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LAW OFFICES

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VIA EMAIL
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CYNTHIA.OSHITA@OEHHA.CA.GOV) AND
OVERNIGHT MAIL

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, CA 95814

Re: NOIL – Ethylene Glycol

Dear Ms. Oshita:

On behalf of the Writing Instrument Manufacturers Association ("WIMA") and The Art and Creative Materials Institute ("ACMI"), I am submitting comments on the proposed listing of ethylene glycol as a reproductive toxicant under Proposition 65, along with copies of studies not considered by the authoritative body cited in OEHHA's April 11, 2014 Notice of Intent to List. WIMA and ACMI also join in the comments submitted by the American Chemistry Council. We appreciate the opportunity to provide comments on this important regulatory proceeding.

The Office of Environmental Health Hazard Assessment ("OEHHA") proposes to list ethylene glycol via the authoritative bodies mechanism based on a 2004 National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction Monograph. As explained further in this letter, the proposed listing does not meet the applicable Proposition 65 regulatory criteria because: (a) there is no substantial evidence that the criteria of 27 California Code of Regulations Section 25306(g) have been satisfied; and (b) scientifically valid data not considered by NTP-CERHR clearly establish that the Section 25305(g) criteria have not been satisfied. Briefly, in the absence of human studies only the rabbit model is relevant to evaluate the biological plausibility of the association between adverse human developmental effects and ethylene glycol, and rabbits exhibited no adverse developmental effects following exposure to this chemical, even at high doses. OEHHA therefore should not list ethylene glycol.

Meaningful warnings begin with meaningful listings. This listing, if it proceeds, would increase the number of Proposition 65 warnings without providing useful information for the public, and would increase frivolous litigation. Such outcomes undermine recent efforts by the California Governor and OEHHA to enhance Proposition 65's effectiveness. Nevertheless, if the agency nevertheless proceeds with listing ethylene glycol, it should limit the listing to ethylene glycol via the oral route of exposure.

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I. EXECUTIVE SUMMARY

WIMA and ACMI are trade associations whose members sell products around the world, including California. Most of these organizations' member companies are small and medium enterprises. Many of these member companies' product lines, including inks and certain art materials, contain ethylene glycol.

Ethylene-glycol containing products are subject to the labeling requirements, and exemptions (if applicable), of the Federal Hazardous Substances Act ("FHSA"). Exemptions from FHSA labeling are based on specified criteria including toxicological safety criteria and limits on total mass of ethylene glycol. WIMA's and ACMI's members' products comply with these requirements.

Both WIMA and ACMI sponsor certification programs, under which member companies' products undergo toxicological evaluations for the assessment of acute and chronic health hazards. These certification programs incorporate federal requirements under the FHSA and the Labeling of Hazardous Art Materials Act, and the requirements of ASTM Standard D4236. Depending on the outcome of the evaluation required under the certification program, member companies are granted the use of the applicable program's certification seal and the certified products bear safety labeling, if any such labeling is required. Consumers have come to rely on these programs' certification seals to obtain information about the certified products' safety and to make purchasing choices.

These certification programs, and the member companies' economic viability, will be jeopardized by the scientifically unsupported listing of ethylene glycol. Listing ethylene glycol ultimately also will lead to unnecessary Proposition 65 warnings and will increase unnecessary litigation. These outcomes are contrary to the California Governor's and OEHHA's efforts to enhance Proposition 65's effectiveness.

OEHHA proposes to list ethylene glycol via the authoritative bodies mechanism based on a 2004 National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction Monograph. There are two independent reasons OEHHA should not list ethylene glycol:

1. There is no substantial evidence that the criteria for listing in 27 California Code of Regulations Section 25306(g)(1) or (g)(2) have been satisfied.

   a. The 2004 NTP-CERHR Monograph, on which the proposed listing is based, does not evaluate any human developmental effects studies and therefore no data exist to satisfy Section 25306(g)(1).

   b. No substantial evidence exists that the criteria in Section 25306(g)(2) are satisfied. The association between the adverse effects in humans and ethylene glycol is not biologically plausible. The animal data in the Monograph demonstrate that rabbits, an animal model more relevant to humans than rodents, do not exhibit developmental toxicity following exposure to high doses of ethylene glycol. The high dose in the rabbit developmental toxicity study reviewed in the Monograph led to 42% maternal mortality and, in humans like the rabbit model, altered pharmacokinetics undermine the plausibility of developmental toxicity in humans.

Based on those data, the association between human adverse developmental effects and ethylene glycol is not biologically plausible within the meaning of the regulatory listing criteria.

2. Section 25306(h) of 27 California Code of Regulations bars OEHHA from listing ethylene glycol. That section prohibits listing if scientifically valid data not considered by the authoritative body clearly establish that the listing criteria of Section 25306(g)(1) and (g)(2) are not satisfied.

a. No human developmental effects studies are available for evaluation, and therefore no data exist to satisfy Section 25306(g)(1).

b. Scientifically valid data not considered by NTP-CERHR clearly establish that there is no biologically plausible association between human adverse developmental effects and ethylene glycol. As explained further below, the rabbit model is the only relevant model for evaluating human developmental effects resulting from ethylene glycol exposure, and no developmental effects were seen in rabbits exposed to ethylene glycol.

It is well-established that glycolic acid resulting from the metabolism of ethylene glycol, and not ethylene glycol itself, is the chemical agent that has the potential to cause developmental effects. Three factors that control the potential for developmental toxicity from ethylene glycol and its metabolism reveal the absence of biological plausibility:

i. Species differences in peak blood concentrations of glycolic acid

As explained in the Monograph, high blood concentrations of glycolic acid that are only achieved with oral bolus doses are associated with enhanced potential for developmental toxicity. Post-Monograph data confirm that the peak concentration of glycolic acid, rather than the area under the concentration versus time curve, is a key driver of developmental toxicity (Corley et al., 2005). High peak glycolic acid concentrations depend on species-specific differences in the rates of two metabolic steps: fast conversion of ethylene glycol to glycolic acid, and slow elimination of glycolic acid via metabolism to glyoxylic acid.

All species evaluated metabolize ethylene glycol to glycolic acid and then glycolic acid to glyoxylic acid; however, metabolic rates differ and the different rates affect the biological plausibility of developmental toxicity following an oral bolus dose of ethylene glycol. Blood concentrations of glycolic acid remain low with exposures to ethylene glycol, except under the extreme conditions of oral bolus exposure when peak blood concentrations of glycolic acid rise to levels that cause developmental toxicity in some species or other toxic effects including death in other species.

The rate of ethylene glycol metabolism to glycolic acid is important because the faster glycolic acid is produced following a high bolus dose, the higher the peak blood concentration of glycolic acid. Booth et al. (2004), using liver slices (i.e., tissues from the organ primarily responsible for metabolism of ethylene glycol), showed that rodent metabolism of ethylene glycol to glycolic acid in the liver occurs faster than rabbit

metabolism, and rabbit metabolism of ethylene glycol to glycolic acid is faster than human metabolism.

The rate of glycolic acid metabolism also is important, because the faster glycolic acid is metabolized, the lower the peak blood concentration of glycolic acid. Booth et al. (2004), using liver slices, showed that human metabolism of glycolic acid is faster than rat metabolism.

Thus, in humans glycolic acid is formed more slowly and is cleared more rapidly than in rodents or even rabbits. As a result, human exposure to ethylene glycol is not likely to result in the glycolic acid peak blood concentrations necessary to cause developmental effects.

ii. Placental structures in each species affect glycolic acid concentrations surrounding the embryo

The physiological structures surrounding the developing human embryo at the stage of development sensitive to ethylene glycol effects (4 weeks) are similar to the structures surrounding the rabbit embryo at the stage of development sensitive to ethylene glycol effects (10-days), and not similar to the rodent structures. Thus, human and rabbit embryos are less sensitive to ethylene glycol exposures than rodent embryos.

- Unlike rodent embryos, the rabbit embryo at this stage is surrounded by, and bathed in, yolk sac cavity fluid (YSCF), which is present in a large volume compared to the size of the embryo and has a slow turnover rate. (Carney et al. 2008.) The human physiological structures that surround the embryo at the developmental stage sensitive to ethylene glycol are similar to the rabbit, in that the human embryo is surrounded by, and bathed in, celomic fluid that has a large volume compared to the size of the embryo, and this fluid has a slow turnover rate. This is not the case for rodent embryos, and means that the glycolic acid concentration to which human and rabbit embryos are exposed is lower than the concentration to which rodent embryos are exposed, even with the same ethylene glycol dose.

- In contrast to the rabbit and human, rodents at the stage of development sensitive to ethylene glycol effects (~9 days) have a visceral yolk sac (VYS) placenta that completely surrounds the embryo and contains a small amount of exocoelomic fluid (ECF) that contacts the embryo. (Ellis-Hutchings et al., 2014.) The glycolic acid concentration in maternal blood rapidly equilibrates with the ECF in the mouse. (Ellis-Hutchings et al., 2014.) The glycolic acid concentration in the ECF rapidly equilibrates with the embryo. These factors lead to higher glycolic acid levels contacting the rodent embryo than would be expected in humans.

iii. Species differences in maternal and embryonic pH in different species affect glycolic acid accumulation in the fetus

Another key characteristic that controls the entry of glycolic acid into the embryo during the window of sensitivity is the relative difference in pH between the maternal circulation and the embryo. Glycolic acid will not partition to the human embryo to the same extent as rodents. Rodent embryos are relatively alkaline compared to maternal blood, and this gradient drives glycolic acid into the ECF, trapping it there. In contrast, human and rabbit embryos are acidic compared to maternal blood, and therefore the reverse pH gradient will not drive glycolic acid to the human celomic fluid. (Carney et al., 2004; Carney et al., 2008; Carney et al., 2011; Ellis-Hutchings et al., 2014.) In the absence of excess glycolic acid exposure to the embryo, developmental effects in humans will not occur, just as developmental effects were not seen in rabbits.

Taken all together, these new scientific data demonstrate that glycolic acid levels necessary to cause developmental effects will not occur in humans. These scientifically valid data not considered by NTP-CERHR clearly establish that the association between adverse developmental effects in humans and ethylene glycol is not biologically plausible. Therefore, under 27 California Code of Regulations Section 25306(h), OEHHA should not list ethylene glycol.

If OEHHA nevertheless proceeds with the listing, it should limit the listing to ethylene glycol via the oral route of exposure. Dermal and inhalation data show that it is not possible for dermal or inhalation exposures to ethylene glycol to lead to the high levels of glycolic acid necessary to cause any developmental effects in any animal model.

Meaningful warnings begin with meaningful chemical listings. Close scrutiny of the available scientific literature shows that developmental effects would not occur in humans as the result of ethylene glycol exposure. At this critical gate-keeping juncture, OEHHA should refrain from listing this chemical – and thereby assure that any perceived “overwarning” and frivolous enforcement actions do not further proliferate.

II. INTRODUCTION AND BACKGROUND

A. WIMA and ACMI Have A Strong Interest in OEHHA’s Proposed Listing

WIMA and ACMI are trade associations whose members sell products around the world, including California. Most of the organizations’ respective member companies employ 10 or more employees and therefore are subject to Proposition 65. Most of the member companies are small and medium enterprises.

Many of these member companies’ product lines, including inks and certain art materials, contain ethylene glycol. For all of these product lines, reformulation would take years of research, development and testing. Accordingly, WIMA and ACMI have a strong interest in ensuring that the proposed listing of ethylene glycol fully meets all regulatory listing criteria, is based on sound science and comports with Proposition 65’s objectives.

WIMA is a non-profit trade association with over 40 members. The organization's mission is to promote the overall interest of the writing instrument industry in the United States, Canada and Mexico and to inform the general public of the importance of writing instruments and their safe and proper use. Consistent with its mission, WIMA sponsors an ink certification program, which ensures that products bearing the program's certification seal conform to the acute and chronic hazard labeling standard ASTM Standard D4236[1] and federal regulations promulgated under the Federal Hazardous Substances Act (the "FHSA") and the federal Labeling of Hazardous Art Materials Act ("LHAMA").

ACMI is a non-profit international trade association comprised of over 175 companies. ACMI's mission is to create and maintain a positive environment for art, craft and other creative materials usage; to promote safety in these materials; and to serve as an information and service resource on such products. Like WIMA, and consistent with its own mission, ACMI sponsors a certification program for art materials encompassing both children's and adult art material products. In its current form, the certification program incorporates the requirements of ASTM Standard D4236, of LHAMA and of the FHSA's acute health hazards provisions. Pursuant to ACMI's certification program, art materials found to contain no materials in sufficient quantities to be toxic or injurious to humans, including children, or to cause acute or chronic health problems, are designated with an "AP" seal. The "CL" seal is used for products that are certified to be properly labeled in a program of toxicological evaluation by a medical expert for any known health risks, and that bear information on their safe and proper use.

Under both WIMA's and ACMI's certification programs, products undergo toxicological evaluations for the assessment of acute and chronic health hazards. These evaluations, which take Proposition 65 safe harbor exposure levels into account, are undertaken by a toxicology consulting team at the Division of Occupational and Environmental Medicine, Department of Community and Family Medicine, Duke University Medical Center in Durham, North Carolina. Based on the outcome of these evaluations, member companies are granted the use of the applicable program's seals on the certified products, and the certified products are required to be labeled in accordance with federal law and the certification programs' requirements.

B. A Scientifically Unsupported Listing Ethylene Glycol Will Jeopardize WIMA's and ACMI's Certification Programs, Which Incorporate Federal Requirements for Ethylene Glycol-Containing Products

WIMA's and ACMI's certification programs incorporate federal toxicity standards and labeling requirements, including those found at 16 C.F.R. Sections 1500.14 and 1500.83 relating to ethylene-glycol containing products. Member companies' products that comply with the Section 1500.83 standards and requirements are not required to bear warnings or other

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[1] ASTM Standard D4236 is an industry standard by which art material products are evaluated by qualified toxicologists, based on current scientific and medical information, for chronic health hazards including cancer and reproductive harm. The standard imposes requirements for chronic hazard precautionary labels and precautionary statements based on the outcome of the toxicological evaluations, if in the toxicologist's opinion there is the potential to produce a chronic adverse health effect. Precautionary labels and statements, when required, must include certain elements, including the signal word "WARNING."

precautionary labeling and, if the products also meet the certification programs' requirements, receive the applicable program's seal denoting that the product is safe to use. Consumers have come to rely on those seals in making purchasing choices. OEHHA's listing of ethylene glycol, which is not supported by scientifically valid data, will jeopardize the utility of the certification programs, diminish the meaning of the seals and result in economic hardship to the member companies, all with no counterbalancing benefit to the public.

The FHSA, 15 U.S.C. §§1261 *et seq*., and its implementing regulations require precautionary labeling on the immediate containers of hazardous household products. Under 16 C.F.R. Section 1500.14(a)(2) and (b)(2), ethylene glycol and mixtures containing it at levels of 10% or more by weight must be labeled with the word "warning" and the statement "harmful or fatal if swallowed." This requirement, which has been imposed since even before 1973 when the Consumer Product Safety Commission was formed, recognizes the acute poisoning hazard of ethylene glycol.

However, the FHSA regulations also recognize that this hazard is not present in certain products containing ethylene glycol. Thus, 16 C.F.R. Section 1500.83(a) provides that certain products containing ethylene glycol are exempt from the FHSA's ethylene glycol labeling requirements, if the products also meet the regulations' specific criteria (including toxicity safeguard requirements and caps on total mass of ethylene glycol). These exempt products include:

- Rigid or semi-rigid ballpoint ink cartridges, 16 C.F.R. § 1500.83(a)(7);
- Porous-tip ink-marking devices, 16 C.F.R. § 1500.83(a)(9);
- Containers of dry ink to be used as liquid ink after the addition of water, 16 C.F.R. § 1500.83(a)(12);
- Felt pads impregnated with ethylene glycol, 16 C.F.R. § 1500.83(a)(28); and
- Rigid or semi-rigid writing instruments and ink cartridges having a writing point and ink reservoir, 16 C.F.R. § 1500.83(a)(38).

Significantly, the FHSA regulations impose toxicity safeguards for the inks in these exempted products, the specifics of which depend on the particular product. For example, inks in rigid or semi-rigid ballpoint ink cartridges must be tested by a specified method to confirm that it does not have an LD-50 single oral dose of less than 500 milligrams per kilogram of test animal body weight. 16 C.F.R. § 1500.83(a)(7)(ii). For rigid and semi-rigid writing instruments and ink cartridges having a writing point and an ink reservoir, the ink must be tested by a specified method to confirm that it does not have an LD-50 single oral dose of less than 2.5 grams per kilogram of test animal body weight. 16 C.F.R. § 1500.83(a)(38)(ii). Dried inks must be tested by a specific method to confirm that the LD-50 single oral dose is not less than 1 gram per kilogram of test animal bodyweight; dried inks also cannot exceed 15% ethylene glycol by weight. 16 C.F.R. § 1500.83(a)(12). Other ethylene glycol-containing products exempted from FHSA toxicity labeling are subject to similar requirements.

WIMA and ACMI members whose products are subject to the FHSA's ethylene glycol-related requirements comply with those provisions and therefore are not required to bear FHSA warnings. The organizations' respective certification programs incorporate those regulatory requirements as part of their toxicological evaluations. If the evaluated products meet the program's certification requirements (and, by extension, the federal regulatory requirements), the products do not need to bear any acute or chronic health hazard labeling[2] and receive the applicable program's certification seal.

These certification seals are valuable to consumers and the member companies alike. Consumers may, and do, rely on those seals to assure themselves that those products are safe to use. School districts nationwide restrict the purchase of school supplies and art materials to those that have been evaluated for toxicity under programs like WIMA's and ACMI's. For the participating companies, the seals represent their commitment to ensure that their products are safe, as evidenced by the toxicological evaluations that are required to be conducted in order for the companies to be granted the use of the seals on their certified products.

The scientifically unsupported listing of ethylene glycol will jeopardize these organizations' certification programs – ironically, not because anticipated exposures would require warnings. Given the nature of WIMA and ACMI members' products it is most unlikely that any user would come into significant, or any, contact with the chemical. Rather, the current enforcement climate makes it enormously expensive for a company to meet the statutory burden of proving that no warning is required, and compels the decision to provide warnings, as the law permits, in order to avoid expensive and disruptive enforcement actions.

Listing ethylene glycol will have a significant economic impact on WIMA and ACMI members, many of which are small and medium enterprises:

- The costs of Proposition 65 compliance and defense are high, with small and medium enterprises disproportionately affected. This is particularly true when a numerical No Significant Risk Level ("NSRL") or a Maximum Acceptable Dose Level ("MADL") has not been developed for a specific Proposition 65 chemical. In those circumstances, the company shoulders the double burden of hiring experts to develop those values and then to conduct exposure assessments of their products. Either task may run well into the five or even six figures, a significant financial burden especially for entities still recovering from the nation's recent economic downturn.

- In an enforcement action, the plaintiff will challenge each assumption and calculation made in developing an NSRL/MADL and the exposure assessment, requiring additional financial resources to resist those challenges.

- Proposition 65 warnings are incompatible with the organizations' respective certification seals; member companies will have to decide whether to turn away

[2] The exception is for products bearing ACMI's "CL" seal; those products bear appropriate hazard labeling based on the outcome of the toxicological evaluation required under the certification program.

from their long-standing investments participating in the certification programs or face the high cost of defending a Proposition 65 lawsuit.

- Because of high costs in administrating state-specific labeling programs in a complex supply chain, products may bear Proposition 65 warnings even if not bound for sale in California; such warnings on WIMA and ACMI members' products may lead to negative consumer reaction in non-California markets.

- School districts, which comprise a significant customer base, will not purchase products bearing Proposition 65 warnings.

C. Listing Ethylene Glycol Will Not Promote Meaningful Proposition 65 Warnings And Will Increase Frivolous Litigation

WIMA and ACMI are aware of recent efforts by California Governor Brown and by OEHHA to achieve the twin goals of reducing unnecessary Proposition 65 warnings and preventing frivolous lawsuits. WIMA and ACMI, and their respective members, applaud these goals and believe they can be achieved by workable measures that ultimately will enhance the law's effectiveness without impeding business operations. However, if OEHHA proceeds with this listing these goals will be further out of reach.

Meaningful warnings begin with meaningful chemical listings. Here, listing ethylene glycol will not result in meaningful warnings. As discussed further below, the rodent models relied upon by OEHHA simply are not relevant to humans. Providing Proposition 65 warnings for ethylene glycol or products containing it will not advance Proposition 65's right-to-know objectives, if there is no biologically plausible connection between the adverse effect in humans and the chemical. And, in these circumstances, listing would be contrary to voter intent that Proposition 65 "singles out chemicals that are ***scientifically known*** to cause cancer or reproductive disorders…" and that the law will require warnings to be provided to individuals prior to exposure "to any of these ***dangerous*** chemicals." 1986 Proposition 65 Ballot Initiative at 54 (emphasis added).

Circumspection in a listing decision will mean fewer frivolous lawsuits entering California's overly burdened court system. In the absence of any discipline imposed on private enforcement of Proposition 65, and in the absence of meaningful guidance on when a warning is not required, discipline must be imposed at the time when the chemical is listed. At this critical gate-keeping step, WIMA and ACMI urge OEHHA to carefully consider these comments, and the comments of the American Chemistry Council, and refrain from listing ethylene glycol.

Too often private enforcers exploit Proposition 65's liberal provisions and the enormous cost of defending an enforcement action to extract monetary settlement payments in the form of plaintiffs' attorneys' fees, payments in lieu of civil penalties, and civil penalties. As OEHHA is aware, the California Attorney General released her report summarizing private enforcement activity for 2013; over 70% of the total money paid in settlements was payment of plaintiffs' fees alone. In a May 13, 2014 letter to Proposition 65 counsel, the Attorney General expresses concern over this development and concern about the "millions of dollars the alleged violators

undoubtedly paid to their own attorneys."[3] In this regard, the Attorney General's correct observation still overlooks the millions of dollars collectively spent by companies like WIMA and ACMI members, to undertake compliance-oriented, pre-60-Day Notice Proposition 65 assessments to calculate the potential level of exposure to a listed chemical – assessments which are viewed by plaintiffs merely as another factual dispute to be adjudicated in litigation.

Sixty-day notices of violation and enforcement actions routinely take a "kitchen sink" approach to alleging violations, including asserting routes of exposure that are entirely unexpected, like ingestion for shoes, faucet valves and rainwear. With the broad scope of allegations made in enforcement actions, the burden of proof imposed on defendants, the numerous unanswered questions about how to calculate exposures, and the cost and business disruption attendant to a full defense, entities must attempt the impossible to avoid an enforcement action: calculate with absolute scientific certainty the level of chemical exposure resulting from any route of exposure, no matter how farfetched, and expect a plaintiff to simply walk away from a potentially financially rewarding lawsuit when faced with that exposure analysis.

Those companies in the trenches of Proposition 65 enforcement know that such efforts are largely futile because the regulations provide no meaningful guidance on when a warning is not required and because the law provides strong monetary incentives to file enforcement actions. The only sure alternative to avoid a lawsuit is to provide Proposition 65 warnings, as the law permits.

As explained in this letter, the proposed listing does not meet the applicable regulatory criteria. But if OEHHA proceeds with the listing, it can surely expect to see increased Proposition 65 lawsuits that do not advance Proposition 65's right-to-know objectives, for long experience has shown that there simply is no downside for a plaintiff to file them. WIMA and ACMI members – like all entities subject to Proposition 65 – will have to assess whether they will provide warnings on their products even if their own exposure calculations would not compel such an action, as the law permits. And these companies will do so to the detriment of the certification seals that they have invested in, for Proposition 65 warnings cannot be used for certified products under WIMA's program or for AP-certified products under ACMI's program. Consumers will be inundated with warnings, sound, science-based certification programs will be eroded, and businesses will suffer financially.

OEHHA may avoid these detrimental outcomes at this gate-keeping juncture with a close scrutiny of available scientific literature discussed further below, which demonstrate that ethylene glycol should not be listed.

III. THE PROPOSED LISTING DOES NOT MEET APPLICABLE REGULATORY CRITERIA

OEHHA proposes to list ethylene glycol pursuant to the Proposition 65 authoritative body mechanism. *See* Health and Safety Code § 25249.8(b). Under that mechanism, "a chemical is known to the state to cause cancer or reproductive toxicity if the lead agency

[3] This letter is posted at posted on the Attorney General's website at http://www.oag.ca.gov/sites/all/files/agweb/pdfs/prop65/ag_letter_prop65_2013rpt.pdf?

determines that an authoritative body has formally identified the chemical as causing cancer or reproductive toxicity." 27 Cal.Code Regs. § 25306(a). The Proposition 65 regulations establish the criteria for listing a reproductive toxicant using this mechanism. 27 Cal.Code Regs. §25306(g). As explained further below, there is no substantial evidence that the criteria identified in Section 25306(g) have been satisfied. Further, scientifically valid data which were not considered by the authoritative body clearly establish that ethylene glycol does not satisfy the criteria of Section 25306(g). Because ethylene glycol does not meet the applicable listing criteria, OEHHA should not list this chemical.

The proposed listing is based on a 2004 monograph published by the National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction, "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol" (the "Monograph"). The NTP-CERHR has been designated as an authoritative body for the identification of reproductive toxins. 27 Cal.Code Regs. § 25306(l)(3). For purposes of this letter, WIMA and ACMI assume but do not concede that the NTP-CERHR is properly designated as an authoritative body and that the Monograph meets the requirements of Section 25306(d).

"As causing reproductive toxicity" in Section 25306(a) means that either of the following criteria has been satisfied:

> (1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
>
> (2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

27 Cal.Code Regs. § 25306(g). Even if the authoritative body's formal identification of a reproductive toxin meets either or both of the Section 25306(g) criteria, OEHHA ***must*** conclude that a chemical does not satisfy the definition of "as causing reproductive toxicity" if "scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)." 27 Cal. Code Regs. § 25306(h).

In listing chemicals under the authoritative body mechanism, OEHHA is required to conduct a certain level of analysis. It must "review those identifications which the [authoritative] body has made, both for their formality and their scientific basis." Final Statement of Reasons, 22 California Code of Regulations Division 2, Section 12306 – Chemicals Formally Identified by Authoritative Bodies (February 1990) (the "FSOR") at 8. OEHHA also must "investigate to make certain that there are sufficient animal or human data." FSOR at 17; *see also id.* at 22. In reviewing monographs from the NTP-CERHR, OEHHA also should review the entire record, including the scientific record upon which the NTP-CERHR relied, to

determine whether that authoritative body made the necessary findings to support OEHHA's listing. *Exxon Mobil Corp. v. OEHHA* (2009) 169 Cal.App. 4th 1264, 1286-87.

OEHHA also must be mindful of the relevant biological mechanisms of action, as between human and animal models. *See Baxter Healthcare Corporation v. Denton* (2004) 120 Cal.App.4th 333. The biological mechanism of action is relevant here, because the rabbit model, and not the rodent model upon which OEHHA bases its proposed listing, is the relevant model for determining whether exposure to ethylene glycol causes developmental effects. As explained in this letter, rabbit studies demonstrate that ethylene glycol exposures do not result in developmental effects, and therefore an association between adverse human developmental effects and ethylene glycol is not biologically plausible.

A. Overview

In its April 11, 2014 Notice of Intent to List Ethylene Glycol, OEHHA concluded that the Monograph presented "…sufficient data to conclude that oral gavage exposure to high doses of ethylene glycol (CD-1 mice, ≥ 500 mg/kg bw/day on gd 6–15; Sprague-Dawley rats, ≥1,000 mg/kg bw/day on gd 6–15) causes developmental toxicity in mice and rats, including axial skeletal malformations, reduced body weights, external malformations, and increased post-implantation loss. (NTP-CERHR, 2004: Summary and Conclusions of Reproductive and Developmental Hazards, page II-116)." However, in contrast to the developmental toxicity reported in rats and mice following exposure to high doses of ethylene glycol, data presented in the Monograph itself demonstrate that rabbits, an animal model more relevant to humans than rodents, do not exhibit developmental toxicity following exposure to high doses of ethylene glycol (page II-71). In addition, no human studies showing an association between ethylene glycol exposure and developmental toxicity are summarized in the Monograph.

Ethylene glycol does not meet the regulatory criteria for "causing reproductive toxicity." The overall conclusion in the Monograph (page II-119, emphasis added) is:

> *The Expert Panel judges the likelihood of adverse developmental toxicity in humans from such levels of exposure to be of negligible concern.*

New data and absence of observed effects in humans support the definitive conclusion that ethylene glycol does not cause developmental toxicity in humans. First, there are no studies in humans available that indicate there is a causal relationship between ethylene glycol and developmental or reproductive toxicity. Second, there are scientifically valid data from laboratory studies clearly establishing that ethylene glycol-induced developmental toxicity identified in rodents is not biologically plausible in humans. The absence of biological plausibility is based on a weight of evidence analysis of the scientific data that demonstrates greater human relevance of the rabbit model for ethylene glycol exposure during development than the rodent model for developmental toxicity of ethylene glycol. Simply, the data available demonstrate that rabbits and humans share the characteristics that protect rabbits from ethylene glycol-induced developmental toxicity.

Briefly, physiological and toxicokinetic characteristics that protect rabbits and humans from developmental toxicity of ethylene glycol include: (1) rabbits and humans appear to have a

slower rate of ethylene glycol metabolism to the active metabolite, glycolic acid, and a faster metabolism of glycolic acid to glyoxylic acide, than rats, which overall results in a lower glycolic acid peak concentration (Booth et al., 2004); (2) a reduced distribution of glycolic acid to the embryo occurs in rabbits and humans because during the time of gestation most sensitive to ethylene glycol (day 9-10 in rabbits and week 4 in humans) a large volume of fluid that has a low glycolic acid concentration bathes the embryo while the rodent embryo is in contact with a small volume of fluid that has a higher glycolic acid concentration (Carney et al., 2004); and (3) humans and rabbits do not have the mechanism for trapping glycolic acid in the embryo that rats and mice have. Thus, humans and rabbits are protected from the developmental effects seen in the rodent models. (Carney et al., 2011.)

Significantly, new data establish higher saturation threshold for glycolic acid in humans than presumed by in the Monograph (Corley et al., 2005). A key factor is faster clearance of glycolic acid in humans than previously presumed (Booth et al., 2004). Faster clearance of glycolic acid means less potential for developmental effects. Based on this and other information that demonstrates the human relevance of the rabbit model showing a lack of ethylene glycol associated developmental toxicity, WIMA and ACMI urge OEHHA to refrain from listing ethylene glycol as a reproductive toxin.

B. There Is No Substantial Evidence That The Section 25306(g) Criteria Have Been Satisfied

It is well-established that it is glycolic acid, the product of ethylene glycol metabolism, and not ethylene glycol itself, that is the developmental toxicant. No human studies are available to evaluate the causal relationship between ethylene glycol and developmental effects. The only animal models discussed in the Monograph, suggesting developmental effects, are rodent models which are not relevant to humans. In fact, studies cited in the Monograph involving rabbit models, which are relevant to humans, demonstrate that there is no biologically plausible association between adverse developmental effects in humans and ethylene glycol, because: (1) rabbits have lower peak blood levels of glycolic acid than rodents; (2) rabbits have lower fetal exposures for a given blood level of glycolic acid than rodents; and (3) ethylene glycol is not a developmental toxicant in rabbits. Thus, there is no substantial evidence in the record that the Section 25306(g) criteria have been satisfied.

1. Developmental Toxicity - Basis in Monograph

A number of ethylene glycol developmental toxicity studies on rats, mice, and rabbits have been conducted and were summarized in the Monograph (CERHR, 2004). Pregnant mice were the most sensitive to gavage exposure to high doses of ethylene glycol, with fetal effects occurring at 500 mg/kg/day and a no-observed-adverse-effect-level (NOAEL) of 150 mg/kg/day. Rats were somewhat less sensitive than mice to the developmental effects of bolus doses of ethylene glycol in pregnant dams, with fetal effects occurring at 1,000 mg/kg/day and a NOAEL of 500 mg/kg/day. Rabbits did not exhibit developmental toxicity following high oral doses of ethylene glycol during pregnancy. The rabbit fetal NOAEL was the high dose tested, 2,000 mg/kg/day. A dermal exposure study of ethylene glycol application to mice demonstrated that exposure by the dermal route is over an order of magnitude less toxic than bolus oral exposure.

The fetal NOAEL for developmental toxicity of ethylene glycol following dermal exposure in the mouse is approximately 3,549 mg/kg/day.

A series of studies summarized in the Monograph were intended to identify the proximate toxicant responsible for ethylene glycol developmental toxicity. These and other mechanistic data have been compiled and evaluated by Slikker et al., 2004. The accepted conclusion of the evaluation based on significant data is that glycolic acid is the proximate toxicant.

2. Mechanism of Developmental Toxicity - Basis in Monograph

The Monograph (NTP Brief p. 2) identifies the mechanism of developmental toxicity as follows:

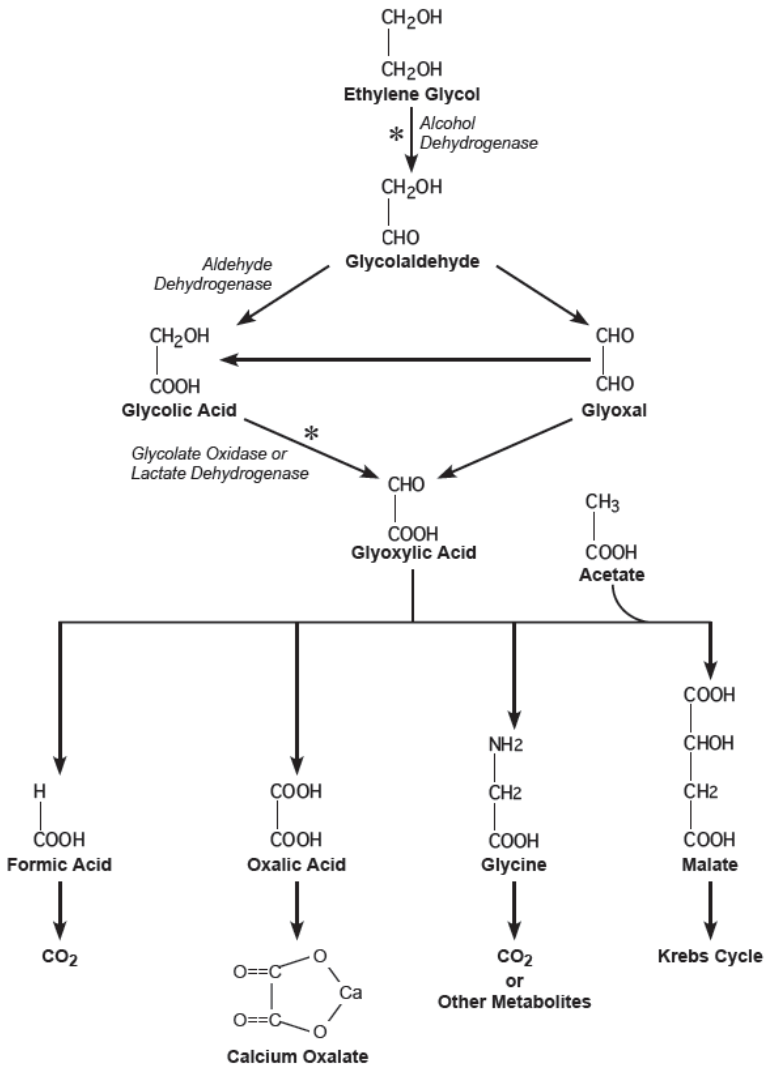
> It appears that EG itself is not directly responsible for developmental toxicity. Rather, developmental toxicity appears to result from the accumulation of glycolic acid, which is formed from the metabolic breakdown of EG. As long as EG exposure does not reach a level that saturates or overwhelms the enzymes that metabolize glycolic acid, there should be no developmental toxicity.

Thus, ethylene glycol (abbreviated EG by CERHR) does not itself cause developmental toxicity; rather, its metabolite, glycolic acid, is responsible for the developmental effects observed in rodents. The Monograph (page II-16) states the following:

> The reviews provide generally consistent descriptions of the metabolic process. Figure 2-1 outlines the metabolic pathway of ethylene glycol, which is qualitatively similar in humans, monkeys, dogs, rabbits, rats, and mice.

Although metabolism is qualitatively similar between species, it is quantitatively different. Figure 2-1 from the Monograph, pasted below, shows that the key steps in the pathway (rate limiting) are conversion of ethylene glycol to glycoladehyde and then conversion of glycolic acid to glyoxylic acid. Although the metabolic processing of ethylene glycol (Figure 2-1) is shared by the key species, *quantitative differences* among species in the rate-limiting steps dramatically affect blood concentrations of glycolic acid, which in turn affects the developmental toxicity potential of ethylene glycol in different species.

Figure 2-1. Metabolism of Ethylene Glycol



*Rate-limiting steps
Adapted from Carney *(35)* and Jacobsen et al. *(51)*

Quantitative differences in metabolism along with mother/fetus distribution differences between species (discussed elsewhere in this submission) are the key factors preventing developmental toxicity in humans following ethylene glycol exposures. The importance of the quantitative effects is captured in the Monograph (page II-119) as follows:

> …ethylene glycol exposures resulting in blood levels below the level of saturation should not result in hazard associated with developmental toxicity in humans.

The "overall conclusions" on the same page of the Monograph also states that saturation occurs in humans but the saturation level is not relevant to even the highest occupational exposure scenarios:

> Limited human in vitro data suggest that saturation of glycolic acid metabolism occurs at ~125 mg/kg bw, but saturation is expected to require much higher doses for slower dose-rate (non-bolus) exposure or for routes characterized by poor absorption (e.g., dermal).
>
> "A comparison of the exposures associated with these scenarios to the dose where saturation of human metabolism is estimated to occur (125 mg/kg bw) shows that all of these exposures in the human are at least 100- to 1,000-fold lower than those expected to result in metabolic saturation.

Thus, none of the high dose saturation kinetics that occur following bolus dose exposures are relevant to human exposures, with the exception of accidental or suicide poisoning scenarios. With the absence of human studies demonstrating a causal effect between ethylene glycol and developmental effects, the record before OEHHA demonstrates that there is no substantial evidence that the Section 25306(g) criteria are satisfied.

Despite the qualitative similarities between species identified in the Monograph, quantitative differences establish the critical distinction, as evidenced by the overall conclusions for developmental toxicity in rabbits (page II-117):

> Developmental toxicity was not observed in rabbits orally exposed to ethylene glycol at doses associated with severe maternal toxicity. Rabbits demonstrated no developmental toxicity following gavage exposure to doses as high as 2000 mg/kg bw/day on gd 6-19, as noted by a lack of malformations, prenatal deaths or decrease in fetal weights.

New data, discussed below, show rabbits are the appropriate model for evaluating developmental toxicity of ethylene glycol in humans. The similarity in the mechanism between rabbits and humans means that developmental toxicity from ethylene glycol is not biologically plausible in humans.

C. Scientifically Valid Data Not Considered by the NTP-CERHR Clearly Establish That Ethylene Glycol Does Not Satisfy Either of The Section 25306(g) Criteria

Both rodents and rabbits accumulate glycolic acid following exposure to high doses of ethylene glycol, yet rodents exhibit developmental toxicity attributed to glycolic acid while rabbits do not. This disparity in response to ethylene glycol suggests there are species-specific differences in the mechanisms of ethylene glycol teratogenicity. Significantly, these mechanisms have been further evaluated in studies not considered by NTP-CERHR and clearly establish that the association between adverse reproductive effects in humans and ethylene glycol is not biologically plausible.

Developmental toxicity occurs when the fetus is more sensitive to the developmental toxicant than the mother, or when pharmacokinetic factors result in the fetus receiving a higher dose than the mother. Accidental or intentional poisonings (e.g., suicides) occur when humans ingest large quantities of ethylene glycol (e.g., antifreeze). Although poisonings are relatively

common (e.g., the Monograph, page II-5, reports more than 5,000 cases of ethylene glycol poisonings in the United States in the year 2000) and human poisonings somewhat resemble oral bolus dose experiments in animals, Corley and McMartin (2005) state that there have not been any reported cases of human developmental effects induced by ethylene glycol.

By way of background, there are three stages in severe human poisonings as follows:[4]

- Stage 1: Decreased reflex responses, seizures, loss of consciousness, and coma.

- Stage 2: Increased rate and depth of breathing; heart damage, including congestive heart failure, resulting in accumulation of fluid in the lungs (pulmonary edema); lung damage, including adult respiratory distress syndrome (ARDS), resulting in a decreased oxygen supply to the body; multi-system organ failure; and death.

- Stage 3: Reduced urine excretion; absence of urine excretion; and acute kidney failure.

Each poisoning stage is attributable to a different chemical present during progressive ethylene glycol poisoning (Corley and McMartin, 2005). Stage 1 is attributable to ethylene glycol, stage 2 is attributable to acidosis, largely due to glycolic acid, and stage 3 is due to calcium oxylate (see Figure 2-1 for metabolic pathway). Thus, enzyme saturation leading to buildup of glycolic acid in blood is the same process that causes both extreme health effects and death in humans and animals, and developmental toxicity in rodents. The high dose in the rabbit developmental toxicity study reviewed in the Monograph led to 42% maternal mortality and, in humans like the rabbit model, altered pharmacokinetics undermine the plausibility of developmental toxicity in humans.

Significant new data enhance the understanding of the mechanisms involved in ethylene glycol-mediated developmental toxicity in rats, mice, and rabbits. The data support the conclusion that the human relevance of the rabbit model is much greater than the relevance of the rodent model, and that developmental effects in humans would not be expected to occur from exposure to ethylene glycol.

Three factors that control the potential for developmental toxicity from ethylene glycol are evaluated below with respect to differences among rodents, rabbits and humans:

1. <u>Species differences peak blood concentrations of glycolic acid</u>

As explained in the Monograph, high blood concentrations of glycolic acid that are only achieved with oral bolus doses are associated with enhanced potential for developmental toxicity. Post-Monograph data confirm that the peak concentration of glycolic acid, rather than the area under the concentration versus time curve, is a key driver of developmental toxicity (Corley et al., 2005). High peak glycolic acid concentration is associated with two metabolic steps: fast conversion of ethylene glycol to glycolic acid, and slow elimination of glycolic acid via metabolism to glyoxylic acid.

[4] Centers for Disease Control and Prevention as viewed on the web on June 5, 2014 at the following URL: http://www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750031.html.

All species evaluated metabolize ethylene glycol to glycolic acid and then glycolic acid to glyoxylic acid; however, metabolic rates differ and the different rates affect the biological plausibility of developmental toxicity following an oral bolus dose of ethylene glycol. Blood concentrations of glycolic acid remain low with exposures to ethylene glycol, except under the extreme conditions of oral bolus exposure when peak blood concentrations of glycolic acid rise to levels that cause developmental toxicity in some species or other toxic effects including death in other species.

The rate of ethylene glycol metabolism to glycolic acid is important because the faster glycolic acid is produced following a high bolus dose, the higher the peak blood concentration of glycolic acid. Just as slower exposure (e.g., as occurs by inhalation) reduces blood concentrations of glycolic acid, slower metabolism of ethylene glycol to glycolic acid reduces blood concentrations of glycolic acid and the potential for developmental toxicity.

Species differences in rates of ethylene glycol metabolism are confirmed by new data. Booth et al. (2004), using liver slices (i.e., tissues from the organ primarily responsible for metabolism of ethylene glycol), showed that rodent metabolism of ethylene glycol to glycolic acid in the liver occurs faster than rabbit metabolism, and rabbit metabolism of ethylene glycol to glycolic acid is faster than human metabolism. (Booth et al., 2004.) Rabbit liver tissue produced an average of 10-fold less glycolic acid from ethylene glycol compared to rats. Human liver tissue from four different donors did not produce detectable amounts of glycolic acid. Given that the tissue was shown to be metabolically active and the precision-cut liver slice system is considered to be a good representative of xenobiotic metabolism in the liver, the authors state that glycolic acid production from ethylene glycol in the human liver would be lower than the rabbit and the rat, given exposure to similar concentrations.

The rate of glycolic acid metabolism also is important, because the faster glycolic acid is metabolized, the lower the peak blood concentration of glycolic acid. Elimination of glycolic acid by metabolism to glyoxylic acid in the liver (i.e., the second rate limiting step shown in Figure 2-1) occurs faster in humans than in rats or rabbits. (Booth et al, 2004.) Thus hepatic clearance and detoxication of glycolic acid is expected to be greater for humans than for rabbits or rats. In agreement with these results, Carney et al. (2008) established that peak blood levels of glycolic acid in rabbits are lower than in rats.

Thus, in humans glycolic acid is formed more slowly and is cleared more rapidly than in rodents or even rabbits. As a result, human exposure to ethylene glycol is not likely to result in the glycolic acid peak blood concentrations necessary to cause developmental effects.

2. <u>Placental structure affects volume and turnover of embryonic fluids in each species and these factors affect glycolic acid concentrations surrounding the embryo</u>

The physiological structures surrounding the developing human embryo at the stage of development sensitive to ethylene glycol effects (4 weeks) are similar to the structures surrounding the rabbit embryo at the stage of development sensitive to ethylene

glycol effects (10-days), and not similar to the rodent structures. The rabbit embryo at this stage is surrounded by, and bathed in, yolk sac cavity fluid (YSCF), which is present in a large volume compared to the size of the embryo and has a slow turnover rate. (Carney et al., 2008). Measurements of glycolic acid in these structures indicated that glycolic acid appeared to diffuse slowly into the YSCF, reaching peak levels 12 hours post-dose, and concentration in the embryo tended to parallel the YSCF concentration. Peak YSCF levels in the rabbit were only 30% of the maximal maternal blood levels. The human physiological structures that surround the embryo at the developmental stage sensitive to ethylene glycol are similar to the rabbit, in that the human embryo is surrounded by, and bathed in, celomic fluid that has a large volume compared to the size of the embryo, and this fluid has a slow turnover rate.

In contrast to the rabbit and human, rodents at the stage of development sensitive to ethylene glycol effects (~9 days) have a visceral yolk sac (VYS) placenta that completely surrounds the embryo and contains a small amount of exocoelomic fluid (ECF) that contacts the embryo. (Ellis-Hutchings et al., 2014.) The glycolic acid concentration in maternal blood rapidly equilibrates with the ECF in the mouse. (Ellis-Hutchings et al., 2014.) The glycolic acid concentration in the ECF rapidly equilibrates with the embryo.

Thus, human and rabbit embryos are less sensitive to ethylene glycol exposures than rodent embryos.

3. <u>The relative maternal and embryonic pH in different species affect glycolic acid accumulation in the fetus</u>

Another key characteristic that controls the entry of glycolic acid into the embryo during the window of sensitivity is the relative difference in pH between the maternal circulation and the embryo. Glycolic acid has a weak acid dissociation constant (pKa of 3.83), which means that if the embryo is relatively acidic compared to the maternal circulation, then glycolic acid will tend to stay in the maternal blood, and if the embryo is relatively alkaline compared to the maternal blood, glycolic acid will preferentially enter the embryo. Rodent ECF and embryos are alkaline compared to the maternal circulation, while rabbit, human, and non-human primate embryos or celomic fluid are acidic compared to the maternal circulation. (Carney et al., 2004; Ellis-Hutchings et al., 2014.) Thus, glycolic acid will not partition to the human embryo to the same extent as rodents.

A pH gradient in rats and mice of 0.2 to 0.4 pH units drives the unionized weak acid, glycolic acid, into the more alkaline ECF and embryonic cells where it becomes ionized at the higher pH and is unable to diffuse back out, thus being trapped. This action is consistent with the peak levels of glycolic acid reported in the rat embryo as high as 2.45 times the maternal circulation. (Carney et al., 2008.) In contrast, the rabbit YSCF is 0.2 to 0.4 pH units acidic compared to the maternal blood, and this property is consistent with the observation of lower peak levels of glycolic acid in the rabbit embryo and YSCF than in maternal blood. (Carney et al., 2008). The human celomic fluid is approximately 0.2 pH units more acidic than the maternal blood early in the pregnancy, which suggests that transfer of glycolic acid to the human embryo during the sensitive

stage for ethylene glycol effects is more like the rabbit (in which no developmental effects were seen) than the rat or mouse. (Carney et al., 2004.)

Taken all together, these scientifically valid data not considered by NTP-CERHR clearly establish that the association between adverse developmental effects in humans and ethylene glycol is not biologically plausible. Therefore, OEHHA should not list ethylene glycol.

IV. IF OEHHA NEVERTHELESS PROCEEDS WITH THE LISTING, IT SHOULD NARROW THE LISTING TO ETHYLENE GLYCOL VIA THE ORAL EXPOSURE ROUTE

New data described above demonstrate that ethylene glycol does not cause developmental toxicity in humans. If OEHHA nevertheless proceeds with listing, the listing should be limited to the oral route of exposure, i.e., **ethylene glycol (oral route)**, because no scientifically valid data exist for a biologically plausible association between adverse effects in humans and ethylene glycol via other routes of exposure**.**

A. Dermal exposure - basis for exclusion

Dermal exposure to ethylene glycol should be excluded from the listing based on the fact that dermal exposure is not included in the Monograph as a route of potential concern for developmental toxicity. A dermal exposure study in mice intended to characterize the potential developmental toxicity of ethylene glycol demonstrated that the fetal dermal NOAEL dose is more than 20 times higher than the fetal oral gavage NOAEL dose. Thus dermal absorption plays a significant role in limiting the potential for developmental toxicity of ethylene glycol. New in vitro data on human skin also show this route is not a concern for developmental toxicity since less than 0.7% of ethylene glycol penetrated within 24 hours (Saghir et al., 2010). As a practical matter, it is unrealistic to believe that dermal exposure to ethylene glycol could cause developmental toxicity in humans, given that the Monograph states as part of its overall conclusions "*…ethylene glycol exposures resulting in blood levels below the level of saturation should not result in hazard associated with developmental toxicity in humans*" and "*saturation is expected to require much higher doses for slower dose-rate (non-bolus) exposure or for routes characterized by poor absorption (e.g., dermal).*"

B. Inhalation exposure - basis for exclusion

Inhalation exposure to ethylene glycol should be excluded from the listing based on the fact that inhalation exposure is not included in the Monograph as a route of potential concern for developmental toxicity. Inhalation exposure studies of ethylene glycol in rodents have been conducted but are confounded by deposition of ethylene glycol on the subject animals' fur. The subjects have groomed the deposited test article off the fur and ingested a large oral dose as well as the inhalation dose. In a nose-only exposure study, sufficient test article was deposited on the nares area in one day to provide a dose of 330 mg/kg of ethylene glycol. (Slikker et al., 2004.). Physiologically-based pharmacokinetic modeling of ethylene glycol inhalation exposure indicated that it would be unlikely that humans can inhale enough ethylene glycol to cause developmental effects. (Corley et al., 2005.)

V. CONCLUSION: OEHHA SHOULD NOT LIST ETHYLENE GLYCOL

No studies are available to evaluate the developmental effects of ethylene glycol directly in humans, and therefore available animal studies must be evaluated to determine whether the association between adverse developmental effects in humans and ethylene glycol is biologically plausible. As discussed in this letter, the requisite biologically plausible association does not exist. Pursuant to 27 California Code of Regulations Sections 25306(g) and 25306(h), OEHHA should not list ethylene glycol.

OEHHA has expressed concerns about perceived "overwarning" and frivolous enforcement actions. Meaningful warnings begin with meaningful chemical listings. In listing chemicals, OEHHA holds a critical gate-keeping role affecting the quality and quantity of both warnings and litigation, a role that must be executed with sound scientific backing. Listing ethylene glycol in the absence of human data and in the absence of any biologically plausible association removes that scientific backing, and ultimately will lead to unnecessary warnings and increased frivolous litigation, to the detriment of the public interest and the regulated community.

Respectfully,

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