Comments to OEHHA in response to the Proposed Rulemaking: Title 27 California Code of Regulations, Section 25705 No Significant Risk Level for Diethanolamine dated August 22, 2025.

Thank you for the opportunity to provide 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. These comments are submitted on behalf of the Personal Care Products Council (PCPC). 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.

Section 1 summarizes our comments, and the subsequent six sections provide detailed explanations with references. PCPC strongly urges the Office of Environmental Health Hazard Assessment (OEHHA) to withdraw the proposed DEA NSRL because the proposal is not based on sound science.

1. Summary.

The proposed NSRL for DEA does not represent "the best available science," as stated in the ISR for several 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.

First, 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.[1,2] However, IARC incorrectly alleged two unconventional studies provides

[1] 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.
[2] IARC (2012). IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Volume 101, pp. 130-131.

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).[3] 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.

Second, 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 prediction.

Third, 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, basing 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, is scientifically indefensible.

Fourth, there are 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 scientifically appropriate methodologies.

Fifth, no matter the modeling approach taken, OEHHA's approach to dermal interspecies adjustments is not supported by the best available data. The ISR correctly notes that DEA has been shown *in vitro* to be poorly absorbed by human skin compared to other species: "mice > rabbits > rats > humans."[4,5] In calculating the proposed NSRL for DEA, OEHHA estimated that the dermal absorption of DEA is 2.19-fold less in humans than in mice based on an unsuitable study by Craciunescu et al. (2009).[6] Fortunately, a much more suitable study (Sun et al., 1996) does exist and that study demonstrates the difference is much greater (i.e., 29-fold less dermal absorption in humans than in mice).[7]

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[3] *Id.*, p. 136.
[4] OEHHA (2025). Initial Statement of Reasons: 1-Bromopropane and Diethanolamine (dermal); Proposition 65 Safe Harbors, p. 12.
[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.
[6] 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.
[7] Sun (1996).

Sixth, 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. Cumulatively, these deficiencies leave no credible scientific basis for OEHHA to do anything other than withdraw the proposed NSRL for DEA. OEHHA's proposed NSRL simply compounds the controversy of Proposition 65 being applied to DEA in personal care products.

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

OEHHA's proposed NSRL is based on the use of a linear model "based on consideration of the available mechanistic information."[8] 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 studies have consistently shown DEA to be non-genotoxic, and this is a strong consensus viewpoint of multiple public health agencies.[9,10,11,12,13,14,15,16,17]

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:

[8] OEHHA (2025), p. 10.
[9] NTP (1999).
[10] 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.
[11] 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.
[12] 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.
[13] 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.
[14] Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen., 5(1):3-49.
[15] NTP (2002) RoC Background Document for Diethanolamine; March 22, 2002.
[16] NICNAS (2016) https://www.industrialchemicals.gov.au/sites/default/files/Ethanol,%202,2'-iminobis-_%20Human%20health%20tier%20III%20assessment.pdf.
[17] EMA (2021) https://www.ema.europa.eu/en/documents/other/chmp-swp-opinion-diethanolamine-and-coconut-oil-diethanolamine-condensate-excipients_en.pdf.

> "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."[18]

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."[19] [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:

> "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."[20]

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."[21] In fact, the study authors chose DEA and two other chemicals for their study because they are "nonmutagenic and nonclastogenic rodent carcinogens."[22]

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

[18] NTP (1999).
[19] IARC (2012), p. 136.
[20] *Id*., p. 136.
[21] 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.
[22] *Id*.

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.[23] 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.

3. 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.[24] According to EPA, this is a serious model deficiency (EPA 2012, 2022).[25]

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

[23] 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].
[24] US EPA (2012). EPA Benchmark Dose Technical Guidance. EPA/100/R-12/001.
[25] Id.; US EPA (2022). BMDS Version 3.3 User Guide. EPA/600/R-21/245.

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**."[26] [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 without acknowledging 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.

4. 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.[27] 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)[28] and others (Lehman-McKeeman et al. (2002)[29], Mellert et al. (2004)[30],

[26] US EPA (2012), pp. 15-16.

[27] 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.

[28] 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.

[29] 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.

[30] 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.

Kamendulis & Klaunig (2005)[31], da Costa et al. (2005)[32], de Camargo et al. (1985)[33], Newberne et al. (1982)[34], and Kiekens et al. (2015)[35]), 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)[36], Haseman et al. (1998)[37], and Wang et al. (2017)[38]). 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.
- 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.

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

[32] 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.

[33] 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.

[34] 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.

[35] 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.

[36] 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.

[37] 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.

[38] 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.

Importantly, compared to mice, humans are known to be more resistant to the effects of choline disruption.[39] 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.[40] 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."[41] 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.[42] NTP is mandated by Congress to include in its ROC chemicals "known to be human carcinogens" or "reasonably anticipated to be a human carcinogen." [43] NTP's decision to exclude DEA from the ROC (11th edition and all subsequent editions to date) underwent three levels of 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.[44] [45] 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."[46] 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

[39] Sidransky H, Farber E (1960). Liver choline oxidase activity in man and in several species of animals. Arch Biochem. Biophys., 87:129-133.
[40] Kamendulis (2005).
[41] IARC (2012).
[42] 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.
[43] *Id.*
[44] NTP (2002). National Toxicology Program Board of Scientific Counselors Report on Carcinogens Subcommittee Meeting, November 19-20. 2002, Bethesda, Maryland. Summary Minutes.
[45] 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/
[46] FDA (2022) Diethanolamine. Available at: https://www.fda.gov/cosmetics/cosmetic-ingredients/diethanolamine.

study are considered to have little relevance to the safety of use of diethanolamine in personal care products."[47]

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.

5. 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 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.[48]

Lehman-McKeeman[49] 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.[50] 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

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[47] 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.

[48] US EPA (2005) Guidelines for Carcinogen Risk Assessment. EPA/640/P-03/001F.

[49] Dr. Lois Lehman-McKeeman is a world-renowned toxicologist and a past president of the Society of Toxicology.

[50] Lehman-McKeeman (2002).

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.

6. A scientifically more appropriate study exists for determining the interspecies skin absorption correction factor.

The ISR correctly notes that DEA has been shown *in vitro* to be poorly absorbed by human skin compared to other species: "mice > rabbits > rats > humans."[51,52] In calculating the proposed NSRL for DEA, OEHHA estimated that the dermal absorption of DEA is 2.19-fold less in humans than in mice based on a study by Craciunescu et al. (2009).[53] However, 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).[54]

OEHHA chose 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."[55] While it may be true that it is the only study that compared plasma DEA concentrations, that does not mean the study is suitable for Proposition 65 purposes because the experimental design of the study was drastically different for human volunteers and mice. 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. Thus, this study is not suitable for determining the interspecies differences in dermal absorption. Additionally, directly multiplying the human plasma concentration by 133.33 (the fold difference of the administered doses between mice and human subjects) to compare it with the plasma concentration in mice is inappropriate. Plasma 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. In the study by Craciunescu et al. (2009), the administered dose for mice is 80 mg/kg/day. 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

[51] OEHHA (2025), p. 12.
[52] Sun (1996).
[53] Craciunescu (2009).
[54] Sun (1996).
[55] OEHHA (2025), p. 12.

the following: 80 mg/kg/day*60kg= 4800 mg DEA/day, 1.8mg DEA/g lotion, 4800 mg DEA=2667 g lotion). A steady state would be reached at a much lower administered dose for humans.

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%

[b] Craciunescu CN et al. (2006)

A much better estimate of the interspecies skin absorption correction factor is provided by Sun et al. (1996).[56] 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.

[56] Sun (1996).

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 fdose absorbed

[a] skin disc size

A limitation of the Sun et al. (1996) study is it is an *in vitro* study rather than an *in vivo* study. However, 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.[57,58] 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.

[57] 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.

[58] 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.

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.[59] In the group 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.

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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.

Sincerely,

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

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

[59] 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.