to integrate evidence as necessary and appropriate based on strengths, limitations, and relevance."[45] Yet unlike the peer-reviewed approaches to systematic review of the Navigation Guide, National Toxicology Program (NTP) and the EPA IRIS program, the TSCA protocol fails to address the steps TSCA risk evaluations will take to determine the strengths and relevance of individual studies, group them into streams of evidence and integrate these streams into a set of judgments about the weight of the evidence as a whole.

In fact, EPA admits that it is proceeding with its first 10 TSCA risk evaluations in the absence of a pre-defined framework for carrying out these basic functions of systematic review:

> … the purpose of the document is internal TSCA systematic review that … sets out general principles to guide EPA's application of systematic review in the risk evaluation process for the first ten chemicals … *EPA had limited ability to develop a protocol document detailing the*

---

[42] Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Review. Washington, D.C.: The National Academies Press.; 2011.

[43] Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [Updated March 2011]: The Cochrane Collaboration. Available from http://www.cochrane-handbook.org.; 2011.

[44] National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014.

[45] Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, 40 CFR 704.33.

systematic review approaches and/or methods prior to the initiation of the risk evaluation process for the first ten chemical substances. For these reasons, the protocol development is staged in phases while conducting the assessment work" (emphasis added). Additional details on the approach for the evidence synthesis and integration will be included with the publication of the draft TSCA risk evaluations.[46]

Despite what EPA says, the PV29 risk evaluation does **not** provide an approach for "evidence synthesis and integration" nor does it attempt these tasks. Thus, the numerical scoring process for study quality exists in a vacuum, unaccompanied by the broader application of professional judgment that would enable an informed assessment of the strengths and weaknesses of the PV29 database as a whole.

This is illustrated by EPA's treatment of the PV29 reproductive/developmental screening study (OECD 421 test) reported by Stark et al., 2013. As noted above, this study is the "point of departure" for EPA's Margin of Exposure (MOE) calculations to determine whether PV29 presents a risk to workers and other exposed populations. Thus, one would expect a careful review of its strengths and weaknesses and suitability for making a risk determination. However, EPA's evaluation of the study was largely limited to its scoring for study quality under the TSCA systematic review protocol. While the EPA reviewer assigned a "high" ranking to the study,[47] this ranking did not speak to the many questions of data interpretation and sufficiency that the study presents. For example, as shown in our groups' initial comments on the draft evaluation, the statistical problems with this study are numerous, very serious, and biased towards making it almost impossible to identify any possible adverse effect.[48] In this regard, the study found statistically significant body weight changes in males and females but disregarded their occurrence.[49] As also addressed in our initial comments, while noting that it was a "screening" study with numerous limitations, the draft evaluation describes these weaknesses as "minor," failing to recognize that EPA's own risk assessment guidelines explicitly describe such screening studies as insufficient for an assessment of reproductive and developmental toxicity.[50]

---

[46] 83 FR 26998 (June 11, 2018); Application of Systematic Review in TSCA Risk Evaluations, available at https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

[47] Some of the scores used in the ranking process are questionable so the "high" ranking should not be accepted at face value. One example is test substance purity (metric #3). The HERO ID: 4731538 study received a 'High' grade for 'test substance purity' (see TSCA SR, p. 30). Yet, the full report states, "Purity: The characterization (study no 11L00104) showed expected values for the test substance". Then, near the end of the HERO ID: 4731538 study, where there is less redacting, on page 385, no actual value for the purity of the material is provided. Although the report does say that the values were expected based on a number of characterization tests that are shown, the purity is never disclosed. There are some values that are not as expected: the value for carbon is too low (p. 391); the value for oxygen is too high (p. 392). However, whether or what the implications for this may be is never mentioned, and, again, no value for the purity of the product is reported.

[48] Initial comments, at 18-20.

[49] Had EPA disclosed the individual animal data and pathology results for this study, a fuller examination of whether the findings in fact demonstrated adverse effects would have been possible, but these important portions of the study report have been redacted (unjustifiably) as CBI.

[50] Initial comments at 26-29. The OPPTS 870.3550 Test Guideline is designed solely to generate information on "reproductive performance such as gonadal function, mating behavior, conception, development of the conceptus, and parturition." https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/epa/epa_870_3550.pdf The Guideline specifically states that, "it is not an alternative nor does it replace the existing test guideline in OPPTS 870.3700" which tests prenatal developmental toxicity." The OPPTS 870.3550 Test Guideline also makes clear that it "does not provide complete information on all aspects of reproduction and development", as it is only designed as a

These important issues would have been carefully considered under a comprehensive systematic review framework but were given short shrift in the PV29 evaluation because the TSCA protocol focuses narrowly on study quality and ignores the more important goal of using a structured and documented process for expert professional judgment to determine the overall weight of the evidence. In the case of PV29, this led to a failure to address the core issue of whether the limited and incomplete data on this substance are sufficient to support a science-based determination that it does not present an unreasonable risk of injury.

D. Continued Use of the Flawed and Incomplete TSCA Systematic Review Protocol in the 10 Risk Evaluations is Unjustified

As our earlier comments emphasize, our groups continue to believe that, because it is fundamentally flawed, EPA should withdraw the TSCA systematic review document and instead implement systematic review methods that have been demonstrated for use in environmental health assessments and endorsed by the NAS. Examples include the NTP Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration; the EPA Handbook for Developing IRIS Assessments; the Preamble to the IARC Monographs; and the Navigation Guide Systematic Review Method. These protocols can be applied immediately because they have already been peer reviewed and are backed by a broad scientific consensus. While EPA has already expended effort to use the TSCA protocol in its ongoing risk evaluations, shifting to a sounder approach will conserve resources in the long run and enhance the credibility and scientific validity of these evaluations.

We do not oppose asking the NAS to peer review the TSCA protocol, as EPA has committed to, but that review should consider the relative merits of the protocol and the Handbook for Developing IRIS Assessments (Draft, Apr 2019). At this point we remain strongly opposed to any use of the TSCA Systematic Review in its current flawed state; the current reliance OPPT is placing on this protocol is severely damaging the quality and credibility of EPA's draft evaluations.

IV. Recent Actions by the EU REACH Program Raise Serious Concerns about PV29's Impacts on Health and the Environment and Highlight the Gaps in Available Data

Unlike EPA's proposed determination that PV29 does not present an unreasonable risk of injury, EU REACH authorities have identified it as a suspected persistent, bioaccumulative and toxic (PBT) substance and a suspected very persistent and very bioaccumulative (vPvB) substance requiring comprehensive evaluation.[51] Earlier this year, the Belgian Competent Authority (BE CA) issued a Justification Document, now endorsed by the REACH authorities, that supports this designation.[52] This

---

screening level test: "In particular, it offers only limited means of detecting postnatal manifestations of prenatal exposure, or effects that may be induced during postnatal exposure" due in part to the small number of test animals, the limited number of endpoints examined, and the short duration of the study. The Guideline states that, "this method will not provide evidence for definitive claims of no effects" (OPPTS 870.3550, p. 3). https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/epa/epa_870_3550.pdf. Yet this is exactly how EPA is using it in the draft PV29 evaluation.

[51] Remarkably, while the draft risk evaluation includes a discussion of activities underway in other countries, it makes no mention of the evaluation and initial conclusions under the REACH program. The final evaluation should rectify this omission. If EPA disagrees with the BE CA Justification Document, it should explain why.

[52] https://echa.europa.eu/documents/10162/387374b8-62fa-c857-e60f-65e1cd9fd821

Document identifies several serious concerns overlooked in the draft EPA evaluation and highlights data gaps that must be filled for an informed assessment of PV29's risks to health and the environment.[53]

The Justification Document elaborates on why PV29 should be considered a potential PBT, observing that "[i]n view of the structure of the substances, it is reasonable to expect that the P and the vP criterion are met for these substances and QSAR estimations support this concern." The Document adds that, for bioaccumulation potential, "the log Kow and log Koa-values are important metrics" and indicate a "high potential for bioaccumulation in air breathers" and that "the substance may accumulate in terrestrial organisms and in mammals." The Document underscores that significant additional testing is needed to better define PV29's P and B properties, in marked contrast to the draft PV29 evaluation, which presumes that PV29 is not a PBT based on the data available.

In its discussion of PV29's PBT potential, the Document observes "that the perylene core of these diisoquinolines is a PAH which shows a structural similarity with PAHs as there are:

> 1. benz[a]anthracene (EC 200-280-6)(identified as carcinogenic, PBT & vPvB),
>
> 2. chrysene (EC 205-923-4)(identified as carcinogenic, PBT & vPvB),
>
> 3. Benzo[a]pyrene (EC 200-028-5)(identified as carcinogenic, mutagenic, toxic for reproduction, PBT & vPvB)/"

The polycyclic aromatic hydrocarbon (PAH) structure of PV29, which we noted in our initial comments,[54] both reinforces its PBT potential and raises concerns about serious health effects like carcinogenicity, for which sufficient data are lacking.

The REACH registrant for PV29 had argued against a PBT designation on the basis of its low solubility, a consideration strongly emphasized as demonstrating lack of risk in the EPA evaluation. However, the Document disagrees that PV29 has been shown to have low solubility and points to disparate solubility levels using different techniques:

> BE CA considers however that the reliability of the water solubility and partition coefficient data for Perylene3,4:9,10-tetracarboxydiimide as[sic] questionable. The registration dossier for this substance indicates that water solubility of 0.01 mg/L at 20° C, while EpiSuite presents two estimation methods for water solubility: WSKOW v.1.42 □ 6.3 mg/L; Wat Sol v1.01 □ 0.64 mg/L. In both estimation methods the various fragments are recognized and the molecular weight is in the applicability domain. Therefore these estimation methods should be accepted in a weight-of-evidence approach.

The Document then emphasizes that, "[b]ecause the estimated values substantially diverge from the value given in the registration dossier and because water solubility is a crucial element, it seems appropriate not to use the value presented by REG as an argument to deny the B-concern." It concludes that "a reliable conclusion on the bioavailability of this substance is not possible based on the currently available data."

[53] The Document addresses two closely related perylene compounds, Perylene-3,4:9,10-tetracarboxydiimide (PV29) and 2,9-dimethylanthra[2,1,9-def:6,5,10d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone.
[54] Initial Comments, at 24-25.

In the draft risk evaluation, EPA places substantial weight on PV29's "low solubility, low vapor pressure, low bioaccumulation potential, and poor absorption across all routes of exposure."[55] However, the Justification Document questions whether these claimed properties of PV29 are in fact demonstrated by the available data and argues that evidence shows that the substance may in fact bioaccumulate. EPA therefore needs to reexamine the presumption of low solubility and bioavailability, which is a critical foundation for its low risk determination. At a minimum, the Agency should reach no conclusions about solubility and bioavailability without requiring additional testing**.**

While the draft EPA evaluation found limited exposure to PV29, the Document presents a different picture, emphasizing the "wide dispersive use, high tonnage and the environmental exposure" of this substance. The Document presents a detailed overview of PV29's conditions of use, which documents a broader range of applications and greater potential for widespread exposure by workers and consumers than is reflected in the EPA draft evaluation. This suggests that EPA has overlooked a number of uses and understated exposure for the uses it has identified. Our initial comments explored this possibility at length, highlighting several areas where EPA's use and exposure analysis was incomplete.[56]

Finally, the Document notes the dearth of ecotoxicity data for PV29 other than for acute aquatic toxicity and concludes that the potential for risk to the environment cannot be addressed meaningfully without further testing, given the evidence of potential biodegradation and bioaccumulation.

In short, the PV29 assessment by EU REACH program is in conflict with the draft EPA evaluation on several fundamental issues. Troublingly, the information that caused the BE CA to raise concerns about PV29's PBT potential was "reasonably available" to EPA yet completely overlooked, and EPA failed to identify the additional studies necessary to address these concerns recommended in the EU Document. Clearly, these omissions require EPA to reexamine its basis for determining that PV29 does not present an unreasonable risk of injury.

V. Despite FOIA Requests, EPA Has Failed to Provide any Supporting Data or Other Justification for the Critical Workplace Air Concentration on Which Its MOE Calculation is Based

As our groups discussed in our initial comments,[57] the sole basis (p.22) in the draft evaluation for estimating worker exposure levels for PV29 is a "personal communication" by a US manufacturer that "an approximate maximum workplace air concentration of 0.5 mg/m3 would be expected over a 12-hour shift (Mott, 2017a)." The draft evaluation indicates that the reported concentration was based on monitoring, but the methods and results are not provided. Without knowing how the concentration was determined and examining the actual data, it is impossible to assess whether it was obtained using accurate and reliable methods and represents maximum worker exposure levels, as EPA claims.

Because no documentation for the reported workplace concentration could be found in the PV29 docket, our groups submitted a FOIA request for "[a]ll workplace air monitoring data or other records, irrespective of date, supporting EPA's statement in the draft Risk Evaluation that "approximate maximum workplace air concentration of 0.5 mg/m3 would be expected over a 12 hour shift." The

[55] PV29 Evaluation, at 5.
[56] Initial Comments, at 13-16.
[57] Id. at 13.

interim response from EPA on March 19, 2019 provided emails between EPA and Sun Chemical that showed that on September 22, 2017 EPA had requested "any additional information on PV29 air release for occupational exposure" and that on September 25 the Sun representative responded that "[i]nhalation testing has shown exposure was ~0.5mg/m3 over a 12 hour work shift+."[58] There is no indication in the FOIA response that EPA followed up by requesting all backup information from Sun, otherwise attempted to substantiate the reported workplace concentration or sought to obtain the results of monitoring of individual worker exposures.

EPA's failure to take these fundamental steps has made it impossible to review the quality and reliability of this single undocumented data point, let alone assess whether it is representative of typical and foreseeable worker exposure levels. Yet the data point is used in the draft evaluation not simply to assess worker exposure during PV29 manufacturing but to support sweeping conclusions about maximum exposure levels during all other industrial, commercial and consumer uses of PV29 and ultimately to calculate an MOE which is EPA's sole basis for determining that PV29 poses no risk of harm to human health. This is wholly unjustified in light of TSCA's requirement to base risk evaluations on the "best available science" and all "reasonably available" information as well OPPT's purported commitment to assuring "information quality" through its systematic review process.

Conclusion

Based on the new information EPA made available after the close of the initial comment period, it is now clearer than ever that the Agency lacks data sufficient to determine whether PV29 presents an unreasonable risk of injury to health or the environment. The Agency should withdraw the draft evaluation and then use its authority under TSCA to obtain and publicly release all reasonably available information necessary to fully assess PV29's hazards and exposures under its conditions of use. The draft PV29 evaluation should be reworked to incorporate this additional information and reissued for public comment and peer review. The fatally flawed TSCA systematic review criteria should not be used in the reworked evaluation or other TSCA risk evaluations and should be replaced by an alternate, peer reviewed systematic review methodology.

We appreciate this opportunity to submit supplemental comments on the PV29 draft risk evaluation.

Please contact SCHF counsel Bob Sussman with any questions at bobsussman1@comcast.net.

Respectfully submitted,

Liz Hitchcock
Acting Director
Safer Chemicals Healthy Families

Jonathan Kalmuss-Katz
Staff Attorney
Earthjustice

Patrick MacRoy
Deputy Director
Environmental Health Strategy Center

Daniel Rosenberg
Senior Attorney
Natural Resources Defense Council

[58] Email from Scott Sherlock of EPA to Jonathan Kalmuss-Katz of Earthjustice re FOIA Requests EPA-HQ-2019-001853 and EPA-HQ-2019-001976 (Earthjustice), March 19, 2019.

Pamela Miller
Executive Director
Alaska Community Action on Toxics

Veri di Suvero
Executive Director
Alaska Public Interest Research Group (AkPIRG)

Linda Reinstein
President and CEO
Asbestos Disease Awareness Organization

Janet Nudelman
Director of Program and Policy
Breast Cancer Prevention Partners

Deanna White
Director
Healthy Legacy Coalition

Madeleine Foote
Legislative Representative
League of Conservation Voters

Raphaela Hsu-Flanders
Program Analyst & Engagement Manager
Oregon Environmental Council

Ted Schettler MD, MPH
Science Director
Science and Environmental Health Network

Kara Cook
Toxics Director
US PIRG

Lauren Hierl
Executive Director
Vermont Conservation Voters

Jamie McConnell
Director of Programs and Policy
Women's Voices for the Earth