May 5, 2009

Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010
1001 I Street, 19th floor
Sacramento, CA 95812-4010

RE: Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee (Notice to Interested Parties: 03/05/09)

Dear Ms. Oshita:

The Alkanolamines Panel of the American Chemistry Council (the Panel) hereby submits its comments to OEHHA regarding the carcinogenicity hazard prioritization of diethanolamine (DEA) and triethanolamine (TEA) under Proposition 65. The Panel is comprised of major producers of alkanolamines, including DEA and TEA. The current members of the Panel consist of: BASF SE, The Dow Chemical Company, and Huntsman Corporation.

On the basis of available scientific evidence concerning the potential carcinogenicity of DEA and TEA, the Panel urges the Carcinogen Identification Committee (CIC) to advise OEHHA to assign a no priority or a low priority for review of each of these substances.

The Panel believes that neither DEA nor TEA should have been identified as a candidate for preparation of Hazard Identification Materials because neither of these chemicals satisfies the specific screening criteria established by OEHHA. Moreover, when all of the available data are considered, there is insufficient epidemiological or toxicological evidence to suggest that either of these substances would be a human carcinogen.
Should you have any questions regarding this submission, or need any further information or references regarding this matter, please contact me (email: jon_busch@americanchemistry.com; telephone: 703-741-5633).

Thank you for the opportunity to comment.

Sincerely,

Jonathon T. Busch

Jonathon T. Busch
Manager, Alkanolamines Panel
Director, Chemical Products and Technology Division

BEFORE THE
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

COMMENTS OF THE ALKANOLAMINES PANEL OF THE AMERICAN CHEMISTRY COUNCIL ON CHEMICALS FOR CONSULTATION BY THE CARCINOGEN IDENTIFICATION COMMITTEE

	)
OEHHA; Proposition 65,	)
Prioritization: Chemicals for Consultation	)
by the Carcinogen Identification Committee	)
(March 5, 2009)	)
	)

Jonathon T. Busch
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EXECUTIVE SUMMARY

The Alkanolamines Panel (Panel) of the American Chemistry Council submits these comments in response to the State of California Office of Environmental Health Hazard Assessment's (OEHHA) March 5, 2009, notice stating that it has applied two data screens (a human data screen and an animal data screen) to roughly half of the chemicals in its tracking database and has identified a list of 38 candidate chemicals to be presented to the Carcinogen Identification Committee. The Panel is composed of major producers of alkanolamines, including producers of diethanolamine (DEA) and triethanolamine (TEA).

The list of 38 candidate chemicals published by OEHHA includes DEA and TEA. The Panel believes that neither DEA nor TEA should have been identified as a candidate for preparation of Hazard Identification Materials because neither of these chemicals satisfies the specific screening criteria established by OEHHA. Moreover, when all of the available data are considered, there is not sufficient epidemiological or toxicological evidence to suggest that either of these substances would be a human carcinogen, and these substances should not be among those selected by OEHHA for preparation of Hazard Identification Materials.

As discussed further in these comments:

- OEHHA incorrectly applied its animal data screening methodology to the available data for DEA.
- The excess incidence of liver tumors following dermal administration of DEA to B6C3F1 mice does not provide meaningful evidence of potential human carcinogenicity.
- Epidemiological data from occupational exposure to metal working fluids involve complex mixtures, and cannot be reliably used to assess any hazard associated specifically with DEA.
- In the aggregate, the available data on the carcinogenicity of DEA are not sufficient to warrant preparation of hazard identification materials.
- OEHHA also incorrectly applied its animal data screening methodology to available data for TEA.
- The excess incidence of combined benign and malignant liver tumors in female mice following dermal administration of TEA does not provide meaningful evidence of potential human carcinogenicity.
- Epidemiological data from occupational exposure during metal working are also inadequate to reliably evaluate any effects from TEA.

- OEHHA should affirm and extend its determination during prior screening that the evidence of potential human carcinogenicity for TEA is not sufficient to warrant preparation of hazard identification materials.

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INTRODUCTION

The Alkanolamines Panel (Panel) of the American Chemistry Council submits these comments in response to the State of California Office of Environmental Health Hazard Assessment's (OEHHA) March 5, 2009, notice stating that it has applied two data screens (a human data screen and an animal data screen) to roughly half of the chemicals in its tracking database and has identified a list of 38 candidate chemicals to be presented to the Carcinogen Identification Committee (CIC).[1] The Panel is composed of major producers of alkanolamines, including producers of diethanolamine (DEA) and triethanolamine (TEA).[2]

OEHHA is providing an opportunity for public comment on the scientific evidence concerning chemicals on this list of 38 candidates. OEHHA has transmitted detailed materials concerning the 38 candidate chemicals to each member of the CIC.[3] At a meeting to be held on May 29, 2009, the CIC will review the information presented by OEHHA and the public comments concerning the 38 candidate chemicals, and will provide its advice to OEHHA concerning prioritization of these chemicals.[4] Based on this advice, OEHHA will select

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1 OEHHA, Proposition 65, Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee (Mar. 5, 2009), *available at* http://www.oehha.org/Prop65/CRNR_notices/state_listing/prioritization_notices/prior030509.html.

2 The current member companies of the Alkanolamines Panel consist of: BASF SE, The Dow Chemical Company, and Huntsman Corporation.

3 OEHHA, Letter to Members of the Carcinogen Identification Committee (Apr. 3, 2009), *available at* http://www.oehha.org/Prop65/CICletter040309.html.

4 The detailed process for prioritizing chemicals is described in a document issued by OEHHA in 2004. OEHHA, Process for Prioritizing Chemicals for Consideration under

particular chemicals for preparation of detailed Hazard Identification Materials. These materials will then be presented to the CIC for review and for use in deciding whether particular chemicals should be added to the list of carcinogens established under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The list of 38 candidate chemicals published by OEHHA includes DEA and TEA. The Panel believes that neither DEA nor TEA should have been identified as a candidate for preparation of Hazard Identification Materials because neither of these chemicals satisfies the specific screening criteria established by OEHHA. Moreover, when all of the available data are considered, there is not sufficient epidemiological or toxicological evidence to suggest that either of these substances would be a human carcinogen, and these substances should not be among those selected by OEHHA for preparation of Hazard Identification Materials. The Panel sincerely appreciates this opportunity to comment on the scientific data concerning DEA and TEA.

Proposition 65 by the "State's Qualified Experts," (Dec. 2004), *available at* http://www.oehha.org/Prop65/CRNR_notices/state_listing/pdf/finalPriordoc.pdf.

COMMENTS ON DIETHANOLAMINE (DEA)

I. OEHHA INCORRECTLY APPLIED ITS ANIMAL DATA SCREENING METHODOLOGY TO THE AVAILABLE DATA FOR DEA

A. An Increased Incidence of Tumors at the Same Site in Both Sexes in the Same Study of Dermal Administration of DEA to B6C3F1 Mice Does Not Constitute Two Positive Animal Cancer Bioassays

Although OEHHA applied both an epidemiology data screen and an animal data screen to roughly half of the chemicals in its tracking database, the epidemiology screen was applied previously and was only reapplied as part of the current screening process.[5] The key screen for the current list of candidates was the animal data screen presented to the CIC at the November 5, 2008, meeting.[6]

The document issued by OEHHA describing how it selected the 38 candidate chemicals describes the animal data screen as follows:

The animal screen identified chemicals with:

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[5] OEHHA, Prioritization: Applying Epidemiology Data Screen and First Animal Data Screen (Nov. 5, 2008) at 5 (slides presented at CIC Meeting (CIC Slides)), *available at* http://www.oehha.org/prop65/public_meetings/pdf/Prioritization110508.pdf.; Transcript, Meeting of the State of California OEHHA Proposition 65 Carcinogen Identification Committee (Nov. 5, 2008) at 169-71 (CIC Transcript), *available at* http://www.oehha.org/prop65/public_meetings/pdf/cictranscript110508.pdf.

[6] CIC Slides at 4; CIC Transcript at 168.

- Two or more positive animal cancer bioassays;
- One positive animal cancer bioassay with findings of tumors at multiple sites or with malignant (or combined malignant and benign) tumors occurring to an unusual degree with regard to incidence, site, type of tumor or age of onset;
- One positive animal cancer bioassay and evidence from a second animal cancer bioassay of benign tumors of a type known to progress to malignancy.[7]

In applying these criteria, OEHHA states that:

> A positive animal cancer bioassay is a study in which a treatment-related increase in the incidence of malignant or combined malignant and benign tumors is observed in a given tissue or organ, or for a given type of tumor (e.g., hemangiosarcoma).[8]

For those individual chemicals selected by this animal data screen, OEHHA then performed an additional literature search to identify additional information relevant to carcinogenicity, including studies on genotoxicity, mechanism of action, metabolism, and pharmacokinetics.[9]

The OEHHA Proposal includes a table summarizing the results of the data screen for each of the candidate chemicals, and identifying other relevant data it has identified for each

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[7] OEHHA, Prioritization of Chemicals for Carcinogen Identification Committee Review: Proposed Chemicals for Committee Consideration and Consultation (Mar. 2009) at 3 (OEHHA Proposal), *available at* http://www.oehha.org/prop65/CRNR_notices/state_listing/prioritization_notices/pdf/Chemicals030509.pdf.

[8] *Id.*

[9] OEHHA Proposal at 4.

candidate.[10] In addition, OEHHA prepared a summary of the data it used for the screening procedures and the other pertinent data it has identified for each candidate chemical.

The table in the OEHHA Proposal identifies DEA as a chemical with two or more positive bioassays. The Panel has attempted to determine why OEHHA has classified DEA in this manner, and has been unable to identify an appropriate scientific basis for this classification. The OEHHA summary for DEA lists three animal bioassays for DEA,[11] including two studies performed for the National Toxicology Program (NTP) and a transgenic mouse study: (1) a two-year study of dermal administration of DEA to F344/N rats,[12] (2) a two-year study of dermal administration of DEA to B6C3F1 mice,[13] and (3) a 14-week study of dermal application of DEA to transgenic female mice.[14] Of these three studies, the rat study and transgenic mouse study were clearly negative.

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10 OEHHA Proposal at 5-6.

11 OEHHA, Screening Data Summary for Diethanolamine (DEA) (OEHHA DEA Summary) (Mar. 2009), *available at* http://www.oehha.org/Prop65/CRNR_notices/state_listing/prioritization_notices/pdf/Diethanolamine.pdf.

12 NTP, Technical Report on the Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies), NTP Technical Report 478 (July 1999) (NTP DEA Studies), *available at* http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr478.pdf.

13 *Id.*

14 Spalding, J.W., French, J.E., Stasiewicz, S., Furefi-Machacek, M., Conner, F., Tice, R., and Tennant, R. (2000). Responses of transgenic mouse lines p53$^{\pm}$ and Tg.AC to agents tested in conventional carcinogenic bioassays. *Toxicol. Sci.* 53:213-23.

The only positive bioassay for DEA was the study of dermal administration to B6C3F1 mice, in which DEA was associated with significant increases in liver tumors in both sexes. Since this was the only positive study, it appears that OEHHA may have decided that this should be construed as two positive bioassays because excess tumors were observed in both male mice and female mice. Such an approach to classification is not consistent with standard scientific convention. Moreover, there is no suggestion either in the OEHHA Proposal, or in the description of the OEHHA methodology presented to the CIC, that increased tumors in the same tissue in the same strain of the same species would be treated as two positive bioassays if the excesses were to occur in both sexes.

The IARC monograph on DEA refers to the NTP bioassay of B6C3F1 mice as "one study."[15] IARC classified the evidence in experimental animals for the carcinogenicity of DEA as "limited evidence."[16] In a report prepared by an NTP Subcommittee for the NTP Report on Carcinogens (RoC), one of the Subcommittee members who was also on the IARC Working Group for DEA stated that IARC classified the evidence as "limited" because "there was clear evidence of carcinogenicity in only . . . one tissue of one species."[17] As shown in the following section, DEA was extensively evaluated by three NTP committees as part of the RoC process,

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[15] International Agency for Research on Cancer (IARC), Chapter on Diethanolamine (pps. 349-79), in IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Some Industrial Chemicals (IARC DEA Monograph), Volume 77 (Feb. 15-22, 2000) at 373, *available at* http://monographs.iarc.fr/ENG/Monographs/vol77/mono77.pdf.

[16] IARC DEA Monograph at 374.

[17] NTP, Board of Scientific Counselors, Report on Carcinogens Subcommittee Meeting, Summary Minutes (Nov. 19-20, 2002) (RoC Subcommittee Minutes) at 14, *available at* http://ntp.niehs.nih.gov/ntp/htdocs/Liaison/111902.pdf.

utilizing criteria similar to those employed for this screening by OEHHA, and all of these committees concluded that DEA was positive for only one site in one species.

Dr. Gordon Hard, another member of the IARC Working Group for DEA, sent a letter to the Panel, which was previously submitted by the Panel to OEHHA on October 19, 2000.[18] Dr. Hard observed:

> Experimental convention and statistical logic determine that the male and female findings within a single species in carcinogenicity bioassays are treated as part of the same bioassay and not as two separate studies. This is the standard approach promulgated by authoritative guideline-setting bodies including IARC and the U.S. Environmental Protection Agency (EPA).[19]

It does not make sense for OEHHA to construe the excesses of liver tumors in both sexes of B6C3F1 mice as two separate bioassays. If these findings are classified as a single positive bioassay, DEA does not pass OEHHA's animal data screen, and DEA would not be one of the 38 candidate chemicals being presented to the CIC.

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[18] Letter from Jonathon T. Busch, Manager, ACC Alkanolamines Panel, to Cynthia Oshita, OEHHA (Oct. 19, 2000).

[19] Letter from Dr. Gordon C. Hard to Jonathon T. Busch, Manager, ACC Alkanolamies Panel (Sept. 14, 2000) at 3.

B. Expert Committees Established for the NTP RoC Repeatedly Decided That DEA Does Not Satisfy Criteria Very Similar to the OEHHA Screening Criteria

DEA was extensively evaluated by several distinguished NTP committees established for the RoC[20] at a time when DEA was one of ten substances nominated for inclusion in the RoC.[21] DEA was the only one of the ten nominated substances not ultimately listed, and all three of the NTP committees voted not to list it.[22]

In deciding whether to list a substance in the RoC, NTP uses the following criteria for animal data:

> There is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset.[23]

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[20] These committees were the NIEHS Review Committee for the Report on Carcinogens (RG1), the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2), and the NTP Board of Scientific Counselors Subcommittee for the Report on Carcinogens (RoC).

[21] NTP, Call for Public Comments on 10 Nominations, Proposed for Listing in the Report on Carcinogens, Eleventh Edition, 68 Fed. Reg. 3033 (Jan. 22, 2003).

[22] 68 Fed. Reg. at 3035.

[23] NTP RoC Listing Criteria, *available at* http://ntp.niehs.nih.gov/index.cfm?objectid=03C9CE38-E5CD-EE56-D21B94351DBC8FC3.

The RoC criteria are strikingly similar to the OEHHA screening criteria, yet OEHHA has now reached a different conclusion concerning DEA than the three NTP committees that evaluated the same body of scientific evidence.

The RG1 committee report states:

> The majority of the RG1 members felt that the carcinogenicity data was a single tumor type (liver) in one species (mice) and thus did not meet the criteria for listing in the Report on Carcinogens.[24]

Similarly, the RG2 committee stated:

> The RG2 felt that there was insufficient evidence of carcinogenicity of DEA in experimental animals. DEA was carcinogenic in one species (mice) and at one tumor site (liver).[25]

Finally, after an extensive discussion of the same studies that have now been considered by OEHHA, the RoC Subcommittee also concluded that DEA did not meet the listing criteria.[26] In light of the consistent findings by expert NTP committees that DEA does not satisfy criteria very

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[24] Review Summary of the National Institute of Environmental Health Sciences (NIEHS/NTP) RoC Review Committee (RG1), Nomination: Diethanolamine (Dec. 10, 2001) (RG1 Report), *available at* http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/DEARG1RevSumm.pdf.

[25] Review Summary of the NTP Executive Committee Working Group for the Report on Carcinogens (RG2), Nomination: Diethanolamine (DEA) (May 2, 2002) (RG2 Report), *available at* http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/DEARG2RevSumm.pdf.

[26] RoC Subcommittee Minutes at 13-16.

similar to the OEHHA animal data screen, the Panel respectfully requests that OEHHA reconsider its initial determination that this screen has been met for DEA.

II. THE EXCESS INCIDENCE OF LIVER TUMORS FOLLOWING DERMAL ADMINISTRATION OF DEA TO B6C3F1 MICE DOES NOT PROVIDE MEANINGFUL EVIDENCE OF POTENTIAL HUMAN CARCINOGENICITY

A. Liver Tumors Are Often Observed in B6C3F1 Mice and Have Dubious Relevance to Human Carcinogenicity

It has long been known that B6C3F1 mice are more susceptible to liver tumors following exposure to chemical agents than mice of other strains.[27] Indeed, because this strain of mouse is so susceptible to liver tumors, the general consensus is that bioassays in this strain of mouse do not meaningfully discriminate between promoters or other epigenetic agents and genotoxic carcinogens. Consequently, the relevance for human risk assessment of liver tumors observed in B6C3F1 mice following exposure to chemical agents has been frequently questioned.[28]

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[27] Rao, G.N., Birnbaum, L.S., Collins, J.J., Tennant, R.W., and Skow L.L. (1988). Mouse strains for chemical carcinogenicity studies; overview of a workshop. *Fundam. Appl. Toxicol.* 10:385-94.

[28] Grisham, J.W. (1996), Interspecies comparison of liver carcinogenesis: Implications for cancer risk assessment. *Carcinogenesis* 18:59-81; Peroxisome Proliferation and Its Role in Carcinogenesis. Views and Expert Opinions of an IARC Working Group, Lyon, 7-11 (Dec. 1994). IARC Technical Report, No 24; Klaunig, J.E., Babich, M.A., Baetcke, K.P., Cook, J.C., Corton, J.C., David, R.M., DeLuca, J.G., Lai, D.Y., McKee, R.H., Peters, J.M., Roberts, R.A., Fenner-Crisp, P.A. (2003). PPARalpha agonist-induced rodent tumors: modes of action and human relevance. *Crit Rev Toxicol.* 33:655-780; Meek, M.E., Bucher, J.R., Cohen, S.M., Dellarco, V., Hill, R.N., Lehman-McKeeman, L.D., Longfellow, D.G., Pastoor, T., Seed, J., Patton, D.E. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Crit Rev Toxicol.*

B. There Is Robust Evidence That the Excess Liver Tumors in B6C3F1 Mice Associated with DEA Are Caused by Choline Deficiency, and This Mechanism Has Little, if any, Relevance to Potential Human Exposures

There is now compelling evidence that DEA induces liver cancer in B6C3F1 mice through induction of a hepatic choline deficiency, which reduces the ability to methylate DNA and increases S-phase DNA synthesis and cell proliferation. Each element of this epigenetic mode of action has been shown through experimental evidence, and the data also demonstrate that B6C3F1 mice have a special susceptibility to DEA-induced choline deficiency. The data also show that this non-genotoxic mode of action is both reversible, and very unlikely to be relevant for humans. A recent comprehensive review assembles all of the scientific information supporting this mode of action for DEA-induced liver tumors,[29] and this review is among the "other relevant data" listed in the OEHHA screening data summary for DEA.[30]

Dietary choline deficiency is an established cause of spontaneous liver tumors in rodents, including B6C3F1 mice.[31] DEA causes hepatic changes similar to those induced by a

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33:591-653; Boatman, R., Corley, R., Green, T., Klaunig, J., Udden, M. (2004). Review of studies concerning the tumorigenicity of 2-butoxyethanol in B6C3F1 mice and its relevance for human risk assessment. *J Toxicol Environ Health B Crit Rev.* 7:385-3 98 (Sept.-Oct.).

29 Leung, H-W., Kanendulis, L.M., and Stott, W.T. (2005). Review of the carcinogenic activity of diethanolamine and evidence of choline deficiency as a plausible mode of action. *Regul. Toxicol. Pharmacol.* 43:260-271.

30 OEHHA DEA Summary at 2.

31 Newberne, P.M., Decarmargo, J.L.V., and Clark, A.J. (1982). Choline deficiency, partial hepatectomy and liver tuimors in rats and mice. *Toxicol. Pathol.* 10:95-109;

choline-deficient diet, including reduction in choline metabolites and reduction of S-adenosyl-methionine (SAM), which is the source of methyl groups for methylation of DNA.[32] Dermal administration of DEA in ethanol (the same method used in the positive NTP bioassay) increases S-phase DNA synthesis and cell proliferation in the livers of B6C3F1 mice, and this effect is reversible when DEA administration is discontinued.[33] The conclusion that DEA induces liver tumors by causing choline deficiency, and thereby disrupting choline metabolism and DNA synthesis, is also corroborated by a variety of *in vitro* data.[34]

DeCarmargo, J.L.V., Punyarit, P., and Newberne, P. (1985). Early stages of nodular transformation of the B6C3F$_1$ mouse liver induced by choline deficiency, *Toxicol. Pathol.* 13:10-17; Rogers A.E., Nields, H.M., and Newberne, P.M. (1987). Nutritional and dietary influences on liver carcinogenesis in mice and rats. *Arch. Toxicol. Suppl.* 10:231-243.

32 Lehman-McKeeman, L.D. (2001). Incorporating mechanistic data into risk assessment, International Congress of Toxicology, Brisbane, Australia; Lehman-McKeeman, L.D., Gamsky, E.A., Hicks, S.M., Vassallo, J.D., Mar., M-H., and Zeisel, S.H. (2002). Diethanolamine induces hepatic choline deficiency in mice. *Toxicol. Sci.* 67:38-45; Stott, W.T., Bartels, M.J., Brzak, K.A., Mar, M-H., Markham, D.A., Thornton, C.M., and Zeisel, S.H. (2000). Potential mechanisms of tumorigenic action of diethanolamine in mice. *Toxicol. Lett.* 114:67-75.

33 Mellert, W., Kaufmann, W., Rossbacher, R., and van Ravenzwaay, B. (2004). Investigations on cell proliferation in B6C3F$_1$ mouse by diethanolamine. *Food Chem. Toxicol.* 42:127-134.

34 Lehman-McKeeman, L.D. and Gamsky, E.A. (1999). Diethanolamine inhibits choline uptake and phosphotidylcholine synthesis in Chinese hamster ovary cells. *Biochem. Biophys. Res. Commun.* 262:600-604; Lehman-McKeeman, L.D. and Gamsky, E.A. (2000). Choline supplementation inhibits diethanolamine-induced morphological transformation in Syrian hamster ovary cells; evidence for a carcinogenic mechanism. *Toxicol. Sci.* 67:38-45; Kamendulis, L.M., and Klaunig, J.E. (2005). Species differences in the induction of hepatocellular DNA synthesis by diethanolamine. *Toxicol. Sci.* 87(2):328-335.

Choline deficiency as the mode of action for the carcinogenic effects of DEA is further supported by observed differences between species and strains. In contrast to the mouse data, scientific evidence reflects that DEA administration does not alter hepatic concentrations of choline metabolites or SAM in rats,[35] a species in which DEA is not carcinogenic at the maximum tolerated dose. The data also establish that B6C3F1 mice are particularly sensitive to the effects of DEA on choline metabolism. When C57B1/6 mice were treated with DEA, choline metabolites were decreased but SAM levels were not,[36] and the effect of choline deficiency on methylation capacity is much greater in B6C3F1 mice than C57B1/6 mice.[37]

There is little reason to consider DEA induced choline deficiency as a potential mechanism for human carcinogenicity. DEA is more readily absorbed through the skin of mice than rats, and the absorption of DEA through human skin is even less than rats.[38] Moreover, rats and mice are both far more susceptible to choline deficiency than humans.[39] When these factors are considered along with the need for chronic administration of DEA to cause choline deficiency even in the most susceptible species and the demonstrated reversibility of that effect,

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35 Lehman-McKeeman (2001).

36 *Id.*

37 Counts, J.L., Sarmiento, J.I., Harbison, M.L., Downing, J.C., McClain, R.M., and Goodman, J.I. (1996), Cell proliferation and global methylation status changes in mouse liver after phenobarbitol and/or choline devoid, methionine deficient diet administration. *Carcinogenesis* 17:1251-1257.

38 Sun, J.D., Beskitt, J.l., Tallant, M.J., and Frantz, S.W. (1996). In vitro skin penetration of monoethanolamine and diethanolamine using excised skin from rats, mice, rabbits, and humans. *Cutaneous Ocular Toxicol.* 15:131-146.

39 Zeisel S.H. and Blusztajn, J.K. (1994). Choline and human nutrition. *Annu. Rev. Nutr.* 14:269-296.

it is very implausible that humans could be exposed to sufficient levels of DEA to involve any carcinogenic risk.

C. The High Incidence of Liver Tumors in Ethanol-Treated Control Mice Raises Serious Concerns about Potential Confounding, Particularly Since Ethanol Also Causes Choline Deficiency in This Species

The observation of excess liver tumors in the NTP bioassay of B6C3F1 mice was likely confounded and exacerbated by the use of ethanol as the vehicle for dermal dosing with DEA. The possibility of such confounding was suggested by the observation that incidences of liver tumors in the ethanol-treated controls were outside of the standard range for historical controls in NTP bioassays.[40]

Chronic ethanol ingestion has been shown to increase hepatic choline requirements,[41] and the principal observed effect is a reduction of hepatic betaine levels.[42] Betaine is a choline metabolite that directly contributes to methylation capacity.[43] The dosage of ethanol used in the NTP bioassay has been specifically shown to reduce hepatic betaine levels.[44]

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40 NTP DEA Studies at 43-44; Stott, W.T. and Bahnemann, R., Diethanolamine: A Conversation with OEHHA Staff on Research Developments (Mar. 26, 2001).

41 Barak, A.J., Tuma, D.J., and Sorrell, M.F. (1973). Relationship of ethanol to choline metabolism in the liver: A review. *Am. J. Clin. Nutr.* 26:1234-1241.

42 Chern, M.K., Gage, D.A., and Petruszko, R. (2000). Betaine aldehyde, betaine and choline levels in rat livers during ethanol metabolism. *Biochem. Pharmacol.* 60:1629-1637.

43 Leung, *et al.* (2005) at Figure 2.

44 Lehman-McKeeman, *et al.* (2002).

Thus, it is highly probable that use of ethanol as the vehicle for DEA administration confounded and/or exacerbated the induction of liver tumors by DEA itself.

In addition, the mice in the NTP bioassay had free access to the dermal application site during their standard grooming activities. Subsequent research has shown that the blood concentration of DEA in mice that had such access was 32% greater than in mice where the dermal application site was occluded.[45] This supports the conclusion that the effect of dermal administration of DEA in the NTP bioassay was probably also confounded by oral administration, and that this study is best characterized as a combined dermal and oral study.

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[45] Stott, W.T., Bartels, M.J., Brzak, K.A., Mar, M-H., Markham, D.A., Thornton, C.M., Kan, L., Curry, S., Purdon, M., and Zeisel, S.H. (2000). Potential mechanisms of tumorigenic action of diethanolamine in mice. *Toxicologist* 54 (abstract #1022).

D. The Available Data Clearly Demonstrate That DEA Is Not Genotoxic, and Choline Deficiency Was Also the Apparent Cause of Positive Results in a SHE Transformation Study

The table in the OEHHA Proposal also suggests that there are positive genotoxicity data for DEA.[46] This is potentially quite misleading in light of the widespread belief that DEA is not genotoxic.[47] Results for DEA are negative in a wide variety of standard genetic toxicity tests,[48] including each of the genotoxicity tests specifically referenced by OEHHA in its data summary for DEA.[49]

The Panel presumes that the box for genotoxicity has been checked in the entry for DEA in the table in the OEHHA Proposal because DEA was shown to induce cell transformation after seven-day treatment in the Syrian hamster embryo (SHE) clonal assay.[50] A subsequent repeat of this assay confirmed that DEA does cause this response, but also demonstrated that the transformation can be prevented merely by supplementing with choline.[51] This finding indicates that the mechanism for cell transformation in the SHE assay also involves

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46 OEHHA Proposal at 5.

47 *See, e.g.,* RG2 Report at 2 ("DEA does not appear to be mutagenic or genotoxic.").

48 NTP DEA Studies at 182-192; IARC Monograph at 369-372.

49 OEHHA DEA Summary at 1.

50 Kerckaert, G.A., Brauninger, R., LeBoeuf, R.A., and Isfort, R.J. (1996). Use of Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.* 104:1075-1084; IARC DEA Monograph at 370.

51 Lehman-McKeeman and Gamsky (2000); IARC DEA Monograph at 372.

choline deficiency. Because this is the same threshold mechanism that has been demonstrated for carcinogenicity in B6C3F1 mice, this result provides an unreliable basis for evaluating human carcinogenic potential.

III. EPIDEMIOLOGICAL DATA FROM OCCUPATIONAL EXPOSURE TO METAL WORKING FLUIDS INVOLVE COMPLEX MIXTURES, AND CANNOT BE RELIABLY USED TO ASSESS ANY HAZARD ASSOCIATED SPECIFICALLY WITH DEA

Although it does not appear that DEA was included among the candidate chemicals based on epidemiological data, the CIC may still wish to consider this information in making its recommendations to OEHHA concerning prioritization of DEA. Although DEA is among the substances used in metalworking fluids, and there are studies showing elevated cancer risk in metalworkers, metalworking fluids are complex mixtures and contain many potential carcinogens. After reviewing the available data from occupational groups with potential DEA exposure, IARC observed that "the mixed and varying exposures may explain the variability of the results of the different studies and also make it difficult to ascribe the excesses of cancer observed to any single agent."[52] The RG2 Committee concluded that "human cancer studies on metalworking fluids are not relevant for the evaluation of the carcinogenicity of DEA,"[53] and the RoC Subcommittee Minutes state that "the specific effects of DEA can not be separated from the effects of other components in metalworking fluids."[54] In light of these limitations, the available epidemiological data cannot be reliably used for evaluating potential human carcinogenicity of

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[52] IARC DEA Monograph at 360.

[53] RG2 Report at 1.

[54] RoC Subcommittee Minutes at 13.

DEA. Thus, OEHHA has correctly characterized these data in its table as "mixed/poorly defined exposures."[55]

IV. IN THE AGGREGATE, THE AVAILABLE DATA ON THE CARCINOGENICITY OF DEA ARE NOT SUFFICIENT TO WARRANT PREPARATION OF HAZARD IDENTIFICATION MATERIALS

Because excesses of liver tumors in both sexes of B6C3F1 mice exposed to DEA in a single NTP study cannot be properly classified as two positive bioassays, DEA should not have passed OEHHA's animal data screen. In any case, the available scientific data clearly demonstrate that the mechanism by which DEA induced these liver tumors was DEA-induced choline deficiency, which resulted in reduced capacity to methylate DNA and increased cell replication in the livers of the exposed mice. This is a threshold and reversible mechanism, and the scientific data also demonstrate that this mechanism has little, if any, relevance to humans exposed to DEA. In these circumstances, the CIC should advise OEHHA that DEA should be assigned no priority or a low priority, and OEHHA should recognize that there is no justification to prepare Hazard Identification Materials for DEA.

[55] OEHHA Proposal at 5.

COMMENTS ON TRIETHANOLAMINE (TEA)

V. OEHHA ALSO INCORRECTLY APPLIED ITS ANIMAL DATA SCREENING METHODOLOGY TO AVAILABLE DATA FOR TEA

A. OEHHA Itself Previously Observed That There Are Substantial Reasons to Discount the Lymphomas Reported in Female Mice Ingesting TEA in the Hoshino and Tanooka Study, Including a Failure to Consider Historical Controls and Possible Degradation Products Caused by Heating

As in the case of DEA, the table in the OEHHA Proposal identified TEA as a chemical with two or more positive cancer bioassays.[56] The OEHHA summary of the pertinent data for TEA lists seven bioassays for TEA.[57] These studies include: (1) a two-year study by NTP of dermal administration of TEA to B6C3F1 mice (which was repeated by NTP due to chronic infection of the mice with *Helicobacter hepaticus*),[58] (2) a two-year repeat study by NTP of dermal administration of TEA to B6C3F1 mice,[59] (3) a two-year study by NTP of dermal

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56 OEHHA Proposal at 6.

57 OEHHA, Screening Data Summary for Triethanolamine (TEA) (OEHHA TEA Summary), *available at* http://www.oehha.org/Prop65/CRNR_notices/state_listing/prioritization_notices/pdf/TEA.pdf.

58 NTP, Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and $B6C3F_1$ Mice (Dermal Studies), NTP Technical Report 449 (Nov. 1999) (NTP 1999 TEA Studies), *available at* http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr449.pdf.

59 NTP, Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in $B6C3F_1$ Mice (Dermal Study), NTP Technical Report 518 (May 2004) (NTP 2004 Mouse Study), *available at* http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr518.pdf.

administration of TEA to F344/N rats,[60] (4) a lifetime study of dietary administration of TEA to ICR-JCL mice,[61] (5) an 82-week study of TEA administered in drinking water to B6C3F1 mice,[62] (6) a two-year study of TEA administered in drinking water to F344/DuCrj rats,[63] and (7) a 14-week study of dermal application of TEA to transgenic female mice.[64]

The 1999 NTP bioassay of TEA in B6C3F1 mice was repeated by NTP because the mice had a chronic infection with *Helicobacter hepaticus,* an organism that is known to induce hepatitis. This infection precluded meaningful interpretation of the relationship between TEA exposure and effects on the liver. The IARC Working Group completely disregarded this study because it was deemed inadequate by NTP, even though the study had not yet been repeated.[65] Now that a 2004 repeat of the 1999 study deemed inadequate by NTP is available, it is difficult to see reason for OEHHA to consider the earlier deficient NTP study.

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60 NTP 1999 TEA Studies.

61 Hoshino, H. and Tanooka, H. (1978). Carcinogenicity of triethanolamine in mice and its mutagenicity after reaction with sodium nitrite in bacteria. *Cancer Res.* 38:3918-3921.

62 Konishi, Y., Denda, A., Uchida, K., Emi, Y., Ura, H., Yokose, Y., Shiraiwa, K., and Tsutsumi, M. (1992). Chronic toxicity carcinogenicity studies of triethanolamine in B6C3F1 mice. *Fundam. Appl. Toxicol.* 18:25-29.

63 Maekawa, A., Onodera, H., Tanigawa, H., Furuta, K., Kanno, J., Matsuoka, C., Ogiu, T., and Hayashi, Y. (1986). Lack of carcinogenicity of triethanolamine in F344 rats. *J. Toxicol. Environ. Health* 19:345-357.

64 Spalding, *et al.* (2000).

65 International Agency for Research on Cancer (IARC), Chapter on Triethanolamine (pps. 381-401), in IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Some Industrial Chemicals (IARC TEA Monograph), Volume 77 (Feb. 15-22, 2000), at 387, *available at* http://monographs.iarc.fr/ENG/Monographs/vol77/mono77.pdf.

Of the remaining six bioassays, four are clearly negative. The only positive bioassay under the OEHHA criteria is the 2004 NTP study, which found an excess of combined benign and malignant liver tumors in female B6C3F1 mice. The 1999 NTP bioassay of F344/N rats found only an excess of benign adenomas in the treated males. Since OEHHA determined using its animal data screen that there are two positive bioassays for TEA, the Panel presumes that the second positive bioassay identified by OEHHA must be the 1978 study by Hoshino and Tanooka.

The Hoshino and Tanooka study was criticized by IARC on two grounds:

> The Working Group noted the lack of historical control data on the incidence of lymphomas in female mice, as well as the possibility that heating of the triethanolamine in the diet may have produced degradation products.[66]

In the 2004 NTP repeat of its bioassay of TEA in B6C3F1 mice, NTP compared the low incidence of tumors in the control group in the Hoshino and Tanooka study to historic control data from another study in the same mouse strain. NTP observed:

> In another long-term study with ICR mice (Inai *et al.*, 1979), the combined incidence of thymic lymphoma and nonthymic leukemia in control females at 109 weeks was 5/15. This rate is 10 times greater than the rate observed in the female control group of the Hoshino and Tanooka study, and is similar to that reported for triethanolamine-treated females.[67]

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66 IARC TEA Monograph at 386.

67 NTP 2004 Mouse Study at 17.

OEHHA itself previously evaluated all available bioassays for TEA in 2004 as part of its prioritization process for candidate chemicals in "Batch # 4." In that review, OEHHA concluded:

> Triethanolamine (CAS No 102-71-6) did not reach a level of carcinogenicity concern sufficient to be placed on the candidate list.[68]

In its 2004 review, OEHHA described the problems with the Hoshino and Tanooka study that had been previously identified by IARC and NTP, and OEHHA appeared to assign little or no weight to this study as well.[69] The Panel does not believe that it is appropriate to conclude that TEA has passed the current OEHHA animal data screen based on an older study with clearly established serious methodological deficiencies. In these circumstances, the most reasonable conclusion is that the only positive bioassay under the stated OEHHA criteria is the NTP study in B6C3F1 mice. Accordingly, OEHHA should reconsider its determination that the animal data screen has been satisfied for TEA.

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68 OEHHA, Final Prioritized Candidate Chemicals under Consideration for Carcinogenicity Evaluation: Fourty Five Batch #4 Chemicals (Mar. 2004) (OEHHA Batch #4 Report) at 67, *available at* http://oehha.ca.gov/prop65/docs_state/pdf/bat4final45sums.pdf.

69 *Id.*

B. Excess Benign Adenomas from Dermal Administration of TEA to Male Rats Do Not Constitute a Second Positive Animal Cancer Bioassay

Although the 1999 NTP bioassay of TEA in F344/N rats found an excess of benign renal adenomas in the treated males, this does not satisfy the OEHHA criteria for a "positive bioassay." As noted above, the OEHHA animal data screening criteria state:

> A positive animal cancer bioassay is a study in which a treatment-related increase in the incidence of malignant or combined malignant and benign tumors is observed in a given tissue or organ, or for a given type of tumor (e.g., hemangiosarcoma).[70]

Thus, the 1999 NTP rat study does not meet the criteria for being a positive bioassay, although it may be a candidate for the alternative OEHHA screen that considers studies with excesses of benign tumors.

[70] OEHHA Proposal at 3.

VI. THE EXCESS INCIDENCE OF COMBINED BENIGN AND MALIGNANT LIVER TUMORS IN FEMALE MICE FOLLOWING DERMAL ADMINISTRATION OF TEA DOES NOT PROVIDE MEANINGFUL EVIDENCE OF POTENTIAL HUMAN CARCINOGENICITY

A. When Benign Lesions Are Excluded, Malignant Liver Tumors Were Not Significantly Elevated in the Treated Female Mice

In the 2004 NTP repeat bioassay of TEA in B6C3F1 mice, there was a significant excess of combined benign and malignant livers in treated female mice. NTP emphasized that there was no significant excess of malignant liver tumors, and based its decision that the study provided "some evidence" of carcinogenic activity only on a significant excess of hepatocellular adenomas in the treated females.[71] Although this NTP study technically satisfies the OEHHA criteria for classification as a positive bioassay because there was a significant excess of combined benign and malignant tumors, the evidence for carcinogenicity of TEA in this study is quite weak. Thus, it appears that OEHHA has concluded that TEA passes its animal data screen based on a combination of one study which is barely sufficient to be classified as positive under the OEHHA criteria and another study which OEHHA has previously acknowledged has severe methodological problems.

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[71] NTP 2004 Mouse Study at 41. There was also an excess of hemangiosarcomas in treated male mice in the middle dose group, but there was no increase in these lesions in the highest dose group and also no dose-related trend. NTP characterized this as an "uncertain finding" and described it as "equivocal evidence" of carcinogenicity. *Id.* at 40-41.

B. Concerns about the Relevance of Liver Tumors in B6C3F1 Mice to Human Carcinogenic Risk Also Apply to This Study

As in the case of DEA, the evidence for the carcinogenicity of TEA is limited to liver tumors in B6C3F1 mice. As explained above, this strain has unusual susceptibility to liver tumors, and such tumors are widely considered to have dubious relevance to potential human carcinogenicity. Moreover, both IARC and NTP have concluded that TEA is not genotoxic.[72] Since the evidence of carcinogenicity for TEA consists primarily of an excess of benign liver tumors in one sex in a strain that is known to be particularly sensitive, there is substantial reason to suspect that the excess liver tumors are attributable to promotion or another epigenetic mechanism.

C. Like DEA, There Is Substantial Evidence That Any Liver Tumors Associated with TEA Exposure Are Attributable to Choline Deficiency

As noted above, there is robust evidence that the carcinogenic effects of DEA in B6C3F1 mice are caused by the ability of DEA to induce choline deficiency. Although the data for TEA are considerably more limited, a recent study of female B6C3F1 mice found decreased levels of choline and its metabolites betaine and phosphocholine in the high-dose group.[73] These findings were supported by an additional study of the effect of TEA on uptake of radiolabeled

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[72] IARC TEA Monograph at 393-396; NTP 2004 Mouse Study at 18.

[73] Stott, W.T., Radtke, B.J., Linscombe, V.A., Mar, M-H., and Zeisel, S.H. (2004). Evaluation of the potential of triethanolamine to alter hepatic choline levels in female B6C3F1 mice. *Toxicol. Sci.* 79:242-247.

choline by cultured Chinese Hamster Ovary Cells.[74] Although the effect of TEA on choline metabolism is less pronounced than for DEA, the evidence that TEA causes liver tumors in B6C3F1 mice is considerably more limited as well. In the aggregate, the scientific data indicate that choline deficiency is also a plausible mode of action for the excess of benign liver tumors associated with TEA.

VII. EPIDEMIOLOGICAL DATA FROM OCCUPATIONAL EXPOSURE DURING METAL WORKING ARE ALSO INADEQUATE TO RELIABLY EVALUATE ANY EFEECTS FROM TEA

As stated in the discussion for DEA, there are some epidemiological data from studies of metalworkers who used fluids containing ethanolamines. These fluids are complex mixtures that may contain numerous potential carcinogens. IARC noted that it cannot be established whether particular workers even used fluids containing TEA.[75] OEHHA has previously concluded:

> There are no adequate human data on which to evaluate the carcinogenicity of triethanolamine.[76]

The Panel agrees that there are no adequate human data that suggest that TEA presents any carcinogenic hazard. As in the case of DEA, OEHHA properly classified the available human data for TEA as "mixed/poorly defined exposures."[77]

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[74] *Id.*

[75] IARC TEA Monograph at 386.

[76] OEHHA Batch #4 Report at 67.

VIII. OEHHA SHOULD AFFIRM AND EXTEND ITS DETERMINATION DURING PRIOR SCREENING THAT THE EVIDENCE OF POTENTIAL HUMAN CARCINOGENICITY FOR TEA IS NOT SUFFICIENT TO WARRANT PREPARATION OF HAZARD IDENTIFICATION MATERIALS

TEA should not have passed the OEHHA animal data screen, because the only two bioassays of TEA that may be construed as potentially positive are a marginal study in which there were no significant excesses of malignant tumors, and an older study with clearly established methodological problems. In any case, there is reason to conclude that the excess of combined benign and malignant tumors in female B6C3F1 mice exposed to TEA is not attributable to genotoxicity and was likely caused by choline deficiency. There is little, if any, basis to suppose that this finding has any relevance in evaluating human carcinogenicity.

As explained above, this is not the first time that TEA has been evaluated by OEHHA for prioritization under Proposition 65. In the earlier review, OEHHA concluded that TEA "did not reach a level of carcinogenicity concern sufficient to be placed on the candidate list."[78] The current data provide even less basis for any concern that TEA may be a human carcinogen, because data on the effects of TEA on choline and choline metabolites were developed since OEHHA made its previous determination. The Panel recognizes that the current prioritization exercise represents a new phase in OEHHA review, but urges OEHHA to extend and confirm its prior determination. Based on all of the available scientific evidence, the CIC

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[77] OEHHA Proposal at 6.

[78] OEHHA Batch #4 Report at 67.

should advise OEHHA that TEA should be assigned no priority or a low priority, and OEHHA should recognize that there is no justification to prepare Hazard Identification Materials for TEA.

CONCLUSION

The Panel appreciates this opportunity to offer its comments. Based on the available scientific evidence concerning the potential carcinogenicity of DEA and TEA, the Panel urges the CIC to advise OEHHA to assign no priority or a low priority to each of these substances. In reliance on the same evidence, OEHHA should decline to include DEA and TEA among those materials for which it will prepare Hazard Identification Materials.