Personal Care Products Council
Committed to Safety, Quality & Innovation

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California Office of Environmental Health Hazard Assessment

Subject: Comments to Notice of Proposed Rulemaking Title 27 California Code of Regulations, Section 25705 No Significant Risk Level for Titanium Dioxide

Dear Ms. Barajas-Ochoa:

I. Introduction

The Personal Care Products Council ("PCPC") respectfully submits this comment in response to the Office of Environmental Health Hazard Assessments proposed safe harbor No Significant Risk Level ("NSRL") for titanium dioxide (airborne, unbound particles of a respirable size) ("Listed TiO2"). PCPC is the leading national trade association representing cosmetics and personal care products companies and serving as the voice on scientific, regulatory, legislative and international issues for the $535.7 billion global industry. PCPC's 600 member companies represent more than 90% of the U.S. beauty industry and are some of the most beloved brands in beauty and personal care today. They manufacture, distribute, and supply the vast majority of personal care products marketed in the U.S. and are global leaders committed to product safety, quality and innovation.

PCPC appreciates the Office of Environmental Health Hazard Assessment's ("OEHHA") attention to this important matter that substantially impacts the cosmetics industry and looks forward to working collaboratively with OEHHA on this proposal.

II. Background

As a threshold matter, Listed TiO2 is not a confirmed human carcinogen and accordingly, OEHHA should promulgate a regulation indicating that there is no significant risk from Listed TiO2 at any level of exposure relevant to realistic human exposure scenarios. On June 12, 2024, Judge Nunley of the Eastern District of California granted PCPC's motion for preliminary injunction to enjoin enforcement of the requirement to warn of exposures to Listed TiO2, reiterating that "Prop 65 is principally concerned about chemicals that are carcinogenic to humans, not animals."

The evidence supporting Listed TiO2's safe use in cosmetics and personal care products is firmly established. To summarize, the tumorigenic effects of TiO2 observed in experimental animal studies are exclusive to rats, which lack the pulmonary clearance mechanisms possessed by humans. Additionally, multiple epidemiological studies have failed to demonstrate any statistically significant link between exposure to TiO2 and carcinogenicity even at the highest foreseeable doses. The epidemiological data overwhelmingly suggests that TiO2 presents no risk of cancer to

humans, and the use of TiO2 in topical products is strongly correlated with the prevention of skin cancer due to TiO2's photoprotective proprieties.

The evidence of TiO2's carcinogenicity is largely, if not entirely, based on studies using rats that observed incidences of tumors and non-malignant pulmonary responses at very high levels of TiO2 exposure. (Heinrich et al. 1995, Lee et al. 1985a, 1985b, 1986, Mule et al. 1989, 1991, 1995, 1998.) Those studies do not support an inference of human carcinogenicity. Additionally, researchers, international toxicology experts, the European Chemicals Agency Committee for Risk Assessment, and the Court of Justice of the European Union have all concluded that the animal studies finding that TiO2 has a tumorigenic effect in rats are scientifically unreliable for determining the potential carcinogenic nature of TiO2 and for predicting effects in humans in non-overload conditions. (Beva et al. 2018, Driscoll and Borm 2020, Driscoll 2022, ECHA RAC 2017, General Court 2022, Warheit et al. 2016.)

Setting aside the above important issue, this comment addresses the absence of specific particle measurement techniques and the use of inactionable criteria in the proposed NSRL documentation. OEHHA relies upon the quantitative risk assessment contained in the National Institute for Occupational Safety and Health ("NIOSH") Current Intelligence Bulletin ("CIB") 63 to conclude that the NSRLs should be 440 and 44 micrograms per day for fine and ultrafine particles. NIOSH CIB 63 contains important references to standard particle size measurement techniques (NIOSH Method 0600 on p.77) and internationally accepted definitions for critically important terms such as "respirable" (CEN 1993; ISO Report No. ISO 7708 [1995] "Air Quality—Particle Size Fraction Definitions for Health-Related Sampling"). To avoid future confusion as the regulated community seeks to comply with the proposed NSRLs, OEHHA should clarify that the NSRL is based upon the same measurement techniques cited by NIOSH in CIB 63 (i.e., NIOSH 0600) and similarly applies internationally accepted definitions for defined terms such as "respirable" when referring to the size fraction of aerosols covered by the NSRL of 440 micrograms per day.

III. Comments

Comment 1

Cosmetic companies may seek to evaluate compliance with the proposed NSRLs by performing exposure assessments based upon the collection and measurement of particles during average product use. OEHHA's proposal does not specify sampling strategies or reference laboratory analytical methods for demonstrating compliance with the proposed NSRL values. However, as noted above, the risk assessment by a federal agency, upon which OEHHA bases its proposed NSRL, references industry standard industrial hygiene approaches for collecting size-fractioned particulates consistent with NIOSH methods (e.g., NIOSH Method 0600) and international

standards (CEN 481:1993, ISO 7708:1995).[1,2,3,4] Numerous U.S. and international regulatory criteria are set according to specific size-fractions of airborne particulates using these sampling methods and generally accepted technical definitions.[5,6,7] Similarly, numerous validated sampling methods employ the use of cyclones for collection of size-fractioned airborne particulates.[2, 8]

It is important to understand that collection of airborne particulates using a cyclone does not provide an absolute cut-off point. Rather, collection of airborne particulates using cyclones separates particles by size, according to an engineered performance curve that is defined by the median-mass aerodynamic diameter ("MMAD") of particles that the cyclone will collect with 50% efficiency (D_{50}). See Figure 1 for the internationally accepted ISO definition of the "respirable" convention curve.

[1] NIOSH. (2011). NIOSH Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. (p.77) Retrieved from https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf?id=10.26616/NIOSHPUB2011160

[2] NIOSH. (1994). NIOSH Manual of Analytical Methods (NMAM), Fourth Edition: Method 0600 - Particulates Not Otherwise Regulated, Respirable. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/niosh/docs/2003-154/pdfs/0600.pdf

[3] CEN [1993].Workplace atmospheres—size fraction definitions for measurement of airborne particles, EN 481. Brussels, Belgium: European Committee for Standardization.

[4] International Organization for Standardization. (1995). ISO 7708: Air quality - Particle size fraction definitions for health-related sampling. Retrieved from https://www.iso.org/standard/14534.html

[5] OSHA PEL for respirable crystalline silica. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1053

[6] OSHA PEL for particulates not otherwise regulated, respirable dust (PNOR). https://www.osha.gov/chemicaldata/801

[7] ACGIH TLV for manganese, respirable particulate matter. https://www.acgih.org/manganese-elemental-and-inorganic-compounds/

[8] UK Health and Safety Executive (HSE) Method 14/4 for sampling of respirable, thoracic, and inhalable aerosols. www.hse.gov.uk/pubns/mdhs/pdfs/mdhs14-4.pdf

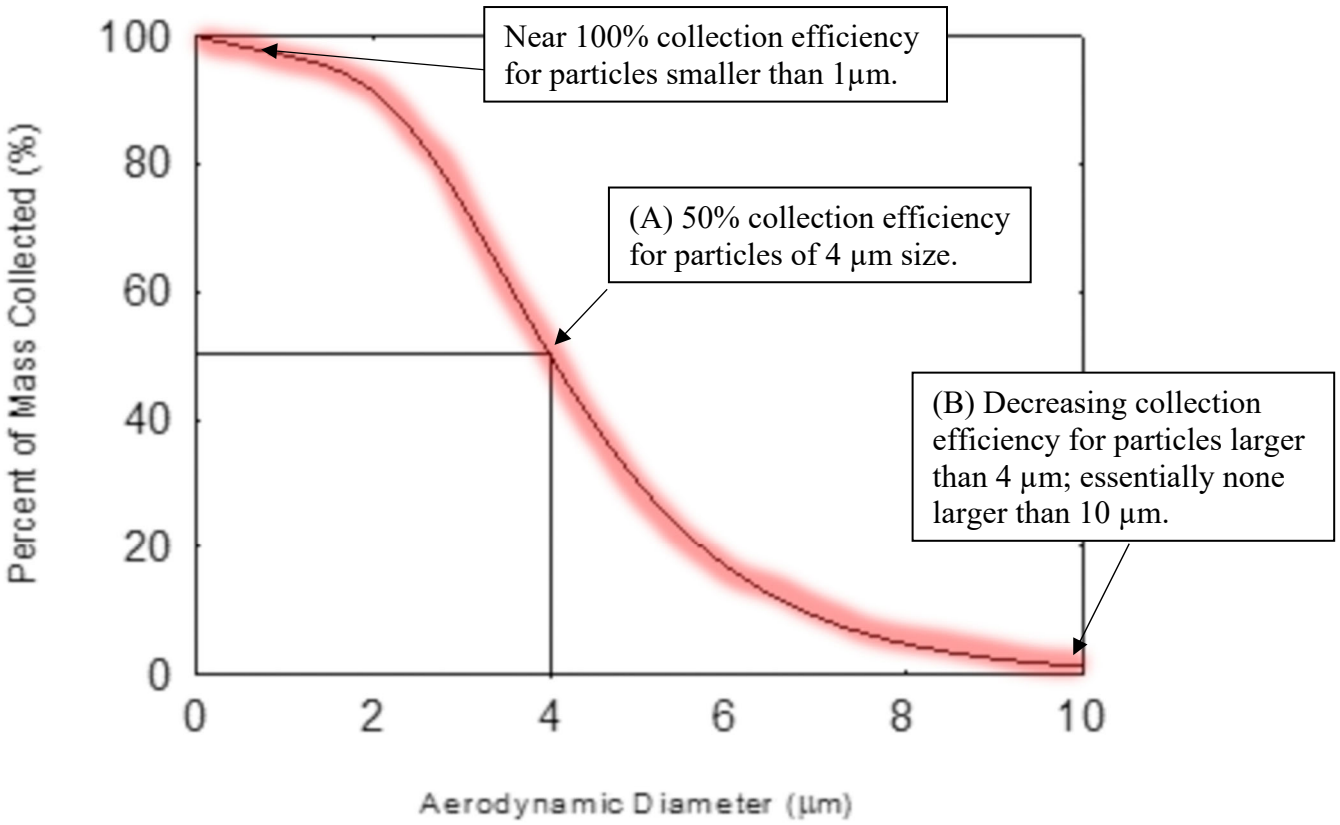

Figure 1- Graphical representation of the size-selective convention for sampling respirable particulates as specified by the International Organization for Standardization ("ISO") in ISO 7708:1995.[9]

In Figure 1, label-A identifies the 50% collection efficiency point (D_{50}) at a particle size of 4 micrometers, and label-B identifies the approximate upper-bound of the ISO respirable curve at approximately 10 micrometers. A cyclone with a performance curve that closely matches the ISO criteria for "respirable" as shown in Figure 1 would meet the definition of collecting particles of "10 micrometers or less" as currently worded in the OEHHA proposed NSRL. The performance of numerous cyclones has been described in peer-reviewed literature, which provides detailed

[9] Source attribution: Graphic modified from original image obtained from OSHA Technical Manual. https://www.osha.gov/otm/section-2-health-hazards/chapter-1.

descriptions of the performance criteria to evaluate conformance with the ISO respirable convention curve shown above.[10,11,12,13]

OEHHA's present proposal does not capture the nuance associated with sampling particles, because the present proposal contemplates precisely capturing all particles at 10 microns or less. Figure 2 below provides a graphical representation of such an interpretation. PCPC does not believe any sampling technique exists that can achieve particle size sampling that is consistent with Figure 2.

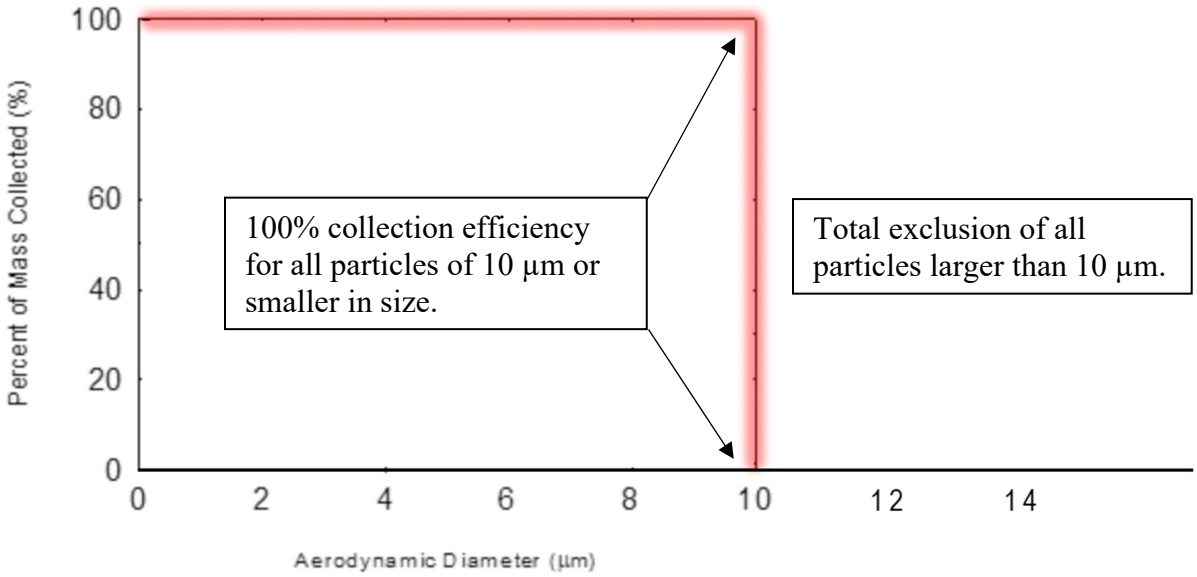

Figure 2- Graphical representation of a size-selective curve with an absolute cut-point at 10 micrometers.

Alternate laboratory analytical approaches may yield the ability to count only particles of precisely 10 microns or less, such as electron microscopy and computer-controlled scanning electron microscopy ("CCSEM") to develop particle-size distribution curves. However, these are particle count-based techniques and not mass-based like cyclone methods, and therefore are not

[10] Lee, et al. (2010). Performance of High Flow Rate Samplers for Respirable Particle Collection. The Annals of occupational hygiene. 54. 697-709. 10.1093/annhyg/meq050.

[11] Lee T, Thorpe A, Cauda E, Tipton L, Sanderson WT, Echt A. Laboratory comparison of new high flow rate respirable size-selective sampler. J Occup Environ Hyg. 2018 Oct;15(10):755-765. doi: 10.1080/15459624.2018.1503670. PMID: 30095363; PMCID: PMC6287257.

[12] Hanlon J, Galea KS, Verpaele S. Review of Published Laboratory-Based Aerosol Sampler Efficiency, Performance and Comparison Studies (1994-2021). Int J Environ Res Public Health. 2022 Dec 24;20(1):267. doi: 10.3390/ijerph20010267. PMID: 36612588; PMCID: PMC9819150.

[13] Stacey P, Thorpe A, Echt A. (2016) Performance of High Flow Rate Personal Respirable Samplers When Challenged with Mineral Aerosols of Different Particle Size Distributions. Ann Occup Hyg. 60(4):479-92. doi: 10.1093/annhyg/mev097. Epub 2016 Feb 10. PMID: 26865560; PMCID: PMC4815938.

appropriate techniques. Neither NIOSH nor the studies upon which it relied used particle-counting as the metric for determining exposure. The animal studies that generated the data upon which NIOSH CIB 63 relies used cyclones to generate Listed TiO2 aerosols with specific particle size characteristics for dosing animals, and the measurement data described in these studies is mass-based.[14]

Using a measurement technique that conforms to the ISO internationally accepted convention for the respirable fraction curve as shown in Figure 1 would be consistent with the human health risk assessment performed by NIOSH in CIB 63, upon which OEHHA based the proposed NSRL values. Within NIOSH CIB 63, section 1.4 "Current Exposure Limits and Particle Size Definitions" provides several citations to authoritative entities that provide working definitions for the term "respirable": CEN 1993; ISO 1995; ACGIH 1994; NIOSH 1998. Further, CIB 63 provides a definition for "fine" particles, upon which the animal tumor incidence data was collected and human health risk assessment are based, as:

> ***"All particle sizes that are collected by respirable particle sampling (i.e., 50% collection efficiency for particles of 4 µm, with some collection of particles up to 10 µm)."***[15]
>
> ***"In this document, the terms fine and respirable are used interchangeably to retain both the common terminology and the international sampling convention."***[15]

Comment 2

With respect to the proposed NSRL of 44 micrograms per day for "unbound titanium dioxide particles with diameters of 0.8 micrometers or less", the same technical feasibility challenges apply to the measurement of "0.8 micrometers or less."[16]

To ensure the 44 microgram NSRL is both measurable and actionable for compliance evaluation purposes, OEHHA should clarify that the selected value of 0.8 micrometers pertains to the D_{50} cut-point on a performance curve for a cyclone. As currently worded, it would appear the value pertains to an upper-bound value, which is inconsistent with data in NIOSH CIB 63. Both Tables 4-4 and 4-6 clearly indicate that the 0.8 micrometer value pertains to a MMAD value for aerosols to which

[14] Heinrich, et al. (1995). Chronic Inhalation Exposure of Wistar Rats and two Different Strains of Mice to Diesel Engine Exhaust, Carbon Black, and Titanium Dioxide. Inhalation Toxicology, 7(4), 533–556. https://doi.org/10.3109/08958379509015211

[15] NIOSH CIB 63. Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide. pg3. https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf?id=10.26616/NIOSHPUB2011160

[16] The 44 microgram proposal originates from within the human health risk data contained in the NIOSH CIB 63 document. In the OEHHA Initial Statement of Reasons, OEHHA relies upon the NIOSH reported 95% lower confidence bound associated with a 1:100,000 risk for occupational exposure to ultrafine Listed TiO2 (0.01 mg/m3) from which calculations on page 9 of the document are performed to convert to an NSRL of 44 micrograms per day, considering continuous inhalation exposure over a 70-year lifetime. OEHHA's reliance on the 0.01 mg/m3 mean airborne exposure value (see Table 4-7 in NIOSH CIB 63), and the animal study data and modeled human lung burden data (Table 4-6), which underpins the values in Table 4-7, meaning that the 44 microgram proposal would be most consistent with particle dimensions described as having a MMAD of 0.8 micrometers and a GSD of 1.8.

the animals were exposed. Notably, applying the 0.8 micrometer value as an MMAD, and not an upper-bound limit, is a more conservative approach as it additionally includes particles, half of which are larger than 0.8 µm.

The No Significant Risk Levels proposed by OEHHA would benefit from added clarification, and ideally identification of an approved sampling device or method, given the absence of an internationally recognized definition for the target particle size fraction associated with this NSRL (as exists for "respirable" in ISO 7708:1995). PCPC is aware of several existing commercially available cyclones that provide the ability to measure particle size fractions with a D_{50} cut point at 0.8 micrometers.[17, 18] As an example, the BGI cyclone model SCC 0.695 for sampling $PM_{0.8}$ meets the performance criteria of providing a D_{50} cut point at 0.8 micrometers. Alternate performance criteria for commercially available cyclones can be derived using an Excel-based calculator tool provided by BGI.[19]

Comment 3

Further, it is clear that measurement of particle size for the purpose of NSRL assessment should be based on secondary particle size (i.e., agglomerates and aggregates), not primary particle size. Table 4-4 in NIOSH CIB 63 definitively states that the ultrafine Listed TiO2 used to dose rats during chronic inhalation studies used ultrafine TiO2 which had a MMAD of 0.8 micrometers for the agglomerates and that individual particles within the agglomerates or aggregates (i.e., primary particles) measured between 0.015 µm - 0.040 µm. Moreover, a footnote of Table 4-6 states: "Agglomerated particle size for ultrafine TiO2 was used in the deposition model." The application of the NSRL to secondary particle sizes is both consistent with the approach described in NIOSH CIB 63 as well as technical means of compliance using exposure assessment methods that rely upon particle size fractioning using a cyclone, which separates particles according to the aerodynamic properties of agglomerated secondary particles. The proposed NSRL would benefit from added clarification that both the 440 microgram per day NSRL value for fines and 44 microgram per day NSRL value for ultrafines pertain to Listed TiO2 as measured using a device that size-fractions aerosols on a mass-basis according to the aerodynamic properties of secondary particles.

Comment 4

Finally, the introductory text to the proposed NSRLs states: "Titanium dioxide (airborne, unbound particles of respirable size). If daily exposure to this chemical is at or below both of the following

[17] L. C. Kenny, A. Thorpe & P. Stacey (2017) A collection of experimental data for aerosol monitoring cyclones, Aerosol Science and Technology, 51:10, 1190-1200, DOI:10.1080/02786826.2017.1341620

[18] BGI Personal Sampling Cyclones Matrix. http://innotechi.com/files/BGI/personal%20cyclones.pdf

[19] BGI (2014). BGI Cyclone Calculator Tool. https://2114285.fs1.hubspotusercontent-na1.net/hubfs/2114285/inmind/public/cyclone_calculator.xlsx

levels, it is deemed to pose no significant risk:" (emphasis added). PCPC recommends the removal of this text for two reasons. Because 27 CCR § 25705(b)(1) already states: "The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk." Thus, the proposed language is unnecessary.

IV. Recommendations

Because OEHHA is applying the process described under section 25705(c)(2) and relying on a "state or federal risk assessment" for purposes of deriving the proposed NSRL values, it is appropriate and consistent with the NIOSH CIB 63 document to promulgate NSRL values that are measured using particle size definitions that are consistent with the human health risk assessment data in NIOSH CIB 63.

Accordingly, the NSRL text should be updated as follows:

- NSRL of 440 µg/day for fine particles as measured using a device with performance criteria meeting that described in ISO 7708 (1995), (e.g., using a cyclone device with a median cut-point of 4 micrometers and upper bound (≤1% collection efficiency) at approximately 10 micrometers).
- NSRL of 44 µg/day for ultrafine particles as measured using a cyclone device with a median cut-point (D_{50}) at 0.8 micrometers.

Respectfully submitted,

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