



January 14, 2019

The Honorable Andrew Wheeler
Acting Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460-0001

**Re: Draft TSCA Risk Evaluation for Colour Index (C. I.) Pigment Violet 29 (PV29);
Notice of Availability (Docket No. EPA-HQ-OPPT-2018-0604)**

Dear Acting Administrator Wheeler:

On behalf of the American Public Health Association, a diverse community of public health professionals that champions the health of all people and communities, I appreciate the opportunity to comment on the Environmental Protection Agency's Draft Risk Evaluation for Colour Index Pigment Violet 29 (PV29). EPA has determined that PV29 does not present an unreasonable risk of injury to health or the environment under the Toxic Substances Control Act.¹ Unfortunately, EPA made this determination in the absence of adequate data on toxicity and exposure. The agency compounded these inadequacies and ignored its own risk assessment guidelines by failing to apply additional uncertainty factors to account for such data gaps and by failing to assess risk across routes of exposure. I respectfully urge the agency to revisit the Draft Risk Evaluation for PV29 and correct these failings, detailed below.

1. EPA lacks adequate data on toxicity and exposure to determine that PV29 does not present an unreasonable risk.

In general, a risk evaluation develops and compares estimates of the *toxicity* of a chemical and estimates of *exposure* to the chemical. If the level of exposure experienced by people is higher than the level of exposure that EPA believes may cause toxicity, the agency will conclude that exposure presents an unreasonable risk. Conversely, if the level of exposure people experience is lower than the level that EPA believes may cause toxicity, the agency will conclude that exposure does not present an unreasonable risk. A risk evaluation therefore depends on estimates

¹ Draft Risk Evaluation for PV29 at 32.

of toxicity and exposure and the data used to derive them. EPA lacks the data needed to develop reliable risk estimates and determine that PV29 does not present an unreasonable risk.

EPA has relied on an extremely limited set of toxicity studies to characterize the hazards associated with exposure to PV29 and to identify the level of exposure that presents an unreasonable risk. The agency does not report any studies of chronic or subchronic exposure, nor does it report any studies of neurotoxicity, respiratory sensitization or other standard domains.² Its human health risk estimate relies on a single toxicity study, a reproductive and developmental toxicity “screening test” conducted according to OECD Guideline 421.³ According to EPA’s *Guidelines for Developmental Toxicity Risk Assessment*, this study design “is insufficient by itself to make an estimate of human risk without further studies to confirm and extend the observations.”⁴ Indeed, the OECD guidelines describe the test as follows:

This test does not provide complete information on all aspects of reproduction and development. ...Due (amongst other reasons) to the relatively small numbers of animals in the dose groups, the selectivity of the end points, and the short duration of the study, *this method will not provide evidence for definite claims of no effects.*⁵

Yet despite the overall lack of toxicity data and reliance on a screening test that that cannot provide evidence for definite claims of no effects, EPA baldly asserts that “a review of the available human health data identified for C.I. Pigment Violet 29 indicates low hazard to human health across all routes of exposure (oral, dermal, inhalation).”⁶ This conclusion simply cannot be supported by these data.

EPA paired this toxicity study with a haphazard assessment of occupational exposure to PV29 in workers employed in the manufacture of this chemical. This assessment relies on “an approximate maximum air concentration of 0.5 mg/m³” provided by Sun Chemical, the manufacturer of PV29.⁷ In support of this value, EPA cites only a personal communication with

² See Appendix D of the Draft Risk Evaluation for PV29 for a table summarizing the human health effects studies considered by EPA. The vast majority of the studies considered by the agency evaluated acute exposures only. The study with the longest duration was the reproductive and developmental toxicity screening test, in which animals were observed between 4 and 57 days. See *id.* at 25-26.

³ The margin of exposure is calculated using the screening test. See Draft Risk Evaluation for PV29 at 29.

⁴ EPA, *Guidelines for Developmental Toxicity Risk Assessment* 21 (1991), https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf.

⁵ OECD, Test No. 421: Reproduction/Developmental Toxicity Screening Test 2 (2016), available at https://www.oecd-ilibrary.org/environment/test-no-421-reproduction-developmental-toxicity-screening-test_9789264264380-en (click on “PDF” link) (emphasis added).

⁶ Draft Risk Evaluation for PV29 at 28.

⁷ See *id.* at 22.

Sun Chemical and presents no further information with respect to how this concentration was determined.⁸ It appears EPA itself may not possess such information: the agency admits that “[i]t is not clear if the monitoring data were for C.I. Pigment Violet 29 or for total dust.”⁹ It is highly unlikely that EPA understands whether the methods used to derive such a value were appropriate if the agency cannot determine whether the data refer to PV29 or total dust. The agency cannot rely on monitoring data about which it knows almost nothing.

2. EPA ignored its own risk assessment guidelines and practices by failing to apply additional uncertainty factors to account for inadequate data.

It is widely understood within the public health community that agencies will need to make decisions without the benefit of complete information. This does not mean, however, that agencies can ignore such “data gaps” altogether. In environmental health, risk assessors bridge data gaps by applying science-based default approaches, such as the uncertainty factors recommended in EPA risk assessment guidelines.¹⁰ Yet EPA has failed to account for the myriad data gaps present in the Draft Risk Evaluation for PV29 and has not applied the appropriate uncertainty factors.

In the PV29 evaluation, EPA compares toxicity and exposure estimates using a margin of exposure (MOE) approach in which a purported “no observed adverse effect level” (NOAEL), which is the highest level of exposure that was not observed to cause an adverse effect in an animal study,¹¹ is divided by an estimate of the level of exposure in people.¹² A MOE > 1 indicates that the level of exposure estimated in people is lower than a level of exposure that was not observed to cause an adverse effect in an animal study (that is, lower than the NOAEL). This, by itself, does not indicate that the level of exposure in people does not pose an unreasonable risk, in part because humans may be more susceptible to chemical toxicity than animals and because some people may be more susceptible than other people are.

In the Draft Risk Evaluation, EPA compares the margins of exposure that it calculates for inhalation and dermal exposures in workers to a “benchmark MOE” of 100, which is the product

⁸ *Id.*

⁹ *Id.*

¹⁰ See National Research Council, *Science and Decisions* 207 (2009) (“[D]efaults need to be maintained for the steps in the risk assessment that require inferences to fill common data gaps.”). The uncertainty factors recommended by EPA are reviewed extensively in EPA, *A Review of the Reference Dose and Reference Concentration Processes* (2002), <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>.

¹¹ According to EPA, a NOAEL is “[t]he highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control[.]” EPA, *Integrated Risk Information System (IRIS) Glossary*, https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary (search for “NOAEL”).

¹² Draft Risk Evaluation for PV29 at 28-29.

of an uncertainty factor of 10 for differences between humans and animals, and an uncertainty factor of 10 for differences among people.¹³ EPA concludes that, because the MOE is greater than the benchmark of 100, meaning that its estimates of the levels of exposure in workers are at least 100 times less than the level not observed to cause an adverse effect in an animal study, that exposure to PV29 does not present an unreasonable risk.¹⁴

EPA errs, however, by failing to include any additional uncertainty factors when calculating the benchmark MOE to account for inadequate toxicity data. Some of the uncertainty factors that the agency should have considered include:

- **Database:** EPA guidelines say it should apply an uncertainty factor when needed to “account for...an incomplete characterization of [a] chemical’s toxicity.”¹⁵ A factor of 10 is applied where, as here, both a prenatal toxicity study and a two-generation reproductive toxicity study are missing.¹⁶ As discussed above, data on the toxicity of PV29 are extremely limited, and the developmental and reproductive toxicity screening test reported by EPA is inadequate for risk assessment. EPA therefore should have considered applying an additional uncertainty factor of 10 to account for database deficiencies.
- **Subchronic-to-Chronic:** EPA guidelines recommend an uncertainty factor of 10 when “only a subchronic study is available to develop a chronic reference value[.]”¹⁷ Here, EPA has evaluated the risk of chronic exposure to PV29 in workers using a screening test that exposed animals over a less-than-chronic duration (4-57 days, or just a small fraction of the two-year lifespan typical of laboratory rodents¹⁸). EPA therefore should have considered applying an additional uncertainty factor of 10 to account for extrapolating from short-term to chronic exposures.
- **Routes of Exposure:** EPA evaluated the risk presented by inhalation and dermal exposure to PV29 in workers using the results of the screening test in which animals were exposed orally.¹⁹ There may be important differences in the toxicity of a chemical based on route of exposure; that is, toxicity may vary when a chemical is swallowed versus

¹³ Draft Risk Evaluation for PV29 at 29.

¹⁴ Draft Risk Evaluation for PV29 at 32.

¹⁵ EPA, A Review of the Reference Dose and Reference Concentration Processes, *supra* note 10, at 4-44.

¹⁶ *See id.* at 4-45.

¹⁷ *Id.*

¹⁸ Draft Risk Evaluation for PV29 at 25-26.

¹⁹ *See id.* at 25, 29.

when a chemical is inhaled.²⁰ EPA therefore should have considered applying an additional uncertainty factor of 10 to account for extrapolating across routes of exposure.

- ***Vulnerable Populations:*** It is widely recognized that pregnant women, infants, and children are more vulnerable to toxic chemicals. In some contexts, EPA applies an uncertainty factor of 10 to account for this vulnerability.²¹ As TSCA requires EPA to evaluate risk in vulnerable subpopulations,²² and the agency lacks data on susceptibility and exposure in pregnant women, infants, and children,²³ the agency should have considered applying an additional uncertainty factor of 10 to protect vulnerable populations.

If EPA had applied all of these uncertainty factors, the benchmark MOE would have been 1,000,000, *not* 100. The margins of exposure for inhalation and dermal exposures in workers are much less than 1,000,000, and EPA thus would have concluded that PV29 presents an unreasonable risk. Such a high benchmark MOE is unusual, as agencies normally do not attempt to conduct risk assessments based on such limited data.²⁴ For this reason, EPA should exercise its authority under TSCA to require the submission of additional studies before it finalizes the risk evaluation. However, if EPA intends to determine whether PV29 presents an unreasonable risk based on the limited information currently in the record, it must follow its own recommendations and apply the necessary uncertainty factors.

3. EPA must combine routes of exposure when evaluating risk.

A person may be exposed to a chemical substance by multiple routes, including ingestion, inhalation and dermal absorption. All of these exposures together contribute to total exposure and risk. Therefore, it is imperative that risk assessments consider all routes of exposure in combination. While EPA acknowledges that workers may be exposed to PV29 by both inhalation

²⁰ Curtin D. Klaassen and John B. Watkins III, *Casarett & Doull's Essentials of Toxicology* 9 (2010) (“Toxic agents typically produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route). An approximate descending order of effectiveness for the other routes would be inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal.”)

²¹ EPA is required to apply an additional uncertainty factor of 10 when assessing risks presented by dietary exposure to pesticides, but the agency has stated that the uncertainty factor should be applied in other risk assessments even when it is not required. *See* EPA, Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields, and Pesticides with No Food Uses 6 (2009), available at <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0889-0002>.

²² *See* TSCA § 6(b)(4)(A).

²³ EPA acknowledges that PV29 is used in watercolor and artistic paint. Draft Risk Evaluation for PV29 at 23. While the agency says these paints “are not directly marketed to infants or children,” *id.*, this cannot be taken to mean that children will not use the paints and be exposed to PV29 as a result. Nonetheless, EPA does not assess exposure to PV29 in children.

²⁴ *See* EPA, A Review of the Reference Dose and Reference Concentration Processes, *supra* note 15, at 4-41.

and dermal absorption, the agency fails to assess risk across these routes.²⁵ This stands in stark contrast to other EPA risk assessments, such as pesticide risk assessments, in which the agency routinely combines inhalation and dermal risks using straightforward methods that easily could be applied here.²⁶ EPA must combine all routes of exposure when making a risk determination.

EPA must conduct a thorough risk evaluation that includes appropriate toxicity and exposure data and, where such data are not reasonably available, science-based defaults recommended by the agency's guidelines. EPA plainly has not done so here. Therefore, I respectfully urge the agency to revisit the Draft Risk Evaluation for PV29 in light of these comments, and the comments of other public health stakeholders, and revise its analysis accordingly.

Please contact me with any questions regarding our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Georges C. Benjamin". The signature is fluid and cursive, with the first name being the most prominent.

Georges C. Benjamin, MD
Executive Director

CC: Alexandra Dunn, Assistant Administrator, EPA/OCSPP

²⁵ Draft Risk Evaluation for PV29 at 22-23.

²⁶ See, e.g., EPA, Atrazine Draft Human Health Risk Assessment for Registration Review 106 (2018), <https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0266-1159>.