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Review of (Some of) the Recently Released BASF Pigment Violet 29 Studies

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The Environmental Protection Network (EPN) is an organization comprised of over 400 EPA alumni volunteering their time to protect the integrity of 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 have the following concerns:

1) The lack of transparency in this risk evaluation will create a precedent of making "no unreasonable risk" determinations based on proprietary information.
2) The most critical study in this evaluation was heavily redacted, which removes the ability to do an independent analysis.
3) A potentially useful and important study was not included in the draft risk evaluation, with no explanation.

Introduction

On November 15, 2018, EPA's Office of Pollution Prevention and Toxics (OPPT) issued a draft risk evaluation for Pigment Violet 29 (PV29) for public review and comment. It was the first of the initial 10 chemicals to undergo a draft risk evaluation by this Administration under the new priority-setting/evaluation system for existing chemicals implemented in response to mandates in the 2016 updated Toxic Substances Control Act (the "new" TSCA). Unlike the other nine substances on the initial top 10 list—Asbestos; 1-Bromopropane; Carbon Tetrachloride; 1, 4 Dioxane; Cyclic Aliphatic Bromide Cluster (HBCD); Methylene Chloride; N-Methylpyrrolidone; Perchloroethylene; and Trichloroethylene—PV29 has received little prior agency or public attention. Furthermore, unlike the other nine on the list, it is a substance for which the extant database is constituted solely of toxicity, physical/chemical characteristics, and environmental fate studies declared by its manufacturer (BASF) to be Confidential Business Information (CBI). As a result, a somewhat non-traditional approach needed to be taken by EPA in order to develop a hazard and risk assessment.

PV29 is one among many substances that are registered in the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program. REACH establishes procedures for collecting and assessing information on the properties and hazards of substances. Data requirements are standardized, driven by the amount of product manufactured and/or imported on an annual basis. As one might expect, as the production/import volume increases, so does the number and nature of the data requirements. Companies can satisfy these requirements by submitting studies from the open peer-reviewed

literature, from other confidential or open sources using a read-across approach and/or conducting new studies to fill remaining data gaps. The European Chemicals Agency (ECHA) is responsible for the review of submissions and maintenance of the REACH database. In the case of PV29, ECHA reviewed roughly 20 submitted CBI studies, prepared "robust summaries" of each and uploaded their findings into a publicly available database.

EPA's OPPT also has access to the summary and study reports that went to ECHA for REACH registration plus several others that had been conducted for other purposes. EPA screened all but one of the REACH studies for the quality of the methods and reporting of results of the individual studies, citing each in the draft evaluation. EPA concluded that the 24 studies it reviewed were of high or medium quality and would be suitable for use in the risk evaluation. Rather than preparing their own summaries of each study, they determined that the ECHA robust summaries adequately captured the findings of the CBI studies and referenced them instead. They did so in a manner similar to that which they and other agency program offices have historically used the Office of Research and Development's (ORD) Integrated Risk Information System (IRIS) hazard assessments as the basis for the hazard component of their programs' risk assessments. As such, this was not as significant of a departure from a common practice than some might assert. ECHA staff scientists possess a level of expertise at a minimum equivalent to EPA staff, so this seemed to be a reasonable and efficient approach to take.

Setting an Unwanted Precedent

EPN has compiled these comments primarily because we are concerned about precedent setting. TSCA gives EPA the authority to require testing that will not be held as CBI before they make a determination of "no unreasonable risk." EPA is not using that authority in this case, and presumably won't do so in future cases. Generally, whether the agency is determining there is risk or no risk, it's important to be able to see the data. That said, it's particularly important for the protection of public health and the environment when a "no unreasonable risk" determination is made.

In the case of PV29, making these data fully available may or may not change EPA's determination, but for other chemicals in the pipeline, relying heavily on confidential data might make a significant difference. EPN urges the agency to use its authority and not make a determination based on proprietary information.

Critical Study Was Heavily Redacted

There have been calls from several sources for the release of all original full study reports for PV29. BASF (and EPA) acquiesced, somewhat. EPA released documentation on the studies in March 2019, but portions of all of the full study reports were redacted. In all cases, redaction obscured the names of individuals involved in the conduct or quality assurance (QA) of the study or were a supply source or testing lab. EPN does not believe this has an impact on the ability to review and assess the study for quality and results. However, in one case, the degree of redaction was far more significant (Study #17, the rat reproduction/developmental screening study). What remains in this case are the summary data for each parameter measured, as is true for all the other studies, but the raw data for each individual animal, which

form the basis of the summaries, is blacked out. So, in this case, although one can judge the quality and integrity of the results of the study, reach conclusions, and do the side-by-side comparison with the related test guideline, one cannot conduct an independent analysis of the data. In addition, no justification was provided for redacting the individual animal data; health and safety studies such as this one, information from health and safety studies, and certain other information, may not be protected as CBI under TSCA.

Potentially Useful Study Was Not Included

Without explanation,EPA did not include a review of, or reference to, a 90-day repeated dose dietary study in rats that also is in the REACH database for this chemical. While this study likely would not have been deemed pivotal for use in characterizing a no-observed-adverse-effect-level (NOAEL) or calculating a margin of exposure, it would have contributed to the weight-of-evidence conclusion that this chemical possesses low hazard and risk potential.

Summary of Findings

We were curious to find out if having access to the full study reports would make any difference in the conclusions reached after reviewing only the robust summaries. That said, EPN members confined their review to those toxicity studies most relevant to human hazard assessment, given that this is where we had the most expertise available.

Studies reviewed:

Studies with summaries only:

- Study #1 Eye Irritation (1975)
- Study #2 Eye Irritation (1978)
- Study #5 Inhalation toxicity study in rats (1975)
- Study #6 Inhalation toxicity study in rats (1978)
- Study #7 Acute intraperitoneal toxicity in mice (1975)
- Study #8 Acute intraperitoneal toxicity in mice (1978)
- Study #9 Acute oral toxicity in rats (1975)
- Study #10 Acute oral toxicity in rats (1978)
- Study #12 Skin irritation study in rabbits (1975)
- Study #13 Skin irritation study in rabbits (1984)

Studies with full reports (but partial redaction):

- Study #3 Acute dermal irritant effects/caustic effects on the rabbit eye (Rupprich and Weigand, 1984)
- Study #4 Acute irritant effects/caustic effects on the rabbit eye (Rupprich and Weigand, 1984)
- Study #11 Acute Oral Toxicity (Acute oral toxicity in the male and female Wistar rat (Rupprich and Weigand, 1984)
- Study #14 Study of mutagenic potential in strains of Salmonella typhimurium (Ames test) and E. coli (1983)

Study #15 Gene Mutation Assay in Chinese Hamster V79 cells *in vitro* (2012)
Study #16 Skin sensitization: Local Lymph Node Assay (mouse) (1999)
Study #17 Reproduction/developmental Toxicity Screening Test in Wistar Rats Oral Administration (Gavage) (2013)

Study NOT included in EPA evaluation:

Study X: 90-day repeated dose, subchronic study in rats (ECHA robust summary only)

Studies not reviewed:

Study #18 Acute Toxicity Zebra Danio (1988)
Study #19 Lemna Gibba Growth Inhibition Test (2012)
Study #20 Daphnia Magna Acute Immobilization Test (2012)
Study #21 Determination of Inhibition of Oxygen Consumption by Activated Sludge (1999)
Study #22 Determination of Biodegradability (1999)
Study #23 Physical Chemical Properties-Log_{KOW} (2013)
Study #24 Physical Chemical Properties-Melting Point (2013)

Approach to review

The review was conducted in three phases.

- Phase 1: Review each study and capture key elements and results. Note agreement or disagreement with study authors' conclusions.
- Phase 2: If an Organization for Economic Cooperation and Development Test Guidelines (OECD TG) was followed, compare elements of the conduct and reporting of the study with requirements/preferences in the TG to judge conformance with the TG.
- Phase 3: Review related ECHA robust summary, if available, to determine similarities or differences between our review and theirs.

Findings

Our assessments of each of the 17 studies reviewed (and included in the EPA evaluation) was consistent with that of ECHA's, with the minor exception of the resulting calculated LD50 in Study #8 (Acute intraperitoneal toxicity in mice). We concluded the LD50 $\geq$ 10,000 mg/kg. ECHA accepted the study report's finding of ~9000 mg/kgbw—a difference of no importance in classification of the endpoint or the overall importance of this study in the assessment of human health because no one is likely to be exposed to this substance by this route in the real world.

A brief word about Study X—the 90-day repeated dose study in rats. This was an old study (1967); therefore, it was not run under Good Laboratory Practice (GLP) or a formal test guideline. Nonetheless, it did possess sufficient integrity so that ECHA declared it a key study at Level 2 (reliable with restrictions), a designation shared by a number of the other 20 ECHA REACH studies that EPA used. Of importance are the reported results: no systemic toxicity effects were seen in male or female rats after 90days of dosing via

the diet at either 500 or 1000 mg/kg/bw/day, a finding consistent with the results of Study #17 (the reproductive/developmental toxicity screening test), that is, the NOAEL $\geq$ 1000 mg/kgbw/day.

Based upon our review, we are not particularly concerned about having only summaries of the 10 short-term assays. We could assess the available information adequately, as little more useful information would have been found in a full study report. The raw data for each animal in each study were included in data tables for all of the studies. Most of these studies are over 30 years old, with seven being conducted before consensus test guidelines were available and/or GLP guidelines were implemented. Documentation was more unstructured and sparse in those days. There are three exceptions. Studies #3, #4 and #13 were conducted after an OECD test guideline became available (OECD TG 404 and 405, each first issued in 1981). Studies #3 and #4 reference the OECD TG they followed (TG 404 and 405, respectively). While the summary of Study #13 makes no reference to any test guideline, the information available suggests that it was conducted in a manner consistent with OECD TG 404, including preferred test species, number of test animals, exposure, and observation durations and documentation of test results in tabular form. Given the amount of information available from each of these 10 studies, there is no reason to exclude them from contributing to the characterization of the substance's hazard profile.

In reviewing the other studies, we found the full reports, too, provided more than enough information to judge the integrity of the study and provide the ability to reach conclusions about the results and their importance. The side-by-side comparison of the study report with the relevant TG shows study compliance with that guideline in all cases.