UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families, Defend Our Health, Earthjustice and Natural Resources Defense Council on EPA's Revised Draft Risk Evaluation for C.I. Pigment Violet 29 under Section 6(b) of TSCA

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Safer Chemicals Healthy Families (SCHF), Defend Our Health, Earthjustice and Natural Resources Defense Council (NRDC) submit these comments on the Environmental Protection Agency (EPA) revised draft risk evaluation for C.I. Pigment Violet 29 (PV29) under section 6(b) of the Toxic Substances Control Act (TSCA).[1] Our organizations are committed to assuring the safety of chemicals used in our homes, workplaces and the many products to which our families and children are exposed each day. We took a leadership role during the TSCA legislative process, advocating the most protective and effective legislation possible to reduce the risks of toxic chemicals in use today.

The draft revised PV29 evaluation is a significant improvement on the initial draft and recognizes the serious risks of lung overload and toxicity to workers who inhale PV29 dust. We support EPA's proposed determinations of unreasonable risk to workers for this endpoint but believe they must be strengthened to fully recognize the magnitude of the risk and coupled with testing to fill vital data gaps. As we demonstrate in these comments:

- EPA is seeking a limited "letter review" of the revised draft evaluation by a small subset of its Science Advisory Committee on Chemicals (SACC) and eliminating the public comment process normally part of SACC review. EPA should reconvene the entire SACC to review the revised draft and afford the public an opportunity to submit comments and make presentations to the SACC.

- Based on new information showing that PV29 particles are significantly smaller and more capable of lung toxicity than previously believed, EPA has selected carbon black as an appropriate surrogate for PV29 and used rodent sub chronic studies on this substance to determine the risk of harmful lung effects to PV29-exposed workers. This is a sound and defensible approach. The suitability of carbon black as an analogue, evidence that PV29 dust contains particles of respirable size, and findings of severe lung damage in studies on carbon black all weigh strongly in favor of providing additional protection to workers from the disabling consequences of lung overload – a goal that can be accomplished by making an unreasonable risk determination for PV29 based on these effects and triggering risk management under section 6(a) of TSCA.

- While relying on the carbon black data-base to assess PV29's lung toxicity, EPA's revised draft incorrectly reaffirms its earlier conclusion that PV29 lacks carcinogenicity potential. This conclusion ignores the fact that that carbon black has produced lung tumors in animal studies and is classified as

[1] EPA announced the availability of the draft revised risk evaluation for public comment on October 30, 2020 (85 Federal Register 68873). The comment period was extended to December 19, 2020 on November 23, 2020 (85 Federal Register 74718).

a likely carcinogen by the International Agency for Research on Cancer (IARC). The mechanism for carbon black carcinogenicity in rodents – impaired lung clearance resulting in particle accumulation and inflammation – is the same mechanism EPA has identified for its non-cancer lung toxicity. If EPA believes that carbon black is an appropriate surrogate for PV29 for one endpoint, it should be a surrogate for other endpoints involving the same target organ and mechanism of action. While additional testing may well provide further insight into PV29's carcinogenicity, the extensive data-base on carbon black now supports a determination of elevated cancer risk from inhalation exposure to PV29. EPA should include this determination in its final evaluation and, as it has done for non-cancer lung effects, use the carbon black cancer studies to estimate cancer risk to PV29-exposed workers.

- In our initial comments, we argued that the many data-gaps for PV29 required EPA to use its TSCA section 4 authority to reliably characterize its toxicological properties. Unfortunately, the revised draft evaluation continues to dismiss concerns for any health endpoint other than inhalation toxicity on the unsupported basis that PV29's purported lack of solubility and bioavailability prevent its systemic absorption and distribution throughout the body. In fact, PV29's insolubility has not been clearly established by available studies and in any case lack of solubility is insufficient in itself to rule out uptake of PV29 and systemic toxicity. We therefore urge that EPA use its section 4 authority to require studies to (1) examine whether there is absorption and uptake of PV29 by all routes (oral, dermal and inhalation) and, if so, whether PV29 causes systemic toxicity, and (2) further elucidate PV29's cancer and non-cancer inhalation effects by testing PV29 directly for these endpoints Once this testing is completed, a supplemental risk evaluation and/or additional risk management may be warranted. In the interim, EPA should finalize unreasonable risk determinations for PV29 based on the known lung toxicity and carcinogenicity of the carbon black surrogate

- Although we support EPA's proposed unreasonable risk determination for PV29, we are concerned that EPA's methodology for calculating Margins of Exposure (MOEs) systematically understates the magnitude of PV29's risks to workers in two respects: (1) the uncertainty factors (UFs) EPA has used to determine its Benchmark MOE of 30 are inadequate and, properly calculated, would require a Benchmark MOE of at least 3,000 and arguably 10,000; and (2) EPA has improperly increased its MOEs to account for the protection provided by respirators despite the limited evidence for respirator use at PV29 manufacturing and processing facilities and the Agency's misinterpretation of OSHA policies and regulations to require respiratory protection for PV29 exposure. If these flaws were corrected, MOEs would be well below the benchmark MOE for high-end and central-tendency exposure scenarios and two of the three median particle sizes for **all 14** of the PV29 conditions of use. Thus, an unreasonable risk determination would be required for all PV29 uses.

I. EPA Should Provide for Peer Review of the Revised Draft by the SACC in a Full Public Process

EPA is seeking a limited "letter review" of the revised draft evaluation by a small subset of SACC members involved in reviewing the initial November 29 draft. The reviewers will not have access to public comments because the review and comment process will proceed simultaneously and there will be no public meeting at which commenters can present their views.

We oppose this unwarranted curtailment of the peer review and public comment process. Standard EPA practice under its peer review guidelines is to share public comments with the reviewers so they can take the views and concerns of the commenters into account. Deviating from this approach will deprive the public of a meaningful role in the peer review process and deny the reviewers access to important information, insight and analysis.

This lack of transparency is apparently intended to expedite completion of the draft evaluation before the new Administration takes office. This is not a legitimate reason for cutting corners on peer review and public comment, particularly when the reason for delay is EPA's own foot-dragging in identifying and obtaining information it should have possessed early in the risk evaluation process. Moreover, the significant changes EPA has made in the draft evaluation underscore the benefits of robust peer review. EPA has reversed is original approach and produced a substantially different document based on a rethinking of its original findings. Not only is public comment essential on the reworked evaluation but a letter review may well narrow the range of expertise brought to bear on the issues that the new draft raises. Experience in inhalation toxicology is critical, for example, but not represented among the selected reviewers.

For these reasons, we urge that EPA reconvene the entire SACC to review the revised draft and afford an opportunity for the public to share their comments with the SACC and make public presentations.

II. EPA Has Properly Determined that PV29 Presents an Unreasonable Risk of Lung Toxicity to Workers

In its initial draft evaluation, EPA concluded that PV29 did not present an unreasonable risk to health despite the limited availability of relevant and reliable health effects data and questionable and unsupportable assumptions about PV29's lack of toxicity.[2] Our groups commented that the draft evaluation was insufficient under the Agency's own risk assessment guidelines to establish the absence of risk and that EPA should have used TSCA authorities to obtain additional hazard and exposure data necessary for a defensible risk evaluation. These concerns were reinforced in the highly critical SACC report on the draft evaluation.

In response, over three years after initiating the risk evaluation, EPA requested additional information from Sun Chemical, PV29's US manufacturer, and finally issued a narrow testing order under TSCA section 4(a) requiring Sun to conduct solubility studies and additional workplace monitoring. To our disappointment, the order did not require additional toxicity studies, as recommended in our comments and the SACC report. However, EPA did use the new information it obtained to revisit and reverse its earlier conclusion of no unreasonable risk. The revised evaluation proposes to determine that PV29 presents an unreasonable risk of harmful lung effects to workers under 11 of its 14 conditions of use.[3] Although it does not go far enough, we support this determination and agree with EPA's proposed approach.

EPA had originally selected barium sulfate as a surrogate for PV29 and used toxicity data for this substance to conclude that PV29 does not have adverse lung effects. However, the presumed similarity between PV29 and barium sulfate assumed equivalent particle size distributions in dust. This assumption was based on BASF measurements of PV29 particle size available to EPA at the time of its draft evaluation. However, in response to EPA's information request, Sun Chemical submitted two new analyses of PV29 dust showing a significantly greater predominance of small particle sizes and thus a greater potential for damage to the respiratory system and human health. As EPA explained:[4]

> "Initially, EPA received particle size information as part of a compilation of physical and chemical properties which indicated an average particle size diameter of 46.9 µm (BASF, 2013). Following the publication of the draft risk evaluation on C.I. Pigment Violet 29, EPA received additional particle size distribution (PSD) data and workplace exposure monitoring data from Sun Chemical. This data indicates that the median diameter of the particles is reported as 43 nanometers (nm), or 1000 times

[2] Draft PV29 Risk Evaluation December 4, 2018, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0007.

[3] Revised Draft Risk Evaluation for C.I. Pigment Violet 29, at https://www.epa.gov/sites/production/files/2020-10/documents/revised_draft_risk_evaluation_for_c.i._pigment_violet_29_public.pdf. (Revised Draft Evaluation)

[4] Revised Draft Evaluation, at 21.

> smaller than the particle size reported in the BASF study report upon which EPA had based its particle size estimate in the draft risk evaluation (BASF, 2013). In an additional characterization of the particle size diameter of C.I. Pigment Violet 29, the mean particle diameter was reported as 10.4 µm (U.S.EPA, 2020a)."

Based on these data, EPA rejected barium sulfate as a surrogate for PV29 and instead selected a more relevant compound, carbon black, on the basis of similarities to PV29 in particle size distribution and other characteristics:[5]

> "Elder et al., (2005) reported a particle size of 0.014 µm for high- surface area carbon black and a particle size of 0.070 µm for low-surface area carbon black; therefore, this range of particle sizes bracket the particle size of C.I. Pigment Violet 29 provided by Sun Chemical (0.043 µm). In addition to similar particle size, carbon black was considered an appropriate analogue for C.I. Pigment Violet 29 because of its similar physical and chemical properties, including insolubility and density (1.97 g/cm^3 for carbon black vs 1.69 g/cm^3 for C.I. Pigment Violet 29) and its similar chemical composition; both chemicals are used as pigments or inks and are predominantly comprised of a planar structure of multiple carbon rings."

EPA's selection of carbon black as a surrogate enables the Agency to account for the greater toxicity of smaller particles because of their deeper deposition in the lung and to base its determination of risk to workers on lung effects data more representative of PV29 exposure in the workplace.

EPA assessed PV29's health risks using a 13-week inhalation toxicity study of carbon black by Elder et al., (2005) which identified an LOAEC of 7 mg/m^3 based on inflammatory and morphological changes in the lungs. The NOAEC was 1 mg/m^3. EPA used this NOAEC as the Point of Departure (POD) to determine Margins of Exposure (MOEs) for workplace exposure levels. To conduct this MOE analysis, the risks from inhalation of PV29 dust were determined for a range of potential particle diameters, reflecting the variability in PV29 particle size in the measurements by BASF and Sun. Risks were estimated based on the three reported median particles from the particle size distribution (PSD) data sets (0.043, 10.4 and 46.9 µm) and the associated estimated deposition fraction in the pulmonary region of the lungs.[6] Concentrations of PV29 dust in the workplace were derived from the two air monitoring studies conducted by Sun (including one under the testing consent order) and risk estimates were developed for central tendency and high-end air concentrations. After estimating risks for workers at the Sun manufacturing facility, EPA extended these estimates to PV29 processing activities at downstream facilities. Without direct data for these facilities, EPA assumed that their operations involved the same PSD ranges and airborne dust concentrations documented at the Sun manufacturing site.

The inhalation effects addressed by EPA's risk analysis represent a serious health concern. As EPA correctly emphasized:[7]

> "As C.I. Pigment Violet 29 is manufactured as a conglomerate solid that is a collection of particles that may be milled to certain particle sizes, humans may be exposed to these particles by inhalation. The respiratory tract has myriad responses to inhaled particles, including neurogenic, cardiovascular, and metabolic dysfunction in addition to inflammation, remodeling leading to asthma, and a host of other respiratory diseases (U.S. EPA, 2019b). One such effect is overload, defined as when the exposure concentration is sufficiently high or the duration sufficiently long to overwhelm alveolar macrophage (AM)-mediated clearance. Inhalation of poorly soluble particles like C.I. Pigment Violet

[5] Id.
[6] Id at 71.
[7] Id. at 67.

29 is associated with adverse effects in the lungs of test animals when AM mediated clearance is overwhelmed."

To increase confidence that the lung overload effects seen in Elder et al were predictive of PV29 toxicity, EPA used the Multiple Particle Path Dosimetry (MPPD) model to compare the predicted alveolar retention of PV29 following 13 weeks of exposure with the measured particle retention reported in Elder. According to EPA, "{t]his modeling analysis and its results support the use of carbon black as an analogue for C.I. Pigment Violet 29 (see Appendix F)."[8]

The variability in particle size data, imperfect monitoring of dust levels by Sun Chemical and lack of any exposure information for downstream processing operations are sources of uncertainty in EPA's risk analysis, as the Agency noted.[9] However, EPA could have reduced these uncertainties by requiring more extensive particle size measurements and monitoring of dust levels early in the risk evaluation process. Similarly, Sun and other companies using PV29 could have anticipated the lung overload concerns that EPA has now acknowledged and proactively developed data to more fully assess inhalation toxicity and exposure.

Moreover, while more data could reduce uncertainty, this is not a reason for inaction. EPA correctly found that "the "data available to characterize human health hazard of C.I. Pigment Violet 29 are sufficient to make a determination of risk."[10] 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 all weigh strongly in favor of providing additional protection to workers from the disabling consequences of lung overload – a goal that can be accomplished by making an unreasonable risk determination for PV29 for these effects and triggering risk management under section 6(a) of TSCA.

III. EPA Should Also Determine that PV29 Presents an Inhalation Cancer Risk Based on the Demonstrated Carcinogenicity of Carbon Black

At the same time that EPA relied on the carbon black data-base to assess PV29's lung toxicity, EPA reaffirmed its earlier conclusion that PV29 lacks the potential for carcinogenicity. After acknowledging the "absence of a chronic carcinogenicity study for C.I. Pigment Violet 29," EPA insisted that:[11]

> "the carcinogenic potential of C.I. Pigment Violet 29 was sufficiently assessed using reasonably available data. This data included two short-term genotoxicity studies (an AMES test and HPRT test; see Appendix E for a summary) as well as a consideration of the structural activity of the compound, which determined that C.I. Pigment Violet 29 is not likely to be carcinogenic. The results of the genotoxicity testing indicate that C.I. Pigment Violet 29 does not demonstrate cytotoxicity or induce gene mutations at the HPRT locus. The very low solubility of C.I. Pigment Violet 29 is expected to lead to negligible absorption and uptake. SAR consideration of the unusual seven fused rings suggests negligible potential for DNA intercalation due to its large size and inability to be metabolized to reactive ring epoxides because ring fusing impedes possibility for epoxidation."

[8] Id., at 68.

[9] For example, interpretation of the Sun Chemical respirable dust monitoring study entails uncertainties because "only modest volumes of air were collected during the task-based sampling periods." In addition, "because the vast majority of the sample results obtained at Sun Chemical were obtained with modest sample volumes and had sample results described as less than the laboratory's reporting limit, it was not possible to determine the employees' actual airborne exposure from those samples." Id. at 52. According to the draft evaluation, when EPA reviewed the monitoring study required under section 4, it "determined that the study did not meet the terms of study plan set forth in the Test Order." Id. at 50.

[10] Id at 74.

[11] Id. at 68.

Astoundingly, this analysis fails to mention that carbon black – EPA's chosen surrogate for PV29 – has produced lung tumors in animal studies. As the International Agency for Research on Cancer (IARC) has described these studies:[12]

> "Two different carbon black products were tested by inhalation exposure in two studies in female rats and in one study in rats of each sex. Significant increases in the incidence of malignant lung tumours or of benign and malignant lung tumours combined were observed in female rats in all three studies. In addition, an increased incidence of lesions described as benign cystic keratinizing squamous-cell tumours or squamous-cell cysts was observed. In one study in female mice exposed by inhalation, carbon black did not increase the incidence of respiratory tract tumours. In two studies of intratracheal administration to female rats using two types of carbon black and in one study using one type, an increased incidence of malignant lung tumours or of benign and malignant lung tumours combined was observed."

IARC also addressed the likely mechanism of action for these lung tumors:[13]

> "The Working Group considered a large body of mechanistic information. For lung cancer in rats, it was concluded that a sequence of events that starts with impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury and production of reactive oxygen species that eventually lead to mutations, was well supported by experimental evidence, although some data also supported alternative pathways. High retained mass lung burdens and decreased lung clearance have been observed in coal miners, which led the Working Group to conclude that animal cancer data obtained under conditions of impaired lung clearance are relevant to humans."

These are the same mechanisms – impaired lung clearance resulting in particle accumulation and inflammation – that EPA has identified as leading to non-cancer lung toxicity by carbon black and, by analogy, PV29. If EPA believes that carbon black is an appropriate surrogate for PV29 for one endpoint, it should be a surrogate for other endpoints involving the same target organ and mechanisms of action. Yet EPA has totally ignored the possibility that PV29, like carbon black, causes lung tumors by inhalation exposure. Given EPA's determination that carbon black and PV29 are similar in particle size distribution and other risk factors, EPA should have treated PV29 as a likely carcinogen in its evaluation of health risks. EPA cannot arbitrarily cherry pick from the carbon black data-base, selecting some findings but glossing over others.

While EPA emphasized that PV29 was negative in Ames and HPRT tests, IARC has noted that carbon black is also negative in most *in vitro* mutagenicity studies (several Ames tests, mouse lymphoma assays and mouse embryo morphological cell transformation assays).[14] This is not surprising given the insensitivity of these test systems to particulates. On the other hand, IARC has cited positive results in other assays:[15]

> "In one study in rats exposed to carbon black by inhalation, the Hprt mutant frequency was elevated in lung epithelial cells following a 15-week exposure. A significant increase in pro-mutagenic 8-oxo-7,8-dihydro-2'-deoxyguanosine induction was observed in the lungs of rats exposed for 13 weeks to one type of carbon black."

More significantly, IARC has postulated a "sequence of events that starts with impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury and production of reactive oxygen

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[12] IARC (2010) Carbon Black, Titanium Dioxide, and Talc. IARC Monogr Eval Carcinog Risks Hum, 93:1–406. IARC Publications Website - Carbon Black, Titanium Dioxide, and Talc

[13] Id at 190-91.

[14] IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. IARC Monogr Eval Carcinog Risks Hum, 65:1–578.

[15] IARC 2010 at 189.

species that eventually lead to mutations" which cause lung tumors. This plausible mechanism of action – which IARC found was "well-supported by experimental evidence" – should receive much greater weight in assessing PV29's carcinogenicity than negative *in vitro* mutagenicity assays.

EPA has also maintained that the "structural activity of the compound" argues against carcinogenicity because PV29 has "negligible absorption and uptake" and "negligible potential for DNA intercalation" due to its unusual seven fused rings. These considerations might be important where the risk of cancer depends on oral and dermal routes of exposure that result in widespread distribution of a compound within the body. However, the concern for PV29, based on analogy to carbon black, is that inhalation and accumulation of small particles in the lung may cause physical changes in lung tissue that progress to inflammation and cell mutations and ultimately to lung cancer. This is a different mode of action entirely.

Moreover, structural considerations that EPA overlooks do in fact raise concern about PV29's carcinogenicity. As discussed in our initial comments, PV29 is a polyaromatic hydrocarbon (PAH), and like PAHs generally, could be problematic for insertion into DNA, which is a demonstrated mechanism for carcinogenicity as described in the EPA Cancer Guidelines.[16] Thus, the public Hazard Data Commons database identifies the PAH subclass 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. [17] [18] The OECD QSAR Toolbox also contains a structural alert for genotoxic carcinogenicity for PV29 based on its classification as a PAH.[19] The SAR concerns associated with PAHs in general and perylenes in particular further warrant heightened scrutiny of PV29's carcinogenicity.

Under EPA cancer guidelines, a conclusion that a substance is "not likely to be carcinogenic to humans" is warranted only "when the available data are considered robust for deciding that there is no basis for human hazard concern." As examples, the guidelines indicate that this standard would be met by "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" and "convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans." [20]

Plainly, no such evidence exists for PV29. Instead, available information – particularly the demonstrated carcinogenicity by inhalation of carbon black, EPA's chosen surrogate for PV29 – raises serious concern about its ability to cause lung tumors. While additional testing may well provide further insight into PV29's carcinogenicity, the extensive data-base on carbon black now supports a determination of cancer risk from inhalation exposure to PV29. EPA should include this determination in its final evaluation and, as it has done for non-cancer lung effects, use the carbon black cancer studies to estimate cancer risk to PV29-exposed workers.

IV. Despite its Claimed Lack of Solubility, More Testing Is Needed to Resolve Questions about PV29's Systemic Toxicity and Elucidate Its Adverse Lung Effects

[16] EPA 2005. Guidelines for Carcinogen Risk Assessment. Section 2.3.5. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf (2005 Cancer Guidelines).

[17] 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

[18] 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.

[19] Organisation for Economic Cooperation and Development (OECD). 2020. OECD QSAR Toolbox for Grouping Chemicals into Categories. Version 4.4. Available: http://toolbox.oasis-lmc.org/?section=download&version=latest

[20] EPA 2005 Cancer Guidelines at. 84-85.

In our initial comments, we argued that the many data-gaps for PV29 required EPA to use its TSCA section 4 authority to better define its toxicological properties and that the Agency lacked a basis to find an absence of unreasonable risk until the results of these studies had been submitted. However, in its revised draft evaluation, EPA continues to maintain that there is no concern for any endpoint other than inhalation toxicity because PV29's purported lack of solubility and bioavailability prevents its systemic absorption and distribution throughout the body.

As discussed below, PV29's insolubility has not been clearly established by available studies and in any case lack of solubility is insufficient in itself to rule out systemic toxicity, necessitating studies on toxicokinetics and representative human health endpoints to clarify whether or not PV29 is bio-available.

A. There Are Unresolved Questions about the Validity of the Method Used to Determine PV29's Solubility in Fat

At the time of its initial evaluation, the only solubility data available to EPA was from a study of PV29's physicochemical characteristics by BASF. In its report on the initial evaluation, SACC found that this study was inadequate to determine solubility and EPA agreed. According to the revised draft evaluation:[21]

> "The values provided for the water solubility (0.011 mg/L) and the octanol solubility (<0.07 mg/L, the Limit of Detection) were found to be unacceptable by EPA due to the fact that the limit of detection for the n-octanol solubility was higher than the measured water solubility. Also, due to the particle-like nature of the substance, EPA questioned as to whether the method of filtration completely removed undissolved material during the study."

To address these flaws, EPA belatedly issued a TSCA Section 4 test order requiring studies measuring solubility of PV 29 in water (OECD 105, flask method) and n-octanol (ETAD method, 2005). The results, reported in Nicolaou 2020, were ranked "high" in quality by EPA and purportedly show low solubility in both water and fat (below the quantification limit of 0.003 mg/L). However, an electronic version of the study is not in EPA's public docket and the results and methods are not available for review.

Moreover, the decision to conduct the n-octanol test not with the established OECD method but with a method developed by the industry trade group ETAD is not explained and justified. The proposed protocol for the study (EPA-HQ-OPPT-2020-0070-0008 Attachment 7) says that this method was "*agreed upon at the "Analytical Experts Meeting" of ETAD (Basel) on January 12, 2005*" (emphasis in original) but provides no information demonstrating that the method was peer reviewed and validated. The protocol does claim that the OECD method was inapplicable for the following reasons:

> "Because of the low solubility of this kind of substances in common solvents used for UV-vis spectrometry and chromatography the standard method for testing solubility (OECD guideline 105) is not applicable. Additionally, solvents in which this substance is readily soluble are not compatible with the equipment required by the OECD guideline." (p. 3)

However, there is no substantiation of these concerns nor any explanation of why the ETAD method is more reliable than the established OECD method.[22] No list of the solvents that are not compatible with PV29 is provided and there is no discussion of why the solvents used in the ETAD method are more appropriate.

[21] Revised Draft Evaluation at 20.

[22] In addition, one limitation of the water solubility test is that the guideline (OECD Guideline 105) does not specify evaluation of solubility under physiological conditions (such as temperature and pH of the gastrointestinal tract/skin/lungs) and it is unclear if any adaptations were made to address these questions.

Under these circumstances, EPA needs to either demonstrate that the ETAD method has been validated and peer reviewed or require the n-octanol solubility test to be repeated using the OECD method. Until then, the n-octanol inolubility of PV29 should not be deemed adequately demonstrated.

B. To Supplement EPA's Unreasonable Risk Determinations, More Testing Is Necessary to Resolve PV29's Systemic Toxicity and Better Understand Its Lung Effects

Even with an adequate demonstration of low solubility, EPA cannot confidently assume that PV29 is not bioavailable and lacks systemic toxicity without additional testing. No toxicokinetic studies have been conducted on PV29 and, accordingly, there is no definitive evidence of lack of uptake and absorption. The limited studies available on PV29 are inconclusive. On the one hand, acute oral studies reported colored feces, indicating excretion of the unchanged test material without absorption. On the other hand, two whole animal experimental single dose studies in mice receiving PV29 intraperitoneally reported clinical effects and deaths after a 14-day observation period.[23] In addition, a reproductive/developmental screening study by gavage using OECD-421 reported black-
discolored feces, black discoloration of the contents of the digestive tract, and body weight gains.[24]

Moreover, some of the inhalable PV29 particles are nanoscale. Nanoscale particles have the propensity to pass between or through cells unhindered, and once inhaled or ingested, can easily travel to all organs of the body via the circulation of blood. Thus, these particles can pass through the placenta into fetal circulation, through the blood brain barrier into neural tissues, and through the blood-testicular barrier into male reproductive cells.[25] Inhaled nanoparticles that are bio-persistent (PV29 has not been tested for this property)[26] have been shown to cause cell damage, inflammation, and other indicators of cell damage.[27] Some types of nanoparticles have significant toxicity potential beyond lung inflammation and pathogenesis and could pose risks of systemic toxicity if exposure is of sufficient magnitude.

In short, there is some evidence of uptake and distribution of PV29 (at least by the intraperitoneal and gavage routes) and indications that inhaled nanoparticles are transported to organs outside the respiratory tract. This calls into question a categorical finding that PV29 is insoluble and, by extension, lacks systemic toxicity. Instead, the evidence of absorption and distribution should spur EPA to use its authorities to require additional studies as necessary to fully characterize concerns about PV29's uptake and potential for health effects.

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[23] Revised Draft Evaluation at 106-107.

[24] Id. at 108.

[25] Oberdörster, G., Elder, A., Rinderknecht, A. (2009) Nanoparticles and the Brain: Cause for Concern? J Nanosci Nanotechnol. 2009 August ; 9(8): 4996–5007. Wang Z, Zhang C, Huang F, Liu X, Wang Z, Yan B. Breakthrough of ZrO2 nanoparticles into fetal brains depends on developmental stage of maternal placental barrier and fetal blood-brain-barrier. J Hazard Mater. 2021 Jan 15;402:123563. doi: 10.1016/j.jhazmat.2020.123563. Epub 2020 Jul 28. PMID: 32745876. Tang Y, Chen B, Hong W, et al. ZnO Nanoparticles Induced Male Reproductive Toxicity Based on the Effects on the Endoplasmic Reticulum Stress Signaling Pathway. Int J Nanomedicine. 2019;14:9563-9576. Published 2019 Dec 4. doi:10.2147/IJN.S223318

[26] See: ECHA EU. chemical profile for Perylene-3,4:9,10-tetracarboxydiimide. Updated 11/11/2020 https://echa.europa.eu/brief-profile/-/briefprofile/100.001.223 A published study of 15 low-soluble nanoparticles found that one-fifth of them were bio-persistent. See: Kononenko V, Warheit DB, Drobne D. Grouping of Poorly Soluble Low (Cyto)Toxic Particles: Example with 15 Selected Nanoparticles and A549 Human Lung Cells. *Nanomaterials (Basel)*. 2019;9(5):704. Published 2019 May 6. doi:10.3390/nano9050704

[27] Oyabu T, Myojo T, Lee BW, Okada T, Izumi H, Yoshiura Y, Tomonaga T, Li YS, Kawai K, Shimada M, Kubo M, Yamamoto K, Kawaguchi K, Sasaki T, Morimoto Y. Biopersistence of NiO and TiO_2 Nanoparticles Following Intratracheal Instillation and Inhalation. Int J Mol Sci. 2017 Dec 19;18(12):2757. doi: 10.3390/ijms18122757. PMID: 29257061; PMCID: PMC5751356.

Therefore, in addition to determining that PV29 presents unreasonable risks of non-cancer and carcinogenic effects by inhalation, EPA must use its section 4 authority to require studies aimed at two objectives: (1) to examine whether there is absorption and uptake of PV29 by any route (oral, dermal and inhalation) which results in systemic toxicity outside the respiratory tract, and (2) to further elucidate PV29's cancer and non-cancer inhalation effects by testing PV29 directly for these endpoints as opposed to relying on data for its surrogate carbon black. At a minimum, these studies should include:

1. Acute inhalation toxicity tests – since EPA has determined that the existing studies are unacceptable;[28]
2. Toxicokinetic studies by all routes of exposure;
3. A 28-day repeat-dose study in rodents by the oral route;
4. A subchronic (90-day) inhalation study in rodents; [29]
5. Consistent with ECHA's evaluation of the REACH dossier for PV29, an *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study;
6. Appropriate shorter-term *in vivo* and/or *in vitro* studies designed to characterize the mode of action of PV29 lung effects and examine the potential for inhalation carcinogenicity, focusing on particle retention kinetics in the whole respiratory tract and the potential for pulmonary inflammation and histopathology as well as systemic toxicity in other tissues; and
7. If warranted by other studies, a two-year carcinogenicity study in rodents.

Once this testing is conducted, a supplemental risk evaluation and/or additional risk management may be warranted. In the interim, EPA should finalize unreasonable risk determinations for PV29 based on the known lung toxicity and carcinogenicity of the carbon black surrogate and follow-up with rulemaking under TSCA section 6(a) to protect workers from these effects of PV29 exposure.

V. EPA's Risk Determinations for Workers Exposed to Carbon Black Are Insufficiently Protective

While we support an unreasonable risk determination for PV29 based on lung toxicity and carcinogenicity, we are concerned that EPA's methodology for calculating MOEs systematically understates the magnitude of 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 3,000 and, arguably, 10,000. Second, EPA increases its MOEs to account for the protection provided by respirators despite the limited evidence for respirator use at PV29 manufacturing and processing facilities and the Agency's misinterpretation of OSHA policies and regulations to require respiratory protection in the absence of a substance-specific workplace standard.

A. EPA's Benchmark MOE of 30 Is Too Small and Must be Increased to 3000 or 10,000

[28] Revised Draft Evaluation, at 105-106.

[29] Based on the potential for lung overload, ECHA requested that the registrants of PV29 REACH dossier conduct additional inhalation toxicity studies on PV29 and its close analogue (C.I. Pigment Red 179), which must include measurements of lung burden and bronchoalveolar lavage fluid (BALF). European Chemical Agency (ECHA). 2019a. Decision on A Compliance Check for Perylene- 3,4;9,10-tetracarboxydiimide (CAS #81-33-4). Available: b12e7c97-c16e-a070-e1b7- 2bf1e683342a (europa.eu); European Chemical Agency (ECHA). 2019b. Decision on A Compliance Check for 2,9- dimethylanthra[2,1,9-def:6,5,10-d'e'f']diisoquinolineL,3,B,LO(2H,9H) -tetrone (CAS # 5521- 31-3). Available: https://echa.europa.eu/documents/10162/df13fee2-32b5-5472-c42b-f07735b18c58

As EPA explains, its benchmark MOE is based on two UFs:[30]

> **Animal-to-human extrapolation (UF_A):** The UF_A accounts for the uncertainties in extrapolating from rodents to humans. In the absence of data, the default UFA of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for toxicodynamic variability. There is no PBPK model for C.I. Pigment Violet 29 to account for the interspecies extrapolation using rodent toxicokinetic data in order to estimate internal doses. In this assessment, a portion of the toxicokinetic uncertainty may be accounted for use of the MPPD model for estimating the retained particle fraction in the alveolar region of the lung (internal dose) based on. A UF_A of 3 is retained to account for toxicodynamic variability (OECD 39).
>
> **Inter-individual variation (UF_H):** The UF_H accounts for the variation in sensitivity within the human population. In the absence of data, the default UFH of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for toxicodynamic variability. Since there is no PBPK model for C.I. Pigment Violet 29 to reduce the human toxicokinetic/toxicodynamic variability, the total UF_H of 10 was retained.

EPA should increase and add to these UFs in three respects:

1. Since there is no toxicokinetic or subchronic data for PV29 itself and the determination of its lung toxicity is based on studies on the analogue carbon black, there is significant uncertainty in extrapolating from rodents to humans. This warrants increasing the UF_A from 3 to 10.
2. EPA recognizes that "[t]ypically, a UF_S of 10 is used to extrapolate a POD from a less-than-chronic study to a chronic exposure," but maintains that this UF is unnecessary because "the available information in animal studies support pulmonary system effects at similar concentrations following chronic exposures to carbon black particles."[31] No data are cited for this statement and it is plausible that inhalation of carbon black (or PV29) for two years as opposed to 90 days would result in greater particle accumulation in the lung, leading to more severe inflammation and other adverse consequences. Thus, a UF_S of 10 is warranted.
3. EPA guidance calls for application of a UF where the absence of adequate data creates uncertainty in determining a chemical's health effects:[32]

> > "The database UF is intended to account for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. In addition to identifying toxicity information that is lacking, review of existing data may also suggest that a lower reference value might result if additional data were available. Consequently, in deciding to apply this factor to account for deficiencies in the available data set and in identifying its magnitude, the assessor should consider both the data lacking and the data available for particular organ systems as well as life stages."
>
> EPA has consistently failed to apply this UF in its TSCA risk evaluations without any explanation or justification. For PV29, the database uncertainty is unusually great, deriving from the use of an analogue to determine PV29's inhalation toxicity, the extremely limited and inadequate data on

[30] Draft Risk Evaluation at 71-72.
[31] Id at 72.
[32] EPA-630-P02-002F, A Review of the Reference Dose and Reference Concentration Processes, at 4-44 (Dec. 2002) https://www.epa.gov/risk/review-reference-dose-and-reference-concentration-processes-document. (RD and RC Review).

PV29 itself and unresolved questions about whether PV29 is absorbed and distributed within the body. These considerations warrant a UF of 10.

If UFs of 10 X for extrapolation from subchronic data to chronic exposure and data-base uncertainty are added, the total UF would be 3000. Adjusting the UF for interspecies extrapolation to 10 would further increase the total UF to 10,000.

B. EPA's Unreasonable Risk Determinations for PV29 Should Not Assume that Exposed Workers Will be Protected by Respirators

As in previous risk evaluations, EPA's risk determinations for workers exposed to PV29 calculate MOEs assuming both the use of respirators and their absence. For some but not all conditions of use, however, EPA factors in the Protection Factors (PFs) provided by respirators, resulting in lower assumed levels of exposure and higher MOEs. It then uses these MOEs as the basis for its determinations of unreasonable risk.

In each of its reviews of draft evaluations, the SACC has repeatedly raised concerns about EPA's undue reliance on personal protective equipment (PPE) for determinations of unreasonable risk. In its report on the initial PV29 draft, the SACC noted that "the analysis in the Evaluation does not discuss or account for the fact that downstream commercial users may be oblivious to chemical risks and lack even rudimentary industrial hygiene measures."[33] Similarly, in reviewing the 1,4-dioxane evaluation, the SACC concluded that the "consensus of the Committee believes that PPE may not be consistently and properly worn, as EPA assumed."[34] As it concluded, "8-hour use of PPE should not be used in the risk characterization of inhaled 1,4-Dioxane. Risk estimates should be presented without the use of PPE as reasonable worst case."[35]

In the case of HBCD, the SACC noted that "it was unreasonable to assume workers would wear PPE for entire 8-hour shifts due to underlying medical conditions, facial hair, discomfort, and other issues" and added that:[36]

> "[M]any members of the Committee believed EPA should place more emphasis on the limited likelihood that respiratory protection will be adopted without specific occupational exposure guidelines for HBCD . . . Dust exposures in the construction trades (especially residential construction) continue to represent an occupational health concern because of the many small-to-medium size operators and the use of temporary (and, not infrequently, undocumented) workers. Workers in these small-to-medium enterprises may not be likely to adopt personal protective equipment (PPE) controls, so EPA's characterization of reasonable risk relying on use of PPE is not sufficiently supported by the practical realities of many workplaces.

The SACC report on the methylene chloride risk evaluation reinforced these points, stating that "[m]ost Committee members agreed that EPA's assumptions of PPE use likely do not reflect actual conditions in most workplaces."[37] The SACC added that:[38]

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[33] SACC Report on PV29 at 37.

[34] TSCA Science Advisory Committee on Chemicals
Meeting Minutes and Final Report No. 2019-02 Peer Review for EPA Draft Risk Evaluations for1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD), at 88.

[35] Id. at 53.

[36] Id at 118.

[37] SACC Report on methylene chloride, at 17.

[38] Id at 36.

> "The Agency's reliance on appropriate use of personal protective equipment (PPE), including both respirators and gloves, is not supported by current research literature or industrial hygiene practice. The mere presence of a regulation requiring respirators does not mean that they are used or used effectively. Inadequacies in respirator programs are documented. Respirators require multiple respiratory protection (RP) compliance factors in order to perform as certified. Brent et al. (2005) used data from the NIOSH and Bureau of Labor Statistics (BLS) joint survey on Respirator Usage in Private Sector Firms, (BLS, 2001) to examine the adequacy of respirator protection programs in private industries. They found "large percentages of establishments requiring respirator use [under OSHA or the Mine Safety and Health Administration (MSHA) regulations] had indicators of potentially inadequate respirator programs." Later, Janssen et al. (2014) reported that 'APFs do not apply to RPD used in the absence of a fully compliant RP program; less than the expected level of protection is anticipated in these situations.' Moving beyond program elements, the frequency of proper use of gloves and respirators is largely unknown."

As in previous draft evaluations, EPA maintains that OSHA regulations require respirator use at PV29 manufacturing and processing facilities:[39]

> "EPA generally assumes compliance with OSHA requirements for protection of workers, including the implementation of the hierarchy of controls. . . EPA does not believe that the Agency must presume, in the absence of such information, a lack of compliance with existing regulatory programs and practices. Rather, EPA assumes there is compliance with worker protection standards unless case-specific facts indicate otherwise, and therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE in a manner that achieves the stated APF or PF."

As we have repeatedly commented, this is a misreading of OSHA regulations and policies. There is no mandatory OSHA standard for PV29 and it is highly uncertain whether the "nuisance dust" standard would require respirator use by PV29-exposed workers. While Sun Chemicals Safety Data Sheet (SDS) for the substance may recommend the use of respirators, OSHA hazard communication regulations do not require employers to follow SDS recommendations, and the preamble to these regulations expressly states that "there is no requirement for employers to implement the recommended controls."[40] Moreover, OSHA regulations give employers wide latitude to interpret evidence of workplace risks and to select worker protection measures they deem appropriate. Thus, OSHA's PPE standard requires employers to assess the hazards workers face but to provide PPE only when the employer deems such measures "necessary."[41]

For PV29, EPA pointed to comments by Sun Chemical and other information indicating "that some employers, particularly in the industrial setting, are providing appropriate engineering or administrative controls or PPE to their employees."[42] However, EPA did not provide any detail except to note that some Sun Chemical workers were reportedly using half-mask respirators for dust protection.[43] In general, EPA admitted that "information [on respirator use] for each condition of use is not known." Nonetheless, it arbitrarily assumed that workers were wearing respirators with PFs of 10 or 25 for some conditions of use but not others:[44]

> "For each condition of use of C.I. Pigment Violet 29 with an identified risk for workers, EPA evaluated the use of a respirator. However, EPA assumes that for some conditions of use, the use of

[39] Revised Draft Evaluation at 47-48.
[40] Hazard Communication, 77 Fed. Reg. 17574, 17693 (Mar. 26, 2012).
[41] 29 C.F.R. § 1910.132(a).
[42] Draft Evaluation at 13.
[43] Id. at 47.
[44] Id. at 14.

> appropriate respirators is not a standard industry practice, based on best professional judgement given the burden associated with the use of supplied-air respirators, including the expense of the equipment and the necessity of fit-testing and training for proper use. For manufacturing, processing, recycling, and disposal conditions of use, respirators with an APF of 10 were assumed. For one condition of use, paints and coatings for automobile (*e.g.*, Original Equipment Manufacturer (OEM) and refinishing), EPA assumed the use of a respirator with an APF of 25. For the remaining industrial, commercial, and consumer conditions of use, EPA assumed no use of a respirator."

EPA's rationale for differentiating among conditions of use is not explained; EPA apparently did not visit any manufacturing or processing sites or solicit detailed information from site owners about worker protection practices. In fact, EPA assumed that in some processing sectors, respirators would not be required "given the burden associated with the use of supplied-air respirators, including the expense of the equipment and the necessity of fit-testing and training for proper use." These are the very factors that have prompted experts (and EPA itself) to conclude that respiratory protection is highly intermittent and ineffective even where OSHA requires its use. This strongly suggests that consistent and reliable use of respirators is unlikely even for the conditions of use where EPA assumes such use; EPA has provided no reason to conclude otherwise. EPA's unreasonable risk determinations should thus rely on an assumed absence of respiratory protection for all conditions of use.

If this approach is utilized, MOEs would be below the current benchmark MOE of 30 for high-end and central-tendency exposure scenarios and two of the three median particle sizes for **all 14** of the PV29 conditions of use. Increasing the benchmark MOE to reflect additional uncertainty factors, as proposed above, would further underscore the seriousness of EPA's findings of unreasonable risk.

Conclusion

We appreciate this opportunity to comment on the draft revised PV29 risk evaluation and urge EPA to finalize the evaluation in accordance with the recommendations in these comments.

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