UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

SUBJECT: Transmittal of Meeting Minutes and Final Report for the TSCA Science Advisory Committee on Chemicals Meeting Held June 18-21, 2019

TO: Jeff Morris, PhD
Director
Office of Pollution Prevention and Toxics

FROM: Todd Peterson, PhD,
Designated Federal Official
TSCA Science Advisory Committee on Chemicals
Office of Science Coordination and Policy

[redacted] 9/18/19

THRU: Steven M. Knott, MS,
Executive Secretary
TSCA Science Advisory Committee on Chemicals
Office of Science Coordination and Policy

[redacted]

Hayley Hughes, DrPH, MPH, CSP
Director
Office of Science Coordination and Policy

[redacted]

Attached, please find the meeting minutes and final report for the TSCA Science Advisory Committee on Chemicals open meeting held in Arlington, Virginia on June 18-21, 2019. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding the Peer Review for the Draft Risk Evaluation of C.I. Pigment Violet 29.

Attachment

cc:

Alexandra Dunn
David Fischer
Tala Henry
Mark Hartman
Cathy Fehrenbacher
Stan Barone
Jafrul Hasan
Garrett Jewett

OPPT Docket

TSCA Scientific Advisory Committee on Chemicals

Henry Anderson, MD
Charles Barton, PhD
Steven Bennett, PhD
Sheri Blystone, PhD
James Bruckner, PhD
Holly Davies, PhD
William Doucette
Kathleen Gilbert, PhD
Concepcion Jimenez-Gonzalez, PhD
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Mark Johnson, PhD
Alan Kaufman
John Kissel, PhD
Craig Rowlands, PhD
Ruthann Rudel, MS
Sheela Sathyanarayana, MD

TSCA Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2019-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29

June 18-21, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Holiday Inn Rosslyn at Key Bridge, 1900 Fort Myer Drive, Arlington, Virginia

NOTICE

The Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals (SACC) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The TSCA SACC provides independent advice and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) on the scientific basis for risk assessments, methodologies, and pollution prevention measures and approaches for chemicals regulated under the Toxic Substances Control Act (TSCA). The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and from time-to-time added on an *ad hoc* basis to assist in reviews conducted by the TSCA SACC. This document constitutes the meeting minutes and final report and is provided as part of the activities of the TSCA SACC.

The TSCA SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the TSCA SACC and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the Agency or any party. The meeting minutes and final report of the June 18-21, 2019, TSCA SACC meeting represent the SACC's consideration and review of scientific issues associated with "Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29." Hayley Hughes, DrPH, Office of Science Coordination and Policy, reviewed the minutes and final report. Kenneth Portier, PhD, TSCA SACC Chair, and Todd Peterson, PhD, TSCA SACC Designated Federal Official, certified the minutes and final report. The report is publicly available on the SACC website (https://www.epa.gov/tsca-peer-review) under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPPT-2018-0604, accessible through the docket portal: https://www.regulations.gov. Further information about TSCA SACC reports and activities can be obtained from its website at: https://www.epa.gov/tsca-peer-review. Interested persons are invited to contact Todd Peterson, PhD, SACC Designated Federal Official, via e-mail at peterson.todd@epa.gov.

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TSCA Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2019-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29

June 18-21, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Holiday Inn Rosslyn at Key Bridge, 1900 Fort Myer Drive, Arlington, Virginia

[redacted]

Kenneth Portier, Ph.D.
TSCA SACC, Chair
TSCA Science Advisory Committee on Chemicals

Date: SEP 18 2019

[redacted]

Todd Peterson, Ph.D.
Designated Federal Official
TSCA Science Advisory Committee on Chemicals

Date: SEP 18 2019

Toxic Substance Control Act
Science Advisory Committee on Chemicals Meeting
June 18-21, 2019

Peer Review for EPA Draft Risk Evaluation of
C.I. Pigment Violet 29

PARTICIPANTS

TSCA SACC, Chair

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Designated Federal Official

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TSCA Science Committee on Chemicals

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Steven Bennett, PhD, Household Commercial Products Association, Washington, DC

Sheri Blystone, PhD, SNF Holding Company, Riceboro, Georgia

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Alan Kaufman, Toy Industry Association, New York, New York

John Kissel, PhD (Retired), Environmental & Occupational Health Sciences, School of Public Health, University of Washington, Seattle, Washington

Craig Rowlands, PhD, Underwriters Laboratories, LLC, Northbrook, Illinois

Ruthann Rudel, MS, Silent Spring Institute, Newton, Massachusetts

Sheela Sathyanarayana, MD, Seattle Research Institute, Seattle, Washington

LIST OF ACRONYMS AND ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and elimination
BMD	Benchmark dose
BW	Body weight
CBI	Confidential Business Information
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CoRAP	Community Rolling Action Plan
COU	Conditions of use
DFE	Design for the Environment
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EPI	Estimation Program Interface
EU	European Union
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FRN	Federal Register Notice
GLP	Good laboratory practices
IH	Industrial hygiene
IRIS	Integrated Risk Information System
LCA	Life cycle assessment
LCSA	Life cycle sustainability assessment
LLNA	Local lymph node assay
MOE	Margin of exposure
MP	Melting point
MPPD	Multiple-Path Particle Dosimetry
MTD	Maximum tolerated dose
NAM	New approach methods
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEC	No adverse effect concentration
NR	Not rated
OPPT	Office of Pollution Prevention and Toxics
OSCP	Office of Science Coordination and Policy
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbons
PECO	Populations, exposures, comparators, and operators
PEL	Permissible exposure limit
PNOR	Particles not otherwise regulated
POD	Point of departure
PPE	Personal protective equipment
REACH	Registration Evaluation and Authorization of Chemicals
SDS	Safety Data Sheet
SR	Systematic review
TWA	Time weighted average
UCSF	University of California, San Francisco

INTRODUCTION

The Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, Science Advisory Committee on Chemicals (SACC) completed its review of the set of scientific issues being considered by the Environmental Protection Agency (EPA) regarding the Draft Risk Evaluation for C.I Pigment Violet 29 (PV29) (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)). The Draft Risk Evaluation, supplemental files, and related documents in support of the SACC peer review meeting are posted in the public e-docket at https://regulations.gov (ID: EPA-HQ-OPPT-2018-0604). The initial notice of availability of the Draft Risk Evaluation and opening the docket for comments was published in the *Federal Register* on November 15, 2018, (83 FR 57473). The notice of meeting and later notice of rescheduled meeting were, respectively, published in the *Federal Register* on November 30, 2018, (83 FR 61629), and May 9, 2019, (84 FR 20354). The review was conducted in an open Committee meeting held in Arlington, Virginia, on June 18 to 21, 2019. Dr. Kenneth Portier chaired the meeting. Dr. Todd Peterson served as the Designated Federal Official.

In preparing these meeting minutes and final report, the SACC (Committee) carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. These meeting minutes and final report address the information provided and presented at the meeting, especially the Committee response to the Agency charge.

The first two days of the four-day meeting included a series of presentations by the Office of Pollution Prevention and Toxics (OPPT) providing an overview of TSCA topics. The presentation topics are described for the meeting in Session 1. The Committee on the third and fourth day conducted deliberations in relation to the charge questions for PV29 during Session 2.

Session 1 - TSCA Overview

On June 18 and 19, 2019, the Committee heard presentations by the Office of Pollution Prevention and Toxics (OPPT), which began with the following:

Opening of Meeting - Todd Peterson, PhD, Designated Federal Official, EPA/Office of Science Coordination and Policy (OSCP)

Introduction and Identification of SACC Members – Kenneth Portier, PhD, TSCA Science Advisory Committee on Chemicals (SACC), Chair

Welcome Hayley Hughes, DrPH, Director, EPA/OSCP

Welcome and Introductory Comments - Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA/Office of Chemical Safety and Pollution Prevention

TSCA Orientation and Overview of Existing Chemicals Program - Jeffrey Morris, PhD,

Director, EPA/OPPT

Risk Evaluation Rule - Susanna Blair, PhD, Special Assistant, EPA/OPPT

TSCA Orientation (Cont.) – Overview of Technical Presentations - Stan Barone Jr, PhD, Deputy Director, EPA/OPPT/Risk Assessment Division (RAD)

SACC Discussion/Clarification from Agency Presenters - Kenneth Portier, PhD, SACC Chair

Risk Evaluation Process Overview Under TSCA – Systematic Review - Iris A. Camacho-Ramos, PhD, Branch Chief, EPA/OPPT/RAD

Risk Evaluation Process Overview Under TSCA:

Technical Elements of Risk Evaluation – Fate Assessment - Mari Lee, PhD, Physical Scientist, EPA/OPPT/RAD

Technical Elements of Risk Evaluation – Engineering - Nhan Nguyen, Branch Chief, EPA/OPPT/RAD

Technical Elements of Risk Evaluation – Exposure - Yvette Selby-Mohamadu, MS, Branch Chief, EPA/OPPT/RAD

Technical Elements of Risk Evaluation – Human Health Hazard - Gino Scarano, PhD, Senior Scientist, EPA/OPPT/RAD

Technical Elements of Risk Evaluation – Ecological Risk Assessment - Karen Eisenreich, PhD, Branch Chief, EPA/OPPT/RAD

SACC Discussion/Clarification from Agency Presenters - Kenneth Portier, PhD, SACC Chair

Session 2 - TSCA SACC Peer Review

On June 20 and 21, 2019, the Committee began a session to cover deliberations in response to the charge questions. This session opened with the following:

Opening of Meeting and Administrative Procedures – Todd Peterson, PhD, Designated Federal Official, EPA/OSCP

PV29 Technical Presentation – Overview of PV29 Risk Evaluation
Jafrul Hasan, PhD, Branch Chief, EPA/OPPT/RAD
Garrett Jewett, PV29 Team Lead, EPA/OPPT/RAD

Public Comments

Charge to SACC (Charge questions were read aloud before each discussion)

PUBLIC COMMENTERS

Oral statements were presented as follows:

Christina Franz, Senior Director, Regulatory & Technical Affairs, American Chemistry Council

Suzanne Hartigan, Senior Director, Regulatory & Technical Affairs, American Chemistry Council

Liz Hitchcock, Acting Director, Safer Chemicals, Healthy Families

Jonathan Kalmuss-Katz, Esq, Staff Attorney, Earthjustice

Patricia D. Koman, PhD, President, Green Barn Research

Jennifer McPartland, PhD, Senior Scientist, Environmental Defense Fund

David Michaels, PhD, Professor, Department of Environmental and Occupational Health, George Washington University

Daniel Rosenberg, Esq, Senior Attorney & Director of Federal Toxics Policy, Health Program, Natural Resources Defense Council

Jennifer Sass, PhD, Senior Scientist, Natural Resources Defense Council

Veena Singla, PhD, Associate Director, Science & Policy Program on Reproductive Health and the Environment, University of California, San Francisco

Tyler Smith, Staff Scientist, Earthjustice

Gary Timm, MS, Environmental Protection Network

Tracey Woodruff, PhD, Professor and Director, Program on Reproductive Health and the Environment, Department of Obstetrics/GYN, University of California, San Francisco

Written statements were provided as follows:

Georges C. Benjamin, MD, Executive Director, American Public Health Association

Richard A. Denison, Ph D,Environmental Defense Fund

Brett Fox, International Union, United Automobile, Aerospace, and Agricultural Implement Workers of America

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American Chemistry

Council

Suzanne Hartigan, PhD, and Christina Franz, JD, Senior Directors of Regulatory & Technical Affairs, American Chemistry Council

Liz Hitchcock, Acting Director, Safer Chemicals Healthy Families, et al.

Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice, et al.

Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice and Randy Rabinowitz, Executive Director, Occupational Safety & Health Law Project

David Michaels, PhD, Epidemiologist, Professor, Environmental and Occupational Health, Milken Institute School of Public Health, George Washington University

Ansje Miller, Director of Policy and Partnerships, Center for Environmental Health, et al.

Natural Defense Council and Safer Chemicals Healthy Families

Kathy Pope, Environmental Protection Network

Swati Rayasam et al., Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco

Rebecca L. Reindel, Senior Safety & Health Specialist, AFL-CIO

Michelle Roos, Environmental Protection Network

Jennifer Sass, PhD,Senior Scientist, Natural Resources Defense Council

Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF), et al.

Stacy Tatman, Director, Environmental Affairs, Alliance of Automobile Manufacturers (Alliance)

Gary E. Timm, MS, Environmental Protection Network

Hanna Vesterinen, PhD, Research Consultant to UCSF PRHE, et al.

David Wawer, Executive Director, Color Pigments Manufacturers Association, Inc.

OVERALL PRE-MEETING SUMMARY

This summary describes the Environmental Protection Agency's activities leading up to the June 2019 Science Advisory Committee on Chemicals peer review meeting.

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA or Agency) to conduct risk evaluations on existing chemicals. In December of 2016, EPA published in the *Federal Register* a list of the initial ten chemical substances that are the subject of the Agency's chemical risk evaluation process (81 FR 91927), as required by TSCA. C.I. Pigment Violet 29 (PV29) (Anthra[2,1,9-def:6,5,10-d'e'f'] diisoquinoline-1,3,8,10(2H,9H)) is one of the first ten chemical substances and the first of the ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC). In response to this requirement, EPA prepared and published a Draft Risk Evaluation for PV29, then solicited comments from the public, and based on comments incorporated information as appropriate in the documents considered in the peer review.

Prior to peer review, the EPA asked for input at several stages of the TSCA process: on the use dossiers, the scopes, and the problem formulations. The EPA received information and comments at each step specific to individual risk evaluations, and information and comments of a more general nature relating to various aspects of the risk evaluation process, technical issues, and the regulatory and statutory requirements. The EPA considered comments and information received at each step in the process and factored in the information and comments as the Agency deemed appropriate and relevant including comments on the published problem formulation of PV29.

The draft EPA Risk Evaluation states that PV29 is an organic pigment that has a low solubility, low volatility, expected to be highly persistent, has low hazard concerns, limited exposure potential and has low bioaccumulation potential in fish and other animals. The pigment is utilized as an intermediate to create or adjust color of other pigments, as well as in commercial paints, coatings, plastics, and rubber products.

In the Draft Risk Evaluation, the EPA states the Agency considered all reasonably available data for PV29 to make a determination of whether risk posed by a chemical substance is unreasonable. The EPA—without considering costs or other non-risk factors—concluded that PV29 does not present an unreasonable risk of injury to human health or the environment including no unreasonable risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use.

The initial notice of availability of the Draft Risk Evaluation for PV29, with supplemental files, and opening the docket for comments was published in the *Federal Register* on November 15, 2018, (83 FR 57473). The information in the 24 individual scientific studies was available to the EPA, however, the studies themselves were not initially posted to the docket because the documents contained information initially identified as protected as Confidential Business Information (CBI).

Appendix A of these minutes and final report includes the transmittal memo regarding the November 15, 2018, notice of availability of the Draft Risk Evaluation and supplemental files. SACC members received TSCA CBI training and were cleared to review the full set of studies as part of their peer review. A transmittal memo dated March 21, 2019, (see Appendix B), along with 15 of the studies released from the claim of CBI and nine studies released with redactions, was posted to the public docket. The notice of rescheduled meeting was published thereafter in the *Federal Register* on May 9, 2019, (84 FR 20354) in advance of the June SACC meeting.

The Agency reviewed the study reports and confirmed that the results are consistent with the physical and chemical characteristics, environmental fate characteristics, and the determination of low environmental and human health hazards as presented in the European Chemicals Agency (ECHA) robust summaries (see the Draft Risk Evaluation Appendices B-D). The EPA review assessed the quality of the methods and reporting of results of the individual studies using the evaluation strategies described in Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a) and concluded that they are of high or medium quality. In addition, the EPA determined that the information presented in these full study reports is consistent with the robust summaries in the publicly available ECHA Database (ECHA, 2017).

As announced in the *Federal Register* published on November 15, 2018, (83 FR 57473), the EPA provided 60 days for public comment on the Draft Risk Evaluation prior to the beginning of the meeting initially scheduled for January 29 to February 1, 2019. This satisfies TSCA section 6(b)(4)(H), which requires the EPA to provide public notice and an opportunity for comment on a draft risk evaluation prior to publishing a final risk evaluation. The meeting was later rescheduled and held June 18 to 21, 2019, in Arlington, Virginia.

An additional 30-day comment period, from April 17 to May 17, 2019, was announced in the *Federal Register* published on April 17, 2019, (84 FR 16011 with correction published 84 FR 16485). The purpose of this 30-day period was to receive comments on the updated *C.I. Pigment Violet 29 (88-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation* (see Appendix C).

Following the publication of the Draft Risk Evaluation, EPA received comments from the Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH) on the risk characterization from inhalation exposure. As a result, two updated approaches were incorporated and presented in a supplemental document to characterize the potential occupational risks from inhalation exposure. With this additional information, the charge to the SACC was amended to add an additional question for the SACC's consideration of inhalation risk. See Appendix D regarding the transmittal memo, updated charge, and the supplemental document, "*EPA-PV29 Inhalation Risk Characterization Summary June 6, 2019*," posted to the docket on June 10, 2019, (https://regulations.gov, Docket ID: EPA-HQ-OPPT-2018-0604).

EXECUTIVE SUMMARY

The EPA requested input and advice from the Science Advisory Committee on Chemicals (SACC or Committee) on several issues posed as questions.

On issues related to the **overall content, organization, and presentation** of the draft risk evaluation of C.I. Pigment Violet 29 (PV29), the SACC (Committee) found that the Draft Risk Evaluation of C.I. Pigment Violet 29 (the Evaluation) required additional text and information to improve clarity and transparency. In general, significantly more detail needs to be provided to better support the risk evaluation conclusions and improve transparency of the decision-making. The Committee identified 11 places in the document where minor changes or additions would significantly improve readability and clarity. Changes include adding a flowchart or decision tree to more adequately describe the flow of the risk evaluation material to including a short description of why PV29 was originally selected for the TSCA workplan.

On the **clarity of the information as presented related to systematic review (SR)** used to support the PV29 risk assessment, the Committee provided recommendations to improve the TSCA systematic review process in general and specific recommendations to improve the PV29 systematic review.

The Committee encouraged the EPA to proceed with its plan to have the National Academy of Sciences (NAS) conduct a peer review of the TSCA SR protocol as soon as practical. In the interim, EPA should improve descriptions of: 1) how the TSCA SR is updated as new science is published, 2) the rationale for decisions applied in the systematic review for specific substances, 3) the rationale for developing a SR specific to TSCA risk evaluations, 4) the rationale for the differences in in the TSCA SR relative to other peer-reviewed SR approaches currently in use, 5) the explicit populations, exposures, comparators, and operators (PECO or problem formulation) used in the SR, 6) the justification for using a weighted scoring system, and 7) the rationale for the metrics selected for differential weighting in its evaluation of studies. Furthermore, additional justification is needed for the use of "not rated" (NR) codes for certain metrics that are not typical of animal studies, and better discussion on how an NR code impacts the quality score. Data quality criteria are needed to assess the quality of information provided via personal communications and other channels not already identified in the TSCA SR that might be considered critical in a risk evaluation. The SR protocol document should discuss why an "indeterminate" designation is not needed in the TSCA SR to account for situations where there is significant lack of data. Finally, EPA should develop, peer review, and publish SRs for substances undergoing TSCA risk assessment prior to release of a draft risk assessment for public comment.

On a related issue, the Committee recommended EPA develop **Confidential Business Information (CBI) requirements and protocols** to ensure that important health-based data identified in the SR, but which are classified as CBI, are made available to the public at the time the draft risk assessment is released.

Regarding the **SR performed for the PV29 risk assessment**, the Committee recommended EPA 1) perform a quality assessment of the exposure data for occupational exposures to PV29, which was provided to the Agency as personal communication from the manufacturer of PV29; 2) include a more thorough and inclusive data integration discussion, including descriptions of how the human health experience, mechanistic information, *in vitro* data, and controlled laboratory animal data were used to support conclusions; 3) include in the discussion how chemical structural considerations, read across approach[1], and other information—including findings from new approach methods (NAMs)—add to the evidence for potential PV29 toxicity; 4) include a better discussion of data uncertainties; and 5) include a discussion on the potential toxicity of byproducts of manufacturing, impurities in PV29, biodegradation and degradation products, and photodegradation (as indicated by the Evaluation Table 3-1).

The Committee requested an improved discussion on why available study data are adequate to reach the conclusions of "no unreasonable risk" from exposure to PV29. This discussion should also justify why additional testing is not necessary to confirm this conclusion.

The EPA reported that PV29 is an organic pigment that has a low solubility, low volatility and is expected to be highly persistent and has low bioaccumulation potential in fish and other animals. In addition, no acceptable studies are available to describe the environmental fate characteristics of PV29 with respect to characterizing the octanol-water partition coefficient (log K_{OW}), organic carbon normalized sorption coefficients (K_{OC}), and bioaccumulation. The Committee was asked to **comment on the characterization of physical chemical properties of PV29 and help identify additional sources or methods to better estimate these properties**. In addition, the Committee was asked to **comment on the determination by the European Chemicals Agency (ECHA) to include PV29 on the 2019-2021 Community Rolling Action Plan (CoRAP) update as a "suspected Potentially Persistent, Bioaccumulative and Toxic/very Persistent and very Bioaccumulative substance."**

The Committee noted that estimates of physical-chemical properties identified in the SR and used throughout the draft evaluation document are not always consistent. The reasons for the discrepancies should be provided and consistent estimates used. The Committee noted that statements that claim that an aqueous solubility of ≤ 11 µg/L precludes oral bioavailability are not correct and should be removed.

High-quality estimates for log K_{OW} or fat solubility are needed to solidify the argument that PV29 is not bioavailable or likely to be absorbed into organisms or tissues. Alternative property estimation methods should be used to generate the additional information needed to strengthen the weight of evidence to conclude that PV29 is not bioavailable. The risk assessment needs improved discussion to support the importance of octanol-air partition coefficient (log K_{OA}) and to better illustrate its implications on determinations of environmental distribution of PV29 and

1 'Read-across and grouping', or 'read-across', is one of the most commonly used alternative approaches for data gap filling in registrations submitted under the REACH Regulation. Read-across involves the use of relevant information from analogous substance(s) (the 'source' information) to predict properties for the 'target' substance(s) under consideration. (see: https://echa.europa.eu/documents/10162/13628/raaf_en.pdf)

resulting exposure to humans and other organisms.

The Committee considered EPA's characterization of Environmental Releases and Exposures (Section 3.2-3.4) as cursory and dependent upon sweeping generalizations that are often unsubstantiated. PV29 may well be poorly bioavailable, and that exposed populations are limited, but that conclusion is based on uncertain (and inconsistent) estimates of physical-chemical properties, and conjecture regarding uses. In addition, overemphasis of the importance of aqueous solubility with respect to bioavailability is problematic especially as it serves as the scientific rationale for the lack of observed toxicity in available studies and conclusion of low toxic potential of PV29. A more thorough analysis is required to appropriately calculate margin of exposures (MOEs).

The Committee's consideration of **occupational exposures, environmental release characteristics, potentially exposed and susceptible subpopulations, and any conclusions regarding aggregate exposure** resulted in the following: 1) EPA needs to more aggressively pursue information from manufacturer(s) of life cycle sustainability assessment (LCSA) targets, purchasers/users of those chemicals, trade associations, and other federal and state regulatory agencies that may have specialized knowledge, 2) incorporate uncertainty analysis into the LCSA risk evaluations and, at a minimum, present screening level calculations when dismissing exposure pathways, and 3) refrain from making sweeping generalizations especially when based on limited and/or uncertain information regarding physical chemical properties or toxicological testing. Projection of environmental fate based on one-at-a-time examination of physical properties is unscientific. For non-ionizable organics, EPA should adopt a screening level fugacity modeling approach as a default under LCSA and further include maximum steady-state dermal flux ($J_{max,ss}$) estimates in their list of physical chemical properties routinely reported in TSCA risk assessments.

Regarding **environmental effects**, given the limited nature of the dataset describing the potential environmental hazards from the manufacture and use of PV29, there are uncertainties associated with risk conclusions to environmental receptors from exposure to PV29 from the uses described in the document.

Many SACC members agreed with EPA's determination that the probability for **environmental releases** is likely low and most likely through wastewater streams from the production facility and downstream manufacturing. The document also indicates that PV29 is used in food packaging and other consumer uses. It is reasonably expected that any environmental releases from consumer uses to be minimal and inconsequential. The SACC recommended that the EPA be clear regarding estimates of toxicity benchmarks developed from these studies where exposures exceeding the water solubility limit are described. The Committee recommended that EPA attempt to explain the inconsistencies where toxicity levels are presented that exceed the water solubility limit in that they could form the basis for misunderstanding regarding the reliability of the water solubility estimate.

Toxicity data to sediment-dwelling organisms have not been presented; therefore, the Committee could not comment on whether concentrations of PV29 could present a low hazard. Potential and probability of release to sediments is likely greatest from the production facility

and should be addressed to help make a determination regarding exposure. Persistence of PV29 in the sediment has not been fully determined; however, if it can be reliably determined that bioavailability is low (e.g., by extrapolation of chemical physical property information), toxicity to sediment dwelling organisms is likely to be low. Therefore, the Committee recommended a level of confidence accompany any judgment regarding toxicity, exposure, and risk to sediment-dwelling organisms. It would also help support this finding to more precisely estimate and describe the manner in which log K_{oc} was determined. Probability of exposure to other ecological receptors through consumer use or trophic transfer is likely to be low given the molecular structure and available chemical physical property information.

The Committee recommended: 1) improving explanations for estimates of toxicity benchmarks developed from those studies where observed exposures exceed the water solubility limit; 2) including a level of confidence statement with judgements of toxicity to sediment dwelling organisms; and 3) providing a better description of the manner by which log K_{oc} was determined in key studies.

To improve the risk evaluation with respect to **human health** and use of a screening reproduction/developmental toxicology screening study the Committee recommended the following: 1) the utility of the screening Developmental and Reproductive Toxicology ***(****repro/dev tox****)*** study for deriving the point of departure (POD) would benefit from additional and better estimates of physical/chemical properties and absorption, distribution, metabolism, and elimination (ADME) data to further strengthen support that PV29 has low bioaccessibility/bioavailability, and therefore, decreased risk for absorption and inhalation and highlight remaining data gaps, since many aspects of toxicity have not been assessed for this chemical; 2) include a table in the Evaluation that compares the endpoints reported in the screening repro/dev tox study used in the Evaluation to endpoints typically reported in a 90-day subchronic tox study—to clarify the value of the screening repro/dev tox study; 3) include the subchronic-to-chronic uncertainty factor in the calculations of the margin of exposures (MOE) or significantly improve the justification/qualifications in the Evaluation for why this uncertainty factor should not be used; 4) wherever in the Evaluation the statement "PV29 … has low hazard potential across all possible routes of exposure" occurs, the statement should be replaced with one that is specific and limited to the routes of exposure observed in the available study data—***thus,*** allowing new data, as it becomes available, to add to and expand hazard conclusions regarding PV29; and 5) regardless of whether PV29 is bioavailable, more justification is needed to conclude that exposures to dusts in occupational settings do not cause lung depositional events or immunological responses sufficient to cause injury.

The committee deferred initially answering a charge question related to use and interpretation of Multiple-Path Particle Dosimetry Model (MPPD v. 3.04) to the discussion on inhalation exposure (see below and charge question 8 in detailed discussion).

When addressing the issue of **absorption via oral, dermal, and inhalation routes**, the Committee concluded that the evidence for low water solubility is not indisputable and available toxicity studies provide conflicting estimates. Public comment indicated PV29 is insoluble in all solvents at room temperature except 96% sulfuric acid, and if true, would support the EPA's position that absorption of PV29 via oral, dermal and inhalation routes would be negligible.

However, this evidence is not clearly presented in the Evaluation and some of the Committee members concluded that additional information was needed to support this conclusion. The Committee's recommendations to improve the Evaluation with respect to absorption via oral, dermal and inhalation routes, include: 1) request an appropriate study to adequately determine bioavailability or bolster the evidence for poor water and octanol solubility in a well-laid out manner to support the Agency's conclusions, 2) given the low confidence in absorption potential based on limited physical-chemical data, present models based on several solubility scenarios and/or NAM *in vitro* testing using tissue adsorption models, and 3) either do not perform MOE calculations or clearly qualify assumptions used in the MOE calculation based on the limited data.

The Committee concluded it was reasonable to assume that, generally **consumer exposures are** less than occupational exposures given that uses include watercolor and artistic paints. The Committee also felt that despite low general exposures, individual consumers may experience high levels of exposures. Overall, the Committee had varied conclusions, and thus, made recommendations to remove uncertainty about consumer exposure. To improve the discussion of the uncertainty surrounding exposures for the general population, EPA should explain clearly why it was initially determined that there were widespread consumer exposures to PV29 but that this did not need to be addressed in the final risk assessment. The EPA needs to clearly acknowledge that there may be certain consumers that receive higher acute and chronic exposures and explain why this is not considered important for this risk assessment. Further, the EPA needs to clarify the statement in the Evaluation (in Section 3.4.1): "there is no evidence of increased or decreased susceptibility for any given population" to acknowledge that there are large data gaps that preclude coming to confident conclusions regarding certain subpopulations.

The Committee agreed that the greatest **exposures to PV29** will likely occur **in manufacturing and occupational workers via inhalation and dermal exposures**. Committee members disagreed on the risk characterization for these workers. Thus, recommendations to improve the Evaluation with respect to hazard to workers via inhalation and dermal exposure, include: 1) clearly acknowledge that there are few data to support a confident conclusion that workers would not be exposed, and therefore, not experience human health hazards via dermal or inhalation routes, and 2) obtain and incorporate into the Evaluation better data and documentation from the manufacturer on conditions of use, exposures, and potential for worker exposures (e.g., collected using standard measurement techniques with adequate temporal and spatial coverage).

Regarding **health hazard concerns for potentially exposed susceptible subpopulations,** the Committee concluded there was a lack of data, and thus, recommended: 1) improve transparency by acknowledging in the Evaluation that there are no specific data supporting the determination of hazards or exposures to children or other susceptible populations to support weight of evidence conclusions regarding risk to these susceptible subpopulations; and 2) do not make statements without additional clarifications and justifications that children or other susceptible populations would be protected. The current data as discussed in the data integration does not clearly support this conclusion and the committee recommended additional data needs and rationale to address this uncertainty. Some Committee members recommended the EPA consider an "indeterminate" categorization and qualify with data that may suggest low toxicity.

Methods to address this would include using more uncertainty factors in MOE calculations or developing multiple modeling scenarios including best case to worst case and presenting these models in the text.

The Committee members were in general agreement that the information presented to support the conclusions outlined in the draft **risk characterization** was not sufficiently robust for this purpose. The Committee comments on charge questions 1 to 6 include recommendations aimed at improving the Evaluation and increasing the clarity and transparency of the information presented and the arguments offered in support of the risk characterization.

The Committee reiterated the data deficiencies that weaken these conclusions, including: 1) inconsistencies in the available physical-chemical properties data and/or lack of high-quality solubility studies in water and octanol, or equivalent tools needed to produce estimates of solubility with sufficiently high confidence to justify their use in establishing exposure potential, 2) lack of details on workplace air monitoring necessary to establishing workplace exposure estimates with confidence, 3) lack of confidence in the readily available animal data's ability to establish with confidence that PV29 has low hazard via inhalation or dermal pathways, 4) poor justification of uncertainties used and no justification for not using a sub-chronic-to-chronic uncertainty factor, and 5) incomplete descriptions of the level of uncertainty in published information, assumptions used, and the impact of these uncertainties on conclusions.

SACC members suggested that the risk characterization would be bolstered by adding additional information related to manufacturing process, exposure, particle size (in the breathing zone) and shape characteristics, release and concentrations in sediments, data on bioavailability, data and modeling on lung toxicity testing on additional species other than rodents, evaluation of PV29 immunotoxicity to assess the potential for sensitization, and a clearer presentation of the limited toxicity database for PV29 and the decision to accept these limitations because of assumptions of limited bioavailability for PV29.

Following the publication of the Evaluation, EPA received comments from the Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH) on the risk characterization from inhalation exposure. As a result, two updated approaches were presented to the SACC to characterize the potential occupational risks from inhalation exposure. The intended use of these approaches is to provide a more appropriate toxicological response to characterize the risks of inhalation of PV29 dust.

Given that no acceptable **inhalation toxicity** studies are available for PV29, the Committee recommended a properly designed inhalation study (e.g., 28-day, aerosol, nose only, inhalable fraction with the high dose achieving toxicity which may be lung overload) would be needed to fill this data gap. Further, PV29 is assumed to not be bioavailable or readily absorbed by any applicable route of exposure since it may have poor water and lipid solubility. No absorption, distribution, metabolism, and elimination (ADME)/toxicokinetic data were presented. However, mouse skin changed color after *in vivo* dosing via intraperitoneal (IP) injection, gavage and dermal application. The mechanism for this has not been ascertained. NAMs such as Organ on a Chip (lung) or skin permeability *in vitro* assay should be considered. The Committee recommended supplementing available data by requesting personal monitoring data from the

manufacturer which should include both respirable dust fraction and total dust in the worker breathing zone.

This first SACC peer review is the first time the TSCA program is making non-TSCA **confidential business information** (CBI) available to peer reviewers. The EPA requested comment on the process, integration, and clarity related to the use of the CBI that was provided. As noted in these meeting minutes and final report Overall Pre-Meeting Summary, SACC members were given TSCA CBI training, and thus, permitted to review the full studies as part of their peer review. More details as to how these studies, which were previously claimed in full as CBI, became partially redacted (sanitized) is presented in Appendix B.

Upon a comparison of the full (unredacted) studies with the redacted studies, the Committee reached consensus that the nature of the redactions do not materially impact the draft risk characterization. The Committee agreed that the summary statistics provided in the unredacted version of the reproduction/development study were consistent with the animal data in the redacted version of the study. The Committee made recommendations to the EPA about how to process CBI information for use by the Committee and the public for future assessments.

DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA or Agency) to conduct risk evaluations on existing chemicals. As required by TSCA, C.I. Pigment Violet 29 (PV29) is one of the first ten chemical substances and the first of the ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC). In response to this requirement, EPA has prepared and published a Draft Risk Evaluation for PV29. The Risk Evaluation process is the second step, following Prioritization and before Risk Management, in EPA's existing chemical process under TSCA. The purpose of risk evaluation is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, exclude consideration of costs or other non-risk factors, use scientific information and approaches in a manner that is consistent with the requirements in TSCA for the best available science, and ensure decisions are based on the weight-of-scientific-evidence.

The SACC was requested to provide advice and recommendations on the following questions.

Question 1: Overall Content, Organization, and Presentation of the Draft Risk Evaluation

EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. To that end, EPA has completed a draft risk evaluation for C.I. Pigment Violet 29.
As part of this risk evaluation for C.I. Pigment Violet 29, EPA conducted an assessment of potential environmental, occupational, consumer, and general population exposures. This analysis considered best available science and reasonably available information, including manufacture, use, and release information, and physical-chemical characteristics. It is important that the information presented in the risk evaluation and accompanying documents are clear and concise and describe the process in a scientifically credible manner.

1	Please comment on the overall content, organization, and presentation of the draft risk evaluation of C.I. Pigment Violet 29. Please provide suggestions for improving the clarity and transparency of the information presented in the documents.

Response

The SACC (Committee) found that the Draft Risk Evaluation of C.I. Pigment Violet 29 (the Evaluation) requires additional text and information to improve clarity and transparency. In general, **significantly more detail needs to be provided to better support the risk evaluation conclusions and improve transparency of the decision-making.** Needed additional information includes: summaries of the systematic review process, better descriptions of exposure and of the efficacy of institutional and engineering controls in the workplace, and more information on likelihood of environmental releases. More detail is provided in the bullets that

follow and in answers to subsequent questions to the Committee.

The risk assessment concluded that PV29 poses "No Unreasonable Risk" at current levels of exposure and based on the limited information on expected health effects. The Committee agreed that current information seems to support the conclusion of "No Unreasonable Risk," but recommended use of a more detailed risk statement that describes the actual parameters considered and includes a statement on the limitations of the risk assessment. The Committee also expressed concern that a determination of "No Unreasonable Risk" for PV29 could preempt states from taking action in the future, if more and better information on chemical properties, workplace and public exposures, and/or health effects of PV29 becomes available. The Committee suggested that EPA clarify that the decision for low risk reflects currently available data and known uses, and so new data and changes in use could alter this determination and could allow for state action on the chemical. Several members also noted that this "no unreasonable risk" designation itself might result in increased use or discharge of this chemical, for example, if it is marketed as having low toxicity.

Recommendations to improve overall content, organization, and presentation:

1. **Define unreasonable risk under the TSCA legislative requirement and describe in general how the threshold between reasonable and unreasonable risk is determined.**

2. I**nclude with the final risk statement a description of the ramifications of the conclusion.**

    2.1. The Public needs to know that if a substance is determined to pose an "unreasonable risk," the Agency will address the identified risk(s) through a risk management process. At a minimum, reference should be made to Agency guidance on how this next step would proceed.

    2.2. Any finding of no unreasonable risk is tied to limitations of currently available data and uses, including industrial hygiene (IH) practices, then the Evaluation should so state. A finding of "no unreasonable risk" should not preclude additional review. Substantial changes in use of the substance under review, and/or the development of new data that alters substantially knowledge of chemical properties, exposures and or toxicity, will alter exposures, toxicity, and will ultimately alter the overall risk.

    2.3. The Committee expressed concerned that a finding of "no unreasonable risk" indicates to the public that nothing further will be done to evaluate or regulate the substance under review (in this case PV29). On the other hand, the prior designation of PV29 as a high priority chemical may suggest to many in the public that additional risk management measures will be enacted regardless of outcome. Additional clarification would be helpful so that manufacturers, state regulators, and the public will understand how the risk assessment finding will impact their current and future activity related to this substance. This statement is needed to clarify report findings and increase transparency of EPA intent following the report finding.

3. **Carefully review and revise the Evaluation to ensure a logical and coherent flow to the discussion, and, to ensure that justifications are near their associated conclusions.** The Committee noted that throughout the document, conclusions are stated without referencing

the appropriate source or analysis that supports it. Sometimes these conclusions occur due to how the Evaluation is organized, forcing the reader to search a later part of the document or an entirely different document for the justification of the conclusion. An example of this occurs in Section 2.4.2 Conceptual Models (page 14) that assumes that PV29 has low hazard and limited exposures (a conclusion) to justify the model before hazard (Section 3) and exposure (Section 4) have been discussed.

4. **Clearly state preliminary suppositions in the final risk determination and ensure that the hazard statement contains associated limitations and uncertainties.** The Committee noted that there is information reported in the Problem Formulation document (U.S. EPA, 2018b) that is referenced in the risk assessment. This information represents preliminary suppositions not discussed in a definitive manner in the Evaluation. Of most concern to the Committee were the preliminary suppositions that impacted Human Exposures (Section 3.3). The Committee concluded that broad statements such as "low hazard was reported for all routes of exposure in human health testing" did not adequately portray the associated uncertainty due to limited data and endpoints considered. The hazard statement at a minimum should identify the animal models and endpoints used.
5. **Describe in more and better detail the systematic review process (Section 2.5) and its results.** The results of systematic review are discussed in prose where one or two diagrams would significantly improve the clarity and transparency of the process. Graphical and/or tabular summaries are needed of the number of abstracts, reports and manuscripts reviewed, and reports and manuscripts accepted and rejected and at what stage in the review process.
6. **Include measures and discussion of uncertainty and variability with all numerical values.** The SACC Committee noted that in the Evaluation, numerical values are presented without associated statements of confidence or measures of variability, especially the physical-chemical values. The Committee noted that risk assessments typically include discussions of uncertainty and variability with reported values. The scientifically reasoned basis for inclusion, exclusion or selection of data values is also expected. For example, is the indirect photodegradation half-life of 7 hours listed in Table 3-1 consistent with overall conclusions that the chemical is very persistent? Estimates of water solubility of PV29 are also inconsistent.
7. **Update the Evaluation to reflect recent changes in confidential business information (CBI) availability.** The Committee noted that there had been significant changes to CBI redacted information upon which the Draft Risk Evaluation relied. These formerly redacted studies are now publicly available for review.
8. **Include a short history or basis on why C.I. Pigment Violet 29 was originally selected for inclusion on EPA's Work Plan and discuss how those concerns have been addressed in the assessment.** The Committee felt that this section is important in establishing the justification for the risk evaluation and provides context and importance for the final risk determination.
9. **Provide cross references to relevant documents and associated information**. The Committee understood that in order to keep the Evaluation relatively short and concise, EPA chose to not repeat information available in other documents or information sources, primarily other EPA documents that provide relevant guidelines. To assist the reader, the risk evaluation document should provide easy reference, and, where possible, internet links to

these key documents or information sources. For example, reviewing the section on "environmental release and exposure," a reader should be able to click on a link to relevant EPA guidance documents on this topic. The SACC noted that recent TSCA legislation established that public review of (including access to) supporting data is part of the process ensuring transparency in the evaluation of health risk from large quantity manufactured chemicals in the US. All documentation and studies used for the assessment, especially health and safety information, should be made available to the public. Access to certified CBI is still problematic.

10. **Include more information on production volume and derivative products**. The Committee discussed the need for better discussion of PV29 production volume in the report. Missing was a discussion of how the quantity of PV29 produced makes this a high production volume chemical, or how the quantity produced relates to production volumes of other priority chemicals or high production chemicals. The Evaluation reports that 90% of PV29 production is used to make another pigment. This, combined with the observation that the European Union (EU) is assessing risks of both pigments together, suggested that the assessment should discuss both pigments in a single assessment. Needed is the rationale for why EPA has chosen to assess PV29 alone. The Committee would have also liked a summary/comparison of the structure, toxicity concerns, and exposure profiles for both chemicals.
11. **Develop a flowchart/decision tree to more adequately describe the risk evaluation**. The Committee concluded that uncertainty in decisions could be more transparently communicated and evaluated using appropriate graphics. The Committee discussed decision tree diagrams as well as logic model diagrams. Such diagrams could be adapted to display associated confidence at each decision point in order to clarify overall confidence in the conclusion (see also discussion in Question 2).

Question 2: Systematic Review:

The Toxic Substances Control Act (TSCA) requires that EPA use data and/or information in a manner consistent with the "best available science" and that EPA base decisions on the "weight of the scientific evidence." The EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726), defines ''best available science'' as science that is reliable and unbiased. This involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). The Final Rule also defines the "weight of the scientific evidence" as a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance (note: PV29 integration was limited because of its overall low-risk profile when compared to other more complex cases).

To meet these scientific standards, EPA applied systematic review approaches and methods to

support the draft risk evaluation of C.I. Pigment Violet 29. Information on the approaches and/or methods is described in the draft risk evaluation as well as the following documents:

- Application of Systematic Review in TSCA Risk Evaluations
- Strategy for Conducting Literature Searches for Pigment Violet 29 (PV29): Supplemental file for the TSCA Scope Document
- Pigment Violet 29 (CASRN: 81-33-4) Bibliography: Supplemental File for the TSCA Scope Document
- *Pigment Violet 29* and the *Pigment Violet 29 (81-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation*
- The updated version of *Pigment Violet 29 (81-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation* (Published April 17th, 2019)

https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0040

2	Please comment on the approaches and/or methods used to support and inform the gathering, screening, evaluation, and integration of information used in the draft risk evaluation of C.I. Pigment Violet 29 and the updated *Pigment Violet 29 (81-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation* (Published April 17, 2019). Please also comment on the clarity of the information as presented related to systematic review and suggest improvements as it applies to PV29.

Response:

Development of the amended TSCA Systematic Review (SR) was a requirement of the life cycle sustainability assessment (LCSA) and is integral and foundational to the development of high confidence risk evaluations of existing chemicals regulated under the LCSA. The EPA OPPT is unique among Federal agencies in its responsibility for regulating a very broad range of industrial chemicals in commerce, with multiple intended uses. In this task, EPA OPPT is supported by a broad array of human and environmental chemical safety information and consumer, occupational and environmental exposure data. Given the unique requirements under TSCA, OPPT developed its own TSCA-specific SR. This was done through a process that involved a review of existing SRs, and in consultation with the National Toxicology Program and the U.S. EPA's Integrated Risk Information System (IRIS) program. Each of these programs have developed their own National Academy of Sciences (NAS) peer-reviewed SR method designed to meet their specific needs.

The SACC (Committee) generally agreed that it is reasonable that the EPA OPPT have and use an SR designed to meet the specific needs of risk characterization and evaluation under TSCA. The Committee strongly encouraged that the EPA obtain a NAS peer review of the TSCA SR protocol as soon as practical. The TSCA SR should be revised and refined as a result of the NAS peer review and further refined as it is used in specific chemical assessments.

The Committee emphasized the importance for the Agency to be as transparent as possible in how the TSCA SR is updated. The rationale and decisions applied in the systematic review for specific chemicals should be clearly described and communicated in the Evaluation. The

Committee noted and congratulated the Agency for updating the TSCA SR of PV29 to include more details.

The Committee recommended that confidential business information (CBI) requirements not be used to prevent important health-based data from being made available to the public. Maximizing transparency by making all non-CBI health information and data from studies publicly available for external review of Agency determinations will expedite Committee review and enhance public confidence in the process and outcome of Agency decisions in its TSCA SR.

While the TSCA SR process appears sound, the Committee identified several places where the TSCA SR deviated from other published processes. The Agency rationale for developing the TSCA SR should include a comparison to other SR approaches and describe the rationale for major differences.

The Committee discussed the need for more discussion of the explicit populations, exposures, comparators, operators (PECO) or problem formulation statements used in formulating the SR for a substance being assessed. Future substance SRs would be enhanced if reliability scores and dose response information are provided, for example using a scatter diagram format as shown in Figure 1.

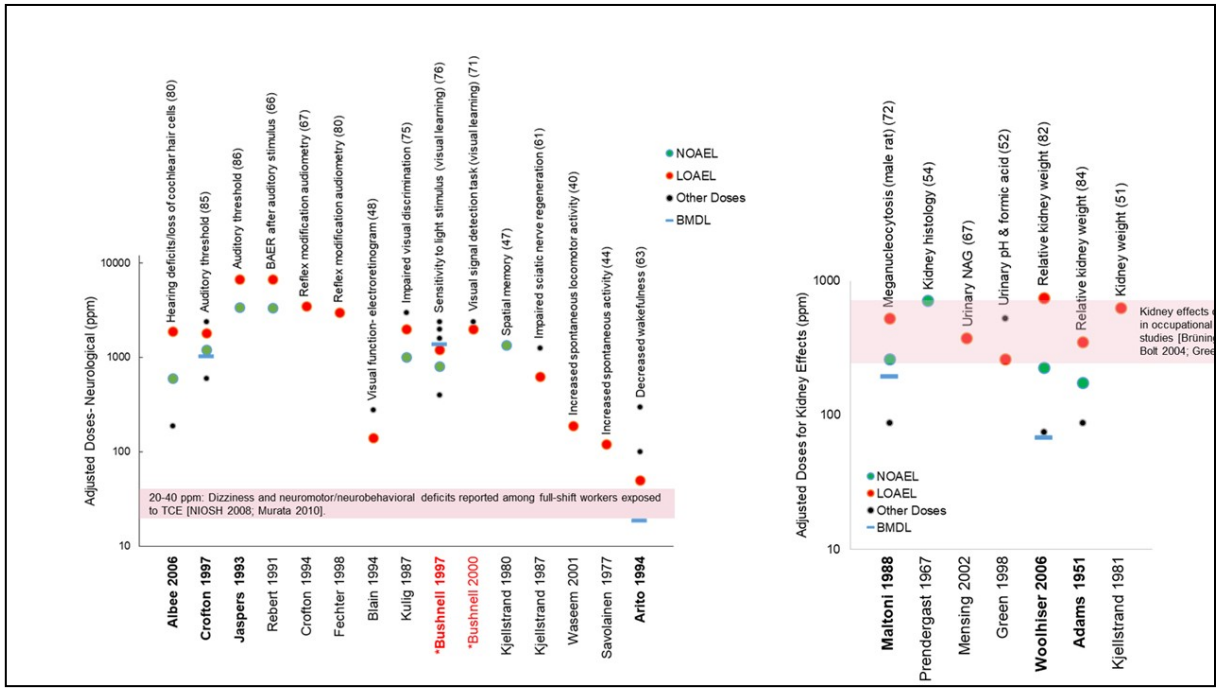

Figure 1: Example scatter diagram (Susan T.E., Leach G.L. and M.S. Johnson (in prep, used by permission M.S. Johnson))

The Committee noted that the TSCA SR weighted scoring system may be inappropriate if there is disagreement in the weighting of different metrics. For example, a certain study characteristic that may be a "fatal flaw" would be weighted equally to other more minor elements. The Agency should provide justification for using a weighted scoring system and the rationale for the specific

metrics used for differential weighting in its evaluation of studies.

Regarding assigning a score of "not rated" (NR) to the metric for "blinding of assessors," the Agency should provide additional rationale to the TSCA SR justification that these are not usually discussed in animal studies. The impact of an NR on the overall quality score should be discussed.

The Committee discussed the need to include data quality criteria in the TSCA SR for evaluating personal communications and other information types not already identified in the TSCA SR that might be considered critical in a risk evaluation. The Committee concluded that the Agency needs to perform a quality assessment of the exposure data for occupational exposures to PV29 that were provided to the Agency as a personal communication from the manufacturer of PV29.

Some Committee members noted that the Agency should provide a rationale for not allowing in the TSCA SR an "indeterminate" designation when there is a lack of data.

The Committee discussed the need to publish peer reviewed pre-established protocols for each of the Agency's reviews prior to performing the actual risk assessment. The protocol for PV29 was created concurrently with the review, which is contrary to best practices for systematic reviews.

Regarding data integration, the Committee discussed the benefits of including a more thorough and inclusive data integration discussion in the TSCA SR for PV29. Improved transparency requires a better description of how the human health experience, mechanistic knowledge, *in vitro* study data, and controlled laboratory animal study data are used to support conclusions. The Committee noted that the available data for PV29 does not lend itself as an adequate example for evaluating the TSCA SR process. Nevertheless, there is a need in the Evaluation for a thorough description and outline for how all evidence and data are integrated into a final weight of evidence conclusion. This was not transparent from reading the documents provided. The diagram in Figure 2 was discussed by the Committee as one example of a conceptual model for data integration that the Agency should include in future TSCA SRs.

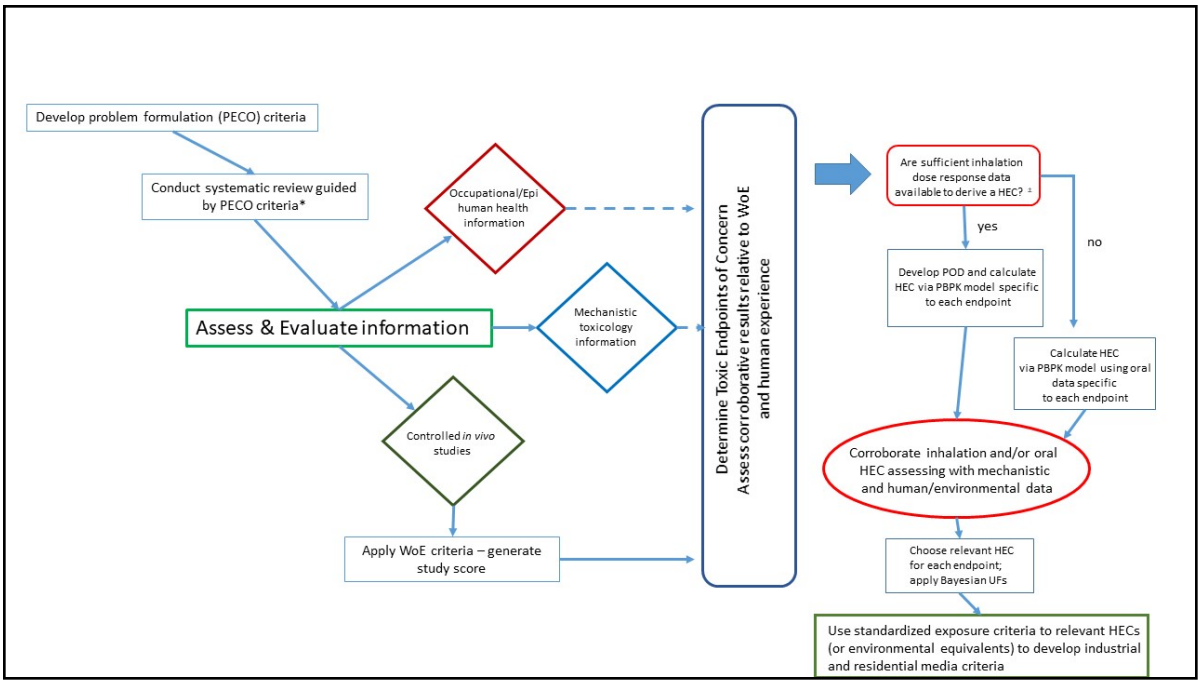

Figure 2: Example data integration diagram (Susan T.E., Leach G.L. and M.S. Johnson (in prep, used by permission M.S. Johnson))

The Committee conferred strengthening the Evaluation by including in the data-integration discussion the evidence for potential PV29 toxicity based on chemical structural considerations, read across, and other sources such as New Approach Methods (NAMs) (e.g., EPA ToxCast program).

The Committee noted many inconsistencies across documents in measured values for chemical properties, especially estimates of the chemical's solubility. These inconsistencies translate into value uncertainty, which was not addressed in the current PV29 TSCA SR data integration discussion. This discussion is critically necessary given the importance chemical solubility plays in supporting assumptions about exposure potential and in establishing the rationale for the adequacy of the toxicity testing database for PV29.

The Committee expressed concerns that the available human health and environmental toxicity data for PV29 were not adequate to support the conclusion of the Evaluation. The Agency needs to improve its rationale for why available study data are adequate to reach the conclusions of "no unreasonable risk," but also why additional testing is not necessary to confirm this conclusion.

Recommendations to improve the general TSCA SR:

1. **As soon as practical have NAS conduct a peer review of the TSCA SR protocol.**
2. **Describe clearly how the TSCA SR is updated and describe the rationale for decisions applied in the systematic review for specific substances.**

3. **Ensure that Confidential Business Information (CBI) requirements do not prevent important health-based data from being made available to the public.**
4. **Describe clearly the rationale for developing a SR specific to TSCA risk evaluations.**
5. **Describe clearly the rationale for the differences in the TSCA SR relative to other peer-reviewed SR approaches currently in use.**
6. **Describe clearly the explicit populations, exposures, comparators, and operators (PECO or problem formulation) used in the SR.**
7. **Describe clearly the justification for using a weighted scoring system and the rationale for the metrics selected for differential weighting in its evaluation of studies.**
8. **Provide additional rationale to the TSCA SR justifying NR codes for certain metrics that are not typical of animal studies and improve discussions on how an NR code impacts the quality score.**
9. **Include data quality criteria in the TSCA SR for evaluating personal communications and other information types not already identified in the TSCA SR that might be considered critical in a risk evaluation.**
10. **Discuss why an "indeterminate" designation is not needed in the TSCA SR to account for situations where there is significant lack of data.**
11. **Develop, peer review and publish SRs for substances undergoing TSCA risk assessment prior to conducting the actual risk assessment.**

Recommendations to improve the PV29 SR:

12. **Perform a quality assessment of the exposure data for occupational exposures to PV29 that was provided to the Agency as a personal communication from the manufacturer of PV29.**
13. **Include a more thorough and inclusive data integration discussion in the TSCA SR for PV29. The discussion should include descriptions of how the human health experience, mechanistic information, *in vitro* data, and controlled laboratory animal data are used to support conclusions. Include in the discussion how chemical structural considerations, read across, and other information including finding from NAMs add to the evidence for potential PV29 toxicity. The discussion should also address data uncertainties.**
14. **Include a discussion on the potential toxicity of byproducts of manufacturing and impurities in PV29.**
15. **Improve the discussion on why available study data are adequate to reach the conclusions of "no unreasonable risk" from exposure to PV29. This discussion should also justify why additional testing is not necessary to confirm this conclusion.**

Question 3: Physical Chemical Properties/ Environmental Fate:

C.I. Pigment Violet 29 is an organic pigment that has a low solubility, low volatility and is expected to be highly persistent and has low bioaccumulation potential in fish and other animals. No acceptable studies are available to describe the environmental fate characteristics of C.I. Pigment Violet 29 with respect to characterizing the Log K_{OW}, K_{OC} and bioaccumulation.

3a	Please comment on the characterization of Log K_{ow}, K_{oc} and bioaccumulation for C.I. Pigment Violet 29, including any suggestions for alternative sources or methods to obtain or derive better estimates of the properties (e.g., use of specific analogs).

3b	Please comment on characterization of the physical chemical properties of C.I. Pigment Violet 29, especially with regard to the determination by the European Chemicals Agency (ECHA) to include C.I. Pigment Violet 29 on the 2019-2021 Community Rolling Action Plan (CoRAP) update as a "suspected PBT/vPvB [Potentially Persistent, Bioaccumulative and Toxic/very Persistent and very Bioaccumulative substance]." The CoRAP justification document for C.I. Pigment Violet 29 is available at: https://echa.europa.eu/documents/10162/13628/corap_justification_201-344-6_226-866-1_be_12079_en.pdf/cf312ff9-6b18-8b76-bc66-d86320faa24a

Response:

The Committee acknowledged the lack of empirical physical-chemical and environmental fate data available to the EPA for assessing the potential environmental impact of C.I. Pigment Violet 29 (PV29). Empirical data were obtained from a BASF study (BASF 2013, No. 11L00105) for melting point (MP), vapor pressure (Pv), water solubility (Sw), and octanol-water partition coefficient (log K_{ow}), but only the melting point information was considered of high quality. However, the melting point information only provided an estimate as "greater than value of 500 C." There was also a study that assessed the ready biodegradability of PV29 that was considered high quality.

To reasonably predict the distribution of a compound within the environment, simple environmental distribution models (e.g., fugacity level I) minimally require the octanol-water partition coefficient (or aqueous solubility since aqueous solubility can be used to estimate K_{ow}) and vapor pressure as input. Values for Henry's law constants (H), organic carbon normalized sorption coefficients (K_{oc}) and octanol-air partition coefficients (K_{oa}) are also critical input properties but can generally be reasonably estimated from ratios of other properties. For ionizable compounds, a pKa value is also critical since the environmental distribution of a compound depends on the charge of the compound at the pH of the environmental compartment of interest. EPA uses empirical data from the BASF study in the Draft Risk Evaluation (Evaluation) for values of aqueous solubility and solubility in octanol despite being judged as lesser quality.

Predicting persistence in the environment requires information on biodegradability, hydrolysis, photolysis and stability to oxidation or reduction reactions. The only experimental data available directly related to persistence was the ready biodegradability study that PV29 did not pass, indicating that it would not be biologically treated under conditions typically found in a wastewater treatment plant. Given the structure of the chemical, its high melting point and its history of commercial uses, PV29 is likely to be environmentally persistent.

Physical-chemical property estimation techniques are often used and appropriate to supplement a lack of experimental data. The EPA used the software program EPI (Estimation Program Interface) Suite™ to estimate values for the octanol-water partition coefficient and Henry's Law Constant. Unfortunately, several different estimated values of the octanol-water partition coefficient can be found in the various supplemental information documents. These estimates are several orders of magnitude apart making it difficult to know which value to use in EPI Suite™ and hence to have a consistent conclusion for the environmental behavior of PV29. For example, EPA selected the EPI Suite™ estimated log K_{ow} of 3.76 to use in the draft fate assessment while the K_{ow} value estimated from a ratio of measured solubilities in octanol and water was approximately 7 (log $K_{ow} \approx 0.85$). Obviously, the almost 3 orders of magnitude difference results in large differences in terms of predicted environmental distribution and bioavailability. The Committee concluded that the estimated log K_{ow} value used in the assessment was reasonable, but indicated that to improve transparency, the document should acknowledge the large differences and provide additional justification for using the EPI Suite™ estimated value.

Other estimation methods could be used to generate additional values in a weight of evidence type approach. For example, the "general solubility equation" (Ran, et al., 2001) yields a log K_{ow} of 3.4, if an aqueous solubility of 0.01 mg/L (2.68E-8 M) and melting point of 500° C is used. The importance of having a good estimate of the melting point value to use in the log K_{ow} estimation methods should also be addressed. The estimated log K_{ow} value reported in the ECHA Community Rolling Action Plan (CoRAP), also determined using the EPI Suite™ software, is much lower (log $K_{ow} = 1.97$) than the EPA selected value, and the difference is likely the result of not using melting point as an input. The larger log K_{ow} value of 3.76 (along with the EPI Suite™ estimated log K_{oc} value of 5) suggests that PV29, when discharged to the environment, would end up in soils or sediments. One Committee member suggested that the EPA should mention the limitations of using K_{oc} values to predict sorption to environmental solids especially for those solids that have low organic carbon and high clay contents. The smaller log K_{ow} value reported in the ECHA CoRAP would suggest that these environmental compartments are less important. The large log octanol-air partition coefficient (K_{oa}) value estimated in EPI Suite™ and used in the ECHA CoRAP also indicates the potential for accumulation in air breathing organisms likely due to particle inhalation. The Committee also mentioned the differences in the aqueous solubility values reported in several of the toxicology studies were also significant.

While some of the differences in estimated physical-chemical property values may be due to errors, the discrepancies among supporting information documents needs to be addressed in the Evaluation. A thorough search for physical-chemical properties values within the supplemental information documents should be conducted and any discrepancies resolved or discussed.

The Committee noted that the Evaluation contains multiple unsubstantiated and scientifically unsupported claims that any substance with aqueous solubility ≤ 11 µg/L implies it is not orally bioavailable. These claims are contradicted by abundant empirical evidence from animal feeding studies and human biomonitoring studies (and even some human feeding experiments). Many PCDDs, PCDFs, PCBs, PBBs, and PBDEs, as well as DDT and all seven of the polycyclic aromatic hydrocarbons (PAHs), that EPA has designated as carcinogens, are compounds having well-documented aqueous solubilities ≤ 11 µg/L and all of which are well-documented to be efficiently absorbed via the gut. This claim should not be allowed to remain in this document, not only because the science establishes it as clearly invalid but also because keeping it in this first TSCA Evaluation could have ramifications on future TSCA risk assessments. Invalid statements and their locations include:

a. "…oral absorption is negligible due to low water solubility" and "…negligible oral absorption due to low water solubility…"**2.3.5.1 Occupational Exposures** (p. 25)

b. "Oral ingestion is expected to be negligible due to the low water solubility…" **2.3.5.2 Consumer Exposures** (p. 25)

c. "…physical-chemical properties indicate that even if ingested, absorption would be expected to be limited due to low water solubility." **2.3.5.3 General Population Exposures** (p. 25)

d. "In addition, oral absorption is negligible due to low water solubility." **2.5.1 Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards** (p. 30)

e. "Furthermore, as described previously, even if oral ingestion occurs, absorption of C.I. Pigment Violet 29 is expected to be limited due to its very low water solubility." **2.5.2.2 Pathways that EPA Plans to Include in the Risk Evaluation but Not Further Analyze** (p. 32)

f. "In addition, oral absorption is poor due to low water solubility." **3.3.1 Occupational Exposures** (p. 22)

g. "Oral ingestion is expected to be limited due to the low water solubility (0.01 mg/L) …" **3.3.2 Consumer Exposures** (p. 23)

h. "Additionally, physical-chemical properties indicate that if ingested, absorption would be expected to be poor due to low water solubility." **3.3.3 General Population Exposures** (p. 22)

The only study providing empirical data establishing the relatively low octanol solubility for PV29 was not of high quality. This reduced the Committee's confidence in statements indicating that PV29 is not likely to be bioavailable. The Committee concluded that this was likely the main reason that the ECHA documents still show PV29 as likely to bioaccumulate. Without a high-quality experimental estimate of K_{ow} or corresponding lipid solubility data, it is difficult to dismiss the potential for PV29 to bioaccumulate. However, additional predictive methods are available that may be used to support a weight of evidence approach to demonstrate that PV29 is not likely to be absorbed by organisms. For example, the publication by Chu and Yalkowsky

(2009) shows that drug absorption is inversely related to melting point. Review of the pharmaceutical literature for techniques that established relationships between the physical-chemical properties of a substance and its bioavailability as an oral drug might also provide addition approaches (Shultz, 2019).

The Committee suggested that EPA consider using a simple fugacity model (Level I or II) to help the reader better understand the potential fate predictions and data input needs. This type of modeling effort could also be used to compare the predicted environmental distribution of PV29 to other well-known and data rich organic contaminants.

One Committee member noted that the structure of PV29 suggests that the compound may also be ionizable, and that the commercial software Chemicalize, by ChemAxon (https://chemaxon.com/), predicts that the compound acts as an acid with a pKa value of 8.46 (Figure 3). The former EPA program SPARC Performs Automated Reasoning in Chemistry (http://archemcalc.com/sparc.html) could be used to corroborate this prediction.

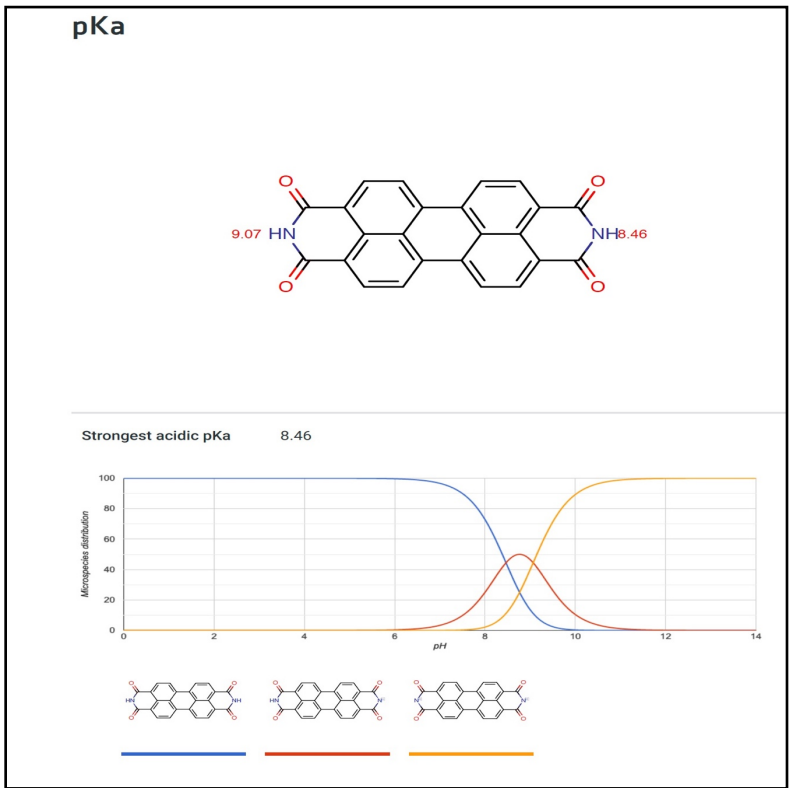

Figure 3. Chem Axon output displaying pKa prediction for PV29.

Assuming this prediction is accurate, then discussion of the potential impact of pH on the environmental behavior of PV29 should be added to the Evaluation.

The Committee also noted that the justification for including PV29 on the initial list of compounds to be evaluated under TSCA is the potential for accumulating in the sediment and in sediment dwelling organisms. This conclusion was based on estimated log K_{ow} and log K_{oc} values. However, no experimental toxicology data for benthic organism is presented in the Evaluation. Without this key piece of information, the case for PV29 being not bioavailable is

weak and needs strengthening.

The Committee discussed the fact that the ECHA CoRAP is evaluating a similar pigment (Pigment Red 179; CAS Number 5521-31-3) along with PV29. This approach seems logical given the high degree of structural similarly between these two substances (one has a methyl group substituted for the potentially ionizable hydrogen atom) and PV29 is a precursor in the manufacturing of Pigment Red 179 and the Evaluation states that 90% of PV29 is used to make Pigment Red 179. At a minimum, available physical-chemical and toxicity data for Pigment Red 179 should be obtained as a structural analog and used to help supplement the lack of data for PV29.

Committee members remarked that the slide presentation given by EPA staff during the introductory comments to the Committee was much easier to follow than the material in the Evaluation. The approach used to organize the technical presentation might be a good model for future draft risk assessment documents as well as serving as a guide to improve readability of the current Evaluation.

Recommendations to improve the Evaluation with respect to Physical-Chemical Properties and Environmental Fate:

1. **Ensure that the physical-chemical properties used throughout the Evaluation are consistent or note the reasons for discrepancies.**
2. **Remove statements that claim that an aqueous solubility of ≤ 11 µg/L precludes oral bioavailability.**
3. **Develop and justify high-quality estimates for log K_{ow} or fat solubility to solidify the argument that PV29 is not bioavailable or likely to be absorbed into organisms or tissues.**
4. **Use alternative property estimation methods to generate the additional information needed to strengthen the weight of evidence to conclude that PV29 is not bioavailable.**
5. **Improve the discussion supporting the importance of K_{oa} and better illustrate its implications on determinations of environmental distribution of PV29 and resulting exposure to humans and other organisms.**
6. **Consider using metabolic pathway prediction software to look for potentially problematic intermediates for PV29. Despite the fact that PV29 seems to have minimal ready biodegradation, the production of toxic and persistent metabolites is always a concern especially for any compound having structure similar to PAHs.**
7. **Consider using the slide presentation given by EPA on Thursday as a guide for organizing the draft risk assessment document.**

Question 4: Exposure and Releases:

To estimate the exposure and environmental releases during manufacturing, EPA used information provided by the manufacturer of C.I. Pigment Violet 29. For the processing and uses, no readily available C.I. Pigment Violet 29 specific information was found. EPA quantitatively evaluated the high-end occupational exposures using airborne monitoring data provided by the manufacturer and an EPA standard approach for occupational dermal exposure. Based on the worker activities, chemical concentration and amount handled, EPA determined that the exposure during the manufacturing will likely represent a high-end exposure scenario. These occupational exposure estimates were proposed to be protective of downstream users of C.I. Pigment Violet 29, which includes exposures to consumers and to the general population. Based on the recommendation by NIOSH, additional characterization of inhalation exposures to workers using the Occupational Safety and Health Administration (OSHA) standard for particles not otherwise regulated (PNOR) will be added as a high-end scenario inhalation exposure to workers.

4a	Please comment on the characterization of occupational exposures (inhalation and dermal) for the manufacturing workers. Is the panel aware of other additional relevant information, including C.I. Pigment Violet 29 specific data, that could be considered?

Response:

In the Evaluation, EPA states that the only occupational exposures that have been deemed relevant under TSCA are those that occur during manufacture, and that those only involve exposure to PV29 in powder form. The Evaluation also states that handling of the pure compound as powder presents a worst-case condition as it represents the highest concentration that can be encountered. The Committee found that both statements lack substantiation (at least through statements in the Evaluation). Any saturated solution or formulation represents roughly the same potential for uptake (i.e., thermodynamic activity) as the pure compound despite lower concentration. In the case of compounds that are solid at exposure temperatures, liquid formulations may present greater opportunity for dermal uptake due to reduced mass transfer resistance. Exclusion of downstream users such as painters from the risk evaluation is therefore unwarranted.

The Committee acknowledged their lack of prior familiarity with the compound, and with the manufacturing facility in question. This compound is apparently produced in only one location in the U.S. Therefore, a site visit would appear to have been feasible (to aid in assessment of in-plant exposures). Despite the compound having been in manufacture for decades, the Committee could find no basic information on the number of exposed workers and whether medical monitoring has historically been conducted. Implicit in the Evaluation is that "absence of evidence is evidence of absence." The Committee could not determine whether the population size or level of attentiveness were sufficient to have revealed health effects even if they exist. No evidence was provided to indicate that EPA queried other Federal or state OSHAs for information on PV29 or requested occupational hygiene or environmental release-related data from the manufacturer that are typically collected and archived.

The Evaluation alternates between a discussion of risk mitigation via engineering controls and personal protective equipment (PPE) and screening level calculations that assume no PPE. The document would be improved by more clearly distinguishing these two lines of thought.

Inhalation: Air quality "data" used in the first version of occupational inhalation risk evaluation, was determined by the Committee to be grossly inadequate, consisting entirely of limited information contained in a brief email from a representative of the manufacturer. A point estimate of the in-plant air concentration was mentioned in this email—without the supporting information typically accompanying such estimates, such as: a statistical confidence statement, a description of sampling locations and the proximity to dust generating activity, a discussion of sampling and/or analytical methods, and documentation of laboratory certification. This point estimate is referred to as a "maximum" value (p. 22) without substantiation.

Because occupational exposures outside the manufacturing facility were not considered, the possibility of inhalation of dust produced by painting-related tasks where PV29 is a component of the paint, for example in automotive paint repair tasks where sanding of coated surfaces is common, were not evaluated. The Committee expressed concern that individual exposures in these scenarios may be greater than for manufacturing exposures and the number of individuals exposed much larger.

Just prior to peer review, the analysis in Sec. 3.3.1.1 was supplemented by consideration of pulmonary obstruction by particle inhalation using alternate methods. Those methods are the subject of Charge Question 8 and thus are not considered here.

Dermal: The Committee considered the protocol used to assess dermal exposure in the manufacturing plant as crude, but in this case probably producing a conservative estimate of dermal exposure. "Fraction absorbed" is a poor metric of propensity for dermal absorption. Fractional uptake is dependent upon loading and not appropriately applied across studies without correction. The Committee wondered why flux-based estimation, a superior method for estimation of dermal exposure and one that is already used by EPA in the drinking water program and water applications under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), was not used. This approach is facilitated via an online calculator sponsored by NIOSH.

EPA's screening level calculation:

$$10\% \cdot 3100 \frac{\text{mg}}{\text{day}} \cdot \frac{1000\ \mu\text{g}}{1\ \text{mg}} \cdot \frac{1\ \text{day}}{24\ \text{h}} \cdot \frac{1}{1000\ \text{cm}^2\ \text{per two hands}} \approx 13 \frac{\mu\text{g}}{\text{cm}^2\ \text{h}}$$

implies a dermal flux of greater than 10 µg/cm^2/h. Based on the physical-chemical properties of PV29, this exposure rate (flux) is very likely an overestimate for human skin for liquid as well as powder exposures. However, it is possible that in an alternative scenario, a lower flux could be partially compensated for by greater surface area involvement.

4b	Please comment on the environmental release characterization for the manufacturing and use as a site limited intermediate. Is the panel aware of other relevant additional information, if any, that could be considered?

Response:

Based on impromptu public testimony by a representative of the manufacturer (identified as Dr. Robert C. Mott of Sun Chemicals) the Committee learned that the overwhelming fraction of manufactured PV29 is immediately converted to Pigment Red 179 via methylation. This does seem to be a terminal sink for PV29. The life cycle assessment (LCA) for PV29 would be much improved if this information was explicitly provided. As mentioned in the Committee's response to the previous question, these compounds were considered together in the CoRAP process.

4c	Please comment on the exposure and release characterization for the downstream processors and users. Is the panel aware of other C.I. Pigment Violet 29 specific data and/or information that could be considered?

Response:

Downstream releases (and, by inference, exposures) were dismissed as likely to be minor due to lesser masses handled. In the Evaluation, this argument was not well justified. Exposures at the manufacturing site are ostensibly mitigated by engineering controls and PPE. 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. Possibly sloppy handling of low masses can produce high exposures to no-negligible numbers of individuals.

In the opinion of many on the Committee, a dearth of information regarding the totality of downstream uses represented a major deficit of the Evaluation. A more generously descriptive LCA would be of great value in evaluating risks presented by use of PV29 in commerce.

4d	Please comment on the screening level approach used in the context of the conclusions associated with potentially exposed susceptible subpopulations (e.g., to children, workers, or pregnant women). Please comment on other additional information or analyses that could be conducted, if any, in light of the screening level approach used in this case?

Response:

The "screening level approach," described in the Evaluation and used for identifying susceptible populations, has two components. First, toxicological susceptibility was dismissed based on available toxicity tests, which the Committee considered quite limited and not adequate for this task without further rationale and scientific justification regarding the Agency's conclusion for minimal PV29 adsorption and bioavailability. Second, potential susceptibility associated with alternative high-exposure scenarios was dismissed on the grounds that in-plant exposures represent worst-case scenarios and thus obviate the need for consideration of other downstream

exposures. This argument was considered by the Committee to be unconvincing as, for example, painters might easily have higher inhalation (in the case of spray application) or dermal (or aggregate) exposures than plant workers. “Painters” should include individuals engaged in occupational conditions of use (COU), such as auto body repair shop workers and professional artists, and users in the general population, such as children.

4e	Please comment on the conclusion regarding the need for aggregate exposure.

Response:

For PV29, the Committee concluded that aggregate exposure should be the default approach. In the case of a dominant pathway of exposure, the sentinel exposure can be demonstrated to essentially be the aggregate exposure via screening level calculation. PV29 is used in food packaging, thus more information about potential exposures by this pathway, and introduction of PV29 into the environment through incineration or other disposal of the packaging, should be included.

Recommendations to improve the Evaluation with respect to Exposures and Releases:

1. **More aggressively pursue information from manufacturer(s) of life cycle sustainability assessment (LCSA) targets, purchasers/users of those chemicals, trade associations, and other federal and state regulatory agencies that may have specialized knowledge.**
2. **Incorporate uncertainty analysis into the LCSA risk evaluations and, at a minimum, present screening-level calculations when dismissing exposure pathways.**
3. **Refrain from making sweeping generalizations especially when based on limited and/or uncertain information regarding physical chemical properties or toxicological testing. Projection of environmental fate based on one-at-a-time examination of physical properties is unscientific.**
4. **For non-ionizable organics, EPA should adopt a screening level fugacity modeling approach as a default under LCSA.**
5. **Include $J_{max,ss}$ (maximum steady-state dermal flux) estimates in their list of physical chemical properties routinely reported in TSCA risk assessments.**
6. **Aggregate exposures should be considered including use of PV29 in food packaging.**

Question 5: Environmental Effects:

Given the limited nature of the dataset describing the potential environmental hazards from the manufacture and use of C.I. Pigment Violet 29, there are uncertainties associated with risk conclusions to environmental receptors from exposure to C.I. Pigment Violet 29 from the uses described in the document.

5a	Please comment on the evidence used to support the characterization of hazard to ecological receptors from acute and chronic exposure as presented in the document.

Response:

Given the information presented in the Evaluation, the probability for environmental releases from manufacturing are likely low, and, most likely to occur in wastewater streams. The Evaluation identifies consumer uses in the PV29 conditions of use, but any environmental releases from consumer uses are reasonably expected to be minimal and inconsequential.

Acute data collected for duckweed (*Lemma gibba*), copepods (*Daphnia magna*), and fish (*Zebra danio*) suggest a low probability for toxicity from acute exposures. Data from these assays appear to be collected in accordance with good laboratory practices (GLP) and as a result considered of good quality. Further, water solubility estimates for PV29 are supported by analytical chemistry information of PV29 in water exposures to these organisms. However, toxicity benchmarks reported in these studies suggest that investigators were successful in greatly exceeding the estimated solubility. Details are provided in these reports that show exposures included loadings (e.g., particulates, precipitates) and extrapolations, and that this helps explain these results. The Evaluation discussion needs improvement for estimates of toxicity benchmarks developed from those studies where exposures exceeding the water solubility limit are observed. These inconsistencies need better explanations in the Evaluation since they can lead to misunderstandings regarding the reliability of the water solubility estimate.

5b	Strong sorption to sediment is indicated as a result of the estimated K_{oc} of 5.0 based on estimations from EPI Suite™. While this indicates that exposures to aquatic organisms in the water column are likely to be low, this also indicates that potential water releases could result in exposure to sediment-dwelling organisms. The EPA assumed low hazard to these organisms due to the lack of toxicity observed in the tests conducted with all other aquatic species, particularly *Daphnia magna*. Given the acute hazard profile for this chemical, limited releases, and the physical-chemical characteristics of C.I. Pigment Violet 29, please comment on the risk characterization for sediment-dwelling invertebrates.

Response:

Toxicity data to sediment-dwelling organisms are not presented in the Evaluation. As a result, the Committee was unable to comment on whether low concentrations of PV29 could present a hazard to these organisms. Potential for, and probability of releases to sediments are greatest for

the manufacturing facility and actual releases should be addressed in greater detail to help make a determination regarding exposures to sediment-dwelling organisms.

Persistence of PV29 in the sediment has not been fully determined, only inferred from modeled chemical physical property data. If bioavailability is low (by extrapolation of chemical physical property information), toxicity to sediment dwelling organisms is likely to also be low. Affinity of PV29 to organic carbon is dependent upon the organic carbon content of the sediment. Organic carbon content will vary considerably depending on the substrate (e.g., low in sandy sediments). Increased organic carbon in the soil implies increased exposure probabilities for these sediments and thus to related aquatic organisms. The Committee suggested that including a level of confidence statement with any judgment regarding toxicity, exposure, and risk to sediment-dwelling organisms. In addition, support for findings on toxicity to sediment dwelling organisms would be increased by better descriptions of how log K_{oc} was determined.

The probability of exposure to other ecological receptors through consumer uses or trophic transfer is likely to be low given the molecular structure and what is known about chemical physical properties of PV29.

Recommendations to improve the Evaluation with respect to Environmental Effects:

1. **Improve explanations for estimates of toxicity benchmarks developed from those studies where observed exposures exceed the water solubility limit.**
2. **Include a level of confidence statement with judgements of toxicity to sediment dwelling organisms.**
3. **Provide better description of how log K_{oc} was determined in key studies.**

Question 6: Human Health:

C.I. Pigment Violet 29 is an organic pigment found in a wide variety of commercial uses EPA believes has a low hazard potential to human health across all possible routes of exposure.

6a	Please comment on the toxicological study which was used to identify the endpoint of concern and derive the associated point of departure (POD). Also, please comment on alternative approaches to estimate the potential for lung effects using analogs for poorly absorbable particles to calculate an inhalation toxicity POD and the screening-level calculation to estimate the potential for lung overload. Please comment on this approach and whether this analog represents useful information to quantify risk for the inhalation route and whether oral developmental study is appropriate for all routes of exposure. If not, please describe what other alternative approaches could be used in lieu of these approaches to serve as the basis for completing the hazard assessment and subsequent risk evaluation for C.I. Pigment Violet 29:

Response:

Several Committee members felt that the statement "low hazard potential across all possible routes of exposure" is too broad of a conclusion, and one that is not based on adequate data. Wherever this statement occurs in the Evaluation, it should be modified to include appropriate qualifying conditions. One option discussed was to use a logic model diagram to visually present confidence in streams of evidence leading to final risk determinations. An example from the Washington State Board of Health is shown in Figure 4 (below).

The Committee recognized that the toxicological study used to identify the POD was a well done reproductive/developmental oral repeated dose screening study (OECD Guideline 421) that measured basic reproductive and limited systemic endpoints in pregnant dams and their pups (e.g., pup weight, and pup gross morphology). But the Committee disagreed on the interpretation and applicability of study results to setting a POD. Some Committee members concluded that data from this study were sufficient to use in setting the POD for final margin of exposure (MOE) calculations when considered in conjunction with additional rationale and scientific justification for minimal PV29 absorption and bioavailability. Most of the Committee felt that while this was the best available data that could address the POD, they had strong reservations about drawing conclusions from this single screening study because many endpoints from general toxicity studies—for example a 90-day study—were never assessed (or publicly reported) for this chemical.

Limitations of the study included: 1) examination of only a few endpoints including body weight of the pups at birth; 2) presence of gross skeletal abnormalities; and 3) histopathology available of only reproductive organs. The study did not examine functional immune or endocrine endpoints, assess behavior or growth, or evaluate other potential endpoints. The study also did not examine chronic health effects—this was not what the study was designed to do. The Committee recognized that to use a study of this kind is acceptable in traditional risk assessment. But in this instance the limitations in the available bioavailability data on PV29 do not support

the use of one oral, screening reproductive/toxicologic study to derive the POD for dermal and inhalation scenarios without additional data demonstrating the lack of absorption of PV29 in animal models and humans. Finally, there is little contextualization of these limitations in the text.

One Committee member expressed that EPA's Evaluation accepts the data gaps from lack of hazard data because of the assumption that very limited bioavailability for this chemical prevents exposure. The Evaluation should clarify the toxicity data gaps, listing in a table of common toxicity endpoints (e.g., from a SIDS data set) that have never been assessed for this high production volume chemical. The Evaluation should explain that despite these gaps the Agency believes additional toxicity testing is not needed because of assumed limited bioavailability.

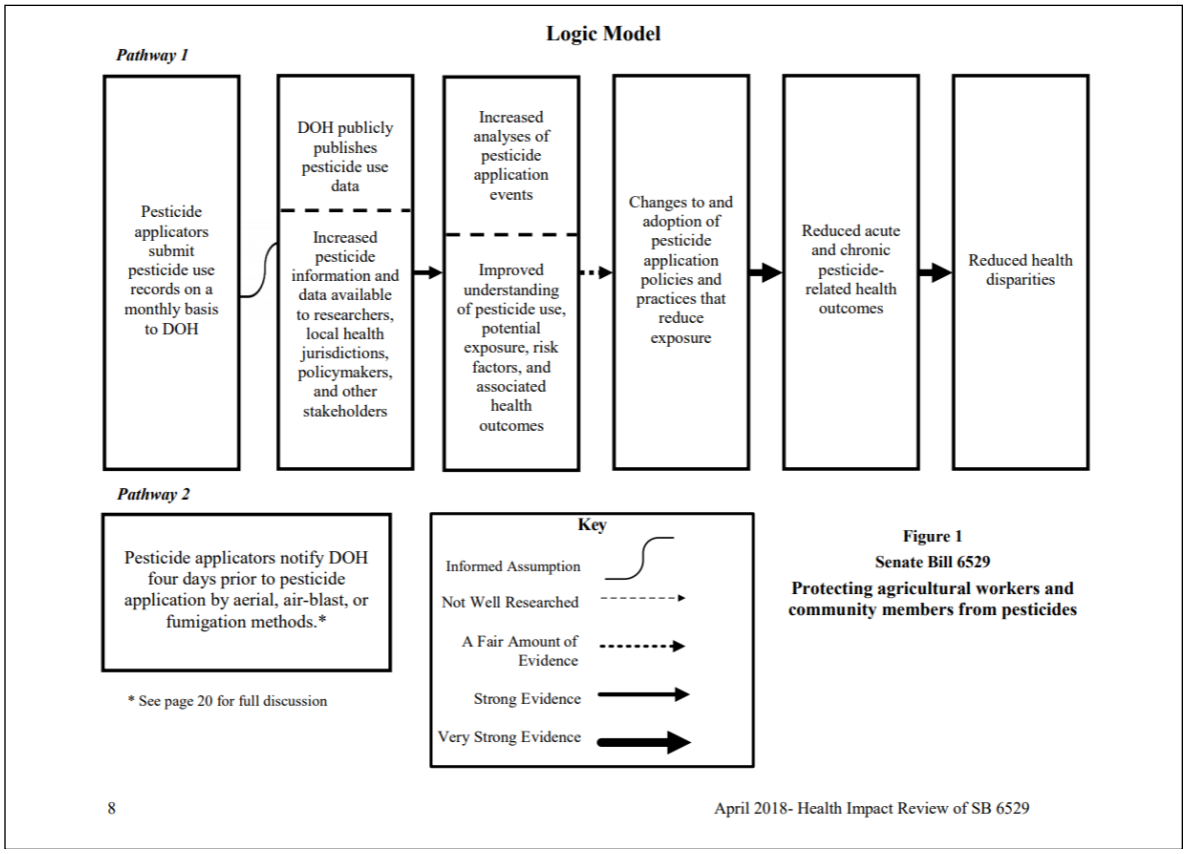

Figure 4: Example of a logic model diagram (used by permission: H. Davies, Washington State Board of Health).

Interpretation of some changes in male/female F0 body weight at middle doses were interpreted as biological variability without toxicological significance because of a lack of a dose-response relationship. There is recognition of non-monotonic dose responses with a physiologic basis for occurrence. For these reasons the Evaluation should be modified to further clarify these results/conclusions.

Mammalian and ecological toxicology testing of PV29 observed no adverse effects up to 1,000

mg/kg body weight (BW) and limit concentrations, respectively. The results indicate that PV29 is not toxic in these models. This could be because PV29 is: 1) not intrinsically hazardous but bioavailable; or, 2) not intrinsically hazardous and not bioavailable; or, 3) intrinsically hazardous but is not bioavailable and the lack of observed effect is due to no significant exposure. In order to determine the real reason for the lack of toxicity, it is necessary to determine with confidence whether or not PV29 is bioavailable in toxicology models. An ADME study for oral, dermal, and inhalation routes would provide greater confidence in PV29 bioavailability and exposure estimates.

In the presentation to the Committee at its meeting, several uncertainty factors were discussed, yet the MOE calculation incorporates only two of these; the intra-species uncertainty and the inter-species uncertainty factors. The uncertainty factor accounting for subchronic-to-chronic toxicity was not used. Some Committee members expressed that it was important that this uncertainty factor be included in calculating the MOE, since a repeated dose reproductive/developmental screening test is not equivalent to a sub-chronic exposures test nor is it equivalent to a long-term chronic toxicity test. Therefore, the available data do not seem to account for this effect.

The Committee also discussed the issue related to lung loading through variations in particle size and the potential for clearance and/or inflammation. The Committee concluded that although the comparison done with BaSO3 attempts this, differences in PV29 particle configurations could present differences that could conceivably cause effects not anticipated.

The discussion on methods to estimate lung effects also requested in Question 6a is included in the responses to Charge Question 8.

Recommendations to improve the Evaluation with respect to use of a screening reproductive/toxicologic study to determine the POD:

1. **The utility of the screening reproductive/developmental toxicological study for deriving the POD would benefit from additional and better estimates of physical/chemical properties and ADME studies to further strengthen support that PV29 has low bioaccessibility/bioavailability and therefore, decreased risk for absorption and inhalation.**
2. **Include a table in the Evaluation that compares the endpoints reported in the screening reproductive/developmental toxicological study used in the Evaluation to endpoints typically reported in a 90-day subchronic tox study or to compare what's available for PV29 vs. a basic SIDS data set–to clarify the value of the screening reproductive/developmental toxicological study and highlight data gaps in the toxicity assessment.**
3. **Include the subchronic-to-chronic uncertainty factor in the calculations of the MOE or significantly improve the justification/qualifications in the Evaluation for why this uncertainty factor should not be used.**

4. **Wherever in the Evaluation the statement "PV29. . . has low hazard potential across all possible routes of exposure" occurs, the statement should be replaced with one that is specific and limited to the routes of exposure observed in the available study data—thus allowing new data, as it becomes available, to add to and expand hazard conclusions regarding PV29.**
5. **Regardless of whether PV29 is bioavailable, more justification is needed to conclude that exposures to dusts in occupational settings do not cause lung depositional events or immunological responses sufficient to cause injury.**

6b	Please comment on the use and interpretation of Multiple-Path Particle Dosimetry Model (MPPD v. 3.04), which has not been formally peer-reviewed, to predict lung deposition of aerosolized C.I. Pigment Violet 29.

See discussion to Charge Question 8.

6c	Please comment on the evidence available to support the agency's conclusion of negligible absorption via oral, dermal, and inhalation routes.

Response:

The Agency's conclusion of negligible absorption via oral, dermal, and inhalation routes is based on several assumptions including: low water solubility, low lipid solubility, high molecular weight, and use of PPE equipment (specifically for manufacturing workers). The Committee concluded that the evidence for low water solubility is not clear and available studies provide conflicting estimates.

Some Committee members felt that additional information presented during the meeting increased confidence in the conclusions. In the oral comments before the Committee by Dr. Robert C. Mott, it was stated that PV29 is insoluble in all solvents at room temperature except 96% sulfuric acid. Assuming this is true, it further supports the low lipophilicity of PV29, implying that absorption of PV29 via oral, dermal, and inhalation routes would be negligible. This further supports other evidence presented in the Evaluation, namely, low water solubility (0.01 mg/ml), no hazards observed in the limited mammalian toxicology and aquatic toxicology studies, not biodegradable, and low bioaccumulation. EPA should compile and evaluate these types of data and include them in the report to support statements about low bioavailability and lack of environmental transformation.

Other Committee members indicated that the information presented during the meeting did not change their finding that available data was not sufficient to support the Agency's conclusion of negligible absorption via oral, dermal, and inhalation routes. Based on bioavailability uncertainty, it was unclear whether there is truly exposure via these routes. Some Committee members indicated that many bioavailability statements are overstated (see response to Question 3). In particular, the claim that low aqueous solubility precludes gastrointestinal (GI) uptake is incorrect. Similar statements exist for dermal and inhalation. The Committee suggested further testing is needed to confirm assumptions, such as modeling using different scenarios as opposed

to the one scenario presented or NAM testing using *in vitro* tissue adsorption models, or in vivo ADME assessments.

In the case of inhalation, the Committee noted it likely that workers would be exposed. Assumed use of PPE to prevent exposures, especially for those workers not directly interacting with the pigment, was not sufficient when assessing potential exposures. Negligible absorption cannot be confidently concluded because the physical chemical properties of PV29, including its octanol-water partition coefficient (log K_{ow}), have not been adequately established as mentioned several times previously in the Committee's discussion. If modeling of absorption is going to happen, there should be several solubility scenarios that should be used.

The animal data examining dermal exposure was sufficient to assume a low likelihood for dermal irritation, but there is no data on dermal absorption. The Committee was conflicted about whether absorption occurred. Some Committee members felt strongly that skin pigmentation noted in the acute oral toxicity study strongly suggested PV29 absorption and migration throughout the body.

Recommendations to improve the Evaluation with respect to absorption via oral, dermal and inhalation routes:

1. **Request an appropriate study to adequately determine bioavailability or bolster the evidence for poor water and octanol solubility in a well-laid out manner to support the agency's conclusions.**
2. **Given the low confidence in absorption potential based on limited physical-chemical data, present models based on several solubility scenarios or NAM *in vitro* testing using tissue adsorption models.**
3. **Either do not perform MOE calculations or clearly qualify assumptions used in the MOE calculation based on the limited data.**

6d	Given the varied nature of the consumer uses, please comment on the agency's characterization of hazard to consumers via inhalation and dermal exposure for different durations of exposure.

Response:

The Committee concluded it was reasonable to assume consumer exposures are generally less than occupational exposures given that uses through watercolor and artistic paints are less than 1% of production volume. The Committee also felt that despite low general exposures, individual consumers may experience high levels of exposures. There are additional consumer exposures identified as a COU but for which risks were not evaluated (see Table 2-2 of the Evaluation) primarily because the volume of manufactured PV29 allocated to these uses is small. In addition, the use in food contact material that is regulated by the Food and Drug Administration (FDA), considered outside of the scope of this assessment, points to possible other uses and exposures. Based on the volumes and materials, such as the use of PV29 in plastics, EPA can make reasonable assumptions on consumer exposures. Consumer uses as listed

include those who would use paints or pigment containing materials. These could include painters or others using pigment containing materials. In addition, EPA could include children who potentially use paints. Children are more likely to have oral, hand-to-mouth behaviors that place them at increased risk of exposure.

Some Committee members were comfortable with the likelihood of exposure being low, and therefore, the risk assessment would be protective of consumers. Other Committee members concluded that the information presented in the Evaluation was insufficient to support with confidence a conclusion of low hazard for consumers exposed via inhalation- and dermal-absorption. For the reason stated previously, the likelihood of inhalation exposure is truly unknown.

The reasonably available information does not support the statement in Section 3.4.1 of the Evaluation that “the results of the available human health data” indicate "there is no evidence of increased susceptibility for any single group relative to the general population." The handful of studies in animal models does not represent sufficient support for this statement. There is no evidence for increased susceptibility in special populations, primarily because there is simply no data to address this.

Of note, there was no discussion of duration of exposures for consumers in the text of the report. Therefore, the committee could not address this point.

Recommendations to improve the Evaluation with respect to hazard to consumers via inhalation and dermal exposure:

1. **Improve the discussion of the uncertainty surrounding exposures for the general population. Explain clearly why it was initially determined that there were widespread consumer exposures to PV29 but that this did not need to be addressed in the final risk assessment. Clearly acknowledge that there may be certain consumers that receive higher acute and chronic exposures and explain why this is not considered important for this risk assessment.**
2. **Clarify the statement in 3.4.1, “there is no evidence of increased or decreased susceptibility for any given population” to acknowledge that there are large data gaps that preclude coming to confident conclusions regarding certain subpopulations.**

6e	Similarly, please comment on the Agency’s characterization of hazard to workers via inhalation and dermal exposure for different durations of exposure.

Response:

The Committee agreed that the greatest exposures to PV29 will likely occur in manufacturing and occupational workers via inhalation and dermal exposures. Committee members disagreed on the risk characterization for these workers. Some Committee members felt that the agency-

computed MOE was protective of workers based on the suggestion of low bioavailability of PV29 and no observed toxicity in the limited readily available animal data and screens.

Most Committee members felt that workers in manufacturing were most vulnerable to exposures and most likely to be highly exposed compared to other populations. Given this exposure scenario, there is no adequate bioavailability data to conclude with confidence that workers would be protected with risk management to the MOE calculated. Therefore, some Committee members expressed little to no confidence in the risk determination for workers.

Recommendations to improve the Evaluation with respect to hazard to workers via inhalation and dermal exposure

1. **Clearly acknowledge that there are few data to support a confident conclusion that workers would not be exposed, and therefore, not experience human health hazards via dermal and/or inhalation routes.**
2. **Obtain and incorporate into the Evaluation better (e.g., collected using standard measurement techniques with adequate temporal and spatial coverage) data/documentation from the manufacturer on conditions of use, exposures, and potential for worker exposures.**

6f	Please comment on the Agency's consideration of health hazard concerns for potentially exposed susceptible subpopulations given the constraints of the available information (e.g., children, workers, or pregnant women).

Response:

The low PV29 exposure potential to consumers including sensitive subpopulations and acceptable MOE based in part on a developmental reproductive toxicity screening study demonstrating no effects in fetuses, provide some data to show that pregnant women may be protected.

Limitations of this study were described in the Committee's discussion to Question 6a above. There are no data on children, and the study did not observe pups beyond birth (however, if shown not to be bioavailable, this may not be an issue). There are also no data on susceptible worker populations and those at higher risk for human health risks such as those with respiratory diseases or other conditions. The MOE calculation does not include additional uncertainty factors to protect these populations.

Recommendations to improve the Evaluation with respect to health hazard concerns for potentially exposed susceptible subpopulations:

1. **Improve transparency by acknowledging in the Evaluation that there are no data supporting the determination of hazards or exposures to children or other**

susceptible populations on which to make confident conclusions regarding risk to these susceptible subpopulations

2. **Do not make statements without additional clarifications and justifications that children or other susceptible populations would be protected. The current data as discussed in the data integration does not clearly support this conclusion and the committee has recommended additional data needs and rationale to address this uncertainty. Some committee members recommended the EPA consider an "indeterminate" categorization and qualify with data that may suggest low toxicity. Methods to address this would include using more uncertainty factors in MOE calculations or developing multiple modeling scenarios including best case to worst case and presenting these models in the text.**

Question 7: Risk Characterization/Risk Determination:

After consideration of all information identified by the EPA that pertains to C.I. Pigment Violet 29, please comment on whether the information presented to the panel supports these conclusions outlined in the draft risk characterization section concerning C.I. Pigment Violet 29. If not, please suggest alternative approaches or information that could be used to develop a risk finding in the context of the requirements of EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).

Response:

Committee members were in general agreement that the information presented to support the conclusions outlined in the draft risk characterization was not sufficiently robust for this purpose. The Committee's comments on charge questions 1 to 6 include recommendations aimed at improving the Evaluation and increasing the clarity and transparency of the information presented and the arguments offered in support the risk characterization.

The Committee reiterated the data deficiencies that weaken these conclusions. Including:

1. Inconsistencies in the available physical-chemical properties data and/or lack of high-quality solubility studies in water, octanol, or equivalent tools, such as ADME studies, needed to produce estimates of solubility with sufficiently high confidence to justify their use in establishing exposure potential.
2. Lack of details on workplace air monitoring necessary to establishing workplace exposure estimates with confidence.
3. Lack of confidence in the readily available animal data's ability to establish with confidence that PV29 has low hazard via inhalation- or dermal-pathways.
4. Poor justification of uncertainties used and no justification for not using a sub-chronic-to-chronic uncertainty factor.
5. Incomplete descriptions of the level of uncertainty in published information, assumptions used, and the impact of these uncertainties on conclusions.

Committee members suggested that the risk characterization would be bolstered by adding the following:

1. A description of the manufacturing process, including worker activities where exposures would occur.
2. Details of particle size (in the breathing zone) and shape and how these characteristics relate to potential inhalation toxicity.
3. Information on outfall/release and concentrations in the sediment at the manufacturing site.
4. Data sufficient to confirm bioavailability of the PV29.
5. Additional *in vitro* or *in silico* data, such as Toxcast and other NAM models to provide needed insight on lung toxicity or respiratory sensitization and further confirm bioavailability.
6. Testing in model organisms other than the traditional rodent models like zebrafish, yeast, and nematode worm, *Caenorhabditis elegans,* to increase knowledge of effects.
7. An evaluation of PV29 immunotoxicity that encompasses immunosuppression or possible respiratory sensitization.

Additional Comments

Committee member 1:

EPA has taken a tiered approach to assessing whether PV29 poses an unreasonable risk. Since this screening level assessment did not identify concerns, no additional information would normally be required. A conservative assessment based on existing information was sufficient to determine no unreasonable risk.

The concerns from public comments that the EPA did not have sufficient information to support the conclusion revolved primarily around three issues.

1. There are insufficient data to assess hazard, primarily for chronic and sub-chronic exposures.

None of the human health studies with relevant routes of exposure indicated adverse effects. This included two mutagenicity studies as a screening assessment for cancer effects and a reproductive/developmental toxicity screening test. None of the acute aquatic toxicity studies in fish, invertebrates, or aquatic plants indicated any toxicity up to the solubility limits. Under a tiered assessment protocol, there is nothing in the data suggesting the need to perform additional studies provided a conservative exposure assessment does not indicate a problem.

2. Not all the data from the studies are publicly available.

Making full study reports publicly available is certainly desirable, but the Committee must also recognize that studies have commercial value. Balancing these needs is a challenging proposition. In Europe, the concept of a robust study summary was developed under the Registration Evaluation and Authorization of Chemicals (REACH) regulation. In this particular

case, EPA was able to review the underlying studies in full, but then asks the public to accept their assessment of the accuracy of those summaries. Ultimately many of the original CBI claims were removed. **EPA should continue to encourage data submitters to review CBI claims closely prior to submission.**

Protecting CBI is important to make sure that EPA will receive as much relevant data as possible, including voluntary submission of data that may be owned by companies not subject to TSCA or subject to data sharing agreements. Having as much information as possible helps reduce the chances of EPA requiring duplicative testing when that data may already be available. **EPA should consider novel ways to make full study reports available to interested members of the public without compromising the investment of the data owner.**

3. Uncertainty in how worker exposures are derived and reliance on company Safety Data Sheets (SDS) for protection downstream.

EPA's assessment of worker exposure was conservative. They assumed no use of PPE for both dermal- and inhalation-exposure and that the concentration of inhalable dust is 100% PV29. The reference MOE included two 10x uncertainty factors.

"How much dust from PV29 is in the air at the manufacturing site?" seems to be an unanswered question.

Originally the EPA used 0.5 mg/m^3 based on information supplied by the manufacturer. Under these conditions, assuming no use of PPE and 100% PV29, the calculated MOE was protective. In fact, the MOE would still be protective even if the OSHA permissible exposure limit (PEL) of 5 mg/m^3 (10x higher) for inhalable nuisance dust was used. EPA recently released updated inhalation assessments based on comments from NIOSH. Both of those alternative assessments indicated that there is a sufficient margin of protection under the worst-case scenario—again assuming maximum dust in the air based on OSHA standard, that 100% of the dust is PV29 and that no PPE is used. Given that three different models did not indicate a concern there is no reason to further refine the assessment.

Many public comments pointed out that the use of the manufacturer Safety Data Sheet (SDS) for PV29 was insufficient to ensure that downstream users were protected. In actuality, given that the assessment was based on no use of PPE, downstream users are as protected as workers at the manufacturing site because the same OSHA limitations apply. The SDS is important and gives users information on how to safely handle the material, but the safety assessment does not rely on what information is provided on the SDS, nor on how that information is implemented by users.

Committee Member 2

The EPA based their conclusion in part on the negative results of the industry-sponsored studies that tested acute oral, acute inhalation, reproductive toxicity and acute intraperitoneal (IP) toxicity, as well as skin irritation, eye irritation, mutagenicity, and local lymph node sensitization. Only acute intraperitoneal exposure to PV29 induced overt toxicity, including

death. Since this exposure route is very unlikely in humans, the EPA discounted the IP toxicity, and determined that PV29 is unlikely to injure human health under the most likely routes of exposure. Based on the negative toxicity data from the available studies, the EPA's characterization of PV29 as not likely to injure human health could be seen as appropriate.

The public comments regarding the overall risk characterization/risk determination raised important concerns. Some of them are reproduced here (bulleted text), and their apparent validity discussed:

- The EPA seeks to demonstrate that PV29 is not hazardous to human health by drawing far-reaching conclusions from a limited dataset that provides minimal information about its potential toxicity.

The human health evaluation was based on twelve whole-animal studies, and two *in vitro* studies. Two studies used single gavage exposure to test the acute oral toxicity of PV29 (6,810 or 10,000 mg/kg) in 5 male and 5 female Wistar rats/group after 14 days. Both studies showed staining of skin and feces, but no deaths or overt organ pathology. Two studies examined acute inhalation toxicity by subjected 6 male and 6 female rats to a single 8-hour exposure to vapor containing 14.74 mg/l PV29, or a single 7-hour exposure to vapor containing 0.31 mg/l PV29. Although some mucous irritation was noted, no deaths had occurred when the experiments were terminated at 7 or 14 days respectively. Eye irritation was examined in two studies (2 female rabbits, or 3 male rabbits). A single application of 50 or 100 µl of PV29 caused some irritation over the course of 3 to 8 days, but with the small sample size it was unclear if the treatment differed from exposure to the talcum control. Acute intraperitoneal toxicity was evaluated in two studies, each using 5 female and 5 male mice/group. The mice were exposed to a single IP injection of 2,150, 4,640, 6,810 or 10,000 mg/kg PV29 in a 50% suspension. The highest concentration induced 70-100% lethality within 24-48 hours. Even the lowest concentration induced 10% lethality by the time the experiment ended at day 14.

Two different assays were used to assess sensitization/irritation. A local lymph node assay (LLNA) was conducted using four male CBA/Ca/Ola mice/group that were exposed to 3%, 10% or 30% solution daily for 3 days. No substantial proliferation was detected in the lymph nodes at day 6, indicating a lack of sensitization. Hexylcinnamaldehyde was used as a positive control. In two addition studies, rabbits (2 females, or 1 female and 2 males) exposed to a 50% suspension of PV29 on intact and/or scarified skin demonstrated no skin irritation by 8 days.

Lastly, reproductive toxicity in Wistar rats (10 male and 10 female rats/group) were exposed by gavage to 100, 300 or 1000 mg/kg/day daily for 14 days. The rats were mated, and exposure continued for an additional 14 days. The experiment was terminated on post-natal day 4. The investigators noted no effects of PV29 exposure on male or female fertility, post implantation loss, live birth, pup numbers or viability, sex ratios or pup body weight. The investigators concluded that PV29 exposure did not cause reproductive or developmental toxicity.

Mutagenicity of PV29 ($\pm$ metabolic activation at concentrations up to 5,000 µg/plate) was tested in strains of *E. coli* and *S. typhimurium*. No PV29-induced mutagenicity was observed in the Ames test after 72 hours. Similarly, 4 or 24-hour exposure to PV29 (at concentrations up to 172

µg/ml; higher concentrations induced precipitation which invalidated the results) did not induce mutation of the HPRT locus in Chinese hamster V79 cells after 7 days (See Study #15 Gene Mutation Assy; Docket ID=EPA-HQ-OPPT-2018-0604-0027). This study tested 4-hour exposure to PV29 in the presence or absence of S-9 liver fractions to control for metabolic activation. A longer, 24-hour exposure to PV29 was also tested for mutagenicity, but not in the presence of S-9 fractions. Both of the *in vitro* experiments had appropriate positive (DMBA) and negative (solvent and water alone) controls.

Ideally, toxicity assessments draw from experiments conducted by federal agencies and academicians, and with results assessable in public databases. These assessments can include animal studies, *in vitro* experiments as well as human epidemiological data. In the case of PV29, the human health assessment conducted by the EPA was based on a limited number of industry-sponsored experiments. It may be unreasonable to demand a full battery of tests for each of the myriad chemicals on the market. However, there are some specific gaps in the existing data that make it difficult to accurately assess PV29 toxicity.

As indicated in the public comments, there is no data concerning the long-term effects of PV29 exposure. None of the studies described extended past 14 days. Even the reproductive study was terminated at post-natal day 4, despite the fact that the more long-term effects of developmental exposure on the pups would have been of legitimate concern. If the solubility, bioavailability and metabolism of PV29 is as low as stated, the long-term effects of long-term occupational exposure may be a moot point. However, there was an apparent lack of consensus regarding PV29 solubility. In addition, despite requests from the EPA, the manufacturers have not provided crucial information concerning the characteristics and fate of PV29. **The Agency needs to compel answers to these questions if they are to accurately assess the potential human and environmental hazards**.

Chronic non-occupational exposure to PV29, and accompanying long-term effects seems unlikely. A bigger concern is the chronic exposure of the personnel who manufacture PV29, or who use it in an occupational setting. Unfortunately, the very minimal occupational inhalation data provided by the manufacturer makes it difficult to estimate the impact on workers via this route of exposure. This means that the statement that PV29 poses a low risk across all exposure routes is not supported. **The EPA needs to obtain documented inhalation data**.

The evaluation of PV29 immunotoxicity effects was limited to the LLNA, which is designed to test only the induction of type IV hypersensitivity. The adaptive immune response, which has now been shown to play a role in many bodily responses including those of the nervous system and gut. In addition to mutagenicity, toxicant-induced suppression of the adaptive immune system is also a major contributor to neoplasia. PV29 is derived from prylene or acenaphthene, both of which are polycyclic aromatic hydrocarbons (PAHs). Since PAHs have been shown to routinely suppress several aspects of the immune system, an evaluation of PV29 immunotoxicity that encompassed immunosuppression would have made the assessment of low toxicity more convincing.

The conclusion that PV29 does not present an unreasonable risk of injury to human health or the environment means that PV29 lacks the potential for unreasonable risk under its conditions of

use. The question becomes how much data is required to show that no such risk exists. **Saying that no unreasonable risks for PV29 were identified may reflect the weakness and limitations of the database.** This is not the same as saying that conclusive evidence exists that PV29 does not present an unreasonable risk. The experimental results regarding PV29 toxicity are limited, especially regarding long-term effects, potential immunotoxicity, and inhalation effects. On the other hand, the conditions of use mean that exposure is also likely limited both occupationally and environmentally. Part of the exposure assessment is based on the assumption that the absorption, bioavailability and metabolism of PV9 is low. As described in the public comments, the EU REACH authorities have described PV29 as persistent with a high potential for bioaccumulation, especially via inhalation. The sparsity of data concerning potential PV29 toxicity is balanced by a similar lack of information concerning the physical characteristics of the compound. Getting sufficient information in either of these two areas would go a long way to mitigating the deficiency of the other. However, the confluency of both deficiencies makes it difficult to agree with the EPA's assessment that PV29 does not pose an unreasonable risk to human health.

As the first SACC evaluation, this is the time and circumstances to demand sufficient information to provide an adequate assessment. This is a template that will be needed to proceed to evaluate other chemicals on the list.

Committee Member 3

It isn't clear how the decision about whether the PV29 data set is adequate to support a low risk finding is related to the assessment of exposure potential. There are many data gaps for PV29 toxicity, pharmacokinetics, and exposure. Are these data gaps acceptable to EPA only because of the apparently limited use and exposure potential for this chemical? What if exposure was widespread? One can't tell from the documents how these elements are connected. This question is relevant to the precedent being set for future assessments and also raises a question of how the assessment would be different if there was widespread use and exposure to the chemical, for example in food packaging or consumer products. How will the Agency adjust its decision if production and exposures increase or if assumptions in this assessment turn out to be incorrect? For example, since FDA has approved PV29 in food contact polymers up to 1%, is it also likely that PV29 is—or in the future—used in consumer product polymers, for example children's toys? The manufacturer may choose to market this pigment as eco-friendly if it receives a low-risk designation, and that could result in increased exposure. Is the data set available for this assessment compatible with a non-toxic or environmentally safe marketing approach? How does the data available for this assessment for low risk under TSCA compare with data requirements for EPA to designate a safer chemical or product in its (former) Design for the Environment (DFE) program? In terms of pre-emption of state action as a result of this assessment, any statement of low-risk finding should be stated more narrowly—reflecting more completely the uncertainties and assumptions about limited exposure—and providing room for states to act in response to new information on exposure or hazard if EPA is not.

Committee Member 4

EPA indicates that PV29 is presented with limited data sets. EPA indicates that under the new

TSCA regulation they are required, based on the reasonably available data, to make a risk determination of whether risks are unreasonable or not unreasonable.

The Evaluation needs to be revised to include greater detail to assist the reader in understanding EPA's interpretation of the data. For example, the data provided included a single air measurement value from the manufacturing site for human exposure to PV29. The Evaluation indicates that workers are exposed to the product in dry powder form. No description of the air sampling procedure or measurement methodology was provided and there was no indication of the particle size measured, sampling location(s) (personal or area), duration, frequency or the sampling program parameters. There is no indication whether the manufacturer has an employee health program and, if so, what it entails. Such information should be obtained and included in the Evaluation. Collectively, there is a need to not just identify uncertainty but provide detail necessary to reduce uncertainty and increase confidence in the interpretation provided in the Evaluation.

Another example of lack of detail was the lack of a description of the manufacturing process, worker activities where exposures would occur and product drying and packaging. Adding this information to the Evaluation would place exposures in the context of the work environment. While other downstream product uses are listed, details concerning exposure circumstances are not provided.

This Committee member recognized that the EPA faces time constraints under the TSCA Rule which may limit the ability to obtain new data resulting in a more robust data base. These time constraints appear to have resulted in an inability to address the identified PV29 data limitations. **If it is not possible to arrive at an "indeterminate" conclusion, the EPA could conclude that the limitations in the data are sufficient to conclude an "unreasonable risk" and, as a regulatory response, order the manufacturer to develop a limited set of new data, the development of which would not be time limited.** Key new studies could increase confidence and result in a change in the unreasonable risk determination.

Committee Member 5

Some of the statements in the Evaluation are too broad and are not supported by the evidence.

For example, consider the statement: "Low hazard was reported in all human testing via all routes of exposure." The low hazard was often from low exposure as an assumption from the physical characteristics that are not supported by the evaluation. Not all routes of exposure were included in the testing and the rationale for not needing them is not supported. Limited tox studies on animal models and the discussion does not include carcinogenicity, neurotoxicity, or endocrine activity or chronic studies.

The evidence does not support "no unreasonable risk to potentially exposed and susceptible subpopulations." A handful of studies in animal models is not sufficient for that statement. There isn't evidence for increased susceptibility in special populations, but it's because of data gaps. **Lack of evidence isn't evidence**.

The discussion the Committee had with EPA staff regarding physical chemical properties was informative, but much of this information is not found in the Evaluation, and hence, is not there to support conclusions and assumptions.

The statement about "limited environmental releases" is not supported by data.

While this Committee member would like some more information on consumer exposures, one generally agreed with EPA's approach that the occupational exposures are higher, and the conservative estimate would be protective of other populations. It is likely that consumer exposures are going to be both at lower levels and in products like paint and plastics where the chemical is less accessible. However, the MOE approach for workers is currently based on unsubstantiated information from the manufacturer.

EPA should acknowledge that PV29 is on the Work Plan and now being evaluated because originally it was assessed as "Widely used in consumer products. Estimated to have moderate releases to the environment" and given an exposure score of 3 out of 3. Now it seems that the assessments as "widely used in consumer products" and "moderate releases to the environment" are wrong, which is great if models and assumptions give way to better information, but it should be addressed.

Committee Member 6

Consider the use of a logic model for risk characterization.

Question 8: Supplemental Analysis:

Following the publication of the draft risk evaluation, EPA received comments from the Center for Disease Control and Preventions' National Institute for Occupational Safety and Health (NIOSH) on the risk characterization from inhalation exposure. As a result of these comments, two updated approaches are presented to characterize the potential occupational risks from inhalation exposure. The first approach involves utilizing analog inhalation toxicity data from poorly-soluble, non-reactive dusts with a similar particle size to C.I. Pigment Violet 29, while the second approach uses a screening-level calculation to estimate lung overload incorporating the particle size data for C.I. Pigment Violet 29 as explained in Oberdörster (1994). Use of these approaches will provide a more appropriate toxicological response to characterize the risks of inhalation of C.I. Pigment Violet 29 dust. The exposure limit for this characterization will be based on a nuisance dust standard adjusted for the deposition fraction of C.I. Pigment Violet 29 to the alveolar region, as predicted by the Multiple Path Particle Dosimetry Model (MPPD, v. 3.04). Please note that the MPPD model has not undergone a formal peer review.

8a	Please comment on whether the use of point of departure from analog data used in conjunction with the adjusted NIOSH-recommended exposure limit or the Occupational Safety and Health Administration (OSHA) standard for Particles Not Otherwise Regulated (PNOR) to develop an MOE provides utility in risk characterization concerning C.I. Pigment Violet 29. If not, please suggest

	alternative approaches or information that could be used to incorporate these values into the human health risk characterization.

Response:

The Committee recognized this method has been used in risk assessments. The point of departure (POD) of 40 mg/m^3 based on the no adverse effect concentration (NOAEC) of analog $BaSO_4$ seems appropriate. The MOE equation inputs also seem appropriate. Thus, the MOE of 101 based on $BaSO_4$ provides some utility considering the lack of direct data for PV29. But some Committee members expressed concern that $BaSO_4$ is not the most appropriate analogue. There are important physical-chemical property differences to be considered, such as the fact that $BaSO_4$ is an inorganic chemical while PV29 is an organic chemical.

Actual toxicity and exposure data for PV29 is preferred. Actual monitoring data needs to be obtained for total and respirable dust. From these data an MOE could be computed and used in a comparison to the PNOR-derived MOE for this question to be definitively answered.

The Committee noted uncertainty in whether lung overload is the critical endpoint that the Evaluation should be based upon since an appropriate inhalation toxicity study has not been performed. There is a profile for PV29 in the Danish QSAR Database. Four out of four QSAR models in the profile predicted respiratory sensitization (an allergic hypersensitivity response). This further raises the issue as to whether lung overload is the appropriate critical endpoint for human risk assessment.

The derivation of the PNOR needs to be summarized in the Evaluation. First, the Evaluation assumes that PV29 has poor water and lipid solubility. Readily available studies provide water solubility estimates for PV29 from 0.01 - 2300 mg/L. The Evaluation is not clear on why one estimate was chosen over others. But the chemical structure suggests that PV29 is essentially insoluble and falls into the category of nuisance dust/PNOR. The assumption was that PV29 will behave like an inert mineral or inorganic dust, and thus, should be categorized as a nuisance dust/PNOR implies that applying the applicable OSHA PELs of 15 mg/m^3 and 5 mg/m^3 respirable time weighted average (TWA) seems appropriate. It seems unlikely that dust levels within the plant would approach the OSHA PEL limits, but PPE could be employed to keep exposure at safe levels if indicated. If all assumptions are valid, adding the OSHA PEL-derived MOE to the analog data-derived MOE adds confidence to the conservativeness of the risk computations.

Recommendations on the use of PNOR to estimate an MOE for PV29:

1. **Given that no acceptable inhalation toxicity studies are available for PV29, a properly designed inhalation study (e.g., 28-day, aerosol, nose only, inhalable fraction with the high dose achieving toxicity which may be lung overload) would be needed to fill this data gap.**
2. **PV29 is assumed to not be bioavailable or readily absorbed by any applicable route of exposure since it may have poor water and lipid solubility. No absorption, distribution, metabolism, elimination (ADME)/toxicokinetic data were presented.**

However, mouse skin staining was observed after dosing by IP injection, gavage, and dermal application. The mechanism for this has not been ascertained. NAMs such as Organ on a Chip (lung) or skin permeability *in vitro* assay should be considered.

3. **Supplement available data by requesting personal monitoring data from the manufacturer which should include both respirable dust fraction and total dust.**

8b	Please comment on whether the screening-level estimate for the potential for lung overload with the NIOSH-recommended exposure limit or the Occupational Safety and Health Administration (OSHA) standard for Particles Not Otherwise Regulated (PNOR) and the predicted deposition fraction to the alveolar region predicted by the MPPD model (v3.04) from Orberdörster (1994), and whether this provides utility in risk characterization concerning C.I. Pigment Violet 29. • Oberdörster, G. (1994). Lung particle overload: implications for occupational exposures to particles. *Regulatory Toxicology and Pharmacology*, *21*(1), 123-135

Response:

The Committee noted the Multiple-Path Particle Dosimetry Model (MPPD https://www.ara.com/products/multiple-path-particle-dosemetry-model-mppd-v-304) provides some utility in risk characterization. The predicted deposition fraction to the alveolar region predicted by the MPPD model appears to be based upon better science than the screening-level estimate for the potential for lung overload with the NIOSH-recommended exposure limit or the Occupational Safety and Health Administration (OSHA) standard for Particles Not Otherwise Regulated (PNOR).

The Committee recognized increased interest in using computational models for estimating pulmonary deposition of particles, in part due to cost, time, and lack of standardization. In the MPPD model, pulmonary asymmetry in branching pattern and path variation are considered, allowing for determination of average deposition fractions. The parameters used by MPPD to calculate deposition include type of airway morphometry, particle properties, and exposures, with the possibility of evaluating the deposition, or the deposition and clearance, of the particles. The physical-chemical property characteristics of the particles, which are used to determine their lung deposition, are density, particle mean diameter, and geometric standard deviation.

Chronic inhalation of poorly soluble particles in all species is associated with localized pulmonary toxicity initiated by a chronic inflammatory response to particle deposition. The rat is a particularly sensitive species in developing pulmonary non-neoplastic and neoplastic lesions under the conditions of lung overload. Humans are less sensitive to lung overload. Epidemiological studies have not found an association between occupational exposure to poorly soluble, low toxicity particles and an increased risk for lung cancer. Also, differences in rodents and primates regarding interstitial particle sequestration and associated retention kinetics needs to be considered.

The delivered dose, not the exposure concentration, is required for consistency, risk assessment, and regulatory relevance of particle inhalation. If only the exposure concentration can be provided, sufficient physical-chemical property characterization of the poorly soluble particle and the experimental conditions are needed for conversion from concentration to dose.

Increased prolongation of lung clearance of poorly soluble particles occurs when the retained lung burden exceeds a certain threshold. This effect on particle clearance is due to an impairment of the alveolar macrophage clearance function. The impaired clearance correlates with the phagocytized volumetric loading of the alveolar macrophages. The impairment starts when the average composite phagocytized volume exceeds 6% of the normal alveolar macrophage volume, and complete cessation of clearance occurs when this phagocytized volume reaches 60% of the normal alveolar macrophage volume. This is the best POD for lung overload.

Alveolar macrophage clearance can be used to design rat chronic inhalation studies to predict exposure regimens and increased pool sizes of alveolar macrophages delivering a NOAEC and the level at which the physiological functions still operate. The modeling of the NOAEC and maximum tolerated dose (MTD) allow for the design of rat inhalation studies to obtain information needed for hazard identification and risk assessment. Alveolar macrophage clearance improves read-across and prevents irrelevant hazard classifications obtained from findings at irrelevant exposure levels.

The NOAEC for increased pool sizes of alveolar macrophages in rats can be used to derive the equivalent human concentration. Applying an uncertainty factor of 10 will allow for human variability to be taken into consideration.

The MPPD model helps fill a void in the extrapolation of effects from rats to humans and in the comparison of animal and human data for the same effects. Comparison of responses at equivalent exposure levels can inform toxicodynamic differences between the two species when both animal and human data are available for the same endpoint. Also, the MPPD model can be used to assess the influence that parameters such as age, exercise, and diseased state have on deposited and retained doses in humans. It can also assess the influence that the characteristics of the particles can have on these doses.

Question 9: Content for Closed Session as Described in Federal Register Notice (FRN) for this Meeting:

This is the first time the TSCA program is making non-TSCA confidential business information (CBI) available to peer reviewers to conduct a review by the SACC. The panel should comment on the process, integration, and clarity related to the use of the CBI which was provided.

Following the CBI substantiation and review process for C.I. Pigment Violet 29, the Agency made publicly available partially redacted (sanitized) copies of nine full study reports used to characterize the physical chemical characteristics, environmental fate, environmental hazard, and human health hazard of C.I. Pigment Violet 29. See Appendix for more details as to how these

studies, which were previously claimed in full as CBI, became partially redacted (sanitized).

The final confidentiality determination by the Agency on the CBI claims can be accessed at FOIAonline at:

- https://foiaonline.gov/foiaonline/action/public/submissionDetails?trackingNumber=EPA-HQ-2019-001853&type=request

  Please comment on whether or not the information contained in the CBI materials provided to the panel is accurately reflected in the sanitized data that are made publicly available and robust summaries used in the risk evaluation for C.I. Pigment Violet 29.

Response:

There was initially a lot of CBI material for the peer review of the PV29 risk evaluation. A large fraction of that material became public during the time the Committee was preparing for its review. Because of these changes, the Committee found it difficult to directly address the issue of whether the sanitized (public) data/summaries accurately reflected the original study data/summaries. In the future, the Committee would like to be provided with a summary of the nature of the redacted information and, in particular, what redacted information is also relevant to the risk evaluation at the time the CBI material is communicated to Committee members.

The need to maintain CBI means that the Committee would have to consider creating two report summaries. One summary of meeting findings would make little or no reference to CBI materials, and the second confidential-to-EPA document would include needed details extracted from CBI materials. This would require a higher level of management of meeting discussions and document preparation than has been the norm for EPA-sponsored scientific peer review meetings in the past. Protocols for this have not been established at this point. A hypothetical situation was used to illustrate this need. It is possible that in the future, CBI data could turn out to be the crucial information needed to confidently estimate the dose response function needed to establish a benchmark dose (BMD) and benchmark dose level (BMDL). Without these being public, the Committee would not be able to publicly publish their analysis, and in the public report the BMD and BMDL estimates would appear without justification (or with analysis text redacted). The Committee found this situation uncomfortable and very un-scientific. This said, the Committee understands that in this situation, these data would be deemed as critically important and EPA would negotiate with the data owner for public release.

The PV29 reproductive/developmental screening study, which contains a significant amount of CBI material, illustrates one issue discussed by the Committee, that of the situation where neither EPA nor the study authors provide enough description or summary tables to sufficiently explain some key results identified by the study authors. Some Committee members felt it was important to look through the CBI individual animal records for anomalies and other results (e.g., detailed comparisons between control animals and treated animals that did not make it into summary tables) to fully understand and gain confidence in the results as presented the public summaries.

To the Committee members, who are accustomed to seeing all these details, the justification for redacting this individual animal data as CBI was not clear. The Committee did note that the summary statistics provided in the unredacted version of the reproduction/development study were consistent with the animal data in the redacted version of the study.

The Committee questioned whether companies are required to justify redactions. They learned that justification of redactions is typically provided in the substantiation process and submitted with the CBI claim. For PV29, the studies were not submitted under TSCA, so they were not subject to release under TSCA as health and safety information. The Committee suggested EPA develop a protocol to include justifications when providing the CBI materials.

The Committee acknowledged that in most cases, portions of the study would be redacted to preserve the ability of the product owners, investors, inventors, etc. to preserve the value of their copyrighted or patented intellectual property while not impeding the registrant's ability to fulfill data requirements needed for product review by regulatory agencies.

In many cases, the Committee found that the redactions (e.g., hiding identifying details about the laboratories, protocols, etc) did not impact their ability to scientifically interpret, use, and have confidence in study findings. The Committee suggested providing, for each study involving CBI, a summary of the differences between the full study report and the redacted study report, with a focus on what information/data is critical to the assessment and how redactions could affect this information. These summaries and comparisons help the Committee put redactions into the context the Committee needs for its peer evaluation.

The Committee noted that there were situations where robust and informative summaries were available in the public portions of study reports that did not appear in the risk assessment report. This issue was also commented upon in a written comment to the Committee prior to its review. The Committee wondered why the risk assessment report used less informative summaries.

The Committee expressed concerns that redactions may create the impression that important information is being hidden from the public, with the result that the Committee may have to address CBI-related questions from the public during the public comment session in their public meeting, without the ability to provide suitable answers. Having the comparison and context document would help the Committee address this issue.

The Committee suggested that EPA come up with a means to allow certain parties to examine full (unredacted) studies. Federal agencies, such as the Census Bureau and the Centers for Disease Control and Prevention (CDC) have and use such guidelines and protocols (e.g., allowing access in secure sites only, and only after successful vetting) to allow limited access to confidential and sensitive information. The Committee learned that EPA has allowed very few and limited access to CBI material through the use of non-disclosure agreements.

One Committee member noticed that for a study describing the physical-chemical characteristics of PV29, the CBI redacted report seemed to have more information than the unredacted study report. One answer given for why this might happen involves the potential to “black out" shaded (but not redacted) text in the process of copying, something that needs to be avoided in the future.

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APPENDIX A: Transmittal Memo Dated November 9, 2018

The Agency published in the *Federal Register* a notice of availability, for the Draft Risk Evaluation for Colour Index (C.I.) Pigment Violet (PV29), on November 15, 2018 (Volume 88, No. 221, pages 57473 to 57475).

The files that appeared in the docket (ID: EPA-HQ-OPPT-2018-0604) are described in the following transmittal memo:

Transmission of Background Materials and Charge to the Committee for the January 29 to February 1, 2019 Session of the Toxic Substances Control Act's Science Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation For Pigment Violet 29 (PV29)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

DATE: November 9, 2018

SUBJECT: Transmission of Background Materials and Charge to the Panel for the January 29 to February 1, 2019 Session of the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation For Pigment Violet 29 (PV-29)

TO: Steven Knott
Executive Secretary
FIFRA Scientific Advisory Panel Staff
Office of Science Coordination and Policy

FROM: Jeffrey L. Dawson, Acting Director
Risk Assessment Division
Office of Pollution Prevention and Toxics

Transmitted with this memo are copies of the EPA Risk Evaluation for PV-29, supplemental material related to data evaluation which can be made publicly available, and the charge to the Panel for the January 29 to February 1, 2019 session of the TSCA SACC reviewing the Draft Risk Evaluation for Pigment Violet 29 (PV-29). These specific documents are attached and can be identified as follows:

- Draft Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f'] diisoquinoline- 1,3,8,10(2H,9H)-tetrone) CASRN: 81-33-4

- C.I. Pigment Violet 29 (81-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation

- EPA Scientific Advisory Committee on Chemicals, Charge to the Panel - PV29 Review, January 29 – February 1, 2019

There are supporting materials (24 individual scientific studies) that contain information claimed as Confidential Business Information (CBI). Twenty of these studies have been submitted to and summarized by the European Chemicals Agency (ECHA) as part of their information on

registered substances and these ECHA summaries are publicly available.[2] These summaries are referred to as "Robust Summaries" in supplied materials and were used to develop the risk evaluation. They were independently verified by EPA using the CBI materials themselves to ensure the publicly available ECHA summaries reflect the findings in the individual scientific studies to ensure the credibility of EPA Risk Evaluation finding. It should be noted there are no ECHA summaries for the remaining 4 studies so they are not specifically referenced in this transmittal memorandum.

Two additional issues should be noted: (1) no materials contain information protected by copyright and (2) all CBI materials (24 scientific studies) will be separately provided to the SACC who will be cleared for TSCA CBI access so that the verification of the ECHA robust summaries and EPA's use of the data for the remaining 4 studies can be considered by the panel.[3] The 20 non-CBI supporting documents are denoted in the table below along with a link to access them. A link has also been provided to EPA's final rule which details the processes under which the PV29 Risk Evaluation was completed.

Supporting Documents For PV29 Risk Evaluation: Non-CBI Robust Summaries prepared by European Chemical Agency (ECHA) For 20 of 24 Applicable Scientific Studies			
Robust Summary Title	Year	OECD Guideline if applicable	Link of Robust Summary in ECHA
1. Eye Irritation	1976	OECD 405	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/3/?documentUUID=0802ac40-50fe-4caf-8b3f-b449b54abb00
2. Eye Irritation	1978	OECD 405	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/3/?documentUUID=1f0835c7-a771-45ab-b085-26bca73f12fe
3. Acute toxicity: inhalation	1976	Performed according to internal test protocol	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/3/?documentUUID=b866744e-5d3a-49d9-8154-64b027eb3c74
4. Acute toxicity: inhalation	1978	Performed according to internal test protocol	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/3/?documentUUID=34aa4522-b714-47b0-9bee-af8052fff73d
5. Acute toxicity: other routes	1976	Performed according to internal test protocol	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/5/?documentUUID=4bbb16ee-268e-40a9-bbbc-e83db0bfba65
6. Acute toxicity: other routes	1978	Performed according to internal test protocol	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/5/?documentUUID=d39b3d4e-e1e5-4b74-ae32-80485a7703c8

2 https://echa.europa.eu/information-on-chemicals/registered-substances provides general information. Links to individual study summaries are provided in the attached table.

3 A separate inventory of the CBI studies will be developed and included when that information is provided to the SACC.

Supporting Documents For PV29 Risk Evaluation: Non-CBI Robust Summaries prepared by European Chemical Agency (ECHA) For 20 of 24 Applicable Scientific Studies			
Robust Summary Title	Year	OECD Guideline if applicable	Link of Robust Summary in ECHA
7. Acute toxicity: oral	1975	OECD 401	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/2/?documentUUID=587b216d-aaa5-4f5d-8421-73c6cd543466
8. Acute toxicity: oral	1978	OECD 401	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/2/?documentUUID=c4047fab-a7d0-40cb-8148-bbb0200ab43d
9. Skin irritation / corrosion	1976	OECD 404	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/2/?documentUUID=36dd6532-3633-4adf-a27b-6c197e768912
10. Skin irritation / corrosion	1978	OECD 404	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/2/?documentUUID=22d8c3ca-d52c-4608-abfd-b2fe8db31d34
11. Genetic toxicity: *in vitro*	1983	OECD 471	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/7/2/?documentUUID=6099e1ed-0a68-42b7-b071-bb34bbf310a7
12. Genetic toxicity: *in vitro*	2012	OECD 476	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/7/2/?documentUUID=3bc9971c-f0b2-4c71-b174-b50c7437658c
13. Skin sensitisation	1999	OECD 429	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/5/2/?documentUUID=38f72189-03fe-402e-9a67-0bf9048bb68b
14. Toxicity to reproduction	2013	OECD 421	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/9/2/?documentUUID=7e96ccce-834d-4219-9bab-f9bd8a8b7e97
15. Short-term toxicity to fish	1988	OECD 203	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/2
16. Toxicity to aquatic algae and cyanobacteria	2012	OECD 201	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/6
17. Short-term toxicity to aquatic invertebrates	2012	OECD-202	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/4
18. Biodegradation in water: screening tests	1999	OECD 301 F	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/5/3/2

Supporting Documents For PV29 Risk Evaluation: Non-CBI Robust Summaries prepared by European Chemical Agency (ECHA) For 20 of 24 Applicable Scientific Studies			
Robust Summary Title	Year	OECD Guideline if applicable	Link of Robust Summary in ECHA
19. Solubility in organic solvents / fat solubility	2001	N/A	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/4/10
20. Melting point/ freezing point	2011	N/A	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/4/3
Link to EPA's Final Rule For Completing Risk Evaluations: Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act - 82 FR 33726			

APPENDIX B: Transmittal Memo Dated March 21, 2019

Transmission of Background Materials Previously Claimed as Confidential Business Information (CBI) for the Toxic Substances Control Act's Science Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

DATE: March 21, 2019

SUBJECT: Transmission of Background Materials Previously Claimed as Confidential Business Information (CBI) for the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29)

TO: Steven Knott
Executive Secretary
FIFRA Scientific Advisory Panel Staff
Office of Science Coordination and Policy

FROM: Mary C. Fehrenbacher
Acting Director
Risk Assessment Division
Office of Pollution Prevention and Toxics

Transmitted with this memorandum are copies of the 24 study reports which are being made available in the public docket[1] prior to the TSCA SACC expert panel peer review of the *Draft Risk Evaluation for C. I. Pigment Violet 29*. These study reports have been reviewed by the Agency to develop the *Draft Risk Evaluation for C.I. Pigment Violet 29* and were originally claimed in full as confidential business information (CBI) by the data owners. For this reason, these study reports were not originally included in the public docket.

The list of the 24 released study reports is attached and explained in Attachment A: C.I. Pigment Violet 29: List of publicly available study reports. Fifteen study reports are completely released without redactions (see study numbers 1 to 14, and 18, Attachment A), while nine study reports remain partially CBI with certain information redacted (e.g., personal information relating to laboratory personnel, certain company-related information and, in one instance, individual test animal data tables, see study numbers 15-17, 19-24, Attachment A).

Consistent with Agency regulations concerning the review of confidential business information claims located at 40 CFR Part 2, Subpart B, the Agency, in December 2018, requested substantiation of the CBI claims from the affected businesses.

[1] https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604

Subsequently these entities provided responses to the substantiation request. In fifteen instances, the CBI claims associated with the study reports were removed in full by the data owners. In nine instances, the CBI claims were reduced in scope. The Agency has made a final determination on the CBI claims and this can be accessed at FOIAonline at https://foiaonline.gov/foiaonline/action/public/home and then searching the FOIA request number, EPA-HQ-2019-001853. In all instances, non-CBI versions of the study reports were made available to the Agency and can now be accessed in the public docket.[1] In eight of the nine full study reports containing information determined to be CBI, robust summaries are available in the public docket. For the one study that is not being released in its entirety (study #21, HERO ID 4731542), for which a robust summary is not available, there is a redacted non-CBI version of the study in the public docket. Three additional studies which had no corresponding robust summaries are now publicly available as indicated in Attachment A.

As background information, twenty of these studies were summarized in the European Chemicals Agency (ECHA) registration dossier for C.I. Pigment Violet 29 and were made available in the public docket.[2] These summaries are referred to as "Robust Summaries" and were used to develop the *Problem Formulation of the Risk Evaluation for C.I. Pigment Violet 29* (June 2018).[3] EPA compared the information contained in the robust summaries to the information contained in the study reports for accuracy.

Two additional matters should be noted: (1) while the information owners have asserted in some instances a reservation of rights for the use of the materials, no materials contain information claimed to be protected by copyright, and (2) all studies containing CBI (i.e., 9 partially-redacted study reports) have previously been provided without redaction to the SACC Peer Review Panel whose members are cleared for CBI access so that the verification of the ECHA robust summaries and EPA's use of the data can be considered.

A link is being provided to EPA's final risk evaluation rule which details the processes under which the PV29 draft risk evaluation was completed.[4]

[2] https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0002
[3] https://www.epa.gov/sites/production/files/2018-06/documents/pv29_problem_formulation_5-31-18.pdf
[4] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act - 82 FR 33726

Attachment A

C.I. Pigment Violet 29: List of Non-Confidential Business Information (CBI) Study Reports

Attachment A

C.I. Pigment Violet 29: List of Non-Confidential Business Information (CBI) Study Reports4

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
CBI claim fully withdrawn (Full study report)	21. Summary of toxicological investigations with CAS 81-33-4, 1.5 Eye Irritation Study. HERO ID: 4731519	BASF	1975	Sun Chemical (The Netherlands)	BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland.	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/3/?documentUUID=355c6cab-5b7e-417f-b083-4c3a890c339e					
CBI claim fully withdrawn (Full study report)	22. Summary of toxicological investigations with CAS 81-33-4, 2.5 Eye Irritation Study. HERO ID: 4731520	BASF	1978	Sun Chemical (The Netherlands)	BASF Report 77/360. Product Safety Basel, BASF Schweiz AG, Switzerland.	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/3/?documentUUID=123b8854-6e8f-4482-9e03-183d6380fcf8					

4 The 24 study reports represent the following disciplines: #1-17 Human Health; #18-20 Environmental Hazard; #21-22 Environmental Fate, and #23-24 Physical Chemical properties. Study reports #1-13 and #18 were translated from German.

5 ECHA Robust summaries were published to the docket at the following link: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0002

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
CBI claim fully withdrawn (Full study report)	23. Perylimid6 Testing the acute dermal irritant effects/caustic effects on rabbits. HERO ID: 4731534	Rupprich, N, Weigand, W	1984	Clariant (Germany)	Hoechst Pharma Research Toxicology, Germany. Report No. 84.0228 (OECD- 404 skin irritation;	No7
CBI claim fully withdrawn (Full study report)	24. Perylimid Testing the acute irritant effects/caustic effects on the rabbit eye. HERO ID: 4731524	Rupprich, N, Weigand, W	1984	Clariant (Germany)	Hoechst Pharma Research Toxicology, Germany. Report No. 84.0229 OECD-405; eye irritation)	No
CBI claim fully withdrawn (Full study report)	25. Summary of toxicological investigations with CAS 81-33-4, 1.2 Acute inhalation toxicity with rats. HERO ID 4731525	BASF	1975	Sun Chemical (The Netherlands)	BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland.	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/3/?documentUUID=2baa5685-0c63-41a2-88e0-6539146fda83					

6 Perylimid-German name for pigment violet

7 Summarized below are the four additional full study reports that were not described in the ECHA database.

- OECD Guideline 401: Acute Oral Toxicity with Rats
- OECD Guideline 404: Acute Dermal Irritation/Corrosion
- OECD Guideline 405: Acute Eye Irritation/Corrosion
- OECD Guideline 209: Determination of the inhibition of oxygen consumption by activated sludge

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
CBI claim fully withdrawn (Full study report)	26. Summary of toxicological investigations with CAS 81-33-4, 2.2 Acute inhalation toxicity with rats. HERO ID: 4731526	BASF	1978	Sun Chemical (The Netherlands)	BASF Report 77/360	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/3/?documentUUID=2064a5d4-7557-4aed-b389-59bae4eb97d7					
CBI claim fully withdrawn (Full study report)	27. Summary of toxicological investigations with CAS 81-33-4, 1.3 Acute intraperitoneal toxicity with mice. HERO ID: 4731527	BASF	1975	Sun Chemical (The Netherlands)	BASF Report XXV/454	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/5/?documentUUID=38e65d5f-6d87-4037-9153-a2a123481983					
CBI claim fully withdrawn (Full study report)	28. Summary of toxicological investigations with CAS 81-33-4, 2.3 Acute intraperitoneal toxicity with mice. HERO ID: 4731528	BASF	1978	Sun Chemical (The Netherlands)	BASF Report 77/360	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/5/?documentUUID=7eed1bdb-9d2c-44ab-9d49-ccb48bfe7ec2					
CBI claim fully withdrawn (Full study	29. Summary of toxicological investigations with CAS 81-33-4, 1.1 Acute oral toxicity with rats. HERO ID: 4731529	BASF	1975	Sun Chemical (The Netherlands	BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland.	Yes

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
report)				)		
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/2/?documentUUID=e73c9b1a-2e30-4c7b-856f-be9c27b62e3a					
CBI claim fully withdrawn (Full study report)	30. Summary of toxicological investigations with CAS 81-33-4, 2.1 Study report for CAS 81-33-4, Acute oral toxicity with rats. HERO ID: 4731530	BASF	1978	Sun Chemical (The Netherlands)	BASF Report 77/360	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/3/2/?documentUUID=2627a9d8-85f8-408a-8a92-7db3e9edbc32					
CBI claim fully withdrawn (Full study report)	31. Testing the acute oral toxicity in the male and female Wistar rat. HERO ID: 4731531	Rupprich, N, Weigand, W	1984	Clariant (Germany)	Report No. 84.0225 (OECD-401)	No
CBI claim fully withdrawn (Full study report)	32. Summary of toxicological investigations with CAS 81-33-4, 1.4 Skin irritation study. HERO ID: 4731532	BASF	1975	Sun Chemical (The Netherlands)	BASF Report XXV/454	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/2/?documentUUID=991935ed-8813-45d4-a578-e985e45529c7					

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
CBI claim fully withdrawn (Full study report)	33. Summary of toxicological investigations with CAS 81-33-4, 2.4 Skin irritation study. HERO ID: 4731533	BASF	1978	Sun Chemical (The Netherlands)	BASF Report 77/360	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/4/2/?documentUUID=787aa890-cd18-4595-832b-7cc30e58641b					
CBI claim fully withdrawn (Full study report)	34. Perylimid Study of the Mutagenic Potential in Strains of *Salmonella Typhimurium* (Ames Test) and *Escherichia coli.* HERO ID: 4731535	Jung, R., Weigand, W	1983	FDA (Food Additive Petition) (Clariant, Germany filing)	Hoechst Aktiengesellschaft, Germany. Report No. 83.0695	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/7/2/?documentUUID=029bc6b6-17f3-49df-8a18-d363003217df					
CBI claim partially withdrawn (Redacted copy)	35. Gene Mutation Assay in Chinese Hamster V79 Cells *In Vitro* (V79/HPRT) With Paliogen Violet 5011. HERO ID: 4731536	Wollny, H	2012	Sun Chemical (The Netherlands)	Harlan Cytotest Cell Research GmbH, Germany. Report No. 1443105.	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/7/2/?documentUUID=ce0e96f3-e018-4a7e-bbfc-07cfdbbc2b9e					
CBI claim partially withdrawn	36. Perylimid F: Local Lymph Node Assay. HERO ID: 4731537	Johnson, I.R.	1999	Sun Chemical (The	Central Toxicology Laboratory, UK. Project No. CTL/P/6194	Yes

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
(Redacted copy)				Netherlands)	(OECD-406)	
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/5/2/?documentUUID=a548f01b-ceec-4805-8bac-9d5b1126db46					
CBI claim partially withdrawn (Redacted copy)	37. Reproduction/developmental Toxicity Screening Test in Wistar Rats Oral Administration (Gavage). HERO ID: 4731538	Stark, D., Treumann, S., Van Raven-zwaay, B	2013	Sun Chemical (The Netherlands)	BASF SE, Germany. Project No. 80R0223/11C162 (OECD-421)	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/7/9/2/?documentUUID=9a37a3a9-d311-48a2-a34b-6359b6bef6e0					
CBI claim fully withdrawn Full study report	38. Perylimid Testing the acute toxicity in the fish model Zebra danio (*Brachydanio rerio*) over the course of 96 hours. HERO ID: 4731539	Market, D.I. Jung, R.	1988	Clariant (Germany)	Study conducted by Pharma Research Toxicology and Pathology, Hoechst Corporation (Study Completion Date: July 1st, 1988), Frankfurt, Germany. (OECD-203)	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/2/?documentUUID=975f8535-c960-4857-b6c3-596d913e5461					
CBI claim partially withdrawn	39. Paliogen Violet 5011, *Lemna gibba* L., CPCC 310 Growth Inhibition Test. HERO ID: 4731540	BASF	2012	Sun Chemical (The	Study conducted by Institute of Industrial Organic Chemistry,	Yes

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries5
(Redacted copy)				Netherlands)	Branch Pszcyna Department of Ecotoxicology. Pszczyna, Poland (OECD-221)	
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/7/?documentUUID=396286a2-97c2-4f76-97e0-6dfd58eb90bc					
CBI claim partially withdrawn (Redacted copy)	40. Paliogen Violet 5011, *Daphnia magna*, Acute immobilization test. HERO ID: 4731541	BASF	2012	Sun Chemical (The Netherlands)	Study conducted by Institute of Industrial Organic Chemistry, Branch Pszcyna Department of Ecotoxicology. (Study Completion Date: May, 2012), Pszczyna, Poland. (OECD- 202)	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/6/2/4/?documentUUID=983ec9ec-9efc-4350-9a86-b6c1f572f5ba					
CBI claim partially withdrawn (Redacted copy)	41. Determination of the Inhibition of Oxygen Consumption by Activated Sludge by Perylimid F in the Activated Sludge Respiration Inhibition Test according to GLP, EN 45001 and ICO 9002. HERO ID: 4731542	BASF	1999	Sun Chemical (The Netherlands)	Study conducted by BASF Aktiengesellschaft Ecology and Environmental Analytics Laboratory of Ecology D-67056 Ludwigshafen	No

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries[5]
					(OECD-209)	
CBI claim partially withdrawn (Redacted copy)	42. Determination of the Biodegradability of Perylimid F in the Manometric Respirometry Test according to GLP, EN 45001 and ISO 9002. HERO ID: 4731543	BASF	1999	Sun Chemical (The Netherlands)	Study conducted by BASF Aktiengesellschaft Ecology and Environmental Analytics Laboratory of Ecology D-67056 Ludwigshafen (OECD 301-F)	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/5/3/2/?documentUUID=c6149dae-22a5-4dda-85f4-34da02afc03f					
CBI claim partially withdrawn (Redacted copy)	43. Physical-Chemical properties of "Paliogen Violet 5011" (LogKOW)[8]. HERO ID: 4731544	BASF	2013	Sun Chemical (The Netherlands)	BASF Study No. 11L00105	Yes

8 Study reports 23 and 24 (see two separate ECHA links) were submitted under one report (BASF Study No. 11L00105) describing the physical chemical properties of C.I. Pigment Violet 29.

Availability of public version	Study Number/Title (and Link to ECHA summary if applicable)	Author(s)	Year	Original Submitter to EPA (e.g., Sun Chemical or Clariant)	Study ID (OECD Guideline if applicable)	Availability of ECHA Robust Summaries[5]
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/4/8/?documentUUID=53829854-0728-48dd-9184-2045facf18f2					
CBI claim partially withdrawn (Redacted copy)	44. Physical-Chemical properties of "Paliogen Violet 5011" (Melting point)[5]. HERO ID: 4731544	BASF	2013	Sun Chemical (The Netherlands)	BASF Study No. 11L00105	Yes
ECHA Link	https://echa.europa.eu/registration-dossier/-/registered-dossier/10330/4/3/?documentUUID=0ed13da2-4ef1-4d4e-b923-4d6b88bc38a2					

APPENDIX C: Transmittal Memo Dated April 4, 2019.

Transmission of Background Materials on Systematic Review for the Peer Review Meeting of the Toxic Substances Control Act's Science Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

DATE: April 4, 2019

SUBJECT: Transmission of Background Materials on Systematic Review for the Peer Review Meeting of the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29)

TO: Steven Knott
Executive Secretary
FIFRA Scientific Advisory Panel Staff
Office of Science Coordination and Policy

FROM: Cathy Fehrenbacher
Acting Director
Risk Assessment Division
Office of Pollution Prevention and Toxics

Transmitted with this memorandum is an updated copy of the *C.I. Pigment Violet 29 (81-33-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation* (hereafter referred to as the Updated SR Supplemental File) which is being made available in the public docket (https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604) for the public and for the peer review meeting of the TSCA SACC reviewing the *Draft Risk Evaluation for C.I. Pigment Violet 29* (hereafter referred to as the Draft PV29 Risk Evaluation). The updated SR Supplemental File contains the data evaluation scoring sheets for the twenty-four full study reports that the Agency used to inform the human health hazard, environmental hazard, environmental fate and physical-chemical properties of PV29. These full study reports were used to develop the Draft PV29 Risk Evaluation. The study reports were originally claimed as confidential business information (CBI). Thus, the EPA reviewer's comments were not included in the data evaluation scoring sheets in the original SR Supplemental File.

In December 2018, EPA received public comments challenging the confidential treatment of the 24 study reports and the overall quality determinations of two acute inhalation toxicity studies (HERO ID 4731525 and 4731526).[9] EPA initiated review of the CBI claims for the study reports

[1] Bibliographic citations for the inhalation toxicity studies:
- BASF. 1975. Acute inhalation toxicity with rats. BASF Report XXV/454. Product Safety Basel, BASF Schweiz

consistent with Agency regulations located at 40 CFR Part 2, Subpart B in response to a Freedom of Information Act (FOIA) request for the studies. During the CBI substantiation and review process, the data owners removed their CBI claims in full for fifteen studies and reduced the scope of their CBI claims for nine studies. The Agency has made a final determination on the CBI claims and this can be accessed at FOIAonline at https://foiaonline.gov/foiaonline/action/public/home and then searching the FOIA request number, EPA-HQ-2019-001853. In the final determination, the Agency upheld the confidentiality claims for the nine studies. EPA recently made available to the public complete copies of the fifteen full study reports and partially-redacted (CBI removed) copies of the nine study reports. Details of this process are provided in the memorandum, *Transmission of Background Materials Previously Claimed as Confidential Business Information (CBI) for the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation for C.I. Pigment Violet 29 (PV29)*. The public will also have access to the Agency reviewer's comments that support the confidence determinations in the data evaluation scoring sheets.

In addition, EPA re-evaluated the study reports and updated the data evaluation scoring sheets based on public comments. The public input was valuable in that it led to review of our systematic review process and revealed both process and technical inconsistencies which led EPA to implement procedures for further optimization. For instance, EPA has made improvements in our quality assurance procedures and training of reviewers. EPA has also corrected technical errors in systematic review data evaluation scoring sheets of some specific studies where toxicological expertise was needed to evaluate specific criteria. The attached Updated SR Supplemental File provides a more transparent approach than previously provided by including the metric scores, weighting, reviewer's comments and the study's overall score.

Inclusion of EPA Reviewer's Comments

As discussed above, EPA initially released the SR Supplemental File without the EPA reviewer's comments due to concerns that the comments might contain information claimed CBI. The Updated SR Supplemental File now makes publicly available the EPA reviewer's comments related to the data quality evaluation of the physical chemical characteristics, environmental fate, environmental hazard and human health studies.

Data Quality Re-evaluation of the Study Reports

EPA received public comments regarding the data quality evaluation of the acute inhalation toxicity studies (HERO ID 4731525 and 4731526) included in the SR Supplemental File. The public comments identified major methodological deficiencies in the studies based on information published in the European Chemicals Agency (ECHA) database. Under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, the chemical industry has the responsibility of assessing the hazards and managing the risks posed

AG, Switzerland. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID 4731525

- BASF. 1978. Study report for CAS 81-33-4, Acute inhalation toxicity with rats. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731526

by substances they manufacture, import and use in Europe. This includes evaluating the reliability of the information using the Klimish scoring system[10] and posting the results of the evaluation in the ECHA database.

For the two acute inhalation toxicity studies, the ECHA database indicated that they were not reliable (Klimisch score=3) because the studies used an unsuitable test system. EPA's initial data quality evaluation determined that the studies were of medium confidence, but deficiencies in methods were also noted in the reviewer's comments following the method described in the *Application of Systematic Review in TSCA Risk Evaluations* document (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations). However, these technical concerns in the data evaluation scoring sheets, not previously made available to the public, were erroneously omitted from EPA's determination on the confidence score of the studies.

Following a closer inspection of the studies and the data evaluation scoring sheets, EPA determined that the two acute inhalation studies (HERO ID 4731525 and 4731526) were *Unacceptable* primarily due to deficiencies in the exposure inhalation methods. Specifically, the studies were not designed for non-volatile substances, such as aerosols of respirable particles as would be expected for PV29. As discussed in the Draft PV29 Risk Evaluation, EPA determined that the LogKOW determination described in the physical chemical properties study report (HERO ID: 4731544) was *Unacceptable* as a result of methodology which did not consider the poor solubility in octanol and in water of PV29, and this conclusion remains unchanged. However, the physical chemical properties study report (HERO ID: 4731544) describing the melting point was considered a separate study report by EPA where a quantification of the melting point was reviewed separately and found to be of *High* confidence. As a result, a total of three studies reviewed for PV29 are determined to be unacceptable- two acute inhalation studies (HERO ID 4731525 and 4731526) and the LogKOW study (HERO ID: 4731544).

In an effort to further optimize the SR approach, EPA reevaluated the data evaluation scoring sheets of all twenty-four full study reports. As a result, EPA also downgraded the confidence of

[10]Definitions of Klimisch scores:
1=reliable without restrictions: "studies or data. generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to Good Laboratory Practice or GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method."
2=reliable with restrictions: "studies or data. (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."
3=not reliable: "studies or data. in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., non-physiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."
4=not assignable: "studies or data...which do not give sufficient experimental details, and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."

two acute oral toxicity studies[11] and two eye irritation studies[12] from *High* to *Medium* confidence. Similarly, two intraperitoneal[13] studies were downgraded from *High* to *Low* confidence. All of these changes are reflected in the Updated SR Supplemental File. In the Draft PV29 Risk Evaluation, EPA's risk determination did not rely on the two acute inhalation toxicity studies or LogKOW study that turned out to be unacceptable upon subsequent reevaluation. EPA plans to update the risk evaluation after receiving peer review input to reflect the outcome of the data quality re-evaluation as well as any other changes resulting from the peer review process and additional public comment.

In summary, EPA provides this Updated SR Supplemental File in the interest of promoting the transparency of the risk evaluation process. The public will have an additional 30-day public comment period to review and provide input to the Agency on these documents. Furthermore, the Agency values the input from stakeholders on the systematic review process and is committed to making improvements that support transparent and scientifically robust assessments to inform risk-based decision making.

[11] Bibliographic citations for the acute oral toxicity studies:

- BASF. 1975. Acute oral toxicity with rats. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland. Report Date: January 31, 2018. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731529
- BASF. 1978. Study report for CAS 81-33-4, Acute oral toxicity with rats. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731530

[12] Bibliographic citations for the eye irritation studies:

- BASF. 1975. Eye Irritation Study. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland. Report Date: January 31, 2018. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731519
- BASF. 1978. Eye Irritation Study. BASF Report 77/360. Product Safety Basel, BASF Schweiz AG, Switzerland. Report Date: January 31, 2018. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731520

[13] Bibliographic citations for the intraperitoneal toxicity studies:

- BASF. 1975. Summary of toxicological investigations with CAS 81-33-4, Acute intraperitoneal toxicity with mice. BASF Report XXV/454. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731527
- BASF. 1978. Study report for CAS 81-33-4, Acute intraperitoneal toxicity with mice. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731528.

APPENDIX D: Transmittal Memo Dated June 6, 2019

Transmission of Background Material and Updated Charge to the Panel for the June 18 to June 21, 2019 Session of the Toxic Substances Control Act's Science Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation For Pigment Violet 29 (PV-29).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

DATE: June 6, 2019

SUBJECT: Transmission of Background Material and Updated Charge to the Panel for the June 18 to June 21, 2019 Session of the Toxic Substances Control Act's Scientific Advisory Committee on Chemicals (TSCA SACC) Reviewing the Draft Risk Evaluation For Pigment Violet 29 (PV-29)

TO: Steven Knott
Executive Secretary
FIFRA Scientific Advisory Panel Staff
Office of Science Coordination and Policy

FROM: Mary C. Fehrenbacher
Acting Director
Risk Assessment Division
Office of Pollution Prevention and Toxics

Transmitted with this memo are copies of the *Draft: OPPT Updated Risk Characterization for Occupational Inhalation of PV29 Based on Updated Approach* based on comments received from the Center for Disease Control and Preventions' National Institute for Occupational Safety and Health (NIOSH) on the risk characterization from inhalation exposure and the *Updated Charge to the Panel* for the June 18 to June 21, 2019 session of the TSCA SACC reviewing the Draft Risk Evaluation for Pigment Violet 29 (PV-29). Copies of the *Draft: OPPT Updated Risk Characterization for Occupational Inhalation of PV29 Based on Updated Approach* and the *Updated Charge to the Panel* can be made publicly available (https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604). These specific documents are attached and can be identified as follows:

- *Draft: OPPT Updated Risk Characterization for Occupational Inhalation of PV29 Based on Updated Approach*

• *EPA Scientific Advisory Committee on Chemicals, Updated Charge to the Panel - PV29 Review, June 18-21, 2019*

Following the publication of the draft risk evaluation (RE), EPA received comments relating to the screening-level characterization of inhalation risks from occupational exposure to PV29. As a result of these comments, two updated approaches are presented to characterize the potential occupational risks from inhalation exposure. The first approach involves utilizing analog inhalation toxicity data from poorly-soluble, non-reactive dusts with a similar particle size to C.I. Pigment Violet 29, while the second approach involves a screening-level estimation of lung overload using particle size data for C.I. Pigment Violet 29. Use of these approaches provided a more appropriate toxicological response to characterize the risks of inhalation of C.I. Pigment Violet 29 dust at the portal of entry. Both approaches were explained in the enclosed document, "*Draft: OPPT Updated Risk Characterization for Occupational Inhalation of PV29 Based on Updated Approach"* with this transmittal memo.

Enclosed with this transmittal memo is also the *Updated Charge to the Panel*. The previously submitted Charges to the SACC Panel (see item 23 in the following link: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0002) were either revised or additional charge questions were added only in the Environmental Fate, Exposure and Releases, and the Human Health segments. In addition, new charge questions were added under "Supplemental Analysis" to address comments from NIOSH and EPA's responses concerning two updated approaches.

It should also be noted that no materials contain Confidential Business Information or information protected by copyright.

In summary, EPA provides these copies of the *Draft: OPPT Updated Risk Characterization for Occupational Inhalation of PV29 Based on Updated Approach* and the *Updated Charge to the Panel* in the interest of promoting the transparency of the risk evaluation process. The public will have an additional 30-day public comment period to review and provide input to the Agency on these documents. Furthermore, the Agency values the input from stakeholders and is committed to making improvements that support transparent and scientifically robust assessments to inform risk-based decision making.