Environmental Protection Network

(202) 656-6229
environmentalprotectionnetwork.org
info@environmentalprotectionnetwork.org

EPN Comments on Revised Draft TSCA Risk Evaluation for Pigment Violet 29
December 19, 2020

The Environmental Protection Network (EPN) is an organization comprised of almost 550 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of EPA, human health, and the environment. We harness the expertise of former EPA career staff and confirmation-level appointees to provide insights into regulations and policies proposed by the current administration that have a serious impact on public health and environmental protections.

EPN appreciates the opportunity to provide comments on the recently-released revised draft Toxic Substances Control Act (TSCA) risk evaluation for I.C. Pigment Violet 29 (PV29). Some of the comments will specifically address some of the Charge questions directed to the peer reviewers. Others will focus on other aspects of the revised draft.

The Process

In the Federal Register of October 30, 2020, EPA announced the availability of the draft revised risk evaluation for PV29. It also announced the opening of a docket for a 30-day comment period, since extended 20 days until December 19, 2020, to allow the public to review and comment upon the revised draft in light of additional information. It also stated that, *concurrently* with the public comment period, EPA will be conducting a letter peer review by external experts of the revised draft risk evaluation. The extension notice is silent on whether or not the peer reviewers have additional time as well.

EPN vigorously objects to the planned peer review process for the following reasons: 1) Even though the public comment period now approaches the 60 days EPA committed to in its risk evaluation framework rule, the peer review will still be completed before the public comment period has closed and all comments are made available to the peer reviewers for their consideration—a backward approach to peer review and inconsistent with EPA's own agency peer review guidance, and 2) the draft revised risk evaluation is essentially a brand-new document, now including new key sections that were not addressed substantively in the original draft. Given this wholesale transformation, this document should be sent back to the full Science Advisory Committee on Chemicals (SACC) for peer review in a public setting, not to a small group of individuals in a closed, non-transparent, letter review process, especially since there is a paucity of experience and expertise on the part of the selected peer reviewers in the scientific area most critically required to best judge the integrity of the revised risk evaluation—inhalation toxicology, particularly dosimetry in the respiratory system. The agency would be better served if it sought consultation with the full SACC, adding a person or two in this key area to the panel.

Overall Comments

In its initial evaluation, EPA concluded that PV29 does not present an unreasonable risk of injury to human health. EPN and other commenters took issue with this conclusion because of the absence of adequate data for nearly all health endpoints of concern and evidence of potential toxicity from the limited data available. After the SACC raised numerous concerns about the initial draft, EPA

issued a narrow test order under TSCA section 4 requiring only solubility studies in water and octanol and dust monitoring at the Sun Chemical workplace (the sole U.S. manufacturing site). The agency did not, however, require a 90-day subchronic study and other health effects studies recommended by commenters, including EPN.

Because the dust monitoring testing and other data demonstrated a greater predominance of small particle sizes in PV29 dust than earlier assumed, EPA reconsidered the appropriateness of barium sulfate as a surrogate to PV29 for purposes of evaluating potential pulmonary system damage and lung overload. Instead, EPA selected carbon black, which has particle sizes closer to those of PV29, to understand the risks from inhalation of PV29 dust. EPN agrees with this decision because smaller-size particles could lead to a greater potential for toxicity, and carbon black is more similar than barium sulfate to PV29 with respect to this and other characteristics.

EPA then chose a 13-week inhalation toxicity study of carbon black by Elder et al., (2005)[1] to assess the inhalation effects of PV29. That study identified a Lowest Observed Adverse Effect Concentration (LOAEC) of 7 mg/m³ based on inflammatory and morphological changes in the lungs. The No Observed Adverse Effect Concentration (NOAEC) was 1 mg/m³. EPA used this NOAEC as the Point of Departure (POD) to determine Margins of Exposure (MOE) when comparing workplace exposure levels based on the two Sun Chemical air monitoring studies for dust exposures for PV29's conditions of use (COUs). Comparing these MOEs to its Benchmark MOE of 30, EPA determined that 11 of PV29's 14 COUs present an unreasonable risk to the health of workers.

EPN supports this determination based on the suitability of carbon black as an analogue, evidence that PV29 dust contains particles of respirable size, and findings of lung damage in studies on carbon black. These factors weigh strongly in favor of providing additional protection to workers; an unreasonable risk determination will provide a vehicle for this protection by triggering risk management under TSCA.

However, EPN is concerned that the updated EPA evaluation still understates PV29's risks to workers. First, the uncertainty factors (UFs) EPA has used to determine its Benchmark MOE of 30 are inadequate; a more defensible Benchmark MOE would be at least 1,000 and, arguably, 3,000 because of lack of data on PV29 itself. Second, EPA's conclusion that PV29 is not likely to be carcinogenic is contradicted by the observed carcinogenicity of carbon black in rodent studies. If this substance is an appropriate analogue to PV29 with regard to lung toxicity, then it must also be used to evaluate other health effects. As carbon black is a carcinogen when inhaled, PV29 should be assumed to be one, too. These concerns are supported more fully below and require EPA to significantly increase its estimates of risks to workers.

We also disagree with EPA's argument that, because of its purported lack of solubility, PV29 lacks the potential for inducing acute and chronic health effects (with the exception of lung toxicity following inhalation based upon its comparison with carbon black). The evidence of insolubility is not clear-cut; there are suggestions of toxicity in the limited number of studies on PV29, and it cannot be assumed that insolubility definitively rules out the possibility that PV29 will be distributed to tissues and organs within the body and cause toxic effects, especially when inhaled. Thus, EPA

[1] Elder, A; Gelein, R; Finkelstein, JN; Driscoll, KE; Harkema, J; Oberdorster, G. (2005). Effects of subchronically inhaled carbon black in three species I Retention kinetics, lung inflammation, and histopathology. Toxicol Sci 88: 614-629. http://dx.doi.org/10.1093/toxsci/kfi327

lacks a basis to determine that PV29 is without health effects other than lung toxicity following inhalation, based upon the chosen surrogate, and it must require testing to make informed judgments on this issue. At a minimum, required testing should include a 90-day subchronic inhalation study along with appropriate shorter-term *in vivo* and/or *in vitro* studies designed to characterize the mode of action of the lung effects and examine the potential for carcinogenicity.

The Charge Questions:

Question #1. Based on the available data, do you agree with the conclusion that C.I. Pigment Violet 29 has extremely low solubility in octanol and water? Do you also agree with EPA's determination that log K_{OW} is not a relevant property for this chemical? Please explain your answers and provide any other information that would inform EPA on the physical/chemical properties of C.I. Pigment Violet 29.

Answer: In EPN's comments on the draft risk evaluation for PV29 (EPN, July 10, 2019),[2] we noted that EPA based its conclusion of "no unreasonable risk" on claims of low exposure, low bioavailability, and low toxicity observed only in short-term studies, none of them carried out acceptably by the inhalation route. We stated that these data seem to support a hypothesis of low risk, but that they were insufficient to establish it. The SACC agreed that EPA needed better data on particle size and PV29's solubility in water and in octanol in order to evaluate the risk posed by PV29. To obtain better (and valid) partition coefficient data and particle size information, EPA issued a test order under TSCA section 4 to obtain new data on PV29's solubility in water and octanol and exposure data in the work setting. Information on these parameters was provided.

Regrettably, it is not possible to answer the question of EPA's initial conclusion of "no unreasonable risk," as the Nicolaou (2020)[3] study is restricted access (presumably meaning Confidential Business Information (CBI)) and cannot be independently evaluated, and the link EPA (2012c)[4] leads to no data on this chemical. However, even if we had access to the details of the Nicolaou study, it would not show that PV29 lacks the potential to produce adverse health effects in the absence of additional, relevant toxicity testing.

Question #2. Does EPA's approach to inhalation exposure estimates make appropriate use of the received test data? Have uncertainties associated with the inhalation exposure estimates been adequately addressed? Please provide a rationale to your answer.

Answer: Since "received test data" are not otherwise defined, it is assumed that the agency means the two Sun Chemical studies, the first submitted voluntarily after the SACC meeting, the second in response to the test order. We believe these data can be used, in the near term, for exposure estimates but also agree with EPA that the data have substantial limitations, leading to a number of uncertainties (see pages 53-54 of the revised draft). The Sun Chemical studies provide support for risk determinations in the absence of better information, but over the long term, they should be

---

[2] EPN (2019). EPN's Third Set of Comments Objecting to EPA'S Draft Risk Evaluation of Pigment Violet 29 under the Toxic Substance Control Act, July 10, 2019.

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

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

replaced with new data collected in a manner consistent with the test order study plan and fully compliant with the NIOSH 0600 test guideline (see below).

Question #3. Do you have any specific recommendations to improve EPA's calculation of inhalation exposures for C.I. Pigment Violet 29 based on the two available sets of breathing zone data?

Answer: Yes. Over the longer term, EPA should get better data by having Sun Chemical conduct another study that is in compliance with the test order study plan and NIOSH test guideline, resolving the Limitations and Uncertainties described on pages 53-54 of the revised draft.

Question #5. Is EPA's determination that carbon black matches the critical properties of C.I. Pigment Violet 29 and is an appropriate surrogate reasonable? If not, please provide suggestions of surrogates that may be better as a surrogate for C.I. Pigment Violet 29, along with additional justification for why the alternative surrogate is better than carbon black.

Answer: As discussed above, we agree that carbon black is a good-enough surrogate, given similarities in particle size distribution and other characteristics to PV29. However, when EPA issued its section 4 test order, it only required information related to physical-chemical properties and occupational exposure and did not call for development of any toxicity or dosimetry data. We continue to believe that EPA should require a subchronic (90-day) inhalation study in rodent(s) along with appropriate shorter-term *in vivo* and/or *in vitro* studies designed to characterize the mode of action of the lung effects and examine the potential for carcinogenicity. As in the Elder et al. 2005 study,[5] the focus should be on particle retention kinetics, but in the whole respiratory tract, with special attention given to examining the potential for pulmonary inflammation and histopathology, as well as the standard evaluation of systemic toxicity in other tissues. While there are notable differences in the respiratory systems of rodents and humans, these have received much attention with other chemical substances. The lessons learned can be applied in this case.

Question #6. Are there other critical characteristics that should be considered in the selection of a surrogate? If so, provide detailed additional substantive information that EPA should consider.

Answer: As noted above, carbon black is an appropriate surrogate in the absence of appropriate toxicity data on PV29 itself and can be employed in this risk evaluation.

Read-across, presumably, was the tool employed when selecting carbon black as the new surrogate for PV29. It is a useful tool, if used properly, which did not happen in the current case. One cannot pick and choose what components of a data set should be looked at and considered when building an equivalency case. One must line up *everything* that is known about potential surrogates against what is known about the substance of interest, in all domains—physical-chemical properties including state (gas, liquid, solid), environmental fate, potential routes of exposure, environmental and human health effects, etc. In this instance, important information has been ignored or given short shrift, which provides additional support for the need for a subchronic inhalation study (and some short-term *in vivo* and/or *in vitro* assays).

1) The agency chose carbon black as a surrogate, arguing strong similarities in physical-chemical properties and particle size and dimensions, which would lead to the expectation of similar

[5] Ibid.

behaviors by PV29 in the respiratory system when inhaled. In light of this, serious consideration should be given to the possibility that PV29, like carbon black, could be carcinogenic following long-term inhalation exposure.

Why? Most *in vitro* mutagenicity studies of carbon black were negative (several Ames tests, mouse lymphoma assays, and mouse embryo morphological cell transformation assays) (IARC, 1996)[6]. PV29 was shown to be negative in an Ames test and HPRT test. These negative results are not unexpected given that these test systems are not going to take up a test substance that is a particulate.

Negative mutagenicity results notwithstanding, there were positive results in long-term inhalation carcinogenicity studies with carbon black in rats that have prompted the hypothesis that there is secondary genotoxicity, based on an overloading situation that leads to the generation of reactive oxygen species from infiltrated inflammatory cells, the oxidation of DNA bases and DNA strand breaks or lipid peroxidation, the secretion of inflammatory mediators that have been independently implicated in secondary genotoxic and proliferating events that lead to formation of tumors from poorly soluble dust (IARC, 2010).[7]

EPA is using one of the hypothesis-supporting studies (Elder et al. 2005), which examined particle retention kinetics, inflammation, and histopathology of the lungs in female rats, mice, and hamsters exposed to carbon black for 13 weeks, to explain what could also occur following inhalation exposure to PV29.

If, indeed, the two substances have similar characteristics as EPA concluded, PV29 and carbon black should be deemed to share not only physical-chemical and particle size and dimension characteristics, but also toxicity profile characteristics, including carcinogenicity.

2) Some of the inhalable PV29 particles are nanoscale. Nanoscale particles have the propensity to be translocated systemically or to the brain, circumventing the blood-brain barrier (e.g., Oberdorster et al. 2009).[8] Some types of nanoparticles have significant toxicity potential beyond lung inflammation and pathogenesis and could pose other risks of concern if there is sufficient exposure.

<u>Additional Comments:</u>

1. Human Health Risk characterization

    a. Margin of Exposure

        1) Page 70 of the revised draft risk evaluation states "MOE calculations and equations are provided in Appendix G and Appendix H." Appendix G has MOEs listed in a column of the first table for both central tendency and high-end exposure scenarios, but no

[6] IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. IARC Monogr Eval Carcinog Risks Hum, 65:1–578.
[7] IARC (2010) Carbon Black, Titanium Dioxide, and Talc. IARC Monogr Eval Carcinog Risks Hum, 93:1–406.
[8] Oberdörster, G., Elder, A., Rinderknecht, A. (2009) Nanoparticles and the Brain: Cause for Concern? J Nanosci Nanotechnol. 2009 August; 9(8): 4996–5007.

calculations or equations. Appendix H has nothing to do with human health (but also contains neither MOE calculations nor equations).

2) Calculation of the Benchmark MOE

EPA's rationale for selecting a UF_S of 1 to account for extrapolation from a subchronic to chronic exposure duration is unconvincing, particularly in light of identifying a potential for carcinogenicity following long-term inhalation exposure to the surrogate, carbon black. In this instance, the UF_S should be at least 3.

EPA selected a UF_A of 3 to account for animal-to-human extrapolation, stating that a portion of the toxicokinetic component of this extrapolation may be accounted for by use of the MPPD model for estimating the retained particle fraction in the alveolar region of the lung, and converting the animal dose (1 mg/m^3) to a Human Equivalent Concentration (HEC).

There is nothing in the text or appendices which describes and illustrates, via the mathematics, the derivation of HEC, particularly the one which should be serving as the POD in determining whether or not the margins of exposure for each COU are adequate. Because the assessment is so poorly documented in the text, Appendix F and the tables of Appendix G, it was initially thought that this step had not been performed. It turns out that the term used conventionally by the agency to define the converted human dose (the HEC) does not appear anywhere in the document. There is no discussion in the text or inclusion of the term in the Appendix G tables. Only by accident was it figured out that a column entitled "POD Adjustment" in Table_Apx G-1 and Table_Apx G 2 in Appendix G apparently contained the presentation of the HEC, the converted human dose (in this case, 0.28 mg/m^3).

We are in agreement with the agency that the Inter-individual variation UF_H should remain at 10.

Once again, for PV29, there is a missing UF—that which accounts for data deficiencies (UF_D). The Office of Pollution Prevention and Toxics (OPPT) claims they don't use this UF. However, as EPN has pointed out on more than one occasion, this omission runs counter to agency guidance as articulated in US EPA, (2002)[9] and US EPA, (2005).[10] In this case, the database for PV29 is so lacking that this UF should be set as its maximum default, 10X.

Calculating the total Uncertainty Factor results in a Benchmark MOE of at least 1,000, or 3,000, if one employs the full default for extrapolation of subchronic data to a chronic exposure scenario.

---

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

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

b. Point of Departure

The POD is generally defined as the measured or modeled dose administered in a toxicity study that did not result in adverse effects of concern. In Table 4-1 on page 71 of the revised draft, EPA presents a POD of 1.0 mg/m^3 as the NOAEC based upon the "lung particle increased burden and inflammation" at the next higher dose (7.6 mg/m3) reported in the Elder et al. (2005) study. Respiratory tract particle burden is NOT a measure of toxicity. It is a measure of exposure dosimetry. If 1 mg/m3 is the highest dose at which no adverse changes such as inflammatory and morphological changes in the lungs are observed, then that dose is the appropriate NOAEC to serve as the POD (once converted to an HEC). Whether or not there is coincident particle overload is irrelevant.

c. Risk Estimation

Table 4-3 on page 73 presents risk estimations for occupational inhalation exposure scenarios.

With a more appropriate Benchmark MOE of 1,000, there are no acceptable MOEs for workers without respirators for any COU; no acceptable MOEs for Occupational Non-Users (ONUs) without respirators, except those with central tendency exposures to the 46.4 ug/m^3 particle size; no acceptable MOEs to workers using Assigned Protection Factor (APF) 10 or 25 Personal Protective Equipment (PPE), except those with central tendency exposures to the 46.4 ug/m^3 particle size; and no acceptable MOEs for workers using APF 50 PPE, except those with high-end or central tendency exposures to the 46.4 ug/m^3 particle size.

With a Benchmark MOE of 3,000, there are no acceptable MOEs for any COU except for workers using APF 50 PPE with central tendency exposures to the 46.4 ug/m3 particle size.

We believe that EPA has not justified the assumption that respirators will be used either in PV29 manufacture or in downstream conditions of use. OSHA regulations do not require respirators for PV29-exposed workers, and EPA has repeatedly acknowledged that respirator use in many workplaces is sporadic and often ineffective. EPA should assume no PPE (in this case, respirators) in calculating MOEs for PV29.

d. Risk Characterization

On Page 75 of the document, EPA states "Because the exposure estimates and hazard assessment for inhalation exposures to C.I. Pigment Violet 29 are considered to be of high uncertainty and low confidence, the confidence in the risk estimation is considered to be low."

EPN agrees with this conclusion but believes that there is an adequate basis for a determination of unreasonable risk. EPA should require additional studies to provide greater certainty in its risk estimates.

2. Environmental Risk Characterization

The initial draft risk evaluation for PV29 provided insufficient information and analysis to allow judgments to be made on the potential of PV29 to pose risk to any aquatic and terrestrial environments.

Given the expanded discussion in the revised draft risk evaluation, we agree with the agency's assessment that no adverse effects were observed in results from laboratory testing for acute exposure to microorganisms, aquatic plants, aquatic invertebrates, and fish up to the limit of PV29 solubility, 3 μg/L.

Furthermore, modeling efforts to predict potential aquatic toxicity following chronic exposure to PV29 found no effects were predicted to occur at levels greater than 10 times the limit of solubility. Using the same approach, hazard levels for sediment-dwelling species was also determined to be low.

We agree with Ecological Structure Activity Relationships (ECOSAR) (ver. 2.0) guidance for predicting acute and chronic effects to aquatic organisms that PV29 may not be sufficiently soluble to measure predicted effects for each species, and that, if effect levels exceeded the water solubility by 10-fold, typically "no effects at saturation" is reported. This approach is consistent with standard practices in the testing industry (Weyman et al. 2012).[11]

Based on PV29's low vapor pressure and volatility and low solubility, exposures to terrestrial species through air and water are not expected, so risk concerns for terrestrial species are not identified.

Given its low solubility in water, its limited environmental releases, and lack of environmental hazard, EPA determined that PV29 does not present an unreasonable risk to aquatic species in the water column and sediment, and to terrestrial species. We agree with EPA's determination that there is no unreasonable risk of injury to the aquatic and terrestrial environment from all conditions of use of PV29.

[11] Weyman, GS, H Rufli, L Weltje, ER Salinas, and M Hamitou. 2012. Aquatic toxicity tests with substances that are poorly soluble in water and consequences for environmental risk assessment. Environ Toxicol Chem. 31(7):1662 1669.