Personal Care Products Council

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Joint Comments to OEHHA in response to the Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File: Title 27 California Code of Regulations, Section 25705 No Significant Risk Level for Diethanolamine dated June 10, 2026.

Thank you for the opportunity to provide comments in response to the Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File: Title 27 California Code of Regulations, Section 25705 No Significant Risk Level for Diethanolamine (DEA) dated June 10, 2026. These comments are submitted on behalf of the Personal Care Products Council (PCPC) and the Consumer Healthcare Products Association (CHPA).

Founded in 1894, the Personal Care Products Council is a leading national trade association representing the cosmetics and personal care products industry. PCPC is dedicated to promoting product safety, quality and innovation, serving as a unifying voice that champions science-based standards and responsible practices to support health, well-being and economic growth. PCPC's global members are some of the most beloved and trusted brands in beauty and personal care today, providing millions of consumers with the diverse products they rely on every day – from sunscreens, toothpaste and shampoo to moisturizer, makeup and fragrance.

CHPA, founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and OTC medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit ***www.chpa.org****.*

Section 1 summarizes our comments, and the subsequent six sections provide detailed explanations with references. Given that "the Proposition 65 warning requirement for cancer as applied to diethanolamine cannot be constitutionally enforced." *see The Personal Care Products Council v. Bonta, Case No. 2:26-CV-00682-DJC-CKD (E.D. Cal.), Order Regarding Final Judgment and Permanent Injunction (June 24, 2026),* ***Exhibit A*****,** we question the scientific merit and basis for

proceeding with finalizing the DEA NSRL. We respectfully request that the Office of Environmental Health Hazard Assessment (OEHHA) withdraw the proposed DEA NSRL.

1. Summary.

The proposed NSRL for DEA does not represent "the best available science," as stated in the ISR for multiple reasons which are detailed herein. Furthermore, the proposed NSRL will not accomplish the stated benefit of "easing compliance" but will likely result in controversy and confusion for the regulated community.

Section 2 of this submission demonstrates it is scientifically inappropriate to use the Craciunescu et al (2009) study to adjust for the comparative differences between mice and humans. The Craciunescu et al. (2009) study of the plasma levels of DEA in three humans is only a pilot study, which should not be used for quantitative risk assessment. In the words of the study authors:

> "**The human data from the present study should be considered as pilot data**; only three subjects were studied (one for 3 weeks rather than a month), and there was significant variability among subjects. **A larger group should be studied prior to making definitive conclusions and quantitative risk estimates using this data.**"[1] [emphasis added]

Using the human plasma DEA data from the Craciunescu et al. (2009) to establish a NSRL does not comply with the Proposition 65 regulations. The extremely limited plasma DEA data in 3 human subjects does not constitute "evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing"[2] and the human pharmacokinetic data cannot "be taken into account with confidence."[3]

OEHHA chose to use data from the Craciunescu et al. (2009) study because it is "the only available study comparing plasma concentrations following dermal application of diethanolamine in human volunteers and mice."[4] But, that is not enough. Simply comparing the results of plasma concentrations in two species without considering the important differences between the test methods and experimental designs used for each species is not appropriate. The comparison of the results in the Craciunescu et al. (2009) is not an apples-to-apples comparison. The test methods used for human volunteers and mice by Craciunescu were completely different. In fact, the experimental designs are so different that it is impossible to make any legitimate comparison between dermal absorption of DEA in mice and humans based on this study.

There is a fatal flaw in how OEHHA calculated the difference in dermal absorption between humans and mice. OEHHA attempted to estimate what the plasma level of DEA would be in humans at the same dose level of DEA applied to mice (i.e., 80 mg/kg/day), even though humans were estimated to receive a dose 133-fold lower. OEHHA multiplied the plasma level of DEA observed in the most

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[1] Craciunescu CN, Niculesu MD, Guo Z, Johnson AR, Fischer L, Zeisel SH (2009). Dose response effects of dermally applied diethanolamine on neurogenesis in fetal mouse hippocampus and potential exposure of humans. Toxicicol. Sci., 107(1):220-226.
[2] 27 CCR Section 25703 (a)
[3] 27 CCR Section 25703(a)(7)
[4] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 12.

sensitive human subject times a 133-fold factor, which suggests there is only a 1.96-fold difference in the plasma DEA levels between mice vs. humans at the same dose. However, directly multiplying the human plasma DEA concentration by 133 to compare it with the plasma DEA concentration in mice is inappropriate because it assumes linearity. The plasma DEA concentration does not increase proportionally with the increase in administered doses, as dermal absorption will reach a maximum steady state at which further increases in dermal dose will not significantly elevate plasma levels. Assuming that the human plasma DEA level at a dose of 80 mg/kg/day can be calculated by simply multiplying the plasma DEA level observed at a dose of 0.6 mg/kg/day by the 133-fold difference in the estimated dose levels of 0.6 and 80 mg/kg/day is not a scientifically correct approach. In reality, the difference between dermal absorption of DEA in mice and humans is much greater than predicted by the erroneous approach used by OEHHA to calculate a NSRL of 5.8 mcg/day. A much more suitable study (Sun et al., 1996) demonstrates the difference is much greater (i.e., 29-fold less dermal absorption in humans than in mice).[5]

Further, the human portion of the study was not well-controlled. It is unclear whether other DEA-containing personal care products were used by the subjects during the 3-4 week study period. The DEA exposure from other products could significantly contribute to the plasma level measurement and make the results unreliable for any quantitative risk assessment. Also, it is unclear how much time elapsed between the time that lotion was applied and the time when the plasma level of DEA was measured. Unfortunately, these details are not provided by Craciunescu et al. (2009). So, even if the approach used by OEHHA to estimate the difference in dermal absorption had been correct (it is not), there is considerable uncertainty in the estimated 133-fold difference in the estimated dose levels received by humans and mice.

OEHHA's recent proposal to limit the plasma DEA data to only the single "most sensitive human subject", thereby basing the NSRL on a single human subject, is unwarranted and scientifically indefensible. Basing the NSRL on only one human subject is preposterous. By this decision, OEHHA has reduced a study with an inadequate 3 human subjects to an even more inadequate study with only one human subject. OEHHA has never based a NSRL on data from a single individual. To the best of our knowledge, there is no precedent for OEHHA to do this. If the goal is to take into consideration human pharmacokinetic variability, using the data from a study involving only three human subjects, and then excluding two of the human subjects because they were not the most sensitive individuals, is no way to accomplish this. In OEHHA's original calculations, an average of the three volunteers' plasma levels was used. However, in the updated calculation OEHHA has determined that it should rely on the results of the most sensitive human subject. While OEHHA claimed that "This practice ensures that even sensitive individuals will be adequately protected.", this approach is not scientifically sound. The number used on the other side of the equation (the mouse plasma DEA level) was an average of five mice (1253 ± 127 nmol/ml). It is not appropriate to compare the highest plasma level from human subjects with an average plasma level from mice.

[5] Sun JD, Beskitt JL, Taliant MJ, Frantz SW (1996) In vitro skin penetration of monoethanolamine and diethanolamine using excised skin from rats, mice, rabbits, and humans. J Toxicol: Cutaneous and Ocular Toxicity 15(2):131-146

OEHHA then compared plasma DEA levels in mice and humans after 11 days of dermal exposure (Day 11), but Craciunescu et al. (2009) did not actually measure the plasma DEA concentration on Day 11 in any human subject. Instead, the human plasma DEA concentration on Day 11 used by OEHHA represents OEHHA's estimate of what the DEA concentration might be for Volunteer 2 on Day 11 based on GetData software. In other words, OEHHA used the GetData software program to extrapolate what the plasma DEA concentration might be on Day 11 based on measurements taken on Days 0, 7, and 28 for Volunteer 2. However, it is unclear how the GetData software modeled the data since it does not appear to be intended for pharmacokinetic data. This comparison of plasma DEA levels on Day 11 in mice and humans is based on extrapolated data for a single human subject, not on an actual plasma measurement in humans on Day 11.

OEHHA has historically expressed skepticism on far more validated *in vivo* data and models than presented in Craciunescu et al. (2009) and OEHHA (2026a)[6] when attempting to extrapolate interspecies toxicokinetics differences from rodents to humans. OEHHA (2008[7], 2009[8], 2016[9], 2026b[10]). For example, for extrapolating interspecies toxicokinetic differences, OEHHA has required review of extensive *in vivo* datasets with multiple PK parameters beyond just simply measuring plasma concentrations including, but not limited to, half-life, area under the curve, maximum concentration, and partitioning coefficients. OEHHA (2008, 2026). All of these are data analysis parameters default expectations for human dermal absorption studies FDA (2019[11]) and none of these parameters were calculated in Craciunescu et al. (2009) or by OEHHA. OEHHA has even previously noted validity issues with using small samples in *in vivo* human studies for interspecies extrapolation. OEHHA has even previously cited the use of best practices for interpretation of dermal absorption (Sullivan et al. 2017[12]) when determining the validity of a dermal absorption factor and one critical element is to ensure all samples are the sample exposure duration and ideally the same dose preparation, none of which is applicable to Craciunescu et al. (2009), OEHHA (2025[13]), Sullivan et al., (2017). In summary, OEHHA is not consistent with what *in vivo* data should be relevant for determining dermal absorption and interspecies differences.

Sections 3 through 7 of these comments re-submit PCPC's comments originally submitted in time to meet the November 7, 2025 deadline. PCPC filed extensive comments in response to the Initial Statement of Reasons (ISR) dated September 19, 2025.[14] OEHHA provided a limited response to

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[6] OEHHA 2026a. Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File. Title 27, California Code of Regulations. Article 7 No Significant Risk Levels. 1-Bromopropane and Diethanolamine (Dermal). 10 June 2026

[7] OEHHA, 2008, Appendix E, Application of Toxicokenetic Modeling and Analysis of Toxicokenetic Differences by Age at Exposure.

[8] OEHHA 2009. Review of Physiologically Based Pharmacokinetic Model for N-Methylpyrrolidone and Implications for Benchmark Analysis.

[9] OEHHA 2016. Pesticide Exposure and Risk Assessment Peer Review. Document Review Department of Pesticide Regulation's Draft Risk Characterization Document for Chlorpyrifos.

[10] OEHHA 2026b. Public Health Goal: Health-Protective Concentration for the Noncancer Effects of Hexavalent Chromium in Drinking Water. February 2026.

[11] FDA (2019), Maximal Usages Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over the Counter Monograph: Study Elements and Considerations.

[12] Sullivan, K.M., Aggarwal, M., Akins, J.M., Fabian, E., Heylings, J.R., Raabe, H., Shah, P.P., Wiemann, C. and Peffer, R., 2017. Dermal absorption for pesticide health risk assessment: Harmonization of study design and data reporting for North American Regulatory submissions. Regulatory Toxicology and Pharmacology, 90, pp.197-205.

[13] OEHHA (2025) Pesticide Exposure and Risk Assessment Evaluation: Comments on DPR's Risk Characterization and Exposure Assessment Documents for 4 Neonicotinoids (Acetamiprid, Clothianidin, Dinotefuran, and Thiamethoxam)

[14] OEHHA (2025) Statement of Reasons, p.12 Initial Statement of Reasons: 1-Bromopropane and Diethanolamine (dermal); Proposition 65 Safe Harbors

the studies used to account for differences in dermal absorption, but, OEHHA did not respond to any of the other comments submitted by PCPC. Many of those comments have the potential to significantly impact the development of the NSRL.

Section 3: DEA is not a genotoxic carcinogen. All standard genotoxicity studies have consistently shown DEA to be non-genotoxic, and this is a consensus viewpoint of multiple public health agencies. The National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) recognized that DEA is consistently negative (not genotoxic) in a large battery of conventional genotoxicity assays.[15,16] IARC cited two unconventional studies as providing some support for genotoxicity; upon review neither study actually provides evidence of genotoxicity or that tumors induced by DEA have a mutagenic mode of action (MOA).[17] Importantly, there is sufficient evidence to demonstrate the MOA for DEA-induced liver tumors in mice involves chronic disruption of choline homeostasis, a known MOA for liver tumors in mice. Unlike mice, humans are much less susceptible to the effects of choline disruption. Applying linear extrapolation for DEA-induced mouse liver tumors is scientifically inappropriate since DEA is non-genotoxic and exhibits a threshold MOA.

Section 4: The liver tumor data in the NTP DEA cancer bioassay show a saturated dose-response curve that cannot be used to reliably estimate a $BMDL_{05}$ or a cancer slope factor. Attempts to predict a dose level that causes a 5% increase in liver tumors is problematic when there are no doses close to the range of interest that would allow for an accurate estimate.

Section 5: The NSRL for DEA should not be based on the liver tumors in B6C3F1 mice in the NTP cancer bioassay. The B6C3F1 strain of mice used by NTP in its cancer bioassay of DEA is uniquely sensitive to liver tumors, and the significance to humans of liver tumors in B6C3F1 male mice has repeatedly been called into question by numerous scientific organizations, including the NTP. No increase in liver tumors was observed in rats in the NTP cancer bioassay. The mouse liver tumors in the NTP cancer bioassay were insufficient for NTP to conclude that DEA is "reasonably anticipated to be a human carcinogen" and to include DEA in the NTP Report on Carcinogens (ROC). In short, OEHHA should not base an NSRL for DEA on a liver tumor response in the uniquely sensitive B6C3F1 mice with an MOA that has a clear threshold, in the absence of data to support human relevance.

Section 6: There are more scientifically appropriate approaches for deriving a dermal NSRL for DEA, which include: (1) basing the NSRL on a relevant precursor endpoint (choline disruption) for liver tumors and applying a threshold model, or (2) basing the NSRL on kidney tumors using a linear model since the MOA of DEA-induced kidney tumors is unknown. OEHHA did not use either of these more scientifically appropriate methodologies.

[18] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 3.
[18] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 3.
[18] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 3.

Section 7: The proposed NSRL assumes that the only route of exposure to DEA in the NTP cancer bioassay is dermal exposure which is not the case. The mice in the NTP bioassay were not collared, which means that, during grooming, the mice were able to lick and ingest DEA from the dermal application site. OEHHA did not account for the contribution of oral exposure to DEA in the NTP cancer bioassay in the proposed dermal NSRL for DEA.

Because of the above limitations and deficiencies, we request that OEHHA withdraw the proposed NSRL for DEA. Any of the above material deficiencies, alone, would constitute sufficient scientific support for OEHHA to withdraw the proposed NSRL.

2. It is scientifically inappropriate to use the Craciunescu et al (2009) study to adjust for the comparative differences between mice and humans.

OEHHA correctly notes that DEA has been shown *in vitro* to be poorly absorbed by human skin compared to other species: "mice > rabbits > rats > humans."[18,19] In revising the proposed NSRL for DEA, OEHHA estimated the dermal absorption of DEA is 1.96-fold less in humans than in mice based on part of a study by Craciunescu et al. (2009).[20] However, the Cranciunescu et al. (2009) study is not scientifically appropriate for comparing the dermal absorption and pharmacokinetics of DEA in mice and humans for multiple reasons.

The Craciunescu et al. (2009) study of the plasma levels of DEA in humans is no more than a pilot study, which should not be used for quantitative risk assessment, as acknowledged by the study authors.

The primary purpose of the Craciunescu et al. (2009) study was to evaluate the embryotoxicity of DEA among the offspring of pregnant mice exposed dermally to DEA. The primary purpose was not to evaluate the plasma levels of DEA in non-pregnant mice and non-pregnant women. Only three human subjects were used for this study, and one of the three dropped out before the completion of the study. Because of the incredibly small number of human subjects used by Craciunescu et al. (2009), their study does not have adequate power to accurately determine the difference in dermal absorption between mice and humans, and it should be regarded as a pilot study, which should not be used for quantitative risk assessment.

The authors of the Craciunescu et al. (2009) study make this very point in the Conclusions section of their publication:

> "**The human data from the present study should be considered as pilot data**; only three subjects were studied (one for 3 weeks rather than a month), and there was significant variability among subjects. **A larger group should be studied prior to making definitive conclusions and quantitative risk estimates using this data.** The human data are

[18] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 3.
[19] Sun (1996).
[20] Craciunescu et al. (2009).

> presented to provide an estimate of the order or magnitude of response to exposure in humans relative to the mouse."[21] [emphasis added]

It is not appropriate to use such limited human data to establish a NSRL for DEA, especially when the primary purpose of the study was to evaluate the developmental toxicity of DEA in pregnant mice. The final conclusion of Craciunescu et al. (2009) is:

> "This study identifies the dose-response relationship for mouse embryotoxicity of DEA, a common commercial ingredient in personal care goods, and we present **pilot data** that suggest that human exposure is likely to be on the order of 100- to 200-fold lower than that needed to perturb brain development in the mouse."[22] [emphasis added]

It is a generally accepted scientific principle that pilot studies should not be used for quantitative risk assessment – and especially not to set regulatory limits.

It is noteworthy that the study authors of the Craciunescu et al. (2009) study appropriately did not draw any conclusion about the magnitude of the difference between dermal absorption of DEA in humans compared to mice. The meager human data in the Craciunescu et al. (2009) study are inadequate to draw any conclusions about the comparative dermal absorption of DEA. And Craciunescu et al. (2009) clearly understood this: "A larger group [of humans] should be studied prior to making definitive conclusions and quantitative risk estimates using this data."[23]

Using the human plasma DEA data from the Craciunescu et al. (2009) to establish a NSRL does not comply with the Section 25703 of the Proposition 65 regulations.

OEHHA's proposed use of the human data from the Craciunescu et al. (2009) study is not in compliance with the Proposition 65 regulations. For example, the Quantitative Risk Assessment section of the Proposition 65 regulations states:

> "A quantitative risk assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk. **The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer.**[24] [emphasis added]

The human data from the Craciunescu et al. (2009) is not "of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer.

[21] Id.
[22] Id.
[23] Id.
[24] Proposition 65 regulations, 27 CCR 25703(a)

Diethanolamine (DEA) was placed on the Proposition 65 list as a carcinogen through the Labor Code listing mechanism on June 22, 2012. OEHHA identified the underlying basis for the Labor Code listing of DEA as the International Agency for Research on Cancer (IARC) classification of DEA as a Group 2B carcinogen ("possibly carcinogenic to humans") based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of DEA. The *sufficient* evidence in experimental animals is the 1999 National Toxicology Program (NTP) technical report entitled "Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies)." In the Initial Statement of Reasons, OEHHA correctly determined "that the two-year dermal studies conducted by NTP in male and female B6C3F1 mice met the criterion in Section 25703 as being sensitive studies of sufficient quality."[25]

The human data from the Craciunescu et al. (2009) study is not "evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical." It is not even close. The NTP cancer bioassay is a large animal cancer study involving hundreds of mice and rats conducted under carefully controlled conditions and conducted according to Good Laboratory Practices (GL P).

In contrast, the human data from the Craciunescu et al. (2009) study is no more than a pilot study involving only three human volunteers. And, one of the three subjects did not complete the study. The dose levels of DEA were not carefully controlled, and there is little information about how the body lotion was applied. There is no information about whether there were other exposures to DEA during the course of the study. It would be surprising if there were not other exposures to DEA during the course of the study since DEA is commonly found in a wide variety of consumer products. There is also no information on whether the skin was occluded. The occlusive conditions could vary between subjects depending on the type of clothing the subjects wore and how much of their body was covered. As such, there is no way to account for these potential confounders. Also, there was no information in the publication on when plasma samples were drawn relative to the timing of the last dermal administration of DEA. By the authors' own admission, the human data from their study should be regarded as a pilot study that must be verified in a subsequent well-controlled study with larger numbers of subjects. The plasma DEA data in a pilot study involving only 3 human subjects is not "of comparable scientific validity" to the NTP carcinogenicity study of DEA in mice and rats. It should not be used to establish a NSRL for DEA.

The Proposition 65 regulations specifically address when pharmacokinetic data, such as data in the Craciunescu et al (2009) study, can be used to determine a NSRL. The regulations state:

> "When available data are of such quality that physiologic, pharmacokinetic and metabolic considerations **can be taken into account with confidence**, they may be used in the risk assessment for inter-species, inter-dose and inter-route extrapolations."[26] [emphasis added]

[25] OEHHA (2025). Initial Statement of Reasons: 1-Bromopropane and Diethanolamine (dermal); Proposition 65 Safe Harbors, p. 7.
[26] 27 CCR Section 25703(a)(7)

Clearly, the human data from Craciunescu et al. (2009) cannot "be taken into account with confidence." A pilot study by its very definition is not a study that can be taken into account with confidence. A pilot study is a study that must be repeated with a much larger study before its results can be taken into account with confidence.

Although the Craciunescu et al. (2009) is the only available study comparing plasma concentrations of DEA, the experimental designs were drastically different for each species, precluding any legitimate basis for comparison of dermal absorption and pharmacokinetics.

OEHHA chose to use data from the Craciunescu et al. (2009) study because it is "the only available study comparing plasma concentrations following dermal application of diethanolamine in human volunteers and mice."[27] But, that is not enough. Simply comparing the results of plasma concentrations in two species without considering the important differences between the test methods and experimental designs used for each species is not appropriate. The comparison of the results in the Craciunescu et al. (2009) is not an apples to apples comparison. The test methods used for human volunteers and mice by Craciunescu were completely different. In fact, the experimental designs are so different that it is impossible to make any legitimate comparison between dermal absorption of DEA in mice and humans based on this study.

Table 1. Comparison of experimental design of the Craciunescu et al. (2009) experiments in mice and humans

Design Factors	Mice	Humans
Occlusion	Unoccluded	Partial occlusion likely
Vehicle matrix	Acetone	Commercial body lotion
Dose	80 mg/kg bw/day	0.6 mg/kg bw/day (assumed by authors)
Concentration	Approx. 4.1%[a]	0.18% w/v (1.8 mg/g)
Surface area of application	2 cm^2 on small region on back of mouse[b]	No specific data reported; assumed to be whole body application (per manufacturer's instructions) of 20 mL lotion per day
Plasma sampling after dosing	At 11 days No information on whether it was 1, 2, 3, etc. hours after dosing	At 7 days and 3-4 weeks No information on whether it was 1, 2, 3, etc. hours after dosing

[a] Based on authors' note of 1.78 mL/g mouse weight and an assumed C57BL/6 pregnant mouse weight of 0.025 kg (0.025 kg x 80 mg/kg bw/day = 2 mg or 1.82 mL – DEA density: 1.097 and a total volume of 44.5 µL (25 g x 1.78 µL to mouse); 1.82 µL / 44.5 µL = 4.1%

[27] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 12.

[b] This value comes from an earlier study by Craciunescu et al. (2006). Craciunescu et al (2009) does not describe the surface area of application. It is assumed that the Craciunescu et al. used the same application method for both studies for purposes of this table.

There are at least six critical methodological parameters beyond species that differ, making this an inappropriate study for interspecies comparisons of dermal absorption, as shown in Table 1.
A much better estimate of the interspecies skin absorption correction factor is provided by Sun et al. (1996).[28] This study demonstrates the difference is much greater (i.e., 29-fold less dermal absorption in humans than in mice).[29] This study is an *in vitro* comparative species dermal absorption study using radiolabeled DEA aligned with OECD Test Guideline 428. In contrast to the Craciunescu et al. (2009) study, the Sun et al. (1996) study tested skin absorption of DEA in mice and humans under the same conditions, as shown in Table 2. Under identical conditions, human skin was shown to absorb 29-fold less DEA (0.23% vs. 6.68% cumulative dose absorbed) than does mouse skin.

Table 2. Comparison of experimental design of the Sun et al. (1996) experiments in mice and humans

Design Factors	Mice	Humans
Test system	Fresh skin samples from CD-1 mice	Fresh skin samples from mammoplasty patients
Test material	[^{14}C]DEA	[^{14}C]DEA
Vehicle (dilution)	Aqueous (37%)	Aqueous (37%)
Dose applied	95 µL	95 µL
Surface area of application[a]	1.77 cm^2	1.77 cm^2
Duration	6 hr exposure period	6 hr exposure period
Occlusion	Yes	Yes
Analytical method	Liquid scintillation spectrometer	Liquid scintillation spectrometer
Sampling timepoints	12 sampling timepoints distributed thru 6 hr	12 sampling timepoints distributed thru 6 hr
Analytical endpoints	Fraction of dose recovered Penetration rates	Fraction of dose recovered Penetration rates
Result	6.68% cumulative dose absorbed	0.23% cumulative dose absorbed

[a] skin disc size

[28] Sun (1996).
[29] Sun (1996).

A limitation of the Sun et al. (1996) study is it is an *in vitro* study rather than an *in vivo* study. However, this *in vitro* test method is widely used to evaluate skin absorption in humans. The fact that this study tested DEA under the same conditions on both human and mouse skin means that this is an apples-to-apples interspecies comparison and makes this study the far better choice for determining the interspecies skin absorption correction factor. In fact, OEHHA has previously used and applied an equivalent *in vitro* study to determine the differences in skin absorption between rats and humans for phthalates.[30,31] Thus, there is precedent in the use of an *in vitro* comparative dermal absorption study for rule-making purposes. Here, for DEA, it is the better scientific approach for OEHHA to rely on the Sun et al. (1996) study and to apply a 29-fold interspecies dermal adjustment factor in any proposed NSRL rulemaking.

There is a fatal flaw in the method chosen by OEHHA to calculate the difference in dermal absorption of DEA in humans compared to mice, based on the Craciunescu et al. (2009) study.

As background, the proposed dermal NSRL for DEA is based on a series of calculations by OEHHA that purport to identify a 1.96-fold difference in dermal absorption of DEA between mice and humans. To accomplish this, OEHHA compared the dermal dose levels received by mice vs. humans in the Craciunescu et al. (2009) study. According to Craciunescu et al. (2009), the mice received daily dermal doses of 80 mg/kg/day of DEA in acetone. Craciunescu et al. (2009) estimated that the human volunteers received a daily dermal dose of approximately 0.6 mg/kg/day of DEA in a body lotion. However, the human dose was not actually measured. The study authors measured the amount of lotion that was missing from each volunteers' bottle of lotion after 3 or 4 weeks, and that sum was divided by the number of days the volunteers were in possession of the lotion. The average amount of lotion missing from the returned bottle (and presumably applied to the skin) ranged from 14.5 to 22.9 ml/day. The average daily dermal dose for the human subjects was estimated to be 0.6 mg/kg/day, assuming a 60 kilogram woman applies 20 ml/day of the lotion containing 0.18% w/v of DEA. The body weights of the human subjects were not reported. Based on the difference between the assumed human dose of 0.6 mg/kg/day of DEA and the reported mouse dose of 80 mg/kg/day, OEHHA calculated that humans received a dermal DEA dose 133-fold less (80 mg/kg/day ÷ 0.6 mg/kg/day = 133)[32] than that received by the mice.

There is a fatal flaw in how OEHHA calculated the difference in dermal absorption between humans and mice. OEHHA attempted to estimate the blood level of DEA in humans at the same dose level of DEA applied to mice (i.e., 80 mg/kg/day).[33] To accomplish this, OEHHA multiplied the blood level of DEA observed in the most sensitive human subject (discussed in greater detail later) times the 133-fold difference between the estimated dose levels given mice vs. humans. This calculation suggests that there is a 1.96-fold difference in blood levels between humans and mice if humans had been given the same dose as mice. However, directly multiplying the human plasma

[30] Scott RC, Dugard PH, Ramsey JD, Rhodes C (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environ. Health Perpect., 74:223-227.
[31] OEHHA (2017). Supporting Materials for a Safe Use Determination for Diisononyl Phthalate (DINP) in Interface GlasBac® and GlasBac®RE Modular Carpet Tiles, p. 11. Available at: https://oehha.ca.gov/proposition-65/crnr/issuance-safe-use-determinations-diisononyl-phthalate-dinp-interface-glasbacr-and-glasbacrre-modular.
[32] OEHHA reported this difference as 133.33 (5 significant figures). For the sake of simplicity, it is rounded herein as 133.
[33] To achieve an equivalent dose for human subjects, a subject would need to apply 2.7 kg of lotion per day. This calculation is based on the following: 80 mg/kg/day x 60 kg = 4800 mg DEA/day and 4800 mg DEA ÷ 1.8 mg DEA/g = 2667 g lotion.

concentration by 133 (i.e., the difference between the estimated doses administered to mice and human subjects) to compare it with the plasma concentration in mice is inappropriate because it assumes linearity. The plasma DEA concentration is not expected to increase proportionally with the increase in administered doses, as dermal absorption will reach a maximum steady state at which further increases in dermal dose will not significantly elevate plasma levels. A steady state would be reached at a much lower dose for humans. In short, the estimated 1.96-fold difference between mouse and human dermal absorption of DEA is based on a false premise that plasma concentration of DEA increases proportionately with administered dose. In reality, the difference between dermal absorption of DEA in mice and humans is much greater than predicted by the erroneous approach used by OEHHA for the proposed NSRL of 5.8 mcg/day. Assuming that the human plasma DEA level at a dose of 80 mg/kg/day can be calculated by simply multiplying the plasma DEA level observed at a dose of 0.6 mg/kg/day by the 133-fold difference in the estimated dose levels of 0.6 and 80 mg/kg/day is not a scientifically correct approach.

In addition, this approach assumes that the estimated human dose from the body lotion is accurate. In reality, there is considerable uncertainty in the human dose estimate of 0.6 mg/kg/day. It is unclear whether the use of other personal care products contributed to DEA exposure or not. Also, it is unclear when the plasma level of DEA was determined in the human subjects relative to when the lotion was applied. The plasma levels of DEA are presumably a function of when the plasma samples were taken relative to the application of the DEA-containing products. Unfortunately, these details are not provided by Craciunescu et al. (2009). So, even if the approach used by OEHHA to estimate the difference in dermal absorption had been correct (it is not), there is considerable uncertainty in the assumed 133-fold difference in the estimated dose levels between humans and mice.

OEHHA's recent proposal to limit the plasma DEA data to only the single "most sensitive human subject," thereby basing the NSRL on a single human subject, is unwarranted.

Another recent proposed change in the derivation of the NSRL is to use the data from only "the most sensitive human subject."[34] OEHHA explained this decision as follows:

> "Additionally, in OEHHA's original calculations, an average of the three volunteers' plasma levels was used. However, OEHHA has determined that it should rely on the results of the most sensitive human subject. This practice ensures that even sensitive individuals will be adequately protected. Volunteer 2 had the largest 11-day treatment-attributable diethanolamine plasma concentration, 4.58 nmol/ml , and given the pharmacokinetic variability observed among the three human volunteers, this value was selected for use in deriving a factor to account for differences in dermal absorption between mice and humans."[35]

First, it is important to note Craciunescu et al. (2009) did not actually measure the plasma DEA concentration on Day 11 in any human subject. So, when OEHHA states that "Volunteer 2 had the

[34] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 5.
[35] Id.

largest 11-day treatment-attributable diethanolamine plasma concentration," it is critical to know Carciunescu et al. (2009) never measured the plasma DEA concentration on Day 11. Craciunescu et al. (2009) did not report any plasma DEA concentration for any human subject on Day 11. The plasma DEA concentration on Day 11 used by OEHHA represents OEHHA's estimate of what the DEA concentration might be for Volunteer 2 on Day 11 using "GetData software", as described by OEHHA in the Initial Statement of Reasons.[36] Apparently the GetData software referred to is GetData Graph Digitizer, which is a program built for getting raw data out of visual graphs for analytical purposes. In other words, OEHHA used a software program to extrapolate what the plasma DEA concentration might be on Day 11 based on measurements on Days 0, 7, and 28[37] for Volunteer 2. However, it is unclear how the GetData software modeled the data since it is not intended for pharmacokinetic data specifically. The bottom line is OEHHA's comparison of plasma DEA levels on Day 11 in mice and humans is based on extrapolated human data, not actual plasma DEA measurements on Day 11.

There are multiple problems with limiting the data to the "most sensitive human subject." Contrast this with the earlier-mentioned warning of Craciunescu et al. (2009):

> "**The human data from the present study should be considered as pilot data**; only three subjects were studied (one for 3 weeks rather than a month), and there was significant variability among subjects. **A larger group should be studied prior to making definitive conclusions and quantitative risk estimates using this data.** The human data are presented to provide an estimate of the order or magnitude of response to exposure in humans relative to the mouse."[38] [emphasis added]

If the goal is to take into consideration human pharmacokinetic variability, using the data from a study involving only three human subjects, and then excluding two of the human subjects, is no way to accomplish this.

OEHHA has historically expressed skepticism on far more validated *in vivo* data and models than presented in Craciunescu et al. (2009) and OEHHA (2025) when attempting to extrapolate interspecies toxicokinetics differences from rodents to humans (OEHHA 2008[39], 2009, 2016, 2026). For example, for extrapolating interspecies toxicokinetic differences, OEHHA has required review of extensive *in vivo* datasets with multiple PK parameters beyond just simply measuring plasma concentrations including, but not limited to, half-life, area under the curve, maximum concentration, and partitioning coefficients (OEHHA 2008, 2026). All of these are data analysis parameters default expectations for human dermal absorption studies (FDA 2019[40]) and none of these parameters were calculated in Craciunescu et al. (2009) or by OEHHA. OEHHA has even previously noted validity issues with using small samples in *in vivo* human studies for interspecies extrapolation. OEHHA has even previously cited the use of best practices for interpretation of

[36] OEHHA (2025) Statement of Reasons, p.12 Initial Statement of Reasons: 1-Bromopropane and Diethanolamine (dermal); Proposition 65 Safe Harbors
[37] Or Day 21 in the case of the one volunteer that dropped out of the study after three weeks.
[38] Craciunescu et al. (2009).
[39] OEHHA, 2008, Appendix E, Application of Toxicokenetic Modeling and Analysis of Toxicokenetic Differences by Age at Exposure.
[40] FDA (2019), Maximal Usages Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over the Counter Monograph: Study Elements and Considerations.

dermal absorption (Sullivan et al. 2017) when determining the validity of a dermal absorption factor and one critical element is to ensure all samples are the sample exposure duration and ideally the same dose preparation, none of which is applicable to Craciunescu et al. (2009), (OEHHA 2025[41]; Sullivan et al., 2017). In summary, OEHHA is lowering its own standards for what *in vivo* data should be relevant for determining dermal absorption and interspecies differences.

3. DEA is not a genotoxic carcinogen, and linear extrapolation is inappropriate for establishing an NSRL for DEA based on the mouse liver tumors.

PCPC filed extensive comments in response to the Notice of Proposed Amendment to Section 25703 Specific Regulatory Levels Posing No Significant Risk and the Initial Statement of Reasons (ISR) for a proposed dermal No Significant Risk Level (NSRL) for diethanolamine (DEA) of 6.4 micrograms/day "µg/day" on September 19, 2025.[42] In the Notice of Modification to the proposed NSRL dated June 10, 2026, OEHHA states: "During the comment period on the original proposal, OEHHA received a number of comments, including comments on design aspects of the two-year dermal carcinogenicity studies conducted in mice by the National Toxicology Program (NTP) that were used to determine the cancer potency of diethanolamine, mechanisms by which diethanolamine induces liver tumors and the dose-response model used to estimate cancer potency, and the studies used to account for differences in dermal absorption between mice and humans." OEHHA provided a limited response to the studies used to account for differences in dermal absorption. However, OEHHA did not respond to any of the other comments submitted by PCPC. Many of those comments have the potential to significantly impact the development of the NSRL. Accordingly, we are re-submitting PCPC's initial comments that were originally submitted in time to meet the November 7, 2025 deadline as Sections 3 – 7 of the present submission.

OEHHA's proposed NSRL is based on the use of a linear model "based on consideration of the available mechanistic information."[43] However, the ISR does not elaborate on why it is scientifically appropriate to employ a linear model, especially since IARC concluded there is only "weak evidence" of genotoxicity, as discussed below. The linear multistage model is typically used for carcinogens with a genotoxic MOA. However, DEA is not genotoxic. All standard genotoxicity

[41] OEHHA (2025) Pesticide Exposure and Risk Assessment Evaluation: Comments on DPR's Risk Characterization and Exposure Assessment Documents for 4 Neonicotinoids (Acetamiprid, Clothianidin, Dinotefuran, and Thiamethoxam)

[42] OEHHA (2025) Statement of Reasons, p.12 Initial Statement of Reasons: 1-Bromopropane and Diethanolamine (dermal); Proposition 65 Safe Harbors

[43] OEHHA (2025), Notice of Modification to Proposed Regulation and Addition of Documents to Rulemaking File, Title 27, California Code of Regulations, Article 7 No significant Risk Levels, 1-Bromopropane and Diethanolamine June 10, 2025, p. 10.

studies have consistently shown DEA to be non-genotoxic, and this is a strong consensus viewpoint of multiple public health agencies.[44,45,46,47,48,49,50,51,52]

NTP conducted an extensive battery of both *in vivo* and *in vitro* genotoxicity studies of DEA, and the results are consistently negative. The NTP summarized the results of its genotoxicity studies as follows:

> "Diethanolamine was not mutagenic in any of four strains of Salmonella typhimurium, in the presence or absence of S9 metabolic activation enzymes. No induction of trifluorothymidine resistance was observed in L5178Y mouse lymphoma cells treated with diethanolamine with or without S9. Diethanolamine did not induce significant sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9. Peripheral blood samples collected from male and female mice exposure to 80 to 1250 mg/kg diethanolamine for 13 weeks showed no increase in micronucleated normochromatic erythrocytes."[53]

Importantly, IARC, the agency whose determination formed the basis for the listing of DEA under Proposition 65, summarized the evidence for a genotoxic mechanism for DEA-induced liver tumors as follows:

> "There is **weak evidence** that a genotoxic mechanism is involved in the induction of liver tumors by diethanolamine."[54] [emphasis added]

To put the above statement into context, IARC uses three categories to categorize the strength of genotoxicity data: weak, moderate, and strong. IARC does not have a "not genotoxic" category. Thus, weak evidence is IARC's lowest level of evidence.

Regarding the genotoxicity of DEA, IARC alleged two studies provide some support for genotoxicity:

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[44] NTP (1999). NTP Technical Report No. 478. Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies). Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr478.pdf.
[45] Witt KL, Knapton A, Wehr CM, Hook GJ, Mirsalis J, Shelby MD, and MacGregor JT (2000). Micronucleated erythrocyte frequency in peripheral blood of B6C3F1 mice from short-term, prechronic, and chronic studies of the NTP carcinogenesis bioassay program. Environmental and Molecular Mutagenesis, 36(3):163-194.
[46] Beevers C, Henderson D, Lillford L (2015). Investigation of sodium arsenite, thioacetamide, and diethanolamine in the alkaline comet assay: Part of the JaCVAM comet validation exercise. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 786:165-171.
[47] Loveday KS, Lugo MH, Resnick MA, Anderson BE, Zeiger E (1989). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro: II. Results with 20 chemicals. Environmental and molecular mutagenesis, 13(1):60-94.
[48] Thorpe E (1982). Studies on the effects of Diethanolamine on the integrity of rat liver DNA in vivo. Available at: https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0520408.
[49] Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen., 5(1):3-49.
[50] NTP (2002) RoC Background Document for Diethanolamine; March 22, 2002.
[51] NICNAS (2016) https://www.industrialchemicals.gov.au/sites/default/files/Ethanol,%202,2'-iminobis-_%20Human%20health%20tier%20III%20assessment.pdf.
[52] EMA (2021) https://www.ema.europa.eu/en/documents/other/chmp-swp-opinion-diethanolamine-and-coconut-oil-diethanolamine-condensate-excipients_en.pdf.
[53] NTP (1999). NTP Technical Report No. 478. Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies). Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr478.pdf.

[54] IARC (2012), p. 136.

> "A genotoxic mechanism is supported by the induction of aneuploidy in Drosophilia [sic] and the elevated frequency of mutations in β-catenin *Catnb* genes in liver tumours induced by diethanolamine. However, diethanolamine was not genotoxic in most *in vitro* systems and did not increase the frequency of micronuclei in exposed mice."[55]

However, neither of these two unconventional genotoxicity studies cited by IARC provides evidence of genotoxicity that is relevant to determining the MOA for DEA. First, in the drosophila (i.e., fruit fly) study, the lowest dose chosen for the study is 5% in the diet, which is an exceedingly high dose. More importantly, according to the study authors, the effect (induction of nondisjunction in fruit fly oocytes) suggested "unspecific cell division perturbations probably due to toxicity. No clear dose effect relationships were observed."[56] In fact, the study authors chose DEA and two other chemicals for their study because they are "nonmutagenic and nonclastogenic rodent carcinogens."[57]

Second, in the *Catnb* gene study, *Catnb* mutations observed in 4/42 control animals are all different with significant overlap of mutations seen in the DEA-exposed mice, which also have a wide range of mutations and no clear dose-response pattern. Of note, it is common to observe mutations in tumor cells; it is a hallmark of cancer. The presence of mutations in cancer cells does not mean the cancer was induced by a genotoxic substance. The mutations may occur for a variety of reasons, including increased cell turnover, shorter cycle, and oxidative stress. In addition, if DEA caused the beta-catenin mutations, we would expect to see a pattern of the mutations formed (i.e., a mutational signature). Yet, no such pattern has been observed, and DEA is negative in the standard genotoxicity assays that look for mutations. In short, neither of these studies provide convincing evidence of genotoxicity, particularly in light of the large number of conventional genotoxicity studies that show no genotoxic effect.

IARC acknowledged that there is stronger evidence that the MOA is disruption of choline homeostasis rather than genotoxicity.[58] In contrast to genotoxicity, the disruption of choline homeostasis is characterized by a threshold. In other words, there is a dose below which no disruption of choline homeostasis occurs. It is inappropriate to use linear extrapolation to assess the cancer risk for a chemical with a threshold. A threshold model should be used instead.

In summary, the scientific evidence demonstrates that DEA is not a genotoxic carcinogen. Applying linear extrapolation to DEA-induced liver tumors with a threshold MOA is scientifically inappropriate.

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[55] *Id*., p. 136.

[56] Munoz ER, Barnett BM (2003). Chromosome malsegregation induced by the rodent carcinogens acetamide, pyridine and diethanolamine in Drosophila melanogaster females. Mutat Res., 539 (1-2):137-44.

[57] *Id*.

[58] IARC stated: "There is **weak evidence** that a genotoxic mechanism is involved in the induction of liver tumours by diethanolamine. There is **moderate experimental support** for choline deficiency as a mechanism for diethanolamine-induced liver cancer in rodents. Weak evidence is IARC's lowest category of the strength of evidence; moderate evidence is IARC's middle category [emphasis added].

4. The liver tumor data in the NTP DEA cancer bioassay show a saturated dose-response curve that cannot be used to reliably estimate a $BMDL_{05}$ or a cancer slope factor.

There is an additional reason why the mouse liver tumor data should not be used to establish an NSRL for DEA. The liver tumor data is not suitable for accurately estimating the benchmark dose or the cancer slope factor for DEA since the liver tumor dose-response curve is saturated. The background incidence of liver tumors among the control male mice is 78%. Trying to predict a dose level that causes a 5% increase in liver tumors is problematic when there are no dose levels in the range of interest that would allow for an accurate prediction. Modeling the combined male liver tumors with US EPA's benchmark dose software (BMDS) multistage model using a 5% benchmark response to establish the proposed NSRL results in a benchmark dose lower limit ($BMDL_{05}$) more than 10-fold lower than the response at the lowest non-zero dose.[59] According to EPA, this is a serious model deficiency (EPA 2012, 2022).[60]

The EPA Benchmark Dose Technical Guidance (2012) similarly describes this situation as follows:

> "**A dataset in which all non-control doses have essentially the same response level (e.g., Dataset B in Figure 2B) provides limited information about the dose-response relationship** since the complete range of response from background to maximum must occur somewhere below the lowest dose; thus, the BMD may be just below the first dose, or orders of magnitude lower. When this situation arises, it is tempting to use a model such as the Weibull with no restrictions on the power parameter (in quantal data, especially if the maximal response is less than 100%); however, this can result in models that are improbably steep in the low-dose region (see Section 2.3.3.3.). **The unfortunate reality in such situations is that the data provides little useful information.** In some cases biological significance may be inferred from other data on the same chemical and endpoint about the dose-response relationship at lower doses; **the ideal solution is to collect further data in the dose range missed by the studies in hand**."[61] [emphasis added]

In male mice, the incidence of combined liver tumors was 78%, 94%, 100%, 100% in the control, low, middle and high dose groups, respectively. However, the ISR used the liver tumor data in male mice as the basis for establishing the proposed NSRL, but does not appear to address the serious limitations and potential inaccuracies in the data set for liver tumors in male mice for estimating cancer potency.

In summary, the NTP liver tumor data shows a saturated dose-response curve, which cannot be used to accurately estimate the $BMDL_{05}$ or the cancer slope factor for liver tumors in mice exposed to DEA.

[59] US EPA (2012). EPA Benchmark Dose Technical Guidance. EPA/100/R-12/001.
[60] Id.; US EPA (2022). BMDS Version 3.3 User Guide. EPA/600/R-21/245.
[61] US EPA (2012), pp. 15-16.

5. The NSRL for DEA should not be based on the liver tumors in B6C3F1 mice in the NTP cancer bioassay for multiple reasons.

The proposed NSRL for DEA is based almost exclusively on the male mouse liver tumors.[62] It is well known that B6C3F1 mice, the strain used by NTP in its cancer bioassay of DEA, are particularly sensitive to the induction of liver tumors. Liver tumors are the most common spontaneous tumor in the B6C3F1 strain of mice used in NTP bioassays. In fact, in the NTP cancer bioassay of DEA, the incidence of liver tumors in unexposed control male mice was 78% (39/50). In addition, liver tumors are the most common type of tumors caused by exposure to test materials (including by many non-genotoxic test substances) in NTP cancer bioassays in B6C3F1 mice.

The significance to humans of liver tumors in B6C3F1 male mice has been called into question by many scientific organizations, including the NTP. Specifically in the case of DEA, the MOA for mouse liver tumors has been identified, and mice are uniquely sensitive to this MOA. Based on evaluations by Leung et al. (2005)[63] and others (Lehman-McKeeman et al. (2002)[64], Mellert et al. (2004)[65], Kamendulis & Klaunig (2005)[66], da Costa et al. (2005)[67], de Camargo et al. (1985)[68], Newberne et al. (1982)[69], and Kiekens et al. (2015)[70]), sufficient evidence exists to demonstrate the MOA for DEA-induced liver tumors involves chronic disruption of choline homeostasis and a sequelae of associated effects (Wiedeman et al. (2018)[71], Haseman et al. (1998)[72], and Wang et al. (2017)[73]). These publications collectively provide the following information:

- Choline depletion is known to cause liver tumors in mice.
- DEA is similar to choline in terms of chemical structure.
- Many studies have demonstrated that DEA, at a sufficiently high dose, will lead to disruption of choline homeostasis in mice.

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[62] The proposed NSRL for DEA is based on the combined cancer slope factors for liver and kidney tumors in male mice. In reality, the data on renal tubule adenomas plays a negligible role in defining the proposed NSRL since the cancer slope factor for the liver tumors before including the renal tumors is 0.0957 $(mg/kg/day)^{-1}$ and the cancer slope factor after including both the liver and renal tumors is 0.0973, a difference of less than 2%. So, the proposed NSRL is determined almost exclusively by the male mouse liver tumors.

[63] Leung H-W, Kamendulis LM, Stott WT (2005). Review of the carcinogenic activity of diethanolamine and evidence of choline deficiency as a plausible MOA. Regul. Toxicol. Pharmacol., 43(3):260-271.

[64] Lehman-McKeeman LD, Gamsky EA, Hicks SM, Vassalo JD, Mei-Heng Mar, Zeisel SH (2002). Diethanolamine induces hepatic choline deficiency in mice. Toxicol. Sci., 67(1):38-45.

[65] Mellert W, Kaufman W, Rossbacher R, van Ravenzwaay B (2004). Investigations on cell proliferation in B6C3F1 mouse liver by diethanolamine. Food Chem. Toxicol., 42(1):127-134.

[66] Kamendulis LM, Klaunig JE (2005). Species differences in the induction of hepatocellular DNA synthesis by diethanolamine. Toxicol. Sci., 87(2):328-336.

[67] da Costa KA, Gaffney, CE, Fischer LM, Zeisel SH (2005). Choline deficiency in mice and humans is associated with increased plasma homocysteine concentration after a methionine load. Am. J. Clin. Nutr., 81(2):440-444.

[68] de Camargo JLV, Punyarit P, Newberne PM (1985). Early stages of nodular transformation of the B6C3F1 mouse liver induced by choline deficiency. Toxicol. Pathol., 13(1):10-17.

[69] Newberne PM, de Camargo JLV, Clark AJ (1982). Choline deficiency, partial hepatectomy, and liver tumors in rats and mice. Toxicol. Pathol., 10(2):95-106.

[70] Kiekens F, Daele, Van Daile F, Blancquaert D, Van Der Straeten D, Lambert WE, Stove, CP (2015). Determination of five folate monoglutamates in rodents. Agricultural Food Chem., 63:10089-10095.

[71] Wiedeman, A.M., Barr, S.I., Green, T.J., Xu, Z., Innis, S.M., and Kitts, D.D. 2018. Dietary Choline Intake: Current State of Knowledge Across the Life Cycle. Nutrients, 10:1513.

[72] Haseman, J.K., Hailey, J.R., Morris, R.W. 1998. Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. Toxicol Pathol, 26(3):428-41.

[73] Wang Y, Sun Z, Szyf M. S-adenosyl-methionine (SAM) alters the transcriptome and methylome and specifically blocks growth and invasiveness of liver cancer cells. Oncotarget. 2017 Dec 5;8(67):111866-111881.

- Multiple studies have demonstrated DEA is incorporated into phosphocholine pathway and produces changes in multiple biomarkers of choline deficiency (e.g., hypomethylation). The B6C3F1 strain of mice used in the NTP cancer bioassay is particularly susceptible to this non-genotoxic MOA for liver tumors.
- DEA selectively alters the hepatic choline pathway in B6C3F1 mice and not in F344 rats (no tumors in the NTP cancer bioassay) or C57BL/6 mice.
- DEA decreased the hepatic choline metabolites and S-adenosylmethionine levels in mice similar to those observed in choline-deficient mice.
- A consistent dose-response relationship was established between choline deficiency and carcinogenic activity since all DEA dose levels that induced tumors in the NTP cancer bioassay were also shown to produce choline deficiency.
- Supplementing the diet with choline was shown to block the effects of DEA, including decreased phosphatidylcholine synthesis, transformation in the Syrian hamster embryo cells, increased S-phase DNA synthesis in mouse hepatocytes, and decreased gap junctional intracellular communication in cultured mouse and rat hepatocytes.
- DEA decreases hepatic choline metabolites and SAM levels in B6C3F1 mice with respect to choline deficiency indicators, liver proliferation (DNA synthesis), and hepatocellular tumors. Choline deficiency and liver proliferation are demonstrated to be reversible events.

In short, there is sufficient scientific evidence to support disruption of choline homeostasis as the most likely MOA for induction of liver tumors by DEA in B6C3F1 mice. This MOA is consistent with a threshold below which no adverse effects occur.

Importantly, compared to mice, humans are known to be more resistant to the effects of choline disruption.[74] Human hepatocytes have been shown to be refractory compared to mouse hepatocytes, so much so that no effect was observed in human hepatocytes at DEA exposures 75-fold higher than those required to affect mouse hepatocytes.[75] It is acknowledged that IARC stated: "The human relevance of this mechanism to humans cannot be excluded, especially for subgroups that are highly susceptible to dietary choline deficiency."[76] However, establishing a NSRL for DEA using a threshold approach would include a 10-fold intraspecies uncertainty factor to account for the possibility of sensitive subpopulations. The threshold approach using uncertainty factors provides ample protection for humans, particularly considering the at least 75-fold greater sensitivity to DEA of mouse hepatocytes compared to human hepatocytes. Also, it is noteworthy that IARC's statement confirms IARC has not established DEA as a known human carcinogen.

NTP voted not to include DEA on its Report on Carcinogens (ROC) based on the scientific evidence.[77] NTP is mandated by Congress to include in its ROC chemicals "known to be human carcinogens" or "reasonably anticipated to be a human carcinogen."[78] NTP's decision to exclude DEA from the ROC (11th edition and all subsequent editions to date) underwent three levels of

[74] Sidransky H, Farber E (1960). Liver choline oxidase activity in man and in several species of animals. Arch Biochem. Biophys., 87:129-133.
[75] Kamendulis (2005).
[76] IARC (2012).
[77] NTP (2002). Report On Carcinogens Background Document for Diethanolamine. Available at: https://ntp.niehs.nih.gov/sites/default/files/ntp/newhomeroc/roc11/deapub_no_appendices_508.pdf.
[78] *Id*.

review. Both the National Institute of Environmental Health Sciences (NIEHS) and the NTP Executive Committee Interagency Review Group for the ROC recommended that DEA not be listed in the 11th ROC. In the third and final review, the NTP Board of Scientific Counselors subcommittee concluded that DEA did not meet NTP's criteria for a possible human carcinogen and voted not to include DEA in the ROC.[79] [80] One of the primary reviewers said "the fact that the only significant tumors in animals are mouse liver tumors detracted from the strength of evidence." In short, the increases in mouse liver tumors were insufficient to allow NTP to conclude that DEA is "reasonably anticipated to be a human carcinogen."

In 2022, the US Food and Drug Administration (FDA) evaluated the NTP cancer bioassay of DEA, and FDA concluded: "The NTP study did not establish a link between DEA and the risk of cancer in humans."[81] DEA has also been assessed by the Cosmetic Ingredient Review Expert Panel, which concluded: "Given that nongenotoxic mechanisms of action have been postulated for diethanolamine-induced carcinogenicity in animal studies, the dermal penetration of diethanolamine is sufficiently well-characterized, the concentration of use of diethanolamine is quite low (≤0.06% in leave-on products), and the hepatocarcinogenicity in mice reported in the NTP study are considered to have little relevance to the safety of use of diethanolamine in personal care products."[82]

The questionable relevance of the liver tumors observed in B6C3F1 mice is underscored by the lack of any increase in tumors in the liver or any site in male and female **rats** in the NTP bioassay. The lack of carcinogenicity of DEA in rats offers additional support that DEA is non-genotoxic and that the liver tumors in mice are unique to mice and not accurate predictors of carcinogenicity in other species, including humans.

The NSRL for DEA should not be based on a linear approach using the liver tumors in B6C3F1 mice. A more reasonable alternative is to base an NSRL for DEA either on the mouse liver tumors using a threshold approach or on the mouse kidney tumors using a linear approach since the MOA of DEA-induced kidney tumors has not been fully elucidated, as discussed below.

6. Scientifically more appropriate approaches to deriving a dermal NSRL for DEA should be based on either (1) a relevant precursor endpoint for mouse liver tumors using a threshold model or (2) kidney tumors in mice using a linear model.

As discussed above, the threshold model is scientifically more appropriate than the linear model OEHHA elected to use in determining the NSRL for DEA, if based on mouse liver tumors. A no-observed-effect-level (NOEL) for disruption of choline homeostasis, a relevant precursor endpoint required in the etiology of DEA-induced mouse liver tumors, may be conservatively used as the

[79] NTP (2002). National Toxicology Program Board of Scientific Counselors Report on Carcinogens Subcommittee Meeting, November 19-20. 2002, Bethesda, Maryland. Summary Minutes.
[80] The Rose Sheet (2002) DEA Exclusion From 11th Report On Carcinogens Advised By NTP Panel. Available at: https://insights.citeline.com/RS010772/DEA-Exclusion-From-11th-Report-On-Carcinogens-Advised-By-NTP-Panel/
[81] FDA (2022) Diethanolamine. Available at: https://www.fda.gov/cosmetics/cosmetic-ingredients/diethanolamine.
[82] Fiume MM, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, Andersen FA (2017). Safety Assessment of Diethanolamine and Its Salts as Used in Cosmetics. Int. J. Toxicol., 36(5, Supp. 2):89S-110S.

point of departure (POD) for deriving an NSRL for DEA. The use of a precursor endpoint, which is observed at doses below those associated with tumors, represents a conservative approach to establishing an NSRL for DEA. The use of a precursor step for cancer risk assessment is recommended by the US EPA 2005 Guidelines for Carcinogen Risk Assessment in circumstances such as these.[83]

Lehman-McKeeman[84] et al. (2002) found that the NOEL for disruption of chlorine homeostasis in B6C3F1 mice exposed dermally to DEA for 4 weeks is 10 mg/kg bw/day.[85] Using virtually the same study design as the NTP cancer bioassay, groups of mice were given 0, 10, 20, 40, 80, or 160 mg/kg bw/day of DEA in ethanol dermally for 5 days per week for 4 weeks. Significant alterations of choline homeostasis were observed at all doses of DEA associated with an increase in liver tumors in the NTP bioassay. Thus, the NOEL of 10 mg/kg bw/day for disruption of choline homeostasis in B6C3F1 mice is expected to be protective of carcinogenicity in mice.

The NOEL of 10 mg/kg bw/day for a DEA precursor effect could be used as the POD for determining a "scientifically more appropriate" NSRL. Appropriate uncertainty factors could be applied to this POD to derive a scientifically more defensible NSRL for DEA. These might include uncertainty factors for interspecies uncertainty, intraspecies uncertainty, and/or uncertainty regarding the duration of exposure, as well as an interspecies skin absorption factor.

Alternatively, IARC's classification of "sufficient evidence" in experimental animals, which formed the basis for the listing, includes the increased incidence of kidney tumors (i.e. renal tubule adenoma) in male mice. The B6C3F1 strain of mice is not known to be uniquely sensitive to kidney tumors, unlike liver tumors. Also, the MOA for the mouse kidney tumors induced by DEA is not fully elucidated, which is not the case for the mouse liver tumors. Therefore, it could be appropriate to use the linear multistage model to establish an NSRL for DEA based on mouse kidney tumors since the default model is used in the absence of a scientifically more appropriate approach. In short, there are scientifically more appropriate alternative approaches using the existing data available, but OEHHA's proposed approach in the ISR is not scientifically defensible for each and all of the many reasons detailed herein.

7. The proposed NSRL is based on an erroneous assumption that the only route of exposure to DEA in the NTP bioassay is dermal exposure.

OEHHA's proposed NSRL assumes that the only route of exposure to DEA in the NTP cancer bioassay is dermal exposure. This is not the case. The mice in the NTP bioassay were not collared, which means that, during grooming, the mice were able to lick and ingest DEA from the dermal application site. There is no question that ingestion played a significant role in the NTP cancer bioassay of DEA. Stott et al. (2000) conducted a study that compared blood levels of DEA in mice administered DEA (1) dermally with no collars, (2) dermally with collars, or (3) orally.[86] In the group

[83] US EPA (2005) Guidelines for Carcinogen Risk Assessment. EPA/640/P-03/001F.
[84] Dr. Lois Lehman-McKeeman is a world-renowned toxicologist and a past president of the Society of Toxicology.
[85] Lehman-McKeeman (2002).
[86] Stott WT, Bartels MJ, Brzak K, Mar MH, Markham DA, Thronton CM, Zeisel SH (2000). Potential mechanisms of tumorigenic action of diethanolamine in mice. Toxicol. Letters, 114:67-75.

of uncollared mice administered DEA dermally, ingestion of the test material accounted for an approximately 30% increase in blood levels of DEA compared to that observed in collared mice given DEA dermally. These results demonstrate that, by not collaring the mice in the NTP bioassay, the ingestion exposure to DEA from grooming contributed significantly to the internal dose of DEA in the NTP bioassay. OEHHA did not account for the contribution of oral exposure to DEA in the NTP cancer bioassay in the proposed dermal NSRL for DEA.

* * *

Considering the deficiencies and limitations described herein, PCPC requests that OEHHA withdraw the proposed NSRL for DEA as there is no credible scientific basis to proceed as proposed.

Sincerely,

/s/ Jaap Venema
Jaap Venema, PhD
Executive Vice President, Science & Chief Scientist
Personal Care Products Council

/s/ Emily Manoso
Emily Manoso
Executive Vice President, Legal & Regulatory & General Counsel
Personal Care Products Council

/s/ Jay Sirois
Jay E. Sirois, Ph.D.
Vice President, Scientific and Regulatory Affairs
Consumer Healthcare Products Association

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF CALIFORNIA

SACRAMENTO DIVISION

THE PERSONAL CARE PRODUCTS COUNCIL,

Plaintiff,

v.

ROB BONTA, IN HIS OFFICIAL CAPACITY AS ATTORNEY GENERAL OF THE STATE OF CALIFORNIA,

Defendant.

Case No. 2:26-CV-00682-DJC-CKD

ORDER REGARDING FINAL JUDGMENT AND PERMANENT INJUNCTION

Judge: Honorable Daniel J. Calabretta
Trial Date: None set
Action Filed: March 3, 2026

The Court has received, read, and considered the Stipulation Regarding Final Judgment and Permanent Injunction in this case filed by Plaintiff The Personal Care Products Council ("PCPC") and Defendant Attorney General Rob Bonta, in his official capacity, which is hereby fully incorporated herein. For good cause shown:

The Court hereby **ORDERS** that Defendant Rob Bonta, in his official capacity as the Attorney General of the State of California, his officers, employees, and agents, and all those acting in privity or concert with the Attorney General and those individuals, are permanently enjoined from filing or prosecuting new lawsuits to enforce the warning requirement under Cal. Health and Safety Code section 25249.6 ("Proposition 65") for diethanolamine in cosmetic and personal care products;

The Court further **ORDERS, ADJUDGES AND DECLARES** that, based on the current state of the relevant science, the Proposition 65 warning requirement for cancer as applied to diethanolamine cannot be constitutionally enforced, consistent with the First Amendment, by the Attorney General of the State of California, his officers, employees, and agents, and all those acting in privity or concert with the Attorney General and those individuals;

It is further **ORDERED** that the Attorney General retains the right to move the Court to dissolve this injunction pursuant to Federal Rule of Civil Procedure 60(b)(5) or (6) in the event he believes a change in the facts or law renders its application inequitable or unnecessary;

It is further **ORDERED** that this Court shall retain jurisdiction over this action for purposes of implementing and enforcing the permanent injunction;

It is further **ORDERED** that PCPC shall have judgment entered in its favor; and

It is further **ORDERED** that the Parties shall each bear their own attorneys' fees,

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costs, and all other expenses incurred in connection with this case.

It is so **ORDERED**.

Dated: June 23, 2026

/s/ Daniel J. Calabretta
THE HONORABLE DANIEL J. CALABRETTA
UNITED STATES DISTRICT JUDGE