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Supplemental Comments on Draft Pigment Violet 29 Risk Evaluation Under the Toxic Substance Control Act

July 10, 2019

The Environmental Protection Network (EPN) is an organization comprised of over 450 EPA alumni volunteering their time to protect the integrity of the U.S. Environmental Protection Agency (EPA), human health and the environment. We harness the expertise of former EPA career staff and confirmation-level appointees to provide an informed and rigorous defense against current administration efforts to undermine public health and environmental protections.

We make three points elaborated on below:

1. The current systematic review process has never been externally peer-reviewed.
2. The Pigment Violet 29 (PV29) database is inadequate and the approach to determine hazardous levels of exposure was computed with four uncertainty factors, missing a crucial fifth to account for database deficiencies.
3. EPA relied on inadequate data to reach the conclusion that PV29 does not present an unreasonable risk to health or the environment.

1. TSCA Systematic Review

On August 16, 2018, the EPN submitted comments on EPA's draft guidance on a new systematic review process that was developed specifically for use in chemical risk evaluations under the Toxic Substance Control Act (TSCA); this process had never been externally peer-reviewed. In our comments, EPN advised against the use of this highly flawed draft methodology, as did numerous other organizations and experts in systematic review, as it departed substantially from accepted scientific principles for systematic review supported by the National Academy of Science's (NAS) Institute of Medicine and adopted by the National Toxicology Program. EPN commented that the draft TSCA process inexplicably did not build upon the years of progress in developing EPA's systematic review process for the Integrated Risk Information System (IRIS) program, which has been endorsed by the NAS. Our comments documented three critical flaws in the TSCA approach: 1) failure to include protocols to synthesize evidence from all the selected studies into a judgment about the weight of evidence as a whole; 2) use of an arbitrary quantitative scoring system for assessing and selecting individual studies; and 3) failure to adopt adequate implementation procedures for conducting the systematic review. EPN believes that these three critical flaws will lead the agency to exclude quality research and to select potentially biased studies for use, in direct opposition to the intent of conducting a systematic review in the first place.

Despite the well-documented flaws in this proposed systematic review process, EPA has not yet subjected the methods to peer review, but EPA has continued using the deficient TSCA review process for the TSCA risk evaluations of the first 10 chemicals and for the Safe Drinking Water Act risk assessment of GenX. At the June 20, 2019 meeting of the TSCA Science Advisory Committee on Chemicals (SACC), an EPA staff presentation indicated that over the next year SACC and the NAS would review the process, but verbal discussion at the meeting clarified that there would not be a formal NAS review. The EPA staff presentation also documented that the TSCA systematic review process would not be revised to include the protocols on how to synthesize evidence from all the selected studies in order to make a determination of unreasonable risk. Instead EPA would address synthesis of studies on a chemical-by-chemical basis and would document the process used in each chemical risk evaluation.

EPN is commenting today on the April 2019 Pigment Violet 29 Systematic Review: Supplemental File for the TSCA Risk Evaluation. This supplemental file documents the changes that EPA made in response to public comments on its original assessment of relevant studies. First, quantitative scores for assessing the quality of an individual study are arbitrary and not science-based; the Cochrane Collaboration and the National Academy of Sciences recommend against such scoring methods.

In the updated supplemental file document, EPA continues to pursue quantitative scoring, which is arbitrary, and the major changes in the scoring of studies support our contention that the TSCA systematic review process is flawed and capricious. Furthermore, the TSCA regulation requires that the systematic review method be applied consistently to each evidence stream, but the TSCA method does not provide clear criteria for rating studies, nor can they. This inconsistency can be seen as approximately one-third of all the ratings of individual study aspects were downgraded from EPA's initial evaluation. This change in ratings was particularly problematic for the acute inhalation toxicity studies since inhalation is expected to be the main exposure pathway for workers. In the PV29 risk evaluation, EPA found no unreasonable inhalation risk for workers based on only two acute inhalation toxicity studies and a personal communication from Sun Chemical that an approximate maximum workplace air concentration of 0.5 mg/m3 would be expected over a 12-hour shift. This finding was despite the fact that EPA was forced to downgrade both acute inhalation toxicity studies from medium to unacceptable in the second round of scoring when public comments pointed out that ECHA summaries labeled them "not reliable." In addition, two acute oral toxicity studies and two eye irritation studies were downgraded to medium, while two acute intraperitoneal studies were downgraded to low confidence. Thus, EPA's systematic review methods should not use numeric scoring and must be improved before a reliable risk evaluation conclusion can be drawn.

EPA told the SACC that each chemical risk evaluation would describe how the agency synthesized the evidence from all the selected studies, but in the PV29 risk evaluation EPA does not adequately describe a specific protocol used to conclude that the chemical does not pose an unreasonable risk. [Biases from financial conflicts of interest were not rated.] There was no discussion of how the agency qualitatively rated the confidence in the overall body of evidence for PV29.

In conclusion, EPN recommends that EPA abandon the flawed TSCA "systematic review." Instead, EPA should implement a systematic review method that is compatible with empirically based existing methods and aligns with the Institute of Medicine's definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review. EPA should consider methods demonstrated for use in environmental health, and which have been endorsed and utilized by the National Academy of Sciences, i.e., the National Toxicology's Office of Health Assessment and Translation systematic review method, and the Navigation Guide Systematic Review Method, and the IRIS program. EPA's TSCA systematic review framework should be peer-reviewed by qualified external experts in the field.

2. Adequacy of the PV29 Database and the Missing Uncertainty Factor

Comments submitted by EPN and other parties during earlier comment periods questioned whether the hazard and exposure information available on PV29 was adequate to allow EPA to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment….." If there was any doubt about the inadequacy of the foundation for making a determination at the time of initial issuance of the November 2018 draft Risk Evaluation for public comment, the recent downgrading by EPA of several of the toxicity studies meant to describe the potential for human hazard, as documented in the Supplemental files presented to the TSCA SACC for consideration during their recent peer review of the

draft Risk Evaluation, completely dispels any myth of adequacy. It's time for the agency to admit that the database for PV29 is too insubstantial to support a risk determination. If EPA wishes to do so in the future, issuance of testing orders to fill the critical data gaps is the only reasonable next step to take.

EPA could have saved a lot of time and effort if it had followed long-standing agency-wide guidance on determining the adequacy of a toxicity database when deriving a Reference Dose (RfD) or Reference Concentration (RfC). The principles in place for RfD and RfC derivation also apply when characterizing a Benchmark Margin-of-Exposure (MOE), as was the approach taken for PV29. Implementation of these principles at an early stage in the assessment process would have led to the conclusion that the database for assessment of human hazard was too sparse to allow for a finding to be made, and that either the assessment should be abandoned or suspended until such time as adequate data have been requested and analyzed.

As pointed out by Dr. Scarano in his presentation to the SACC on June 19, 2019, there are a number of Uncertainty Factors that may be appropriate for application to a data set when deriving an RfD, RfC or Benchmark MOE as an estimate of "acceptable" human exposure to a chemical substance. He cited the following:

UF_H–Intraspecies –human-to-human variability/uncertainty
UF_A–Interspecies -animal-to-human variability/uncertainty
UF_S–Subchronic to Chronic extrapolation
UF_L–LOAEL-to-NOAEL extrapolation

What he did not mention was a fifth category of Uncertainty Factor:

UF_D_Database deficiencies

Each of these, when applied, generally does not exceed 10X, and may be lower; 3X is common. Agency application of this guidance is predicated upon a determination that, for a chronic exposure situation, a minimum database on which to estimate a high confidence reference value/MOE based upon animal studies would consist of chronic dog and rat studies, along with reproductive and developmental bioassays (Dourson et al 1992; Dourson, et al 1996, US EPA, 2002). As a matter of policy, the composite UF should not exceed 3000 (US EPA, 2002).

Looking once more at the PV29 Draft Risk Evaluation, EPA used a MOE approach to assess data describing only non-cancer hazards. As a reminder, the MOE is the ratio of the point of departure (POD) dose from a toxicity study divided by the estimated or measured human exposure dose. This MOE is compared to a benchmark MOE. If the MOE exceeds the benchmark MOE, this indicates that risks to human health are not expected. EPA determined the Benchmark MOE to be =100, incorporating only the interspecies (UF_A), intraspecies (UF_H) and LOAEL-to-NOAEL (UF_L) Uncertainty Factors. However, because they were assessing a longer-term occupational exposure scenario, they also should have included an Uncertainty Factor for Subchronic to Chronic extrapolation (UF_S), as the study from which they selected the POD was of limited duration. Finally, because the toxicity database is so poor, they should have included an Uncertainty Factor for Database deficiencies (UF_D). Thus, the composite Uncertainty Factor would have been (UF_A x UF_H x UF_L x UF_S x UF_D) or (10 x 10 x 1 x 10 x 10)=10000. But since the agency's policy is that no composite UF should exceed 3000, the Benchmark MOE, in this instance, should be 3000. While this might not change the conclusions about risk associated with inhalation exposures, it would alter the conclusions reached with regard to dermal exposures. A comparison of the MOE for inhalation with the benchmark MOE (14,933/3000) and the MOE for the worst-case dermal exposure with the benchmark MOE (361/3000) indicate that risks may not be identified for workers based on inhalation exposure but

would identify risks based upon dermal exposure, as only the inhalation MOE was greater than the benchmark MOE of 3000.

3. Additional Testing Is Necessary Under TSCA

The data insufficiency finding under TSCA is

> there is insufficient information and experience upon which the effects of manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted.

The converse of the data inadequacy finding under TSCA is that data should be adequate for reasonable determination or prediction of the substance's effects. As noted above, EPA relied on inadequate data to reach the conclusion that PV29 does not present an unreasonable risk. In addition, TSCA requires that health and safety information cannot be claimed as Confidential Business Information and must be made available to the public. These studies for PV29 are not fully available to the public.

EPN recognizes, as does TSCA, that comprehensive testing for every effect for every chemical is not feasible. However, it is critical that, for those relatively few chemicals selected for TSCA risk evaluations, sufficient data is available to support science-based determinations of risk. For PV29, EPA has based its conclusion of "no unreasonable risk" on insufficiently supported claims of low exposure, low bioavailability, and low toxicity observed only in short term studies. The available information is suggestive of a hypothesis of low risk, but it is woefully insufficient to establish it. As tiered testing is encouraged by TSCA, EPA should, at a minimum, seek to confirm or reject this hypothesis by requiring acute inhalation toxicity studies, workplace monitoring, basic pharmacokinetic (PK) data measuring levels of PV29 in blood and distribution in fat, solubility studies and a 90-day subchronic test as directed by PK results. If these studies demonstrate PV29's potential for exposure and provide evidence of toxicity, further higher-tier testing would be necessary to address a broader range of end-points.

In addition, EPA noted that PV29 was expected to partition to soil and sediment. It, therefore, has no basis to conclude that there is no unreasonable risk to the environment without biodegradation data and data on the toxicity to benthic organisms.

EPA should use its testing authority under TSCA section 4. The Lautenberg amendments gave EPA authority to require testing by rule, order, or consent agreement when data are needed to conduct a risk evaluation or even to establish the priority of a chemical for risk evaluation. These amendments were designed to ensure that EPA can obtain the data needed to assess the risk of chemicals in commerce. In other words, the amendments were tailor-made for just this kind of situation.

The risk evaluation of PV29 is critical because it will be precedent setting and should signal the agency's commitment to identifying and filling significant data-gaps before it makes determinations of unreasonable risk. We recognize that, from the standpoint of the extent of testing required, PV29 may be an exception in the first group of chemicals selected for risk evaluation since its production and exposure are more limited than many other chemicals in this group. For high production volume, high exposure chemicals included in these initial and future risk evaluations, EPA should have data addressing the full spectrum of effects (e.g., mutagenicity, cancer, chronic effects, reproductive and developmental effects) before it concludes that there is no unreasonable risk to human health. Similarly, the agency should have the full range of data on relevant environmental effects when a chemical is released to the environment in substantial amounts.

EPA needs to establish criteria to determine the minimum data set necessary to make a risk determination. Without such criteria, it will appear to be an arbitrary judgment call on each chemical.

References:

Dourson, ML; Knauf, LA; Swartout, JC. (1992) On reference dose (RfD) and its underlying toxicity database. Toxicol Ind Health 8:171–189.

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U.S. EPA. 2002. Review of the Reference Dose and Reference Concentration Processes. Final Report December 2002 EPA/630/P-02/002F Washington, DC.