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Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010
Sacramento, California 95812-4010

Submitted electronically via https://oehha.ca.gov/comments

RE: SUPPORT FOR MODIFIED DERMAL NSRL FOR DIETHANOLAMINE, TITLE 27, CALIFORNIA CODE OF REGULATIONS, SECTION 25705(B)(1)

Dear OEHHA,

Greenbaum Law Firm ("GLF") submits this comment in support of OEHHA's proposed modification establishing a dermal No Significant Risk Level ("NSRL") for diethanolamine ("DEA") of 5.8 micrograms per day. GLF supports adoption of the modified NSRL because it is grounded in the Proposition 65 implementing regulations, reflects OEHHA's reasoned response to the scientific record and public comments, and better advances Proposition 65's public-health and right-to-know purposes than the substantially less protective alternatives urged by PCPC, IBA, and Kirman et al. GLF submits this comment because its attorneys represent members of the public who use Proposition 65 to enforce consumer-safety protections in the public interest.

This comment addresses three principal points. First, OEHHA's modified 5.8 microgram per day dermal NSRL is supported by the direct DEA dermal carcinogenicity evidence and the Proposition 65 quantitative risk-assessment framework. Second, the objections advanced by PCPC and IBA depend on methodological substitutions that would make the safe-harbor level substantially less protective without resolving the key scientific uncertainties in the record. Third, adoption of an OEHHA-derived NSRL will provide useful compliance guidance while preserving Proposition 65's central public-health and right-to-know functions.

Summary of Key Scientific Evidence

The scientific record supports OEHHA's modified 5.8 microgram per day dermal NSRL. The key evidence is straightforward: DEA is listed under Proposition 65 as a carcinogen; the National Toxicology Program conducted two-year dermal carcinogenicity studies in B6C3F1 mice; those studies showed statistically significant treatment-related tumor increases, including liver tumors

in male and female mice and renal tubule adenomas in male mice; and OEHHA determined that the NTP dermal mouse studies were sensitive studies of sufficient quality for quantitative cancer risk assessment.

OEHHA's modified calculation also rests on a protective and transparent treatment of dermal absorption. After considering comments, OEHHA reevaluated the species dermal absorption factor, subtracted background DEA levels, used treatment-attributable plasma concentrations, selected the most sensitive human subject from the available comparative in vivo study, and derived a 1.96-fold dermal absorption adjustment. That revised adjustment produced a human cancer slope factor of 0.12 per mg/kg-day based on the male mouse multisite analysis and a resulting dermal NSRL of 5.8 micrograms per day.

The mechanistic record further supports OEHHA's decision not to adopt PCPC's threshold-only theory or Kirman et al.'s 3,400 microgram per day alternative. IARC identified mechanistic evidence relevant to DEA-induced liver tumors, including choline-related effects, but also found that human relevance could not be excluded and that no mechanistic data were available for DEA-induced kidney tumors. In that setting, OEHHA reasonably relied on the Proposition 65 quantitative risk-assessment framework, modeled the treatment-related tumor findings, and selected the most health-protective male mouse multisite result.

Introduction

OEHHA initially proposed a dermal NSRL for DEA of 6.4 micrograms per day and, after reviewing comments, modified the proposed value to 5.8 micrograms per day. OEHHA explained that the modification resulted from reevaluating the factor used to account for species differences in dermal absorption, including subtracting background DEA levels and using data from the most sensitive human subject. That revised analysis produced a dermal absorption adjustment factor of 1.96, a human cancer slope factor of 0.12 per mg/kg-day based on the male mouse study, and a resulting dermal NSRL of 5.8 micrograms per day.

OEHHA's modification strengthens the rulemaking because it demonstrates reasoned engagement with the scientific comments rather than disregard of them. OEHHA reconsidered the dermal absorption adjustment, refined the calculation by using treatment-attributable plasma concentrations and the most sensitive human subject, and adopted a more health-protective value. OEHHA also stated that it carefully considered comments on study design, mechanisms by which DEA induces liver tumors, dose-response modeling, and dermal absorption before modifying the proposed DEA NSRL.

OEHHA should adopt the 5.8 microgram per day NSRL because it reflects the best available evidence in the regulatory record and furthers Proposition 65's public-health and right-to-know purposes. DEA was listed as a carcinogen under Proposition 65 on June 22, 2012. OEHHA relied on the National Toxicology Program's 1999 dermal carcinogenicity study and IARC Monograph Volume 101, which summarize rodent carcinogenicity data and other information relevant to DEA's carcinogenic activity. OEHHA determined that the two-year dermal NTP studies in male and female B6C3F1 mice were sensitive studies of sufficient quality under Section 25703. In

male mice, OEHHA identified statistically significant increases in renal tubule adenomas, hepatocellular adenomas, hepatocellular carcinomas, hepatoblastomas, and combined hepatocellular adenomas, carcinomas, and hepatoblastomas. In female mice, OEHHA identified statistically significant increases in hepatocellular adenomas and hepatocellular carcinomas.

This rulemaking should be evaluated as what it is: a science-based safe-harbor determination for a listed carcinogen. OEHHA explained that an NSRL provides assurance to the regulated community that exposures at or below the level are not considered to pose a significant risk of cancer. OEHHA also explained that adopting NSRLs using the best available science provides more accurate and current information about risk to Californians, which is a scientific and public-health benefit. Where the record contains unresolved mechanistic questions, human-relevance uncertainty, and no mechanistic data for DEA-induced kidney tumors, Proposition 65's public-health and right-to-know purposes support a protective safe-harbor determination rather than a less protective value derived from additional assumptions that reduce estimated potency.

The objections submitted by PCPC and IBA do not undermine OEHHA's conclusion. They do not identify a superior chemical-specific dermal carcinogenicity study, nor do they show that OEHHA's modified calculation is inconsistent with Proposition 65's implementing regulations. Instead, they ask OEHHA to replace its health-protective, regulation-grounded analysis with a less protective industry-preferred approach that depends on different datasets, different dose metrics, and different low-dose extrapolation assumptions.

I. OEHHA Reasonably Applied the Proposition 65 Quantitative Risk-Assessment Framework

OEHHA's approach is grounded in the Proposition 65 implementing regulations and the available carcinogenicity evidence. OEHHA stated that the proposed DEA dermal NSRL conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about DEA. OEHHA reviewed available rodent carcinogenicity data and selected the two-year NTP dermal studies in male and female B6C3F1 mice as sensitive studies of sufficient quality. OEHHA used tumor incidence data for male mouse renal tubule adenomas and combined hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas to estimate cancer potency.

OEHHA also appropriately selected the most health-protective result. OEHHA's initial analysis derived a human cancer slope factor of 0.11 per mg/kg-day from the male mouse multisite model and used that value to calculate the original 6.4 microgram per day dermal NSRL. OEHHA's modified analysis revised the dermal absorption factor and selected the male mouse multisite human cancer slope factor of 0.12 per mg/kg-day because it was the most health protective. Using that revised human cancer slope factor, OEHHA calculated a dermal DEA NSRL of 5.8 micrograms per day.

That approach is more defensible than the regulated industry's preferred approach because it uses the direct DEA dermal carcinogenicity study, addresses multisite tumor risk, applies a transparent interspecies adjustment, and produces a health-protective safe-harbor value.

II. OEHHA Reasonably Rejected PCPC's Threshold-Only/Non-Genotoxicity Theory

PCPC's objections begin with a threshold-mode-of-action theory. That theory does not justify abandoning OEHHA's multistage modeling approach.

PCPC argues that "DEA is not a genotoxic carcinogen," that DEA-induced liver tumors in mice involve "chronic disruption of choline homeostasis," and that applying linear extrapolation is "scientifically inappropriate." OEHHA should reject PCPC's attempt to convert those mechanistic arguments into a categorical bar against a dermal NSRL derived under the Proposition 65 quantitative risk-assessment framework.

OEHHA did not ignore mechanistic evidence. OEHHA considered IARC's discussion of possible mechanisms, including choline deficiency, diacylglycerol accumulation, activation of protein kinase C, incorporation of DEA into membrane phospholipids, generation of lipid second messengers, and induction of aneuploidy. OEHHA also considered IARC's conclusion that there is weak evidence that a genotoxic mechanism is involved in DEA-induced liver tumors, moderate experimental support for choline deficiency as a mechanism for DEA-induced liver cancer in rodents, that the human relevance of that mechanism cannot be excluded, and that no mechanistic data are available for DEA-induced kidney tumors. That mixed mechanistic record does not support PCPC's threshold-only approach. It supports OEHHA's decision to use the multistage model consistent with the Proposition 65 implementing regulations.

PCPC's argument also fails because it focuses on liver tumors while minimizing the broader tumor record. In male mice, OEHHA found statistically significant increases in renal tubule adenomas, hepatocellular adenomas, hepatocellular carcinomas, hepatoblastomas, and the combined incidence of hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas. OEHHA used both renal tubule adenomas and combined liver tumors from the male mouse study to estimate cancer potency. OEHHA noted that IARC found no mechanistic data available on the induction of kidney tumors by DEA. PCPC's threshold-only theory therefore does not address the full basis for OEHHA's proposed NSRL.

OEHHA's approach is more faithful to the regulatory task before the agency. Based on the available mechanistic information, OEHHA applied the multistage model and concluded that there were no principles or assumptions scientifically more appropriate than that approach. After further review, OEHHA reaffirmed use of the male mouse multisite result and selected the human cancer slope factor of 0.12 per mg/kg-day because it was the most health protective. PCPC may prefer a threshold model, but its preference does not make OEHHA's health-protective application of the Proposition 65 framework scientifically unsound.

III. Kirman et al.'s 3,400 Microgram Per Day Value Rests on Less Defensible Methodological Choices

PCPC's threshold theory is implemented most directly through its reliance on Kirman et al., which does not merely apply OEHHA's framework differently. It substitutes a different dataset, dose metric, and low-dose extrapolation structure.

PCPC argues that OEHHA should withdraw the proposed NSRL and instead use alternative approaches, including a threshold model based on choline disruption or a linear model based on kidney tumors. IBA states that it aligns with PCPC's evaluation of the scientific literature and asks OEHHA to withdraw the proposed DEA NSRL. Kirman et al. derived an NSRL of 3,400 micrograms per day for dermal DEA exposures and described that value as protective of human health. But Kirman et al.'s result rests on methodological substitutions that are less scientifically defensible than OEHHA's approach.

First, Kirman et al. pooled data across four different cancer bioassays involving DEA and DEA-containing condensates, rather than deriving potency from the NTP dermal DEA study itself. Kirman et al. state that "dose-response data were pooled across four cancer bioassays conducted for DEA and DEA-containing condensates" to characterize dose-response relationships. The pooled dataset included neat DEA, coconut oil acid DEA condensate, lauric acid DEA condensate, and oleic acid DEA condensate, with free DEA content ranging from 100% to 0.19%. That pooling decision materially changes the dataset being modeled. It treats chemically different test materials, with different free-DEA content and potentially different matrices, as interchangeable measures of DEA carcinogenic potency. By contrast, OEHHA relied on the actual NTP two-year dermal DEA studies, which directly tested DEA by dermal application. Under the Proposition 65 safe-harbor framework, direct reliance on sensitive, chemical-specific DEA studies is more defensible than reshaping the dose-response relationship through pooled condensate studies.

Second, Kirman et al. used the pooled dataset to replace the direct DEA tumor response with a reconstructed, modeled dose-response curve. Kirman et al. justified pooling by stating that lower tumor incidence values were reported in bioassays using test condensates with lower free DEA content and that pooled data could provide a more robust characterization of the dose-response relationship. That justification assumes that tumor responses across condensates are biologically and quantitatively interchangeable with tumor responses from DEA itself once adjusted for free DEA content and absorbed dose. OEHHA's approach avoids that assumption. OEHHA used tumor incidence data from male mice for renal tubule adenomas and combined hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas to estimate cancer potency. OEHHA then used multisite modeling for the male mouse liver and kidney tumor data and selected the resulting human cancer slope factor because it was the most health protective.

Third, Kirman et al. treated liver tumors nonlinearly despite the Proposition 65 record supporting OEHHA's multistage modeling approach. Kirman et al. concluded that the weight of evidence for DEA-induced liver tumors was sufficient to support a nonlinear approach, resulting in an NSRL of 30,000 micrograms per day for liver tumors. Kirman et al. then selected the 3,400

microgram per day NSRL based on kidney tumors using low-dose linear extrapolation while treating liver tumors under a nonlinear approach. This selectively removes the most sensitive liver-tumor endpoint from the linear cancer potency calculation. OEHHA reasonably declined to do that. OEHHA considered IARC's mechanistic conclusions, including weak evidence for a genotoxic mechanism, moderate experimental support for choline deficiency, that human relevance cannot be excluded, and that no mechanistic data are available for kidney tumors. Based on the available mechanistic information, OEHHA applied a multistage model and concluded that no principles or assumptions were scientifically more appropriate than that approach. Where human relevance cannot be excluded and mechanistic gaps remain, OEHHA's default health-protective cancer modeling is more defensible than Kirman's threshold-based treatment of liver tumors.

Fourth, Kirman et al.'s absorbed-dose reconstruction introduces additional uncertainty that OEHHA's approach avoids. Kirman et al. calculated mouse absorbed DEA dose by multiplying administered dose by the fraction of DEA in the condensate and a mouse dermal absorption fraction, then calculated human applied dose by dividing mouse absorbed dose by a human dermal absorption fraction. Kirman et al. relied on absorbed dose values and assumed a human dermal absorption value of 0.9% to convert absorbed dose to applied dose. That approach requires multiple modeled conversions across species, doses, and product matrices. OEHHA instead used the NTP administered-dose data and made a focused interspecies dermal absorption adjustment using in vivo plasma data comparing mice and humans. OEHHA determined that Craciunescu et al. is the only available study comparing plasma concentrations following dermal application of DEA in human volunteers and mice. OEHHA used treatment-attributable plasma concentrations, subtracted background DEA levels, selected the most sensitive human volunteer, and derived a 1.96-fold mouse-to-human dermal absorption adjustment.

Kirman et al.'s final 3,400 microgram per day value therefore reflects a chain of methodological choices that systematically reduce estimated potency. Kirman et al. pooled DEA and DEA-containing condensate studies, expressed doses as absorbed dose, treated liver tumors nonlinearly, used low-dose linear extrapolation for kidney tumors, and selected 3,400 micrograms per day as protective of both liver and kidney tumors. OEHHA made the more health-protective and regulation-grounded choices: it used the direct DEA NTP studies, modeled treatment-related liver and kidney tumors in the most sensitive study, accounted for dermal absorption using comparative in vivo data, and selected the male mouse multisite result. OEHHA's modified analysis selected the male mouse multisite human cancer slope factor of 0.12 per mg/kg-day as the most health protective and used it to calculate a 5.8 microgram per day dermal NSRL.

The dermal absorption component of Kirman et al.'s analysis overlaps with PCPC's separate argument that OEHHA should have relied on Sun et al. rather than Craciunescu et al. That issue is addressed in detail below.

IV. Modeling Difficulty Does Not Justify Ignoring Treatment-Related Tumors

PCPC separately argues that the NTP liver tumor data are difficult to model because of high background incidence and saturated response. That criticism does not justify discarding treatment-related tumors or adopting Kirman's pooled alternative.

PCPC argues that the NTP liver tumor data show a saturated dose-response curve and that the background incidence of liver tumors among control male mice was 78%. PCPC further argues that the combined male liver tumor incidence was 78%, 94%, 100%, and 100% in the control, low-, mid-, and high-dose groups, respectively. Those points identify a modeling issue. They do not justify discarding statistically significant, treatment-related tumor findings or withdrawing the NSRL.

OEHHA recognized and addressed modeling limitations in the NTP dataset. For female mice, OEHHA explained that 100 percent incidences of hepatocellular adenomas and combined hepatocellular adenomas and carcinomas in the low-dose group created modeling issues, including BMDS messages that the BMD computation failed and the BMDL was not estimated. Because of those modeling issues, OEHHA estimated cancer potency for the female mouse study based solely on hepatocellular carcinoma incidence data. This demonstrates that OEHHA did not mechanically model every tumor endpoint without judgment. It evaluated the dataset, identified limitations, and selected endpoints that could be used for quantitative risk assessment.

For male mice, the tumor findings remain highly relevant. OEHHA found statistically significant increases in male mice for renal tubule adenomas, hepatocellular adenomas, hepatocellular carcinomas, hepatoblastomas, and combined liver tumors. OEHHA used a multisite model to estimate cumulative cancer risk from male mouse liver and kidney tumor data. The male mouse multisite model produced a higher human cancer slope factor than the female mouse hepatocellular carcinoma model, and OEHHA selected the male mouse result as the most health protective. PCPC's saturated-dose critique does not negate the treatment-related increases, and it does not provide a more regulation-grounded alternative than OEHHA's use of the sensitive male mouse multisite data.

PCPC uses this modeling criticism to justify replacing the direct DEA bioassay with Kirman's pooled DEA/condensate dataset. That substitution is not warranted. A difficult dose-response dataset does not authorize replacing chemical-specific tumor data with a pooled construct involving different test materials and additional assumptions.

PCPC's argument would effectively require OEHHA to disregard the most sensitive tumor data because the tumor response was strong. The proper response to a strong tumor response in a sensitive, sufficient-quality carcinogenicity study is not to ignore the study, but to apply a transparent, health-protective risk-assessment method. OEHHA did exactly that by deriving cancer potency estimates under Section 25703 and selecting the most health-protective human cancer slope factor. OEHHA's modified calculation then produced a dermal NSRL of 5.8 micrograms per day.

V. PCPC's Oral-Grooming Argument Does Not Undermine the Dermal NSRL

PCPC further contends that OEHHA's NSRL is flawed because mice in the NTP dermal bioassay were not collared and may have ingested DEA from grooming the application site. PCPC argues that the NTP mice were not collared, that mice could lick and ingest DEA from the dermal application site during grooming, and that OEHHA did not account for the contribution of oral exposure. This argument does not support withdrawal of the NSRL or adoption of PCPC's preferred 3,400 microgram per day value.

The NTP study remains a dermal-application carcinogenicity study. OEHHA relied on the NTP technical report titled "Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies)." In the NTP mouse studies, groups of 50 mice of each sex were exposed to DEA by dermal application at doses of 0, 40, 80, or 160 mg/kg body weight, five days per week for 103 weeks. The fact that grooming may have contributed to internal dose is a study-design consideration, not a basis to discard the study. The relevant tumor findings arose under the actual dermal-application conditions of the NTP study.

PCPC's position is also incomplete. If grooming contributed to internal dose, that point may be relevant to uncertainty in extrapolating from animal dermal application to human dermal exposure. But PCPC does not identify a superior chemical-specific dermal carcinogenicity study in humans or animals that OEHHA should use instead, nor does it show that the NTP dermal study ceases to be probative of cancer risk under dermal-application conditions. OEHHA used the available dermal carcinogenicity study and separately adjusted for species differences in dermal absorption using comparative data. OEHHA determined that Craciunescu et al. is the only available study comparing plasma concentrations following dermal application of DEA in human volunteers and mice. OEHHA used treatment-attributable plasma concentrations, subtracted background DEA levels, relied on the most sensitive human subject, and derived a 1.96-fold factor to account for dermal absorption differences between mice and humans.

Nor does the grooming argument justify PCPC's proposed reliance on Kirman et al. Kirman et al. acknowledged that contributions from oral exposure by grooming following topical application were possible under the NTP bioassay conditions. Kirman et al. also stated that the contribution of the oral pathway to total DEA dose in mice was not included in its NSRL calculation. PCPC cannot isolate one feature of the NTP study conditions and use it to nullify OEHHA's analysis while relying on an alternative analysis that also depends on the same NTP record and did not quantitatively resolve the same issue. At most, grooming is one uncertainty for OEHHA to consider within its risk-assessment judgment. It is not a scientific basis for withdrawing the NSRL.

VI. OEHHA Properly Relied on Craciunescu et al. Rather Than Sun et al. for the Dermal Absorption Adjustment

PCPC's criticism of OEHHA's dermal absorption adjustment depends heavily on its claim that OEHHA should have used Sun et al. (1996), not Craciunescu et al. (2009). PCPC argues that Sun et al. (1996) demonstrates a 29-fold difference in dermal absorption between humans and mice and that OEHHA should apply that 29-fold interspecies dermal adjustment factor. PCPC characterizes Craciunescu et al. (2009) as unsuitable and argues that Sun et al. is the better

scientific approach because it tested DEA under the same conditions on human and mouse skin. OEHHA reasonably rejected that position because PCPC's preferred study answers a narrower in vitro penetration question, while Craciunescu provides the only available comparative in vivo data on systemic DEA levels following dermal application in mice and humans.

The most important distinction is that Craciunescu measured internal DEA levels after dermal application in living organisms, while Sun measured penetration through excised skin in vitro. OEHHA determined that Craciunescu et al. is "the only available study comparing plasma concentrations following dermal application of diethanolamine in human volunteers and mice." OEHHA acknowledged that Sun et al. quantified differences in skin absorption of a single application of DEA between human and mouse skin, but found Sun more limited because of its single-application, shorter-duration, in vitro study design. For a cancer risk assessment based on systemic tumor outcomes following long-term dermal application, comparative plasma concentrations in vivo are more directly relevant than short-term penetration through excised skin.

Exposure duration also favors Craciunescu. Craciunescu exposed mice dermally to DEA for 11 days and human volunteers dermally to DEA for three to four weeks. OEHHA explained that Craciunescu's repeated daily applications more closely resemble the exposure patterns in the NTP DEA carcinogenicity studies and expected human exposure patterns. By contrast, OEHHA described Sun as involving a single application and shorter exposure duration. That matters because the NSRL addresses ongoing daily exposure, not one-time penetration. A repeated-application study better captures systemic availability and time-dependent exposure dynamics relevant to chronic risk assessment.

Craciunescu is also more relevant to the route and endpoint OEHHA had to evaluate. OEHHA's DEA NSRL applies only to dermal exposure and is based on the NTP dermal carcinogenicity studies. In the NTP mouse studies, animals were exposed to DEA by dermal application five days per week for 103 weeks. The relevant question is not merely how much DEA crosses excised skin in a short in vitro system, but how dermal application translates into internal systemic dose in mice and humans. Craciunescu supplied plasma concentration data from mice and human volunteers following dermal application. That makes Craciunescu better suited to estimating the interspecies adjustment for a dermal cancer potency calculation.

PCPC's "same conditions" argument for Sun is incomplete. PCPC argues that Sun is an "apples-to-apples interspecies comparison" because it tested DEA under the same conditions on both human and mouse skin. But identical in vitro test conditions do not necessarily make a study more relevant to human risk from repeated dermal product use. In vitro systems lack the full biological context of intact skin in living subjects, including systemic uptake, distribution, clearance, metabolism, tissue binding, and repeated-exposure effects. OEHHA reasonably gave greater weight to the study that measured plasma DEA after dermal exposure in living mice and humans. OEHHA stated that no other studies in exposed humans were identified. OEHHA further stated that the human data in Craciunescu provide an estimate of the order of magnitude of response to exposure in humans relative to the mouse.

OEHHA also did not rely on Craciunescu uncritically. It modified its analysis in response to comments and made it more health-protective. OEHHA revised its calculation by subtracting background DEA levels present in subjects' blood before treatment began. OEHHA also used data from the most sensitive human subject rather than averaging the three human volunteers. OEHHA selected Volunteer 2 because that volunteer had the largest 11-day treatment-attributable DEA plasma concentration, 4.58 nmol/mL. OEHHA explained that using the most sensitive human subject helps ensure that even sensitive individuals will be adequately protected. These refinements directly address variability and sensitivity concerns while preserving Craciunescu's core advantage: comparative in vivo plasma data.

PCPC's proposed 29-fold adjustment would substantially reduce the estimated human cancer potency based on an in vitro study that is less aligned with the exposure scenario. PCPC argues that Sun supports a 29-fold lower dermal absorption in humans than mice. OEHHA instead derived a 1.96-fold mouse-to-human difference using treatment-attributable plasma concentrations from Craciunescu. For a Proposition 65 safe-harbor level, OEHHA was not required to choose the adjustment that produces the least protective result. It was required to use a scientifically defensible approach consistent with the implementing regulations and protective of public health. The repeated-application in vivo Craciunescu data meet that standard better than PCPC's short-duration in vitro alternative.

Finally, the practical exposure context supports OEHHA's choice. OEHHA stated that dermal exposure is a common route of exposure for DEA and expected the dermal NSRL to be valuable for the majority of businesses with products containing DEA. Craciunescu's human volunteers applied a leave-on lotion containing DEA for up to four weeks. That type of repeated topical application is closer to consumer product exposure than a single in vitro skin-penetration experiment. OEHHA therefore reasonably concluded that Craciunescu's repeated-application in vivo design was more appropriate for deriving the dermal absorption adjustment used in the DEA NSRL.

VII. OEHHA's Proposition 65 Framework Independently Supports the NSRL Regardless of Other Agency Evaluations

PCPC may argue that OEHHA's proposed dermal NSRL is inconsistent with how other agencies or scientific bodies have evaluated DEA. That argument should be rejected. Proposition 65 assigns OEHHA an independent role in determining safe-harbor levels under California's risk-assessment framework. OEHHA is the lead state entity responsible for implementing Proposition 65 and has authority to adopt and amend regulations to implement and further the purposes of the Act. As the lead agency for Proposition 65, OEHHA may determine an NSRL based on its own risk assessment conducted according to Section 25703 or a risk assessment reviewed by OEHHA and determined to be consistent with that section. The relevant question is therefore not whether every outside agency has used the same assumptions, but whether OEHHA's NSRL is supported by the Proposition 65 record and the implementing regulations.

OEHHA's proposal is grounded in the specific California regulatory framework for determining no-significant-risk levels. OEHHA explained that, under Proposition 65, the NSRL is calculated

as one excess case of cancer per 100,000 people exposed, expressed as 10^-5. In the modified notice, OEHHA revised the dermal absorption factor, derived a human cancer slope factor of 0.12 per mg/kg-day based on the male mouse study, and calculated a modified dermal NSRL of 5.8 micrograms per day. That is the analysis OEHHA was required to perform under Proposition 65, and it independently supports the proposed value.

Nor did OEHHA ignore IARC. OEHHA relied on IARC Monograph Volume 101, which summarizes available data from rodent carcinogenicity studies and other information relevant to DEA's carcinogenic activity. OEHHA considered IARC's conclusion that there is weak evidence of a genotoxic mechanism, moderate experimental support for choline deficiency as a mechanism for DEA-induced liver cancer in rodents, that human relevance cannot be excluded, and that no mechanistic data are available for DEA-induced kidney tumors. Those conclusions do not preclude OEHHA's approach. The unresolved human relevance of the liver-tumor mechanism and the absence of mechanistic data for kidney tumors support OEHHA's decision not to adopt PCPC's threshold-only theory.

PCPC's reliance on statements from other bodies also does not overcome the tumor data OEHHA evaluated. PCPC argues that NTP did not include DEA in the Report on Carcinogens and that FDA stated the NTP study did not establish a link between DEA and cancer risk in humans. But the Proposition 65 rulemaking is not a listing proceeding and does not require OEHHA to prove human cancer causation anew. DEA was listed as a carcinogen under Proposition 65 on June 22, 2012. The task here is to establish a safe-harbor exposure level for dermal DEA exposures based on the available carcinogenicity evidence and California's quantitative risk-assessment rules. OEHHA determined that the two-year NTP dermal studies in male and female B6C3F1 mice met Section 25703's criterion as sensitive studies of sufficient quality. OEHHA identified statistically significant treatment-related tumor increases in male and female mice.

EPA-related arguments likewise do not require a different result. PCPC cites EPA guidance selectively to criticize OEHHA's modeling choices, while OEHHA's analysis relied on recognized cancer risk-assessment tools and principles. OEHHA used U.S. EPA's Benchmark Dose Software to calculate the dose associated with a 5% increased tumor risk and the lower bound for that dose. OEHHA stated that the multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in U.S. EPA's 2005 cancer risk assessment guidelines. OEHHA then applied the Proposition 65 no-significant-risk calculation using the human cancer slope factor. Thus, OEHHA's approach is not an unexplained departure from accepted risk-assessment practice. It is an application of Proposition 65's specific safe-harbor methodology using appropriate modeling tools.

Most importantly, the existence of different evaluations by other agencies or scientific bodies does not displace OEHHA's duty to protect Californians under Proposition 65. OEHHA stated that adopting NSRLs using the best available science provides more accurate and current information about risk to Californians and is a scientific and public-health benefit. OEHHA stated that the proposed NSRL will ease compliance, reduce the likelihood of over-warning, and

further Proposition 65's right-to-know purposes. Other agencies may apply different statutory mandates, risk thresholds, evidentiary standards, or regulatory objectives. OEHHA's obligation here is to apply California's Proposition 65 framework to the rulemaking record. That framework independently supports the 5.8 microgram per day dermal NSRL.

VIII. Industry Opposition Is Not Scientific Controversy

Having failed to show that OEHHA's scientific approach is unsound, PCPC reframes the proposal as "controversial." That label should carry no weight.

PCPC asserts that OEHHA's proposed NSRL "will likely result in controversy and confusion for the regulated community" and that the proposal "compounds the controversy of Proposition 65 being applied to DEA in personal care products." But the existence of industry opposition does not create a scientific controversy. Nor does a regulated industry's disagreement with OEHHA's risk-assessment choices transform an agency's science-based safe-harbor determination into an improper or unreliable regulatory act.

The record shows a straightforward regulatory question: whether OEHHA can derive a dermal NSRL for DEA under the Proposition 65 implementing regulations. OEHHA determined that the proposed DEA dermal NSRL conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about DEA. OEHHA relied on the NTP 1999 dermal carcinogenicity study and IARC Monograph Volume 101. OEHHA determined that the two-year NTP dermal mouse studies met Section 25703's criterion as sensitive studies of sufficient quality. PCPC may prefer different assumptions, different models, and a less protective numerical value, but that preference is not evidence that OEHHA's analysis is scientifically controversial.

PCPC's own comments confirm that its objection is directed not only to risk assessment, but also to the Proposition 65 enforcement consequences of the proposed NSRL. PCPC argues that OEHHA's proposal "will not accomplish the stated benefit of 'easing compliance'" and asks OEHHA to withdraw the NSRL. PCPC also contends that OEHHA's proposed NSRL has "no credible scientific basis" and would create "controversy and confusion for the regulated community." Those are advocacy positions from entities whose members are subject to Proposition 65 compliance obligations. They are not neutral scientific findings, and OEHHA should not treat regulated-party opposition or compliance concerns as equivalent to scientific uncertainty.

The proposed NSRL also does not impose the burden PCPC suggests. OEHHA explained that an NSRL "does not create a requirement or a mandatory threshold" and instead allows businesses to rely on the NSRL, if they choose, rather than developing their own analysis. OEHHA likewise stated that businesses are not required to rely on an NSRL to demonstrate that a product does not require a Proposition 65 warning and remain free to use other evidence, standards, methodologies, principles, assumptions, or levels to establish no significant risk. Thus, PCPC's claim of "controversy and confusion" is overstated. The rulemaking provides compliance assistance, not a new substantive exposure prohibition or a mandatory warning trigger.

Nor may OEHHA subordinate its public-health role to the regulated community's compliance preferences. OEHHA is the lead state entity responsible for implementing Proposition 65 and has authority to adopt and amend regulations to implement and further the purposes of the Act. Proposition 65 requires warnings for exposures to chemicals listed as known to the state to cause cancer or reproductive toxicity, unless the exposure does not pose a significant risk. OEHHA stated that adopting NSRLs using the best available science provides more accurate and current information about risk to Californians, which is a scientific and public-health benefit. That obligation does not yield because regulated entities would prefer a higher safe-harbor number, less enforceability, or a litigation posture that preserves arguments against DEA warnings.

Whatever positions regulated entities may take in other forums, this rulemaking should be decided on the scientific record before OEHHA. A public-health risk assessment does not become scientifically unsound merely because it may affect future enforcement or compliance strategy. The relevant question is whether OEHHA's proposed NSRL is supported by the scientific record and governing risk-assessment framework. Here, it is. After reviewing comments, OEHHA reevaluated its dermal absorption analysis, used treatment-attributable plasma concentrations, selected the most sensitive human subject, and modified the DEA dermal NSRL from 6.4 to 5.8 micrograms per day. OEHHA explained that the revised factor produced a human cancer slope factor of 0.12 per mg/kg-day based on the male mouse study and a resulting dermal NSRL of 5.8 micrograms per day.

IX. The NSRL Assists, Rather Than Burdens, Smaller Businesses

IBA frames the proposed DEA NSRL as a concern for small and mid-sized businesses in the beauty and personal care sector. IBA states that its membership includes entrepreneurial companies, brands, suppliers, finished product manufacturers, retailers, and service providers in the cosmetic and personal care industries. IBA states that it seeks additional context regarding the interpretation, implementation, and impact of the proposed NSRL on small to mid-sized businesses in the beauty and personal care product sector. That concern does not justify withdrawing or weakening the proposed NSRL.

OEHHA has already explained that the NSRL is compliance assistance, not a new mandatory requirement. OEHHA stated that businesses are not required to rely on an NSRL to demonstrate that a product does not require a Proposition 65 warning. OEHHA stated that an NSRL does not create a requirement or mandatory threshold and instead allows businesses to rely on the NSRL rather than developing their own analysis. OEHHA further stated that the proposed regulation does not impose mandatory requirements on businesses or state or local agencies.

The NSRL should help smaller businesses, not harm them. OEHHA stated that the proposed DEA NSRL is necessary to assist businesses that prefer to rely on OEHHA's analysis rather than calculating their own safe-harbor level. OEHHA explained that small businesses covered by Proposition 65 benefit from NSRL development because the underlying scientific analysis may require resources that smaller businesses lack. Regulated businesses choosing to rely on the NSRL will therefore have clearer guidance for determining whether their products expose people to DEA at a level that poses no significant risk of cancer.

IBA's position would leave smaller businesses with less guidance. IBA asks OEHHA to withdraw the proposed DEA NSRL and reconsider the data and references used to derive the proposed value. But withdrawal would not eliminate Proposition 65 obligations for DEA. OEHHA stated that products causing significant exposure to DEA already required Proposition 65 warnings before this rulemaking. OEHHA explained that the standard for when a warning is required remains the same regardless of the rulemaking: no warning is needed if the responsible person can show that the exposure poses no significant risk assuming lifetime exposure. Without an OEHHA-derived NSRL, businesses, including smaller businesses, would have to evaluate DEA exposure without the benefit of the agency's safe-harbor analysis. That outcome would increase uncertainty, not reduce it.

X. OEHHA's Modified Notice Demonstrates Meaningful Consideration of Public Comments

Any suggestion that OEHHA failed to engage with the comments submitted during the initial comment period should be rejected. The modified notice shows that OEHHA reviewed the substantive scientific objections, reconsidered its analysis, added materials to the record, and revised the proposed DEA dermal NSRL in response to the issues raised.

First, OEHHA expressly identified the categories of scientific comments it received and considered. OEHHA stated that, during the comment period on the original proposal, it received comments on design aspects of the two-year NTP dermal carcinogenicity studies in mice, mechanisms by which DEA induces liver tumors, the dose-response model used to estimate cancer potency, and the studies used to account for differences in dermal absorption between mice and humans. Those categories correspond directly to the principal objections raised by PCPC and IBA. PCPC challenged the NTP mouse bioassay, the mode-of-action analysis, linear dose-response modeling, and OEHHA's dermal absorption adjustment. IBA asked OEHHA to reconsider the data and references used to derive the DEA NSRL, particularly with respect to percutaneous penetration data, and stated that it aligned with PCPC's evaluation.

Second, OEHHA changed the proposed NSRL after reconsidering the comments. OEHHA stated that modifications to the original regulatory text were needed after reviewing the comments, and it revised the proposed DEA dermal NSRL from 6.4 micrograms per day to 5.8 micrograms per day based on a reevaluation of the species dermal absorption factor. That change demonstrates reasoned consideration, not predetermined decision-making.

Third, OEHHA directly addressed the dermal absorption issue that PCPC and IBA emphasized. PCPC argued that OEHHA should have used Sun et al. (1996) rather than Craciunescu et al. (2009) and should have applied a 29-fold interspecies dermal adjustment factor. IBA asked OEHHA to reconsider the NSRL calculation, particularly with regard to percutaneous penetration data. OEHHA responded by explaining why it continued to rely on Craciunescu while modifying the calculation. OEHHA determined that Craciunescu et al. is the only available study comparing plasma concentrations following dermal application of DEA in human volunteers and mice. OEHHA explained that Craciunescu's repeated daily applications more closely resemble the exposure patterns in the NTP carcinogenicity studies and expected human

exposure patterns than Sun's single-application, shorter-duration in vitro study. OEHHA then revised its calculation by subtracting background DEA plasma levels and using the most sensitive human subject rather than averaging the human volunteers.

Fourth, OEHHA addressed variability and sensitive-population concerns in a health-protective way. OEHHA selected Volunteer 2 from Craciunescu because that volunteer had the largest 11-day treatment-attributable DEA plasma concentration. OEHHA explained that relying on the most sensitive human subject ensures that even sensitive individuals will be adequately protected. OEHHA also stated that variability in DEA plasma levels among the human participants captured some variability that exists within the human population. These statements show that OEHHA considered the limitations of the human data and made a protective methodological choice.

Fifth, OEHHA addressed the mode-of-action and modeling objections by reaffirming, with additional explanation, the use of the male mouse multisite cancer potency estimate. OEHHA stated that comments addressed mechanisms by which DEA induces liver tumors and the dose-response model used to estimate cancer potency. In the modified analysis, OEHHA again presented human cancer slope factors based on the male mouse multisite data and the female mouse hepatocellular carcinoma data. OEHHA selected the male mouse human cancer slope factor because it was the most health protective. OEHHA used the revised human cancer slope factor of 0.12 per mg/kg-day to calculate the 5.8 microgram per day dermal NSRL. Thus, OEHHA did not ignore the modeling comments. It reconsidered the analysis and explained why the male mouse multisite result remained the appropriate basis for the NSRL.

Sixth, OEHHA expanded the rulemaking record. OEHHA stated that it was relying on several additional documents and adding them to the rulemaking file. The added documents included materials addressing skin penetration, DEA genetic alterations, human skin penetration, hepatic choline deficiency, DEA absorption and disposition, chromosome malsegregation, and OEHHA's BMDS model run. Adding these documents further demonstrates that OEHHA engaged with the scientific issues raised in the comments rather than dismissing them.

Finally, OEHHA provided an additional public comment opportunity limited to the modifications and newly added record documents. OEHHA opened a public comment and public availability period from June 10, 2026, through June 25, 2026. OEHHA stated that it would address comments received during that period that concern the modified regulatory text or the documents added to the record. This process gave commenters a further opportunity to address OEHHA's revised analysis.

Taken together, the modified notice documents a careful and reasoned response to the first-round comments. OEHHA identified the substantive scientific objections, reconsidered the dermal absorption calculation, explained why Craciunescu remained the better comparator than Sun, used the most sensitive human subject, revised the numerical NSRL, reaffirmed the health-protective male mouse multisite potency estimate, added relevant scientific materials to the record, and opened a further comment period. That record shows meaningful public-comment

engagement; it does not support any claim that OEHHA failed to address the regulated community's scientific objections.

XI. Public Health and the Right to Know Must Remain Central

The purpose of this rulemaking is not to preserve regulated entities' preferred litigation defenses or to maximize industry flexibility at the expense of public health. OEHHA stated that the DEA dermal NSRL will ease compliance for businesses while furthering the right-to-know and public-health purposes of Proposition 65. OEHHA stated that the proposed NSRL may encourage businesses to reduce exposures to listed chemicals to levels that do not pose a significant risk, thereby providing a public-health benefit to Californians. OEHHA also stated that adopting NSRLs using the best available science provides more accurate and current information about risk to Californians.

That public-health function is especially important where the regulated community argues for a safe-harbor value hundreds of times higher than OEHHA's proposed value. Kirman et al. derived a dermal DEA NSRL of 3,400 micrograms per day. OEHHA's modified analysis derived a dermal DEA NSRL of 5.8 micrograms per day. OEHHA should not adopt a less protective value based on methodological choices that pool different test materials, reconstruct absorbed doses across studies and species, and exclude treatment-related liver tumors from linear low-dose extrapolation.

The final rule should reflect OEHHA's independent scientific judgment. OEHHA considered comments on study design, mechanisms, dose-response modeling, and dermal absorption before modifying the DEA NSRL calculation. OEHHA revised its analysis by subtracting background DEA levels, using the most sensitive human subject, and applying a modified dermal absorption factor of 1.96. Those revisions resulted in the proposed 5.8 microgram per day dermal NSRL. That process demonstrates careful consideration, not controversy.

The record therefore presents a clear choice: OEHHA may adopt a transparent, health-protective NSRL based on the direct DEA dermal carcinogenicity evidence and the Proposition 65 implementing regulations, or it may accept industry's request for a much higher value built on pooled datasets, absorbed-dose reconstructions, nonlinear treatment of liver tumors, and other assumptions that reduce estimated potency. Proposition 65 supports the former.

Conclusion

OEHHA should adopt the modified dermal NSRL for DEA of 5.8 micrograms per day. The 5.8 microgram per day value reflects OEHHA's revised dermal absorption analysis, use of the most sensitive human-subject data, selection of the male mouse multisite human cancer slope factor of 0.12 per mg/kg-day, and health-protective calculation under the Proposition 65 framework. It is grounded in direct DEA dermal carcinogenicity evidence, treatment-related liver and kidney tumor findings, comparative in vivo dermal absorption data, and OEHHA's reasoned evaluation of the comments submitted during the rulemaking process. That is precisely the type of agency determination contemplated by the Proposition 65 implementing regulations: a lead-agency risk

assessment, conducted or reviewed under Section 25703, that establishes a level of exposure deemed to pose no significant cancer risk under Section 25705.

As a legal matter, OEHHA is not required to withdraw a proposed NSRL merely because regulated entities prefer a higher value or because commenters identify uncertainty inherent in cancer risk assessment. Section 25703 expressly provides default principles and assumptions for quantitative risk assessment in the absence of scientifically more appropriate alternatives based on the available data. Those defaults include reliance on the most sensitive study of sufficient quality and use of no-threshold modeling when a carcinogenic threshold has not been established. The opposing comments do not overcome that regulatory structure. They do not demonstrate that OEHHA was legally required to abandon the NTP dermal study, disregard treatment-related tumor findings, adopt a threshold-only theory, or substitute Kirman et al.'s substantially higher value for OEHHA's own analysis. Withdrawing the NSRL would not eliminate Proposition 65 obligations for DEA. It would simply leave businesses, consumers, public enforcers, and private enforcers without OEHHA's authoritative safe-harbor guidance for dermal DEA exposure. Finalizing the 5.8 microgram per day value therefore advances both compliance clarity and public-health protection.

PCPC's and IBA's objections do not justify withdrawal, delay, or adoption of the 3,400 microgram per day value advanced by Kirman et al. Those objections depend on methodological substitutions that would move OEHHA away from the direct DEA dermal carcinogenicity record and toward a substantially less protective safe-harbor value. They do not establish that OEHHA's selected studies, modeling approach, dermal absorption adjustment, or final calculation are scientifically unsound under the Proposition 65 implementing regulations. Nor do they show that OEHHA's modified analysis is arbitrary, unsupported by the record, or inconsistent with the statutory purposes of Proposition 65. To the contrary, OEHHA identified the governing regulatory framework, evaluated the available carcinogenicity and mechanistic evidence, considered the comments, modified its calculation in response to the record, and selected the most health-protective value supported by its analysis.

OEHHA should therefore finalize the modified NSRL because it is supported by the record, assists regulated businesses, preserves the integrity of Proposition 65's risk-assessment framework, encourages reduction of exposures to listed carcinogens, and advances Californians' right to know about chemical exposures that may affect their health.

Respectfully submitted,

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