

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

**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 (January 14, 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 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).<sup>1</sup>

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.

The PV29 draft is the first risk evaluation EPA has released under the 2016 TSCA amendments. The new requirements for risk evaluations were added to the law in order to establish a rigorous process for assessing the hazard and exposure profile of chemicals of concern and making a science-based determination 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. It also required a transparent public process with extensive public input and peer review. The number of risk evaluations EPA must conduct at any given time is limited, underscoring that each evaluation is expected to be comprehensive and authoritative. EPA’s evaluations function not only to identify chemical risks that warrant regulation under TSCA but also to provide the public with credible judgments on the safety of chemicals to which it is exposed.

The PV29 evaluation falls woefully short of meeting these expectations and the requirements established by Congress. 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 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 yet failed to

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<sup>1</sup> Throughout these comments, the draft evaluation is referenced as the “PV29 evaluation.”

do so, instead reaching categorical conclusions about the absence of risk that cannot be supported by the inadequate data in the record.

In the body of these comments,<sup>2</sup> we show that:

- EPA has violated TSCA and deprived the public of a meaningful opportunity to comment by denying access to the 24 studies on which its risk evaluation is based and withholding other critical information about PV29's uses and exposure profile.
  - EPA must disclose the 24 studies and other information and extend the comment period so that the public can review and analyze these materials and provide informed feedback to the Agency.
- A determination of no unreasonable risk under TSCA must be supported by substantial evidence establishing that exposure to a substance will not result in adverse human or environmental effects under its conditions of use.
  - Conjecture or limited data are not enough to support this determination. Instead, EPA must make an affirmative showing that no unreasonable risk exists.
  - Given the Agency's ample TSCA information collection/development authorities, EPA cannot sit on its hands and fail (or refuse) to obtain reasonably available information and then determine that a chemical does not present an unreasonable risk in the absence of data necessary to support such a finding.
- Under section 26(k) of TSCA, when conducting TSCA risk evaluations, EPA "shall take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available."
  - In its final "framework" rule for risk evaluations, EPA underscored that information that either exists or "can be obtained through testing" is "reasonably available" and that the Agency may be obligated to require "data [to be] generated in response to EPA data gathering, including testing, authorities" to meet its obligation to consider reasonably available information.
  - Under section 4(a)(2)(A)(i), EPA is expressly authorized to use testing orders, rules or consent agreements where it "determines that information is necessary . . . to perform a risk evaluation under section 6(b)."
  - A risk evaluation that fails to utilize information that is readily obtainable upon request or through TSCA testing or reporting requirements violates EPA's obligation to consider "reasonably available information."

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<sup>2</sup> Our comments incorporate by reference previous comments by these organizations on the PV29 scoping document and problem formulation. These include Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act (September 19, 2017) EPA-HQ-OPPT-2016-0725-0042, and Comments of Safer Chemicals Healthy Families et al. on Risk Evaluation Problem Formulation Documents for Ten Chemical Substances under the Toxic Substances Control Act (August 16, 2018) EPA-HQ-OPPT-2016-0725-0068.

- EPA’s assessment of PV29’s conditions of use is cursory and incomplete and fails to include basic information about human exposure and environmental release critical for a meaningful assessment of PV29’s risks to health and the environment.
  - EPA’s 1992 Guidelines for Exposure Assessment illustrate the breadth and depth of information that the Agency typically requires in determining the nature and extent of chemical exposures.
  - The absence of this information on PV29 is the direct result of EPA’s failure to obtain “reasonably available information” as required by TSCA.
  - For example, EPA’s determinations of worker and consumer exposure for all PV29 uses are based on a single undocumented determination of PV29 air concentrations during manufacturing which EPA then extrapolated to downstream industrial and consumer uses based on the unsubstantiated and likely erroneous claim that unsubstantiated manufacturing exposures represented a “worst case” and exposures during all other conditions of use would be necessarily much lower.
  - Similarly, EPA asserted that PV29’s low solubility equated to an absence of absorption by the dermal and inhalation routes of exposure, but did not provide confirmatory data, which could have been readily obtained using EPA’s section 4 testing authority.
  - Research undertaken for our organizations demonstrates that EPA erroneously concluded that PV29 is not being imported, ignored known uses and greatly underestimated the exposure potential of uses it had identified.<sup>3</sup>
  
- The limited studies on which EPA based its determination of no unreasonable risk not only fail to demonstrate that PV29 lacks adverse human health effects but in fact raise significant concerns.
  - EPA relied on acute inhalation studies deemed “unreliable” by the PV29 manufacturer that conducted them.
  - The reproductive/developmental effects screening study that EPA cites to derive a No Observed Adverse Effect Level (NOAEL) and Point of Departure (PoD) used biased and faulty statistics, disregarded statistically significant body weight changes in males and females, and dismissed gross lesions in the treatment groups.
  - EPA improperly placed no reliance on two single dose studies in mice by the intraperitoneal (i.p.) route that report clinical effects and deaths at doses below the oral, inhalation, and dermal doses that are reported to be “no effect” levels for PV29.
  
- EPA has disregarded longstanding EPA guidance, policies, and practices specifying the evidence necessary to demonstrate the absence of hazard and risk.
  - At a minimum, consistent with Agency policy and practice, EPA could not have determined that PV29 lacked adverse health effects without –
    - Toxicokinetic information (metabolic and excretion rates, etc.) for PV29 that could help inform predictions about its toxicity profile

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<sup>3</sup> This research is summarized in the attached Supplemental Information.

- High-quality, reliable experimental test results for acute inhalation toxicity
    - A respiratory sensitization study
    - A 90-day repeated dose toxicity study for oral, inhalation, and dermal routes of exposure
    - A full battery of tests for genetic toxicity, including in vivo tests for chromosome damage, cytotoxicity, and other relevant endpoints
    - A whole animal carcinogenicity study
    - A developmental neurotoxicity study (which includes possible neurobehavioral effects)
    - A neurotoxicity study
    - Two generation reproduction toxicity studies
    - Studies for acute and chronic endocrine effects
  - These studies are necessary not only based on EPA risk assessment guidelines but because Structure Activity Relationships (SAR) and modeling provide indicators of concern for PV29's carcinogenicity, developmental/reproductive effects and endocrine effects.
  - When it selected PV29 for a risk evaluation in December 2016, EPA could have required initiation of the necessary studies under a testing order or consent agreement and results for most of these studies would have been in hand well before the June 2020 deadline for completing the PV29 risk evaluation.
- EPA's Margin of Exposure (MOE) analysis does not properly account for all uncertainty factors and, if these factors were applied, EPA could not conclude that PV29 lacks adverse effects at expected exposure levels.
  - The extensive and fundamental gaps in available exposure and hazard data call into question whether an MOE analysis for PV29 has any value in assessing risk.
  - In any event, the MOE calculation in the draft evaluation deviated from established policy and practice by EPA and other authoritative bodies that call for the application of uncertainty factors (UFs) based on data gaps, reliance on a short duration study (subchronic to chronic extrapolation), use of an oral study to calculate inhalation and dermal risks and the presumed increased vulnerability of pregnant women, infants, and children.
  - With these additional uncertainty factors, the revised benchmark MOE would be 1,000,000 rather than 100 as calculated in the draft risk evaluation.
  - In the draft risk evaluation, the inhalation margin of exposure is 14,933 and the dermal margin of exposure is 361 (p. 29-30). Because both are greater than 100, EPA has determined that PV29 does not present an unreasonable risk.
  - However, since the dermal and inhalation MOEs are well below 1,000,000, a revised benchmark MOE would fail to support EPA's determination that PV29 is not expected to cause adverse health effects at anticipated levels of exposure.
- EPA has failed to justify its determination that PV29 does not present an unreasonable risk of injury to the environment

- EPA guidelines for ecological risk assessment typically call for studies of acute and chronic effects in a range of invertebrates, aquatic species, and terrestrial species – well beyond the limited studies available for PV29.
  - EPA could readily have required additional ecotoxicity testing when it selected PV29 for a risk evaluation in December 2016. Its failure or refusal to obtain “reasonably available information” should not now enable it to base a finding of no unreasonable risk to the environment on insufficient data.
  - As EPA acknowledged, it lacked any measured data on PV29 releases to the environment and concentrations in environmental media. This information, too, could have been obtained by requiring PV29’s manufacturer to conduct monitoring and therefore was also “reasonably available.”
- Reliance on the TSCA “systematic review” criteria is a serious shortcoming in both the PV29 evaluation and the 9 other risk evaluations now underway, since these criteria are in conflict with other established, peer-reviewed systematic review methodologies used by EPA and other agencies and have not themselves received external peer review.

Given these many flaws, EPA should withdraw its draft risk evaluation for PV29 and recognize that insufficient evidence is available to determine whether it presents an unreasonable risk of injury to health or the environment. The Agency should then use its authority under TSCA to obtain the information necessary to fully assess PV29’s hazards and exposures under its conditions of use and reach defensible, science-based conclusions about its risks to humans and ecological receptors. The draft PV29 evaluation should be reworked to incorporate this additional information and reissued for public comment and peer review.

**I. EPA HAS VIOLATED TSCA AND DEPRIVED THE PUBLIC OF A MEANINGFUL OPPORTUNITY TO COMMENT BY DENYING ACCESS TO THE STUDIES AND OTHER CRITICAL INFORMATION ON WHICH ITS RISK EVALUATION IS BASED**

**A. The 24 Studies Withheld by EPA are “Health and Safety Studies” that must be Disclosed under TSCA**

The 24 studies, conducted by PV 29’s manufacturers, purport to address its physical and chemical properties, environmental fate, human health effects and toxicity to aquatic organisms. According to the draft risk evaluation, 20 of the studies were submitted to the European Chemicals Agency (ECHA) in support of registration under the European Union (EU) REACH Regulation. The other four studies were not provided to ECHA but were apparently submitted to EPA by an unnamed data owner. EPA has made available the “robust summaries” prepared by the data owners for the 20 studies submitted to ECHA but has withheld all 24 studies based on “a claim of business confidentiality by the data owners.” PV29 Evaluation at 6.

**1. Required Disclosure of Health and Safety Studies under TSCA Section 14(b)**

Section 14(b) of TSCA is titled “Information Not Protected from Disclosure.” Section 14(b)(2) provides that the law’s restrictions on the release of confidential business information (CBI) do not “prohibit the disclosure . . . of any health and safety study which is submitted under this Act” for a chemical substance

which “has been offered for commercial distribution.” The absence of CBI protection extends to both the study itself and “any data reported to, or otherwise obtained by, the Administrator from” the study.

EPA’s long-standing position is that it lacks any legal basis for withholding health and safety studies from the public. As stated in 40 C.F.R. § 716.55(a)(1): “Section 14(b) of TSCA provides that EPA may not withhold from disclosure, on the grounds that they are confidential business information, health and safety studies of any substance or mixture that has been offered for commercial distribution . . .”

EPA reaffirmed this position in its May 27, 2010 Policy on CBI Claims for TSCA Health and Safety Studies (75 Federal Register 29754) as follows:

“Section 14(b) of TSCA does not extend confidential treatment to health and safety studies, or data from health and safety studies, which, if made public, would not disclose processes used in the manufacturing or processing of a chemical substance or mixture or, in the case of a mixture, the release of data disclosing the portion of the mixture comprised by any of the chemical substances in the mixture.”

“Section 14(b)(1) of TSCA provides that health and safety studies and data from health and safety studies are not entitled to confidential treatment unless such information, if made public, would disclose processes used in the manufacturing or processing of a chemical substance or mixture or in the case of a mixture, the portion of the mixture comprised by any of the chemical substances in the mixture. (15 U.S.C. 2613(b)(1))”

“The TSCA section 14(b) exclusion from confidential protection for information from health and safety studies indicates the importance attributed by Congress to making such information available to the public.”

## **2. TSCA Definition of Health and Safety Study**

Section 3(8) of TSCA defines “health and safety study” as “any study of any effect of a chemical substance or mixture on health or the environment or on both, including underlying information and . . . toxicological, clinical and ecological studies . . .” EPA regulations at 40 CFR 716.3 state that “[i]t is intended that the term health and safety study be interpreted broadly” and encompass “[a]ny data that bear on the effects of a chemical substance on health or the environment.” The regulations are explicit that tests to determine the chemical and physical properties and fate and transport behavior of a substance fall within the definition, along with studies of a chemical’s human health effects and ecotoxicity.

Thus, the 24 studies on PV29 are “health and safety studies” that cannot receive CBI protection under TSCA. Moreover, EPA’s obligation to disclose these studies cannot be satisfied merely by releasing “robust summaries” but requires public access to the full studies.

EPA has not described the claim(s) of confidentiality that it believes justifies withholding the 24 studies, but with respect to chemical substances, the only portion of a health and safety study that can be treated as CBI under section 14(b)(2) is information “that discloses processes used in the manufacture or processing of a chemical substance.” The 24 studies likely contain little, if any, information meeting this description, and in the unlikely event any of the studies contain legitimate and substantiated CBI of this

type, it can be redacted while all health and safety information is disclosed as provided for in section 14(b)(1).

It is possible that the data owners are basing their CBI claims on an alleged “proprietary interest” in the studies under REACH. However, EPA could only honor these CBI claims if they have a basis in section 14 of TSCA. Nothing in section 14 allows EPA to avoid its unconditional obligation to disclose health and safety studies because of property right claims under European Union (EU) law.

### **3. Robust Summaries Cannot Substitute for the Studies Themselves**

EPA has suggested that public access to the 24 studies is unnecessary because it “has confirmed that the results of these full study reports are consistent with the corresponding robust summaries available in ECHA.” (PV29 evaluation at 6.) However, this puts the public in the untenable position of accepting EPA’s findings on faith. Without access to the full studies, the public cannot form its own judgments about the quality of the studies and the proper interpretation of the results. Moreover, as described below, the robust summaries provide general evidence that PV29 may in fact have adverse effects but the lack of critical data precludes a full analysis of the basis for this concern. Thus, the public cannot adequately comment on whether EPA’s reliance on the studies is or is not justified and whether they in fact support the Agency’s conclusion that PV29 does not present a risk of harmful effects on health and the environment. EPA’s withholding of the studies effectively shuts the public out of the comment process because the 24 studies comprise the sole scientific basis for EPA’s determination that PV29 is not toxic to humans or aquatic species.

EPA’s indication that it will allow members of the Scientific Advisory Committee on Chemicals (SACC) to review the 24 studies but deny access to the public only compounds this lack of transparency. An essential element of peer review under EPA’s Peer Review Handbook is a process to provide public input to the reviewers. This will be impossible if the public lacks access to the 24 studies. Moreover, by treating portions of the peer review process as CBI, EPA will deny the public full access to the peer reviewers’ conclusions and recommendations on a central element of the PV29 evaluation, further blocking meaningful public participation in the review process. It also will constrain the peer reviewers’ ability to engage in a robust debate and discussion during the peer review process.

#### **B. The Docket for the PV29 Evaluation Does not Provide Any Documentation for Critical Exposure Information on Which EPA Has Relied**

Examples of this information include:

- 1) The sole basis for EPA’s estimates of worker and consumer exposure to PV29 is the assertion that “an approximate maximum workplace air concentration of 0.5 mg/m<sup>3</sup> would be expected over a 12-hour shift” during PV29 manufacture. The basis for this assertion is a communication from Sun Chemical, PV29’s producer, referenced in the draft evaluation as “Mott, 2017a.” However, neither the docket nor any other publicly available source

documents this communication and explains how the air concentration of 0.5 mg/m<sup>3</sup> was derived.<sup>4</sup>

- 2) EPA has also relied on industry communications to identify uses of PV29 and related volumes and exposure scenarios. These communications are apparently also the basis for determining that several previously reported uses of PV29 no longer exist in the US and do not need to be assessed. According to the docket, EPA met with the Color Pigments Manufacturers Association (CPMA) and Sun Chemical on February 13, 2017 and they provided “information on the processing, manufacturing, and use of Pigment Violet 29.” EPA-HQ-OPPT-2016-0725. However, the information provided is nowhere to be found. Similarly, other cited communications from industry are unavailable.
- 3) A critical driver of EPA’s assessment of PV29 levels in the environment in EPA’s statement in the draft risk evaluation is that “of the NPDES-permitted TSS discharges for this sole domestic manufacturing facility, it is estimated that 0.6 lb/day of C.I. Pigment Violet 29 is being discharged (<0.1 percent of produced C.I. Pigment Violet 29).” However, no documentation of the basis for this estimate and the underlying calculations is available.

The absence of these critical supporting materials has impeded meaningful public scrutiny of the technical and scientific basis for the PV29 risk evaluation.

### **C. EPA Must Disclose the 24 Studies and other Information and Extend the Comment Period to Enable the Public to Review and Provide Feedback on Them**

There is no legal or policy basis for withholding the studies and other information described above. Accordingly, several of our organizations requested their disclosure under the Freedom of information Act (FOIA) on December 4 and 7, 2018 and submitted a detailed letter to Deputy Assistant Administrator Beck and her senior staff underscoring the need for access to the 24 studies on December 6, 2018. The comment deadline has now passed without any response to these requests. As a result, our organizations and other members of the public have been deprived of a meaningful opportunity to comment on the draft evaluation, as required by the Administrative Procedure Act (APA) and section 6(b)(4)(h) of TSCA. EPA should rectify this violation of law by disclosing the withheld materials as soon as possible and then reopening and extending the comment periods so that the public can review and analyze these materials and provide informed feedback to the Agency.

## **II. A Determination of No Unreasonable Risk under TSCA Must be Supported by Substantial Evidence Establishing that Exposure to a Substance Will Not Result in Adverse Human or Environmental Effects under its Conditions of Use**

The PV29 draft is a limited screening-level evaluation which relies on a small and incomplete dataset to reach overbroad, poorly documented and largely qualitative conclusions about PV29’s absence of risk to

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<sup>4</sup> For these and other communications, the evaluation provides links to EPA’s HERO data-base. However, these links open to summary sheets that reference the cited communications and dates when they occurred but do not provide the substance of the communications or other information.



health and the environment. It thus fails to provide the definitive evidence and rigorous analysis that TSCA requires to support a determination that PV29 does not present an unreasonable risk of injury.

**A. Risk Evaluations under TSCA are Intended to Make a Definitive Determination Whether a Substance Does or Does Not Present an Unreasonable Risk of Injury**

Under section 6(b)(4), the goal of risk evaluations is stated in unconditional terms:

“The Administrator shall . . . determine whether a chemical substance presents an unreasonable risk to injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use.”

The burden on EPA to exonerate a chemical at the risk evaluation stage is a high one. As the Senate report explains, the unreasonable risk standard in the new law is one that “ensures, without taking into consideration cost or other non-risk factors, that no unreasonable risk of injury to health or the environment will result from exposure to a chemical substance under the conditions of use . . .” S. Rep. No. 94-698, 114<sup>th</sup> Cong, 1<sup>st</sup> Sess. (2015) at 17.

Congress structured TSCA so that risk evaluations are the culmination of a multi-step process that includes information collection under Section 8, testing and information development under section 4 and prioritization under section 6(b)(2). This process is designed to assure that chemicals undergoing risk evaluations are carefully selected and that the data available to conduct such evaluations are sufficient for an in-depth analysis of hazard, exposure and risk. As described in the Senate report on the new law, risk evaluations were intended to “look comprehensively at the hazards associated with the chemical,” S. Rep. No. 94-698, at 2. Congress thus expected that, at the risk evaluation stage, EPA would conduct a thorough analysis, informed by comprehensive information, to support a determination that a substance does not pose an unreasonable risk to health or the environment.

Under section 6(b)(2)(B), Congress required EPA to conduct risk evaluations on only 20 chemicals every 3.5 years and provided up to 3.5 years to complete each evaluation under section 6(b)(4)(G). By requiring EPA to conduct risk evaluations on a small subset of chemicals and allowing ample time to complete them, Congress underscored the importance it attached to rigorous analysis and definitive judgments about risk and signaled that a screening-level assessment using limited data and highly uncertain assumptions about hazard and exposure would not pass muster under the law.<sup>5</sup>

**B. The Preliminary Risk Findings Required Under Other TSCA Provisions Underscore the Definitive Nature of Unreasonable Risk Determinations under Section 6(b)(4)**

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<sup>5</sup> In section 18 of TSCA, Congress for the first time gave EPA the authority to preempt states based on a finding of no unreasonable risk. However, it conditioned that authority on EPA doing a thorough, fully informed risk evaluation of all conditions of use, based on all reasonably available information. Congress did not intend for EPA to preempt the states – curtailing long-standing state authority -- using a slipshod risk evaluation process that fails to meet the law’s requirements for transparency, documentation or scientific rigor.

The contrast between section 6(b)(4) and several other provisions of TSCA confirms the high bar EPA must meet in determining that a chemical undergoing a risk evaluation does not present an unreasonable risk of injury.

For example, the standard for identifying a chemical as “high priority” under section 6(b)(1)(B) is a finding that it “may present an unreasonable risk . . . because of a potential hazard and a potential risk of exposure.” Since the purpose of high-priority designations is to select chemicals for risk evaluations, Congress expected that the ensuing risk evaluations would provide considerably more certainty regarding whether an unreasonable risk does or does not exist.

Similarly, “low priority” listings under section 6(b)(1)(B) identify chemicals “for which risk evaluations are not warranted.” The standard for low-priority designation is that there is “*sufficient information to establish*” that a substance lacks the potential for unreasonable risk under its conditions of use (emphasis added). Congress clearly expected risk evaluations to provide at least as much (if not greater) certainty about the absence of risk as low-priority designations. Thus, EPA cannot base a determination that a substance “does not present an unreasonable risk of injury” on conjecture or limited data. Instead, it must make an affirmative science-based showing that no such risk exists. Career federal cancer experts have warned that “Declaring a chemical as not hazardous, or reducing a level of health protection, should require validation, not speculation.”<sup>6</sup> Serious public health consequences may follow if chemicals are misclassified as low risk or non-toxic based on untested hypotheses, poorly validated tests, or incomplete data sets.

In TSCA’s new chemical review provisions, section 5(a)(3)(C) authorizes EPA to allow a new substance to enter commerce without restriction if it determines that the substance “is not likely to present an unreasonable risk of injury.” By contrast, an existing substance will escape regulation under section 6(a) only if EPA conducts a comprehensive risk evaluation and determines that that it *does not* present an unreasonable risk of injury. A preliminary finding of “unlikely risk” based on limited information will not meet this high standard.

Further underscoring the need to affirmatively demonstrate the absence of unreasonable risk is EPA’s obligation under section 19(c)(1)(B)(i)(II) to support such determinations “by substantial evidence in the record taken as a whole.” A determination of no unreasonable risk based on conjecture or incomplete data will lack substantial evidence and a reviewing court would be required to set it aside.

Both TSCA and longstanding EPA risk assessment guidance and precedent speak to the data required for science-based conclusions about the absence of hazard and risk. As shown below, these touchstones underscore the inadequacy of the PV29 risk evaluation and its failure to meaningfully demonstrate the absence of unreasonable risk.

### **III. EPA Has the Tools under TSCA to Obtain Comprehensive Data for Risk Evaluations and is Obligated to Use These Tools Rather than Rely on Inadequate Information**

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<sup>6</sup> Melnick RL, Kamel F, Huff J. Declaring chemicals “not carcinogenic to humans” requires validation, not speculation. *Environ Health Perspect.* 2003 Apr;111(4):A203-4.

Section 4 of TSCA provides EPA with broad authority to require chemical manufacturers to conduct testing. EPA is also empowered to require submission of existing data and information under the reporting provisions of section 8 and the subpoena and inspection provisions of section 11. These authorities give the Agency the means to assure that comprehensive data are available to inform its risk evaluations. Indeed, recognizing the need for more testing to support risk determinations, the 2016 TSCA amendments streamline section 4 by authorizing EPA to issue orders in addition to rules requiring development of data. Significantly, under section 4(a)(2)(A)(i), EPA is expressly authorized to use testing orders, rules or consent agreements where it “determines that information is necessary . . . to perform a risk evaluation under section 6(b).”

EPA also has an obligation to use these or other tools to obtain the information necessary for informed determinations of risk. Under section 26(k) of TSCA, when conducting risk evaluations under section 6, EPA “shall take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonable available to the Administrator.” EPA’s risk evaluation “framework” rule defines reasonably available information as “information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation.” 40 C.F.R §702.33. The preamble to the rule underscores that information that either exists or “can be obtained through testing” is “reasonably available” and that the Agency may be obligated to require “data [to be] generated in response to EPA data gathering, including testing, authorities” to meet its obligation to consider reasonably available information. 82 Fed. Reg. 33726, 33732 (July 20, 2017).

EPA’s obligation to obtain “reasonably available information” is aligned with its responsibility under section 26(h) to “use scientific information . . . in a manner consistent with the best available science.” Section 26(h)(1) provides that, in carrying out this responsibility, EPA must consider whether scientific information is “reasonable for and consistent with the intended use of the information” and “relevant for the Administrator’s use in making a decision about a chemical substance or mixture.” Where the data on a chemical are insufficient for a science-based assessment of a chemical’s risks to human health and the environment, EPA will lack the “best available science” for decision-making and will be required to obtain more extensive and reliable data that are “reasonably available.”

EPA has itself recognized that it must take steps to obtain the information necessary for a robust risk evaluation as early in the process as possible:

“EPA will seek to generally ensure that sufficient information to complete a risk evaluation exists and is available to the Agency prior to initiating the evaluation. . . . EPA also recognizes that there may be circumstances where additional information may need to be developed within the time frames of the risk evaluation process.”

*Id.* Given the Agency’s ample TSCA information collection/development authorities and its obligation to consider reasonably available information, EPA cannot sit on its hands and then determine that a chemical does not present an unreasonable risk in the absence of data sufficient to support that determination. Yet this is exactly what EPA is doing in the PV29 risk evaluation.

#### **IV. EPA Failed to Fulfill Its Obligation under TSCA to Obtain “Reasonably Available Information” on Human and Environmental Exposure to PV29**

The draft risk evaluation's description of PV29's conditions of use is cursory and incomplete and fails to include basic information about human exposure and environmental release critical for a meaningful assessment of PV29's risks to health and the environment. These shortcomings are the direct result of EPA's failure to obtain "reasonably available information" as required by TSCA and its reliance on broad assumptions about exposure and use that are nowhere substantiated in the draft evaluation or accompanying docket. EPA's 2016 draft Guidelines for Exposure Assessment illustrate the breadth and depth of information that the Agency typically requires in determining the nature and extent of chemical exposures.<sup>7</sup> The absence of this information for PV29 underscores the inadequacy of EPA's exposure assessment and its failure to utilize "reasonably available information" and "the best available science."

### **A. EPA Lacks Adequate Information on Human Exposure to PV29**

Several examples highlight "reasonably available information" on human exposure that is missing in the PV29 risk evaluation and is essential for a credible exposure characterization:

#### **1. Engineering Controls**

EPA asserts (PV29 evaluation at 22) that engineering controls used in the manufacture of PV29 and its use as a site-limited intermediate limit exposure. However, the evaluation provides no specific information about the nature of these controls and the degree to which they reduce exposure. While it cites two Safety Data Sheets (SDSs), they are not available in the docket or elsewhere on the EPA website<sup>8</sup> and in any event would not document the specific process steps and control equipment used in the manufacture of PV29. EPA asserts (p.29) that a "[c]hemical manufactured and used as a site limited intermediate typically requires minimum handling, resulting in limited releases and exposure." However, this generalization is far from universal and EPA offers no specific information to demonstrate that it is correct for PV29.

#### **2. PPE**

Similarly, EPA touts the role of personal protective equipment (PPE) in reducing worker exposure, maintaining (p. 22) that this equipment "includes safety glasses with side-shields, dust goggle under certain circumstances, chemical resistant impervious gloves, and particulate respirators if needed." EPA's assumptions about PPE use are solely based on the recommendations in PV29's manufacturer's SDS, which is not available in the docket and in any case is not binding on that manufacturer or PV29's processors and users. The Agency does not provide the details of workplace protection programs requiring the use of PPE or document that PPE is consistently used by workers. As EPA has elsewhere emphasized, PPE utilization in the workplace is highly uneven and cannot be assumed to provide adequate worker protection.<sup>9</sup> That is why OSHA policy and accepted industrial hygiene practice is to

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<sup>7</sup> [https://www.epa.gov/sites/production/files/2016-02/documents/guidelines\\_for\\_human\\_exposure\\_assessment\\_peer\\_review\\_draftv2.pdf](https://www.epa.gov/sites/production/files/2016-02/documents/guidelines_for_human_exposure_assessment_peer_review_draftv2.pdf)

<sup>8</sup> To document these SDSs, the risk evaluation contains links to the HERO data-base but, as discussed above, these links do not open to the SDSs or any other information of substance. Moreover, one of the SDSs is from BASF, which does not manufacture PV29 in the US.

<sup>9</sup> In the preamble to its proposed rule banning methylene chloride paint removers, EPA discussed at length the shortcomings of relying on respirators for effective worker protection as well as the uneven implementation of warning levels and PPE recommendations in SDSs. 82 Federal Register 7464, 7445, 7473-4 (January 19, 2017).

examine whether engineering controls, standing alone, are effective in preventing unsafe worker exposures – an analysis conspicuously absent from the PV29 evaluation.<sup>10</sup>

### **3. Workplace Exposure Levels.**

EPA's sole basis (p.22) 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/m<sup>3</sup> would be expected over a 12-hour shift (Mott, 2017a)." As noted above, the substance of this communication is not publicly available. 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 meaningfully represents maximum worker exposure levels, as EPA claims.

Clearly, the detailed basis for the industry estimate was "reasonably available" to EPA. The Agency could have requested all backup information from the manufacturer voluntarily or used its subpoena and inspection authority to obtain it directly, but the Agency apparently did neither. Moreover, despite its central role in the risk evaluation, EPA did not subject the reported workplace concentration to a review for quality and reliability through its systematic review process. The draft evaluation seeks to excuse this lapse (p.18) on the cryptic rationale that its systematic review framework "is not well suited for the review of these types of references." However, this framework in fact provides extensive data quality criteria for occupational exposure and release data.<sup>11</sup> In any case, apart from its systematic review process,<sup>12</sup> EPA had an obligation under TSCA section 26(h) to determine the reliability of reported workplace concentrations or refrain from relying on them because they do not represent the "best available science."

Finally, the best evidence of workplace exposure is monitoring of individual worker exposure concentrations. It does not appear that EPA inquired about the availability of this information or made any effort to obtain it. To the extent that worker monitoring data do not exist, EPA could have exercised its authority under section 4 to require PV29's manufacturer to conduct such monitoring. This would have provided a far more defensible basis to assess worker exposure than an unsubstantiated manufacturer report of an "approximate workplace air concentration" obtained using unspecified methods.

### **4. Downstream Processing and Use**

Based on industry communications, EPA estimates (pp. 9-10) that 10 percent of PV29's production volume (~60,000 lbs) is processed and used in either commercial paints and coatings (~30,000 lbs) or commercial plastic and rubber products (~30,000 lbs). It asserts (p.28) that "worst case" worker exposures would occur during PV29 manufacturing and that worker exposure levels during downstream processing and use would necessarily be lower.

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<sup>10</sup> <https://www.osha.gov/shpguidelines/hazard-prevention.html>

<sup>11</sup> See *Application of Systematic Review In TSCA Risk Evaluations*, May 2018, EPA Document# 740-P1-8001, Appendix D, available at [https://www.epa.gov/sites/production/files/2018-06/documents/final\\_application\\_of\\_sr\\_in\\_tsc\\_05-31-18.pdf](https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tsc_05-31-18.pdf)

<sup>12</sup> As described below, we do not support EPA's systematic review criteria but believe that EPA cannot justify failing to apply them in this instance.

No information is presented to support this claim. It appears that EPA did not contact downstream users to investigate their operations even though the trade association representing PV29's US manufacturer informed EPA that it and its members "do not possess information regarding worker or consumer exposures to downstream products containing the pigment (e.g., coatings, plastics and artist paints)."<sup>13</sup> Thus, there is no information in the docket about the process by which PV29 is formulated into commercial paints and coatings or the types of operations in which these products are applied. EPA notes that PV29-containing paints and coatings are used in the manufacture and refinishing of automobiles but does not address the possibility that these products are spray applied to vehicle parts and bodies in open processes with significant potential for inhalation and dermal exposure. Similarly, EPA identifies PV29 as a component of "merchant ink for commercial printing" but does not address the potential for significant exposure during printing operations. EPA asserts (p.22) that "occupational exposures from these downstream users are likely to be limited due to the expected use of PPE" but offers absolutely no evidence for either this "expectation" or that in reality PPE is in use.

The details of downstream processing and use activities were clearly "reasonably available" and could easily have been obtained but were not. Nor did EPA request or require submission of monitoring or other data documenting worker exposure levels in these operations – information that would have been of considerable value in assessing risks to workers.

## 5. Consumer Exposure

EPA recognizes (at p.9) that "an unknown volume of C.I. Pigment Violet 29 is used in consumer watercolor and acrylic paints." According to the draft evaluation, "there are no explicit age-related restrictions on the purchase of professional artistic paints such as watercolors and acrylics [and] consumer products that are widely available, like watercolor and acrylic paints, could be reasonably foreseen to be used by children."<sup>14</sup> EPA nonetheless concludes (p. 23) that its "exposure scenarios . . . for occupational exposure via inhalation and dermal are expected to greatly exceed any potential consumer exposure to paints."<sup>15</sup>

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<sup>13</sup> Comments of Color Pigments Manufacturers Association, Inc., September 19, 2017, EPA-HQ-OPPT-2016-0725-0039

<sup>14</sup> According to our research, Blick, a major catalog for art educators, whose products are intended for use by "students of all ages," and whose cover features a young person on a skateboard, lists 3 perylene violet products. Supplemental Information, at 3.

<sup>15</sup> Using this logic, EPA then concludes (p. 24) that it need not address any "potentially exposed or susceptible subpopulations" in the PV29 evaluation:

"Exposures of C.I. Pigment Violet 29 would be expected to be higher amongst workers using C.I. Pigment Violet 29 as compared to the general population, so the exposure calculation for workers is based on full immersion and is therefore protective of all other subpopulations, such as children and pregnant women in the general population, which are not expected be exposed to C.I. Pigment Violet 29 at similarly high levels."

However, since EPA has not demonstrated that manufacturing workers experience the highest exposures, it cannot assume that pregnant women or children exposed during downstream use have lesser exposures and are adequately protected. Nor can it assume (as discussed more fully below) that pregnant women and children are not "susceptible" to PV29 given both the absence of adequate data and indications in the available studies that it may pose reproductive and developmental risks.

Again, this claim is entirely unverified. EPA presents no information on the concentrations of PV29 in consumer paints, how these products are used and by whom and the routes and duration of exposure.

EPA also notes the extensive use of PV29 in rubber and plastic materials used in the automobile industry and carpet manufacture, both of which could result in consumer exposure. However, with no supporting data, it concludes (p. 23) that PV29 is “encapsulated” in these materials and thus could not be ingested, touched or inhaled by consumers.

Our research revealed that:

“At least three of the world’s largest carpet companies sell products containing PV29 pigment. This pigment is likely used in the face fiber, as it is the only visible part of carpet. J+J Flooring, now owned by Engineered Floors, sells a tile carpet line called Kinetex, which contains PV29 as an additive at up to 0.1% of the product by weight. Interface’s Graphlex carpet tile, made in the Netherlands and sold in the United States, contains up to 0.1% PV29. Milliken manufactures a carpet in Jiangsu Province, China, called B2 Manaaki Broadloom that contains up to 1% PV29.”<sup>16</sup>

Contrary to EPA’s claims, it is well-known that pigments frequently migrate from plastics.<sup>17</sup> Thus, as our research concluded:

“Young children, crawling on carpet fibers containing this pigment, can potentially be exposed to additives through dermal contact and ingestion. Further, this pigment, and other additives, can also become dispersed into the indoor environment through routine abrasion and cleaning.”<sup>18</sup>

EPA has also ignored the potential for exposure to PV29 when products, including plastics, enter the waste and recycling streams, where any “encapsulated” compound may be released. According to our research, it is well-established that any plastic additive, including pigments, can “be released from plastics during the various recycling and recovery processes and from the products produced from recyclates.”<sup>19</sup>

## 6. Other Uses

EPA’s May 5, 2017 Use and Market Profile for Pigment Violet 29 identifies numerous additional uses, including in odor agents, cleaning/washing agents, surface treatment, absorbents and adsorbents, laboratory chemicals, light-harvesting materials, transistors, molecular switches, solar cells, optoelectronic devices, paper, architectural uses, polyester fibers, adhesion, motors, generators, vehicle components, sporting goods, appliances, agricultural equipment and oil and gas pipelines.<sup>20</sup> In identifying these uses, the Agency consulted a wide variety of commercial and regulatory sources, including materials developed by PV29’s European manufacturer, BASF, and by ECHA.<sup>21</sup>

While acknowledging that some PV29 uses are “unknown,” the draft risk evaluation concludes (p.11) that “no further evidence was found during the problem formulation and risk evaluation to support”

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<sup>16</sup> Supplemental Information, at 3.

<sup>17</sup> *Id.* at 4.

<sup>18</sup> *Id.* at 3.

<sup>19</sup> *Id.*

<sup>20</sup> EPA-HQ-OPPT-2016-0725-0035

<sup>21</sup> European Chemicals Agency (ECHA). 2016. Substance Information: Perylene-3,4:9,10tetracarboxydiimide. Available at <https://echa.europa.eu/substance-information//substanceinfo/100.001.223>.

these uses and therefore they were not further assessed. EPA does not detail the efforts it made to research all reported PV29 uses and explain why uses it initially identified were dropped. For example, it does not appear that the Agency asked Sun Chemical for a list of all its customers or contacted PV29 distributors who might be knowledgeable about the activities of end-users.

Moreover, as EPA acknowledges, CDR reports would not have captured imports of PV29 or products containing it in volumes under 25,000 pounds because these imports would be exempt from CDR reporting requirements. While EPA asserts that its search of US Customs' records did not reveal any imports of PV29, this search likely did not include formulated products containing PV29. European or Asian companies manufacturing or formulating PV29 might well have provided useful information about products exported to the US but apparently were not contacted. Research conducted for our organizations found evidence in the Panjiva trade data-base of imports of both PV29 specifically and pigment products likely containing PV29.<sup>22</sup>

Here again, EPA's failure to obtain "reasonably available information" likely resulted in failure to identify uses with significant exposure potential and an underestimate of the magnitude of exposure.

## 7. Dermal Absorption

Central to EPA's conclusion that human exposure to PV29 is negligible is its presumption of "low absorption by all routes of exposure" (p.6). This presumption is based on the physical-chemical properties of PV29 and not on actual dermal or inhalation exposure data.<sup>23</sup> For example, EPA states:

"Workers may be exposed via inhalation and dermal routes during handling of neat materials. However, absorption via inhalation pathways is expected to be poor due to low water solubility and dermal absorption is estimated to be negligible for the neat material because it is a solid of high molecular weight, use of PPE, and due to poor absorption in solution based on low solubility" (p. 21-22).

EPA has no scientific basis for using low solubility to conclude there would be no human absorption. In fact, ECHA guidance states that for substances that are poorly soluble in water and fats, "absorption may occur via facilitated diffusion, active transport or pinocytosis, processes that are more actively directed and therefore require energy."<sup>24</sup> EPA has apparently failed to consider or ruled out these other mechanisms that facilitate absorption without explaining why. According to the draft evaluation, PV29 "is presented with limited data sets and one of the factors that is missing is the absorption potential" (p.30). This gap could easily have been filled over the last two years by issuing a section 4 testing order

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<sup>22</sup> Supplemental information at 1-2. Relevant Panjiva documentation is attached to these comments.

<sup>23</sup> EPA arbitrarily rules out oral exposure on the following basis:

"Oral ingestion is not a relevant pathway for workers manufacturing C.I. Pigment Violet 29 since there is no foreseeable route of exposure. Standard workplace practices prohibit eating and smoking in manufacturing facilities. In addition, minimal incidental oral exposures are avoided by the use of personal protective equipment (PPE) that are discussed below."

There is no PV29-specific information presented to justify dismissal of an otherwise plausible route of exposure.

<sup>24</sup> Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c: Endpoint specific guidance Version 3.0 June 2017, a page 176.

[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r7c\\_en.pdf](https://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf)



requiring PV29's manufacturer to conduct absorption studies. EPA's failure to take this simple and obvious step is yet another example of its failure to utilize "reasonably available information."

## **B. EPA's Draft Evaluation Lacks Critical Information on PV29's Release to and Presence in the Environment**

### **1. Manufacturing Releases**

According to the draft evaluation, "EPA concludes that approximately 1-2 percent of the [production] volume is potentially released to air, landfill and surface water" (p20). No calculation or data are presented to support this conclusion. Citing communications from Sun Chemical, EPA also "estimate[s] that 0.6 lb/day of C.I. Pigment Violet 29 is being discharged (<0.1 percent of produced C.I. Pigment Violet 29)" (p. 21). The basis for this estimate is not explained in the docket and, as described above, the cited industry communication is not publicly available.

Apart from these unverified estimates of environmental release, the draft evaluation relies on PV29's physical-chemical characteristics (low water solubility, solid physical state and high sorption) and limited manufacturing and use information "to determine that environmental exposures are likely to be limited for C.I. Pigment Violet 29" (p.21). These conclusions are purely qualitative. EPA admits (p. 27) that "the lack of environmental monitoring data means that the limited predicted environmental concentrations cannot be verified empirically." EPA seeks to minimize the absence of monitoring data on the ground that "lack of environmental hazard means that it would be unlikely for environmental concentrations to reach a level where adverse effects could be observed in environmental receptors" (*Id*). However, this claim ignores EPA's own recognition that the available ecotoxicity data on PV29 are extremely sparse.

It would have been simple for EPA to issue an order under TSCA section 4 requiring PV29's manufacturer to measure PV29's concentration in plant effluent and conduct monitoring to determine its presence in environmental media. However, this straightforward step to obtain "reasonably available information" on environmental releases and concentrations was not taken, leading EPA to rely on speculation and unsupported estimates to assess environmental exposure levels.

### **2. Processing and Use Releases**

EPA also lacks any environmental release information on downstream sites processing and using PV29. It nonetheless concludes (p.21) that:

"Because per site volumes handled by downstream users are likely to be much less than the manufacturer (i.e., less than 5 percent each), it is expected that potential C.I. Pigment Violet 29 discharges per site to water and its related sediment, infiltration to groundwater via land application of biosolids, other landfill leaching, and air emissions will be proportionally lower."

However, while downstream sites may handle lower volumes of PV29 than its site of manufacture, it does not automatically follow that environmental releases will be lower. This depends on the nature of the process employed at the downstream site, how much PV29 is lost during site operations and how process wastes and discharges are managed. None of this information is provided in the draft risk evaluation because EPA apparently made no effort to investigate downstream operations. Here again, EPA's evaluation is based on speculation and inference rather than "reasonably available information."

## **V. The Limited Studies Available on PV29 Do Not Support EPA's Claim that It Lacks Adverse Human Health Effects**

EPA seeks to demonstrate that PV29 is not hazardous to human health by drawing far-reaching conclusions from a limited dataset that provides minimal information about its potential toxicity. 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 human health studies found in the ECHA Database and in an FDA Food Additive Petition that, according to EPA, found "that no adverse effects were observed for all routes of exposure (oral, dermal, inhalation), nor were dermal or eye irritation effects reported." Although the full studies have been withheld (erroneously) on CBI grounds, the "robust summaries" of these studies do not support the findings that EPA attributes to them and in fact provide evidence of adverse health effects that EPA has overlooked.

### **A. EPA Lacks Reliable Acute Inhalation Data on PV29**

EPA's assertion that "no adverse effects were observed for" the inhalation route of exposure is based solely on two experimental studies ("Non-Guideline Acute Toxicity: Acute Inhalation Toxicity with Rats (two studies)" conducted by BASF four decades ago (in 1976 and 1978). EPA ranked these two studies as of "medium" quality" in its systematic review.<sup>25</sup> However, according to the robust summary of the studies, *BASF itself labeled them "not reliable" due to use of an "unsuitable test system" and said the studies should be "disregarded due to major methodological deficiencies."* Plainly, the studies cannot be used to conclude that PV29 lacks acute toxicity by the inhalation route. At any time over the last two years, EPA could easily have required PV29's manufacturer to conduct additional inhalation acute toxicity studies that provide valid and reliable data. Its failure to do so violated the Agency's obligation under TSCA to base its risk evaluation on "reasonably available information." Given the absence of reliable acute inhalation studies, EPA's claim that PV29 is not acutely toxic by all routes of exposure is incorrect.

### **B. The Reproductive/Developmental Screening Study on which EPA Bases a NOAEL In Fact Provides Evidence of Adverse Effects**

As the Point of Departure (POD) for its determination of a Margin of Exposure (MOE) for PV29, EPA uses a No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg/day from a reproduction/developmental screening study (OECD 421 test) reported by Stark et al., 2013.<sup>26</sup> The statistical problems with this study are numerous, very serious, and biased towards making it almost impossible to identify any possible adverse effect:

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<sup>25</sup> The surprising finding of "medium quality" during EPA's 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.

<sup>26</sup> The OECD screening Guideline 421 I has been updated to include endocrine endpoints, but the PV 29 test does not include these. See: Test No. 421: Reproduction/Developmental Toxicity Screening Test "This screening Test Guideline describes the effects of a test chemical on male and female reproductive performance. It has been updated with endocrine disruptor endpoints, in particular measure of anogenital distance and male nipple retention in pups and thyroid examination." <http://www.oecd.org/env/test-no-421-reproduction-developmental-toxicity-screening-test-9789264264380-en.htm>

- 1) The “robust summary” fails to provide information on individual animals, and the statistics only compare treatment group means to control group means. With only ten animals per sex per dose, reporting only group averages is the crudest and least sensitive statistical approach, and makes it nearly impossible to detect an effect if one occurs. Typically, EPA IRIS experts would use both the litter and individuals as a statistical unit. The “best available science” would be to use both.
- 2) The study uses only pairwise statistics, comparing each treatment group to the control group, which is a weaker statistical method than a trends analysis to identify a possible trend across all treatment groups. The EPA Cancer Guidelines say that, "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."<sup>27</sup>
- 3) The study uses only two-sided statistical tests (which presume the treatment is like a drug, and could be either harmful or beneficial), instead of one-sided tests that are more appropriate since the alternative hypothesis (to no effect) is harm, not benefit. EPA IRIS scientists normally utilize one-sided tests for this reason. The EPA Cancer Guidelines state, “A two-tailed test or a one-tailed test can be used. In either case a rationale is provided.”<sup>28</sup> EPA has failed to provide any rationale for relying only on the weaker and less-sensitive statistical analysis, which makes it less likely to identify possible significant adverse effects.

As a potent example of the biased use of statistics, the study found statistically significant body weight changes in males and females that were disregarded:

“The mean body weight gain of the F0 males in test group 2 in the entire pre-mating 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.” (note test group 2= 300 mg/ kg bw/ d and test group 1 = 100 mg/ kg bw/ d).

Disregarding these results is inappropriate given that different effects in males and females are often seen with sexually dimorphic responses, and the lack of traditional dose response is often seen with non-monotonic dose response curves. This may be especially relevant to PV29 given the evidence that it may be a reproductive toxicant and an endocrine disruptor, as discussed herein.

Further limiting the weight it should receive, the PV29 screening study was of shorter duration than called for by OECD screening Guideline 421. The OECD 421 test Guideline says: "Females should be

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<sup>27</sup> EPA 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Section 2.2.2.1.2. Statistical considerations. [https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf)

<sup>28</sup> EPA 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Section 2.2.2.1.2. Statistical considerations. [https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf)

dosed throughout the study, so approximately 63 days."<sup>29</sup> However, The ECHA robust summary says, "The duration of treatment covered pre-mating 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 [21 to 23 days] as well as 4 days of lactation in females."<sup>30</sup> This would result in exposure for 54 days total, 9 days less than the Guideline specifies. This makes the study non-compliant with the Guideline and unreliable.

Since the study reports no adverse effects at even the highest dose tested, this makes it a no-effect study, raising concern about whether the study could in fact detect an effect if one occurred. Supporting these concerns, the robust summary notes that:

*"Several animals of test group 2 and 3 revealed a black discoloration of the contents of the glandular stomach, jejunum and colon. These findings are regarded to be treatment related. All other gross lesions noted were single observations and they were regarded to have developed spontaneously and unrelated to compound and treatment"* (emphasis added).

The summary does not address whether there was a dose-related trend in the pathology observations, the type or size of the lesions, the location or affected organs of the lesions, the biological systems affected by the lesions, whether or not they were malignant, or any other relevant details. Moreover, 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. At a minimum, therefore, this cannot be considered a "no effect" study as EPA claims.

These serious questions underscore the need for public review of the study itself since the "robust summaries" do not provide individual animal data and additional critical information needed for an informed interpretation and reanalysis of the study results – underscoring again the importance of making all the PV29 studies available for review and comment.

### **C. EPA Improperly Disregarded Intraperitoneal Studies Reporting Clinical Effects and Death**

It is concerning that EPA places no reliance on two whole animal experimental single dose studies in mice dosed intraperitoneally (i.p.) with PV29 and observed for two weeks after dosing. Both studies report clinical effects and deaths at doses below the oral, inhalation and dermal doses that are reported to be "no effect" levels for PV29. EPA categorizes the two studies as "high" quality under its systematic review criteria (p. 41, Appendix D).<sup>31</sup>

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<sup>29</sup> See OECD screening Guideline 421 at <http://www.oecd.org/env/test-no-421-reproduction-developmental-toxicity-screening-test-9789264264380-en.htm>

<sup>30</sup> EPA-HQ-OPPT-2018-0604-0002, 14\_Toxicity\_to\_Reproduction\_2013; PV29 ECHA Registration Dossier, Toxicity to Reproduction, 002 Key Experimental Study.

<sup>31</sup> Under the category of "Toxicological Information - Acute toxicity, other routes," the ECHA Registration Dossier for PV 29 lists 10 studies. None are key; all are supporting studies only. Studies 001 to 008 are read-across. The last two, 009 and 010, discussed here, are experimental, reliable with restrictions, single dose intraperitoneal (i.p.) routes of dosing in mice with 14 days post-dosing observation.

As described in the robust summary, the 009 experimental study reported deaths as follows: 2/5 males and 5/5 females treated with 10,000 mg/kg, and 1/5 females treated with 6,810 mg/kg died. Clinical signs were as follows:

“Dyspnea, apathy, unsteady gait and ruffled fur were reported until day 4 in mice given 10,000 and 6,810 mg/kg. Death occurred on day 2 and 3, bad general health until and including day 4. Mice given 4640 mg/kg showed dyspnea and ruffled fur only on the first day of treatment.”

The gross pathology was reported as follows:

“Diseased animals - intra-abdominal precipitation of the substance and coloration. Euthanized animals - intra-abdominal precipitation of the substance and coloration, thickening of the edges of the liver.”

The robust summary also noted that:

“In a pretest 2 male mice per dose group were treated with dose levels of 215, 1000 and 4640 mg/kg. No deaths occurred, animals of the high and medium dose showed dyspnea and ruffled fur on the first day of treatment.”

The 010 experimental study used three doses, 2150, 4640 and 10000 mg/kg. The robust summary identifies an LD50 of 7,000 mg/kg. Importantly, it notes that, “At 10,000 mg/kg, all animals died within 7 days. At 4,640 mg/kg, 2/5 males and 1/5 females died; 1/5 males died when treated with 2,150 mg/kg.” This i.p. study reports several clinical signs, “Dyspnoea, apathy, agitation, lying on the stomach, tumbling, bradykinesion, paresis of the hind extremities, spastic walk, shivering, tremors, roll cramps, flexing cramps, tonic cramps, tonic-clonic cramps, systemic red coloration of the skin and bad general health.”

These two experimental studies – both classified as high quality by EPA – report results that are in conflict with the acute oral dose studies that reported no effects at all at up to 10,000 mg/kg! They therefore call into question the accuracy of the acute oral dose studies that fail to report effects as obvious as lethality. Moreover, these data provide evidence that PV29 can be absorbed and metabolized and is toxic, thus challenging EPA’s pervasive presumption that PV29 is not absorbed.

EPA’s rationale for disregarding the two studies is that “the nature of this route of exposure is not relevant for C.I. Pigment Violet 29 because the test material is injected directly into the intra-peritoneum (body cavity) and C.I. Pigment Violet 29 is poorly absorbed by all routes due to its low solubility” (p.25). However, as noted above, EPA lacks any absorption data on PV29 and low solubility is not necessarily indicative of low absorption. Moreover, i.p. dosing studies are considered as part of the overall evidence by ECHA, as evidenced by a category for studies of “other routes” of exposure, and ECHA’s inclusion of both these studies in the PV 29 dossier.<sup>32</sup> The World Health Organization’s cancer research experts at IARC fully consider studies using all routes of exposure, including i.p. dosing: “Route of exposure was considered a less important factor in the evaluation of experimental studies, in recognition that the

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<sup>32</sup> ECHA Registration Dossier for Perylene-3,4:9,10-tetracarboxydiimide. EC number: 201-344-6 | CAS number: 81-33-4. Toxicological Information. <https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/1>

exposures and target tissues may vary across experimental models and in exposed human populations.”<sup>33</sup> There is a strong scientific basis for treating intraperitoneal dosing studies similarly to oral dosing studies:

“Although intraperitoneal delivery is considered a parenteral route of administration, the pharmacokinetics of substances administered intraperitoneally are more similar to those seen after oral administration, because the primary route of absorption is into the mesenteric vessels, which drain into the portal vein and pass through the liver. Therefore substances administered intraperitoneally may undergo hepatic metabolism before reaching the systemic circulation. In addition, a small amount of intraperitoneal injectate may pass directly across the diaphragm through small lacunae and into the thoracic lymph (Turner et al 2011).”<sup>34</sup>

Thus, the two i.p. studies should not have been rejected as irrelevant but instead treated as reliable experimental evidence of PV29’s toxicity and ability to be absorbed and metabolized.

## **VI. EPA Requires Significantly More Data to Support a Determination that PV29 Does not Present an Unreasonable Risk of Injury to Human Health**

Not only do the data cited by EPA fail to support its conclusion that PV29 is not hazardous to human health but, even if accepted at face value, they fall 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 could have required testing under section 4 of TSCA to obtain “reasonably available information” to fill these gaps but instead chose to reach overbroad and unsupported conclusions about the absence of health risk on the basis of inadequate evidence. We explain below why the omitted studies are necessary for informed science-based determinations of no unreasonable risk under established EPA guidance and policy.

### **A. The EPA Safer Choice Program Establishes Detailed Data Requirements for Identifying Chemicals of Low Concern**

For several years, EPA’s chemical safety office has implemented the Safer Choice Program. According to the Agency, “Safer Choice is EPA’s label for safer chemical-based products. Every chemical, regardless of percentage, in a Safer Choice-labeled product is evaluated through EPA’s rigorous scientific process and only the safest ingredients are allowed.”<sup>35</sup> To qualify for EPA’s Safer Choice Green Circle label, a chemical must be “verified to be of low concern based on experimental and modeled data.”<sup>36</sup> EPA looks to several endpoints in applying this standard, including carcinogenicity, reproductive and developmental effects, systemic or internal organ toxicity, mutagenicity, acute toxicity, sensitization,

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<sup>33</sup> Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, Christiani DC, Beland FA, Smith MT. Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis*. 2018 Apr 5;39(4):614-622. see <https://www.ncbi.nlm.nih.gov/pubmed/29562322>

<sup>34</sup> Turner PV, Brabb T, Pekow C, Vasbinder MA. Administration of substances to laboratory animals: routes of administration and factors to consider. *J Am Assoc Lab Anim Sci*. 2011;50(5):600-13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189662/>

<sup>35</sup> <https://www.epa.gov/saferchoice/frequently-asked-questions-safer-choice>

<sup>36</sup> <https://www.epa.gov/saferchoice/safer-ingredients#greencircle>

neurotoxicity and endocrine effects.<sup>37</sup> For each end-point, 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.”<sup>38</sup>

The table below describes the availability of data on PV29 using the criteria and test methods in the Safer Choice program:<sup>39</sup>

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

<b>Health Hazards</b>	<b>Suitable Empirical Data Available for Pigment Violet 29?<sup>40</sup></b>
Acute mammalian toxicity	
Oral	In vivo experimental study
Dermal	No.
Inhalation	Experimental study unreliable and deficient. Inadequate.
Respiratory sensitization	No.
Skin sensitization	In vivo experimental study
Eye irritation/ corrosivity	In vivo experimental study
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 PV 29, EPA has identified suitable experimental data for only 5 of the 15 critical end-points in Safer Choice (see Table above). Since EPA will not award a Safer Choice Green Circle label without experimental data demonstrating the absence of these adverse effects, 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.

**B. EPA Risk Assessment Guidelines and Other Policies Confirm the Necessary Evidence to Establish the Absence of Risk for Major Health End-Points**

EPA’s positions on the data necessary to establish the absence of health hazard and risk are firmly established in the detailed risk assessment guidelines and other statements of policy it has issued over

<sup>37</sup> [https://www.epa.gov/sites/production/files/2014-01/documents/aa\\_criteria\\_v2.pdf](https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf)

<sup>38</sup> Id.

<sup>39</sup> 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](http://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf)

<sup>40</sup> 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>

many years. As shown below, they demonstrate that the Agency would reject the available data on PV29 as insufficient to conclude that it lacks adverse health effects. Equally important, EPA has ignored findings based on Structure Activity Relationships (SAR) and modeling that provide important additional reasons why further testing of PV29 is essential to assess its potential for hazard and risk.

### 1. Carcinogenicity

EPA acknowledges (p.31) that the “absence of a chronic exposure carcinogenicity study resulted in some uncertainty regarding the carcinogenicity of C.I. Pigment Violet 29.” However, it asserts (p.28) that “negative genotoxicity results, SAR considerations and the expected negligible absorption and uptake of C.I. Pigment Violet 29, support EPA’s conclusion that C.I. Pigment Violet 29 is unlikely to be a carcinogen.”

On its face, the evidence EPA cites fails to provide a basis to conclude that PV29 is not carcinogenic.

First, negative results in two in vitro genotoxicity assays (one in mammalian and one in bacterial cells) cannot rule out carcinogenicity. EPA typically requires a more robust set of assays to screen for genotoxicity.<sup>41</sup> For example, a chromosomal aberration test for mutagenicity has not been performed on PV29. This short-term in vitro mammalian cell test measures asymmetrical structural chromosome aberrations; it is used by regulatory agencies including EPA to assess the potential genotoxic hazard of test substances. Lacking this test is a serious data gap. Moreover, even if PV29 were shown to be non-genotoxic, this would not rule out carcinogenicity by an epigenetic mechanism.

Second, as described above, there are no data demonstrating that P29 cannot be absorbed and the two intraperitoneal studies in fact provide reliable experimental evidence of absorption. Moreover, absorption and uptake (or bioavailability) are exposure, not hazard, considerations, and do not bear on whether PV29 is intrinsically toxic or carcinogenic.

Third, the structure-activity relationship (SAR) considerations EPA cites are not further explained or documented and in fact PV29’s chemical structure and some published reports raise concerns about its potential risk for chronic toxicity, including cancer and endocrine disruption. PV29 is a polyaromatic hydrocarbon (PAH), and like PAH’s generally could be problematic for insertion into DNA, which is a demonstrated mechanism for carcinogenicity as described in the EPA Cancer Guidelines.<sup>42</sup> ATSDR states that, “the most significant endpoint of PAH toxicity is cancer.”<sup>43</sup> ATSDR’s scientific summary and conclusions regarding PAH cancer risk is as follows:

“The carcinogenicity of certain PAHs is well established in laboratory animals. Researchers have reported increased incidences of skin, lung, bladder, liver, and stomach cancers, as well as injection-site sarcomas, in animals. Animal studies show that certain PAHs also can affect the

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<sup>41</sup> See U.S. Environmental Protection Agency, Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: *Using EPA’s 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*, External Peer Review Draft, September 2007, <https://archive.epa.gov/osa/mmoaframework/web/pdf/mmoa-erd-final-83007.pdf>

<sup>42</sup> EPA 2005 Cancer Guidelines, Section 2.3.5

<sup>43</sup> 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>



hematopoietic and immune systems and can produce reproductive, neurologic, and developmental effects [Blanton 1986, 1988; Dasgupta and Lahiri 1992; Hahon and Booth 1986; Malmgren et al. 1952; Philips et al. 1973; Szczeklik et al. 1994; Yasuhira 1964; Zhao 1990].”<sup>44</sup>

“It is difficult to ascribe observed health effects in epidemiological studies to specific PAHs because most exposures are to PAH mixtures. Increased incidences of lung, skin, and bladder cancers are associated with occupational exposure to PAHs.”<sup>45</sup>

Moreover, the public Hazard Data Commons database identifies the chemical class of perylenes (CAS 198-55-0) - which includes PV29 - as having high carcinogenicity potential (high cancer hazard, high confidence) based on over 600 PubMed references and inclusion on authoritative lists.<sup>46 47</sup> The SAR concerns associated with perylenes based on their PAH structure are reasons to require chronic toxicity data for PV29, including in vivo and whole animal carcinogenicity tests. The lack of such tests represents a serious data gap for PV29.

Most importantly, the evidence on PV29 is plainly insufficient under the EPA cancer risk assessment guidelines. According to the guidelines, a determination of “Not Likely to Be Carcinogenic to Humans” requires robust data 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:

- 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.

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<sup>44</sup> 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>

<sup>45</sup> 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>

<sup>46</sup> DataCommons hazard summary for Anthra[2,1,9-def;6,5,10-d'e'f'] diisoquinoline-1,3,8,10(2H,9H)- tetrone (Pigment Violet 29) CAS 81-33-4. Available at <https://commons.healthymaterials.net/chemicals/2028146>

<sup>47</sup> The German Research Foundation’s (DFG) Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK Commission”) is considered an authoritative list by GreenScreen, OECD, EPA and other governments.

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 not relevant to humans, the narrative discusses why the results are not relevant.”<sup>48</sup>

In short, EPA needs data from male and female animals of at least two species in well-designed and conducted studies before it can determine that PV29 is not likely to be carcinogenic. Because no such data are available, EPA lacks any basis to make a determination that PV29 does not present an unreasonable risk of cancer.

## 2. Developmental Toxicity and Endocrine Effects

PV29 is listed on the Danish Advisory List as a reproductive toxicant, “Suspected of damaging fertility or the unborn child”, based on modeled information.<sup>49</sup> The TEDX database of endocrine disrupting chemicals identifies publications in the US National Library of Medicine that report a potential for perylene (CAS 198-55-0) and benzo-a-perylene (CAS 191-85-5) to have endocrine activity based on structural alerts.<sup>50</sup> Moreover, ATSDR emphasizes that although the PAHs, of which PV29 is a member, “generally have a low degree of acute toxicity to humans,” a comprehensive review and assessment of the available data lead ATSDR to conclude that, in addition to cancer risks, “Animal studies show that certain PAHs affect the hematopoietic, immune, reproductive, and neurologic systems and cause developmental effects.”<sup>51</sup>

Given the potential for developmental toxicity and endocrine effects, it is a serious concern that EPA is proceeding with its hazard evaluation of PV29 despite a complete lack of any subchronic studies,<sup>52</sup> 2-generational studies, or endocrine studies. These are serious data gaps.

EPA acknowledges (p.31) that the single repeated dose developmental/reproductive effects study available on PV29 was a “screening-level test” that “provides a limited means of detecting post-natal manifestations of pre-natal exposure, or effects that may be induced during post-natal exposure.”

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<sup>48</sup> EPA 2005. Guidelines for Carcinogen Risk Assessment. Pg. 84-85. Available from:

[https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf)

<sup>49</sup> DataCommons hazard summary for Anthra[2,1,9-def:6,5,10-d'e'f] diisoquinoline-1,3,8,10(2H,9H)- tetrone (Pigment Violet 29) CAS 81-33-4. Available at <https://commons.healthymaterials.net/chemicals/2028146>

<sup>50</sup> Bigelow SW, Nebert DW. 1982. The Ah regulatory gene product. Survey of nineteen polycyclic aromatic compounds' and fifteen benzo[a]pyrene metabolites' capacity to bind to the cytosolic receptor. *Toxicol Lett* 10(1):109-118. DOI: 10.1016/0378-4274(82)90276-4.

Tamura H, Ishimoto Y, Fujikawa T, Aoyama H, Yoshikawa H, Akamatsu M. 2006. Structural basis for androgen receptor agonists and antagonists: Interaction of SPEED 98-listed chemicals and related compounds with the androgen receptor based on an in vitro reporter gene assay and 3D-QSAR. *Bioorg Med Chem* 14(21):7160-7174. DOI: 10.1016/j.bmc.2006.06.064.

<sup>51</sup> 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>

<sup>52</sup> PV29 is a polyaromatic hydrocarbon that is stable and “highly persistent” in the environment (Evaluation p. 19), so while EPA should have a 28-day repeat dose study, this is not enough; EPA should also insist on 90-day repeat dose studies by multiple routes of exposure. The lack of these studies is unjustifiable and represents a serious data gap.

Nonetheless, the draft evaluation asserts that these are “minor uncertainties and the results were sufficiently robust to make a determination of low hazard.” These conclusions are refuted by the Agency’s own risk assessment guidelines, which underscore that the limited data available to EPA are insufficient to make a finding of “low” developmental hazard.

The 1991 EPA Guidelines for Developmental Toxicity Risk Assessment advise that the Agency must meet a high standard to conclude that a substance lacks adverse developmental effects:

“More evidence is necessary to judge that an agent is unlikely to pose a hazard for developmental toxicity than that required to judge a potential hazard. This is because it is more difficult, both biologically and statistically, to support a finding of no apparent adverse effect than a finding of an adverse effect. For example, to judge that a hazard for developmental toxicity could exist for a given agent, the minimum evidence necessary would be data from a single, appropriate, well-executed study in a single experimental animal species that demonstrate developmental toxicity, and/or suggestive evidence from adequately conducted clinical/epidemiologic studies. On the other hand, when no data are available on developmental toxicity, as well as for databases from studies in animals or humans that have a limited study design (e.g., small numbers, inappropriate dose selection/exposure information, other uncontrolled factors), or data from a single species reported to have no adverse developmental effects, or databases limited to information on structure/activity relationships, short-term tests, pharmacokinetics, or metabolic precursors.”<sup>53</sup>

According to the guidelines, “to judge that an agent is unlikely to pose a hazard for developmental toxicity, the minimum evidence would include data from appropriate, well-executed laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no adverse developmental effects at doses that were minimally toxic to the adult animal.”

The Guidelines also provide that short-term tests in general are insufficient for assessing developmental risks, which is particularly relevant to PAHs like PV29 which may have a “low degree of acute toxicity to humans” but a significant risk of cancer and other chronic systemic toxicity.<sup>54</sup> The EPA Guidelines state:

“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*” (emphasis added) p. 19.

More specifically, the Guidelines are clear that the OECD 421 protocol is insufficient for risk assessment:

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<sup>53</sup> EPA 1991. Guidelines for Developmental Toxicity Risk Assessment. Pages 40-41. Available at [https://www.epa.gov/sites/production/files/2014-11/documents/dev\\_tox.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf)

<sup>54</sup> ATSDR 2008. *ibid*

“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.*” (emphasis added) p. 20-21

By relying on the flawed and unreliable OECD 421 screening test on PV29 to demonstrate the absence of developmental toxicity, EPA is ignoring its own express recognition that this test is “is insufficient by itself to make an estimate of human risk.”<sup>55</sup>

### 3. Reproductive Toxicity

The same considerations call into question EPA’s use of the OECD 421 repeated dose study to determine the absence of reproductive risk from exposure to PV29.

The draft PV29 evaluation acknowledges (p. 31) that “this test does not provide complete information on all aspects of reproduction and development, but rather provides a limited means of detecting post-natal manifestations of pre-natal exposure, or effects that may be induced during post-natal exposure.” The evaluation also recognizes that a “smaller number of animals and endpoints are utilized in the dose groups, and the duration of the study is shorter than a full chronic toxicity study” and “[u]ncertainties in the way that this reproductive/developmental screening test was conducted . . . included the expression of test concentrations in terms of nominal concentrations, and a lack of reporting of the stages of spermatogenesis in the testes.”

To then dismiss these limitations as “minor uncertainties” and claim “the results were sufficiently robust to make a determination of low hazard” flies in the face of the 1996 EPA Guidelines for Reproductive Toxicity Risk Assessment.<sup>56</sup> For example, the Guidelines highlight (p.7) the importance of an adequate duration of dosing:

“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

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<sup>55</sup> OECD itself notes that the 421 screening test “offers only limited means of detecting post-natal manifestations of pre-natal exposure” and “will not provide evidence for definite claims of no effects.” <https://www.oecd-ilibrary.org/docserver/9789264264380-en.pdf?expires=1547057183&id=id&accname=guest&checksum=AC7A8AC90849FA79A31A9ECAC1239E35>

<sup>56</sup> EPA, Guidelines for Reproductive Toxicity Risk Assessment, June 1996, available at [https://www.epa.gov/sites/production/files/2014-11/documents/guidelines\\_repro\\_toxicity.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf)

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.”

Commenting on screening studies, the Guidelines advise (p.12) that “[t]heir 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.”

The Guidelines also underscore (p.10) EPA’s position that “a comprehensive reproductive risk assessment should include results from a two-generation test or its equivalent” and explain that:

“[A] one generation study is insufficient to identify all potential reproductive toxicants, because it would exclude detection of effects caused by prenatal and postnatal exposures (including the prepubertal period) as well as effects on germ cells that could be transmitted to and expressed in the next generation. For example, adverse transgenerational effects on reproductive system development by agents that disrupt endocrine control of sexual differentiation would be missed. A one-generation test might also miss adverse effects with delayed or latent onset because of the shorter duration of exposure for the P generation. These limitations are shared with the shorter-term “screening” protocols . . .”

Thus, the Guidelines confirm that the PV29 reproductive screening study is insufficient for assessing reproductive risks and a two-generation reproductive study was required.

### **C. The Data Gaps on PV29 Were Avoidable and Resulted from EPA’s Failure to Use Its Statutory Authorities**

As shown above, EPA guidance and policy preclude EPA from determining that PV 29 does not present an unreasonable risk to human health in the absence of reliable experimental studies on:

- toxicokinetics<sup>57</sup>
- acute inhalation toxicity
- subchronic toxicity
- inhalation sensitization
- neurotoxicity
- developmental neurotoxicity
- two-generation reproductive toxicity
- in vivo genetic toxicity and mutagenicity<sup>58</sup>

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<sup>57</sup> No studies are available investigating the toxicokinetic properties of PV29. This is especially relevant given the lack of whole animal or chronic tests.

<https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/2/1>

<sup>58</sup> For chromosomal damage, the standard tests are either a chromosomal aberration test or a bone marrow micronuclei test. Either are fine. Both are done by treating rodents and then examining blood samples. Other in vivo chromosomal damage tests include the DNA strand break assay, DNA covalent binding assay, and liver unscheduled DNA synthesis assay.

- chronic whole animal carcinogenicity and
- endocrine effects

These are all standard “guideline” studies with established EPA and OECD protocols. In themselves, they may not be sufficient for a comprehensive risk evaluation, but they represent minimum requirements without which no conclusions about the absence of risk are justified.<sup>59</sup>

The major data gaps on PV29 are in large measure the result of EPA’s failure to assure that sufficient data were available for its risk evaluation. At the time EPA decided to conduct its evaluation in December 2016, it could have required PV29’s manufacturer to conduct studies using its broad authority under section 4(a)(2)(A)(i) to compel testing where it “determines that information is necessary . . . to perform a risk evaluation under section 6(b).” Such testing could have been initiated expeditiously under a testing order or consent agreement. The results for many of the studies could have been in hand before the June 2020 deadline for completing the PV29 risk evaluation. Having failed to discharge its obligation under TSCA to obtain “reasonably available information” necessary for an informed risk evaluation, EPA cannot now claim that the absence of that information justifies a determination that PV29 does not present an unreasonable risk of injury.

## **VII. EPA’s MOE Analysis Does Not Properly Account for All Uncertainty Factors and, if these Factors Are Applied, PV29 Could not be Deemed Safe at Expected Exposure Levels**

### **A. How EPA Conducted its MOE Analysis**

EPA typically assesses the risks of non-cancer effects in humans by determining the margin of exposure (MOE) between an actual exposure level and the dose or exposure level at which adverse effects have been observed in animal or human studies (the “point of departure”) and then comparing this MOE to a “benchmark MOE.” If the MOE is greater than the benchmark, the exposure is considered to be without an appreciable risk of deleterious effects during a lifetime in human populations including sensitive

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See for example FDA Guidance for Industry on testing pharma drugs for human use:

<https://www.fda.gov/downloads/drugs/guidances/ucm074931.pdf>

<sup>59</sup> These industry-sponsored guideline studies are typically conducted to satisfy regulatory requirements and are required to follow specific off-the-shelf methods to make it easy for governments to evaluate them and to compare across studies. They must be compliant with Good Laboratory Practices (GLP) which describes how the study information is collected, recorded and reported. GLP requirements were imposed on industry regulatory studies following evidence of widespread animal abuses, fraudulent practices, and false reporting among industry testing laboratories. In many cases GLP and Guideline studies are not published, not subjected to public scientific scrutiny, and not independently peer reviewed. Guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight gain or loss, body weight gain or loss, skeletal malformations, loss of fur, tremors and convulsions, diarrhea, and obvious signs of lethargy. However, guideline studies aren’t designed to grapple with the issues of low-dose exposures, formulations and chemical mixtures, endocrine or hormonal effects, and subtle but significant neurobehavioral impacts including learning and memory impairment. Often more sophisticated and sensitive test systems are necessary to address these critical issues.

subgroups.<sup>60</sup> In other words, if the MOE is greater than the benchmark, EPA concludes that exposure to the chemical will likely be without harm.<sup>61</sup>

For PV29, EPA's MOE calculation (pp.28-30) used the NOAEL of 1000 mg/kg/day from the 28-day reproductive/developmental toxicity screening study as the POD. The Agency then determined a benchmark MOE of 100, based on a UF of 100 to account for variability between species (Interspecies Uncertainty factor (UF) = 10X) times the variability within the human population (Intraspecies Uncertainty Factor = 10). EPA determined separate benchmark MOEs for dermal and inhalation exposure (assuming a dermal absorption rate of 10 percent). The benchmark MOE was then compared to the MOE for predicted exposure, using the approximate maximum workplace concentration of 0.5 mg/m<sup>3</sup> reported by PV29's US manufacturer.

EPA found that the inhalation MOE is 14,933 and the dermal MOE is 361 (p. 29-30). Because both are greater than the benchmark MOE of 100, EPA determined that PV29 does not present an unreasonable risk of injury to human health.

## **B. Multiple Flaws in EPA's MOE Calculation**

Several aspects of EPA's MOE calculation call into question its validity and utility:

- 1) The calculation is entirely based on a single undocumented report of air concentrations in a manufacturing facility. There is no explanation of how the concentration was measured and why it might be representative of "worst case" employee exposure conditions at the facility.
- 2) The application of this reported air concentration to other exposed populations is highly questionable given the lack of any meaningful information on exposure conditions at downstream user facilities or during consumer use of watercolor and acrylic paints.
- 3) The screening study on which the calculation is based is not appropriate to determine the absence of reproductive and development risk and in any event provides evidence of a LOAEL below the dose level of 1000 mg/kg/day that EPA treats as a NOAEL.
- 4) The screening study was conducted by the gavage route and there are uncertainties regarding whether and how to extrapolate the results to dermal and inhalation exposures.

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<sup>60</sup> This is roughly EPA's definition for a Reference Dose or Reference Concentration in the IRIS Glossary of Terms and Acronyms. A definition of Benchmark MOE is not provided in that list. See [https://ofmpub.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/termsandacronyms/search.do](https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/termsandacronyms/search.do)

<sup>61</sup> In general, our organizations do not support using MOE analysis for assessing non-cancer health effects in the TSCA risk evaluation process. The MOE is not an estimate of risk—it is a single number that is a version of the "bright line" approach like the Reference Dose (or Reference Concentration for inhalation doses) and does not address the magnitude of the risks above, at, or below this line. Further, it implies that there is a "safe" level of exposure below which no harm will occur. The NAS Science and Decisions report recognizes that this is not a valid assumption for all chemicals and has recommended moving away from such "bright line" approaches. which do not capture the spectrum of risks across the full range of exposures. National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. We recommend that, in lieu of MOEs, EPA utilize available analytical methods such as PODs based on a Benchmark Dose (BMD) to develop quantified estimates of risk.

- 5) Because of the many data gaps on PV29, the benchmark MOE cannot be assumed to be protective against other as-yet undetermined adverse health effects.

These many flaws indicate that the MOE calculation is not meaningful and credible and should not be used to determine whether PV29 presents an unreasonable risk of injury.

### **C. Apart from its Other Flaws, the Benchmark MOE of 100 Is Grossly Understated and Fails to Reflect Appropriate UFs**

Even if it were not fundamentally flawed in other respects, EPA's selection of a benchmark MOE of 100 would be unjustified. EPA guidance and other authorities call for multiple additional 10X uncertainty factors under the circumstances relevant to PV29.

As summarized in a 2002 report developed for EPA's Risk Assessment Forum:<sup>62</sup>

"UFs are intended to account for (1) the variation in sensitivity among the members of the human population (i.e., interhuman or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the database is incomplete." (p. 4-38)

OECD guidance<sup>63</sup> similarly recognizes that the UFs used to "calculate a criterion or standard that is considered safe or without appreciable risk" should account for:

"the uncertainty in extrapolating from mammalian laboratory animal data to humans, i.e., interspecies uncertainty factor; - the variability in sensitivity among the members of the human population, i.e., intraspecies uncertainty factor; - the uncertainty in extrapolating from effects observed in a short-term study to potential effects from a longer exposure, i.e., subchronic-to-chronic uncertainty factor; - the uncertainty associated with using a study in which health effects were found at all doses tested, i.e., LOAEL-to-NOAEL uncertainty factor; and - the uncertainty associated with deficiencies in available data, i.e., database uncertainty factor."

The PV29 MOE calculation only reflects the first two UFs but, as discussed above, the other three are equally warranted given the PV29 dataset.

In addition, the Food Quality Protection Act (FQPA) requires EPA to apply a 10X default safety factor for the protection of infants and children in the absence of reliable data that support use of a different safety factor.<sup>64</sup> EPA's 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens provides the policy and scientific rationale for extending this approach to all chemical

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<sup>62</sup> USEPA, Reference Dose/Reference Concentration (RfD/RfC) Technical Panel, A Review of the Reference Dose And Reference Concentration Processes, December 2002, available at <https://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes>

<sup>63</sup> <https://www.oecd.org/chemicalsafety/testing/45799595.pdf>,

<sup>64</sup> EPA, Consideration of the FQPA Safety Factor and Other Uncertainty Factors In Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity, February 28, 2002, available at <https://www.epa.gov/sites/production/files/2015-07/documents/apps-10x-sf-for-cra.pdf>



assessments across the Agency.<sup>65</sup> Such a safety factor is appropriate for PV29 in light of TSCA requirements to protect potentially exposed or susceptible populations (including infants and children) from unreasonable risks and the presence of PV29 in consumer watercolor and acrylic paints accessible to infants and children.

Thus, EPA's MOE calculation for PV29 should apply additional uncertainty factors for toxicity and exposure data gaps, use of a short-duration study (subchronic to chronic extrapolation),<sup>66</sup> extrapolation from an oral study to dermal and inhalation routes of exposure (for which there is significant scientific support for a UF of at least 10X)<sup>67</sup>, and the increased vulnerability of pregnant women, infants, and children (as per the EPA 2005 Supplemental Guidance). If EPA applied a 10X factor for each source of uncertainty, the revised benchmark MOE would be:

- UF 10 for a lack of a NOAEL in the key study
- UF 10 for subchronic to chronic extrapolation
- UF 10 for extrapolation from an oral study to other routes of exposure and the absence of any toxicokinetic or toxicodynamic information to inform this extrapolation
- UF 10 for human interspecies variability
- UF 10 for intraspecies extrapolation
- UF 10 for database gaps and increased risks to sensitive populations due to concern with developmental and endocrine risks from PAH chemicals and the absence of any chronic, two-generation or endocrine studies

Total UF = 1,000,000.<sup>68</sup> Since the dermal and inhalation MOEs are far lower, such a benchmark MOE calculation would in fact show the potential for adverse effects at expected exposure levels – and not establish PV29's safety as EPA claims.

The bottom line is that given the need for multiple UFs, EPA is simply not in a position to make credible science-based conclusions about the absence of risk based on the meager database available for PV29. Thus, EPA cannot and should not use an MOE analysis as a basis to determine that PV29 does not present an unreasonable risk of injury to human health.

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<sup>65</sup> EPA 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance, SG). <https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens>; Barton HA, Cogliano VJ, Flowers L, Valcovic L, Setzer RW, Woodruff TJ. Assessing susceptibility from early-life exposure to carcinogens. *Environ Health Perspect.* 2005;113(9):1125-33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1280390/>

<sup>66</sup> For example, in the EPA (2003) IRIS assessment of Acrolein inhalation RfC. "A UF of 10 was applied for adjustment from subchronic to chronic duration because the principal study involved a 13-week dosing period and because there are insufficient inhalation data to preclude an increase in severity (or incidence) with an increase in exposure duration from subchronic to chronic." See [https://cfpub.epa.gov/ncea/iris/iris\\_documents/documents/subst/0364\\_summary.pdf#nameddest=rfc](https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0364_summary.pdf#nameddest=rfc)

<sup>67</sup> Rennen MA, Bouwman T, Wilschut A, Bessems JG, Heer CD. Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment. *Regul Toxicol Pharmacol.* 2004 Feb;39(1):5-11. <https://www.ncbi.nlm.nih.gov/pubmed/14746775>

<sup>68</sup> Furthermore, EPA should combine inhalation and dermal exposures as workers may experience both. EPA combines inhalation and dermal exposures in occupational handlers of pesticides, for example, as follows:  
 $1 / (1 / \text{MOE}_{\text{inhalation}} + 1 / \text{MOE}_{\text{dermal}}) = \text{MOE}_{\text{total}}$

If this method were used for PV29, the calculation would be:  $1 / (1 / 14,933 + 1 / 361) = 352$

In the case of PV29, the risk determination is not affected by combining routes of exposure, but this an important policy issue and an extension of our insistence that EPA consider all exposures. Notably, in the pesticides context, exposure by multiple routes can pose a risk of concern where exposure by a single route does not.

## **VIII. EPA Has Failed to Justify Its Determination that PV29 Does not Present an Unreasonable Risk of Injury to the Environment**

The draft risk evaluation also concludes (p. 26) that PV29 “demonstrates a low hazard to environmental receptors.” The basis for this conclusion is that “[n]o effects were observed in acute toxicity testing with fish, aquatic invertebrates, and aquatic plants up to the limit of solubility of C.I. Pigment Violet 29.” Acknowledging that it lacks data measuring releases of PV29 to the environment and its concentrations in environmental media, EPA nonetheless concludes that environmental exposures “are expected to be limited” based on “qualitative consideration of reasonably available physical-chemical, environmental fate, manufacturing and release, and exposure data.”

EPA acknowledges (p.27) the many uncertainties in these conclusions:

“The EPA has determined there is low hazard to environmental receptors based on a ecotoxicity dataset that is comprised of acute testing with three aquatic species. As a result, there are no data that characterize the hazard of C.I. Pigment Violet 29 to aquatic species following chronic exposure, nor are there toxicity testing with terrestrial species data available to characterize the hazards of C.I. Pigment Violet 29, so there is some uncertainty regarding the environmental risk following acute exposure to sediment-dwelling invertebrates, chronic exposure to aquatic species, and exposure to terrestrial species. In addition, the lack of environmental monitoring data means that the limited predicted environmental concentrations cannot be verified empirically.”

As these statements reflect, EPA guidelines for ecological risk assessment typically call for studies of acute and chronic effects in a range of invertebrates, aquatic species, and terrestrial species.<sup>69</sup> For example, the Safer Choice program requires test data in algae, aquatic invertebrates and fish as well as data on persistence and bio-accumulation. The limited data available on PV29 would thus not be deemed sufficient for a determination that a substance does not present risks to ecological receptors.

Again, EPA could readily have required additional ecotoxicity testing when it selected PV29 for a risk evaluation in December 2016. Its failure to obtain “reasonably available information” should not now enable it to base a finding of no unreasonable risk on insufficient information.

## **IX. The TSCA Systematic Review Criteria Are Unsound Scientifically, Contrary to Other Established Systematic Review Approaches and Lacking in Peer Review**

The TSCA office has developed its own “systematic review” criteria for evaluating the quality of data. These criteria were used in conducting the draft PV29 risk evaluation and are being applied in the other 9 risk evaluations now underway.<sup>70</sup> Our organizations have previously commented that the TSCA

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<sup>69</sup> EPA, Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, January 23, 2004, available at <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/ecological-risk-assessment-pesticides-technical>

<sup>70</sup> 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\\_tzca\\_05-31-18.pdf](https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tzca_05-31-18.pdf)

systematic review document represents a deeply flawed and unscientific approach to systematic review that will compromise the quality, validity and public health value of the 10 risk evaluations.<sup>71</sup>

“Systematic review” is a well-established approach for evaluating and integrating scientific evidence to arrive at judgments about hazard, exposure and risk. However, the TSCA document departs radically from accepted scientific principles for systematic review adopted by the Institute of Medicine (IOM),<sup>72</sup> the National Toxicology Program (NTP)<sup>73</sup> and EPA’s Integrated Risk Information System (IRIS)<sup>74</sup> and endorsed by the National Academy of Sciences (NAS)<sup>75</sup> and other peer review bodies.

The TSCA approach applies a rigid scoring system to grade the “quality” of studies on chemicals. This system could result in many studies being arbitrarily classified as “poor” or “unacceptable” based on a small number of reporting or methodology limitations that do not negate their overall value for assessing health risks. The consequence will be that important evidence of public health impacts -- particularly epidemiological studies demonstrating harm in human populations -- will be either disregarded or given limited weight in the 10 risk evaluations. Other systematic review methodologies do not use numerical scoring systems for assessing study quality and the NAS recommends strongly against such scoring methods.

The TSCA approach also focuses on one limited aspect of systematic review – study quality – but fails to address other critical elements that the Agency itself recognizes are essential for science-based risk judgments. 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.”<sup>76</sup> Yet the TSCA document lacks any protocol for these important tasks. Experts agree that systematic review methods 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’s failure to take this necessary step *before conducting risk evaluations* will compromise the scientific validity of the 10 initial TSCA risk evaluations.

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<sup>71</sup> Comments of Safer Chemicals Healthy Families et al. on Application of Systematic Review in Risk Evaluations under Section 6 of the Amended Toxic Substances Control Act, August 16, 2018, Docket ID EPA-HQ-OPPT-2018-0210. We incorporate these comments by reference.

<sup>72</sup> Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Review. Washington, D.C.: The National Academies Press.; 2011.

<sup>73</sup> National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2015.

<sup>74</sup> National Research Council. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014.

<sup>75</sup> National Research Council. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014; National Research Council. Review of the Environmental Protection Agency’s State-of-the-Science Evaluation of Non Monotonic Dose–Response Relationships as They Apply to Endocrine Disruptors. Washington, DC: National Academies Press; 2014; National Academies of Sciences, Engineering, and Medicine. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: 2017.

<sup>76</sup> 40 C.F.R. 704.33.

Because it is “novel, controversial, [and] precedent-setting [and] has significant interagency interest”, the TSCA document clearly qualifies as a Highly Influential Scientific Assessment (HISA) under the EPA Peer Review Handbook<sup>77</sup> and Influential Scientific Information (ISI) under the OMB Peer Review Bulletin.<sup>78</sup> Thus, external peer review with public participation should have occurred before the TSCA document was used for the 10 risk evaluations. According to a recent letter from Acting Administrator Wheeler to Senator Tom Carper, Chair of the Senate Environment and Public Works Committee, EPA has now committed to peer review of the TSCA systematic review document through both its Scientific Advisory Committee on Chemicals (SACC) and the NAS. These reviews should be expedited so they can inform completion of the 10 risk evaluations. Until the reviews are completed, the TSCA systematic review criteria should not be used by the Agency.

## CONCLUSION

EPA should withdraw its draft risk evaluation for PV29 and acknowledge that it lacks data sufficient to determine whether this substance presents an unreasonable risk of injury to health or the environment. The Agency should then use its authority under TSCA to obtain reasonably available information necessary to fully assess PV29’s hazards and exposures under its conditions of use and reach defensible, science-based conclusions about its risks to humans and ecological receptors. The draft PV29 evaluation should be reworked to incorporate this additional information and reissued for public comment and peer review. The TSCA systematic review criteria should not be used in the reworked evaluation until and unless they are affirmed in the forthcoming peer reviews.

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

Please contact SCHF counsel Bob Sussman with any questions at [bobsussman1@comcast.net](mailto: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

Pamela Miller  
Executive Director  
Alaska Community Action on Toxics

Linda Reinstein  
President and CEO  
Asbestos Disease Awareness Organization

Katie Huffling  
Executive Director  
Alliance of Nurses for Healthy Environments

Nancy Buermeyer  
Senior Policy Strategist  
Breast Cancer Prevention Partners

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<sup>77</sup> U.S. Environmental Protection Science and Technology Council. Agency Peer Review Handbook 4th Edition; October 2015.

<sup>78</sup> Office of Management and Budget. Final Information Quality Bulletin for Peer Review; December 16, 2004

Ansje Miller  
Director of Policy and Partnerships  
Center for Environmental Health

Anne Hulick  
Connecticut Director  
Clean Water Action

Cynthia Luppi  
New England Director  
Clean Water Action

Melanie Benesh  
Legislative Attorney  
Environmental Working Group

Rachel Gibson  
Director, Safer Chemicals  
Health Care Without Harm

Bill Walsh  
Founder & President  
Healthy Building Network

Deanna White  
Director  
Healthy Legacy Coalition

Madeleine Foote  
Legislative Representative  
League of Conservation Voters

Beth McGaw  
President, LDA of America  
Learning Disabilities Association of America

Jennifer Coleman  
Health Outreach Director  
Oregon Environmental Council

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

Laurie Valeranio  
Executive Director  
Toxic-Free Future

Kara Cook  
Toxics Director  
U.S. PIRG

Dr. Andrew Rosenberg  
Director, Center for Science and Democracy  
Union of Concerned Scientists

Lauren Hierl  
Executive Director  
Vermont Conservation Voters

Paul Burns  
Executive Director  
Vermont Public Interest Research Group

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