June 25, 2014

Via E-Mail

Ms. Cynthia Oshita
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Re: Notice of Intent to List Under Proposition 65: Ethylene Glycol

Dear Ms. Oshita:

I. Introduction

The Ethylene Glycols Panel[1] (Panel) of the American Chemistry Council appreciates the opportunity to comment on the California Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) notice of intent to list ethylene glycol (EG) pursuant to the Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65 (Prop. 65), as a chemical known to the State to cause reproductive toxicity (developmental endpoint). OEHHA bases the proposed listing on a 2004 report by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR).

Panel members include manufacturers of EG, which is used in many commercial and industrial applications including antifreeze and coolant. EG also is used as a raw material in the production of a wide range of products including polyester fibers for clothes, upholstery, carpet and pillows; fiberglass used in products such as jet skis, bathtubs, and bowling balls; and polyethylene terephthalate resin used in packaging film and bottles. ACC also joins in the comments submitted by the Writing Instrument Manufacturers Association and the Art and Creative Materials Institute. We appreciated the opportunity to provided comments on this important regulatory proceeding.

In the notice of intent, dated April 11, 2014, OEHHA states:

> A chemical must be listed under the Proposition 65 regulations when two conditions are met:

[1] The EGs Panel is comprised of the following companies: Celanese, The Dow Chemical Company, Eastman Chemical Company, Huntsman Corporation, LyondellBasell Industries N.V., and Shell Chemical LP

1. An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)).
2. The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)).

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)). (emphasis added)[2]

OEHHA also states:

> The studies cited by NTP-CERHR in support of these conclusions were reviewed by OEHHA with regard to the sufficiency of evidence criteria in regulation (Section 25306(g)(2)). Information reviewed for each of the cited studies included parameters related to biological plausibility in humans, including adequacy of experimental design, pattern of dosing, route of administration, numbers of test animals, choice of species, choice of dosage levels, and maternal toxicity. On the basis of the studies, effects and species identified above, OEHHA concluded that the sufficiency-of-evidence criteria in the regulation were met. (emphasis added)

However, EG should not be included on the Proposition 65 list of chemicals that cause reproductive toxicity (developmental endpoint) because eleven peer-reviewed, mechanistic reports have been published since 2004 that were not available to NTP-CERHR. This new information clearly establishes that the sufficiency-of-evidence criteria are not met because adverse developmental effects in humans are not biologically plausible at non-lethal doses of EG.

II. OEHHA Should Consider Additional Scientifically Valid Data

OEHHA should consider the substantial new information that has been published in peer-reviewed journals since the 2004 NTP-CERHR report. In addition, a number of regulatory authorities have considered how human exposures to EG would relate to developmental toxicity seen at high doses in rodents.

In 2004, NTP-CERHR reviewed all pertinent studies on EG through 2003 and concluded

- "The NTP concurs with the CERHR EG/PG Expert Panel that there is negligible concern of adverse developmental toxicity from EG at exposures below 125 mg/kg bw." (page 3, NTP-CERHR, 2004)
- "The NTP concurs with the CERHR EG/PG Expert Panel that there is negligible concern of adverse reproductive toxicity from EG." (page 3, NTP-CERHR, 2004)
- "There is no direct evidence that exposure of people to EG adversely affects reproduction or development." (page 2, NTP-CERHR, 2004)

[2] http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/041114NOILethyleneglycol.html

From 2003 to 2014, eleven mechanistic peer-reviewed investigations have been published that provided important insights into EG kinetics of uptake and metabolism, formation and elimination of the proximate developmental toxicant, glycolic acid (GA), and new information on species differences for mode of action (MOA). The key mechanistic studies are presented in the following table.

Year	**Title**	**First Author**	**Major Findings**
2004	Comparison of the metabolism of ethylene glycol and glycolic acid *in vitro* by precision-cut tissue slices from female rat, rabbit, and human liver.	Booth	"The results…indicate that levels of glycolic acid, if formed *in vivo*, following exposures to similar concentrations of ethylene glycol, would be lower in humans than in rabbits and rats."
2004	Mechanisms regulating toxicant disposition to the embryo during early pregnancy: an interspecies comparison.	Carney	This article presents reasons why EG is a developmental toxicant in rats but not in rabbits. "The dose of toxicant reaching the embryo is a critical determinant of developmental toxicity…." "The rabbit…shares several characteristics in common with humans, such as large embryonic and extraembryonic fluid volumes, a yolk sac that is free floating in the yolk sac cavity…, and a relatively large mass of chorionic tissue present from very early in pregnancy."
2004	Dose-dependent transitions in mechanisms of toxicity: case studies	Slikker	"In animal studies using high doses of EG,…All of these factors converge to bring about very high levels of parent EG, which is rapidly converted to GA. The resultant high levels of GA saturate the enzymatic conversion of GA to glyoxylic acid, leading to a disproportionate rise in GA levels….For workplace, consumer, or other typical human exposures, the large capacity of metabolizing systems available to completely metabolize EG without ever approaching saturation of GA oxidation are thought to effectively preclude the possibility of EG induced developmental effects in humans."

2005a	Development of a Physiologically Based Pharmacokinetic Model for Ethylene Glycol and Its Metabolite, Glycolic Acid, in Rats and Humans	Corley	"…a physiologically based pharmacokinetic (PBPK) model was developed to integrate the extensive mode of action and pharmacokinetic data on EG and GA for use in developmental risk assessments….When internal dose surrogates were compared in rats and humans over a broad range of exposures, it was concluded that humans are unlikely to achieve blood levels of GA that have been associated with developmental toxicity in rats following occupational or environmental exposures." "After inhalation exposures, however, where species differences in respiratory rates and cardiac output become more important (as compared with bolus oral dosing), the Cmax levels for GA are significantly higher in rats than in humans (Fig. 10b). For occupational exposures, this route of exposure is more important than bolus oral dosing." "Given the low volatility of EG (0.06 mm Hg at 20°C), the theoretical maximum vapor concentration for ethylene glycol is only ~79 ppm (~200 mg/m3). This low volatility, coupled with the potential irritancy of EG aerosols, effectively limits the possibility for developmental toxicity in humans after inhalation exposures to EG."
2005b	Mode of Action: Oxalate Crystal-Induced Renal Tubule Degeneration and Glycolic Acid-Induced Dysmorphogenesis—Renal and Developmental Effects of Ethylene Glycol	Corley	**"**The initial steps in the postulated MOA for developmental toxicity involve metabolism of EG to GA, saturation of GA oxidation leading to its accumulation, distribution of GA to the conceptus, and induction of developmental toxicity, the hallmark of which is malformation of the axial skeleton and craniofacial structures."
2005c	Incorporation of Therapeutic Interventions in Physiologically Based Pharmacokinetic Modeling	Corley	"…the modifications to the human PBPK described in this article to include various treatment regimens used clinically to treat accidental or intentional ingestions

	of Human Clinical Case Reports of Accidental or Intentional Overdosing with Ethylene Glycol		of EG enabled Corley et al. (2005a) to compare internal dose surrogates of the intermediate metabolite, glycolic acid, over a broad dose range in rats and humans with a greater degree of confidence" in the PBPK model.
2008	Species-specificity of ethylene glycol-induced developmental toxicity: toxicokinetic and whole embryo culture studies in the rabbit.	Carney	"High-dose gavage exposure to ethylene glycol (EG) is teratogenic in rats, but not rabbits. To investigate the reason for this species difference, toxicokinetic and whole embryo culture (WEC) studies were conducted….The toxicokinetic profile suggested that the lower GA levels in rabbits were due to a slower rate of maternal metabolism of EG to GA, slow uptake of GA into the yolk sac cavity fluid which surrounds the embryo, and negligible transfer via the visceral yolk sac (VYS) placenta….Integration of these findings with published human data suggest that the rabbit is the more relevant model for human EG exposure,…"
2010 (online) 2011a (pub)	The Impact of Dose-rate on Ethylene Glycol Developmental Toxicity and Pharmacokinetics in Pregnant CD Rats	Carney	"Toward the goal of developing EG risk assessments based on internal dose metrics this study examined the differences between fast (bolus) and slow (continuous infusion) dose-rate exposures to EG on developmental outcome and pharmacokinetics…..In the sc bolus groups, increases in… malformations…and variations…were seen…. In contrast, equivalent daily doses of EG given slowly via infusion did not cause any developmental effects….In the case of EG, we can see clearly that high-dose gavage studies cause a shift from linear to nonlinear GA kinetics, which appears to be a prerequisite for EG-induced developmental toxicity. However, most human exposures involve much lower doses occurring via the dermal or inhalation routes, which are non-bolus. Given our understanding of GA kinetics, it is clear that gavage studies greatly overestimate the risk…."

2010	Dermal Penetration of Ethylene Glycol Through Human Skin *In Vitro*	Saghir	"…exposure of EG… to intact skin, either through dermal routes that may occur during normal working hours or by accidental exposure of the whole body for a short duration, will not elevate the systemic levels of toxic metabolites….Likely these kinetic explanations account for the lack of any developmental toxicity in mice after dermal exposure, even though total penetration of the dermally applied dose is much higher in rodents than humans. Overall, these findings demonstrate that EG dermal penetration in humans is expected to be very low and to be slow, indicating very limited systemic or internal dose of EG due to dermal exposure."
2011b	Book chapter, Ethylene Glycol	Carney	"By using an integrated approach which combined animal developmental toxicity studies, whole embryo culture experiments and an extensive array of toxicokinetic data, a strong body of evidence was compiled to implicate GA as the proximate toxicant. Furthermore, studies in rats supported a proposed threshold of at least 2mM GA in maternal blood (4 mM in conceptus) which must be exceeded in order to induce developmental effects. Achievement of such high internal concentrations of GA is favored by some specific conditions, namely: high dose, route characterized by rapid absorption (e.g., oral) and/or high dose-rate (Figure 45.5). These three variables converge to bring about very high blood levels of EG, which is readily metabolized to GA. The resulting high GA levels saturate the metabolism of GA to glyoxylic acid, such that GA production exceeds the rate of its further metabolism, resulting in a disproportionate or non-linear increase in blood GA concentrations. In species such as the rat and mouse, which concentrate weak acids within the conceptus, exposure of the embryo to GA is further increased, whereas in species such

			as the rabbit, GA is poorly distributed to the conceptus and embryonic GA levels are less than those of maternal blood. Given similarities in conceptus fluid volumes and pH gradients, GA disposition in the human is more likely to mirror the rabbit."
2014	Disposition of glycolic acid into rat and rabbit embryos *in vitro*	Ellis-Hutchings	"This research explored the mechanisms of GA disposition into rat and rabbit conceptuses using whole embryo culture (WEC)….Results for this research study suggest GA disposition into rat and rabbit embryos is energy- and pH-dependent, and carrier-mediated….These support and further refine an existing body of data indicating that the pregnant rat model is not relevant to humans due to fundamental differences in maternal metabolism coupled with qualitative differences in the direction of pH-dependent transport."

An excellent summary of all the crucial studies to better understand EG risk assessment for developmental toxicity is included in the textbook, Reproductive and Developmental Toxicology, edited by Ramesh C. Gupta (2011). The chapter, Ethylene Glycol, was authored by Edward W. Carney, a leader in the field of reproductive and developmental toxicology and is being submitted to OEHHA under separate cover. This publication includes the complete history (except for the most recent study by Ellis-Hutchings in 2014) of the research conducted on developmental toxicity pertaining to dose-rate and species differences, toxicokinetics, and mechanism of action with studies substantiating the differences between rats and humans.

The chapter's Introduction explains why EG is a case study to better understand why mode of action including specific studies on kinetics of metabolism and internal dose metrics are so important for determining human risk from high dose-rate gavage rodent studies. In addition, "EG also provides an excellent example of how *in vivo* developmental toxicity studies, toxicokinetics and *in vitro* methods can be integrated to understand mode-of-action (MOA) and to define specific internal dose metrics delineating safe vs. unsafe exposures in humans."

Presented below are key points based on Carney's (2011) chapter reviewing the integrated assessment of EG and the relevance (or lack thereof) to humans.[3]

[3] For more details, including supporting data and figures, please refer to Edward W. Carney (2011). Ethylene Glycol. In: Reproductive and Developmental Toxicology, edited by Ramesh C. Gupta (Elsevier Inc., ISBN: 978-0-12-382032-7).

TOXICOKINETICS

- Glycolic acid (GA) is the proximate toxicant in the developmental toxicity of EG. The conversion of GA to glyoxylic acid is of critical importance in the developmental toxicity of EG, as this is the key rate-limiting step in the EG metabolic pathway. At low EG doses, GA is readily changed to downstream metabolites, leading ultimately to CO_2, and at high EG doses and/or high dose-rates, the resulting high GA levels saturate the metabolism of GA, such that GA production exceeds the rate of its further metabolism, resulting in a disproportionate or non-linear increase in blood GA concentrations.
- Research has identified this shift in GA kinetics as a required step in the progression toward developmental toxicity. Furthermore, research shows several significant differences between rats and rabbits.
- Pregnancy does not appear to have significant effects on the toxicokinetic profile of EG, GA, or oxalic acid (another major metabolite), in maternal blood.
- GA distribution to the conceptus shows marked differences between rats and rabbits
- The higher levels of GA in rat embryo and exocoelomic fluid appear to be due to a phenomenon called ion-trapping. If embryonic dosimetry was based solely on pH gradients, the GA concentration in the human embryo would be expected to be about half that of maternal blood, which contrasts with the opposite situation in the rat.

LINKING DEVELOPMENTAL TOXICITY AND KINETICS

- GA kinetics exhibit saturation at dose levels just below those associated with developmental toxicity in rats
- *In vivo* dose-rate studies demonstrated that the relevant internal dose metric for defining a threshold was peak GA in embryo in rats.
- Based on these integrated data, threshold values of 2mM GA in maternal blood and 4mM GA in embryo were derived for rats.

SPECIES DIFFERENCES

- EG is not developmentally toxic in the rabbit. Knowledge of the mechanisms behind this discordance between rat and rabbit aids in the understanding of the relevance of EG developmental toxicity to humans.
- Interspecies difference was not explained by differences in
    - absorption of EG,
    - elimination of EG or GA,
    - GA protein binding
- The lower tissue levels of GA in the rabbit embryo in comparison to the rat embryo were related to a combination of slower rates of GA formation and decreased disposition of GA from the maternal circulation to the rabbit embryo.
- Concentration of GA in the rat is likely due to ion-trapping driven by a pH gradient between maternal blood and the exocoelomic fluid.
- The pH gradients between maternal blood and conceptus fluids of rabbits are in the opposite direction to those of rats, thus favoring retention of GA in maternal blood.

- Concentration of GA in the conceptus fluid in the rat is favored because of the small volume, which is conducive to rapid equilibrium occurring between maternal blood and exocoelomic fluid and embryo. In contrast, the volume of fluid surrounding the rabbit embryo is quite large relative to the size of the embryo.

IMPLICATIONS FOR HUMANS

- It appears that maternal blood GA levels from as well as disposition of GA to the embryo are likely in humans to be more similar to rabbits than rats.
- Concentration of GA in the embryo is mediated by pH gradients between maternal blood and conceptus fluid compartments, which drives transplacental distribution.
- The pH gradient between human maternal blood and the coelomic fluid is opposite to that of rats and mice, but similar to that of the rabbits.
- Small exocoelomic fluid volumes facilitate rapid concentration GA levels.
- Human coelomic fluid is similar to the rabbit yolk sac cavity fluid in that it directly bathes the embryo and as with the rabbit, appears to be a slower turnover compartment thus attenuating sharp peaks in GA concentration.

GA disposition in the human is more likely to mirror the rabbit than the rat.

	Rat	**Rabbit**	**Human**
Developmental toxicity noted	yes	none	none has ever been reported
Rate of formation of GA from EG metabolism	rate faster than human		
GA is distributed to conceptus		not as well as rat	not as well as rat
Concentrates GA within the conceptus		less than rat	less than rat
Conceptus fluid		more than rat	more than rat
pH gradient			more similar to rabbit
Resulting GA blood and tissue levels	higher than humans		

To go from the PBPK model-predicted concentrations of GA in maternal blood to GA concentrations in the embryo, the target organ, a 0.5x factor must be applied.[4] Hence, a 20 g exposure of EG to a 58 kg pregnant woman (=350 mg/kg) would result in only 1 mM GA to the embryo. Therefore, to obtain the threshold value of 4 mM GA in the embryo, four times more EG (i.e., 80 g to a 58 kg pregnant woman, or 1400 mg/kg) would be required to reach the threshold, which is a dose within the published range of minimal lethal doses for humans.[5]

Therefore, there are scientifically valid data which were not considered by NTP in 2004 which demonstrate:

- Given exposure to EG results in much higher GA in rats vs. humans;
- Concentration of GA within conceptus is much lower in humans; and
- Trapping of GA in the rat leads to higher levels of GA in the embryo than for humans.

Taking all new disposition, metabolism, and kinetic data together, research on EG suggests there is negligible concern for developmental or reproductive toxicity in humans exposed to EG. In addition, developmental toxicity has never been reported in human exposure. If human developmental toxicity can occur, these doses would be in the reported humans' lethal range, and therefore, an association between adverse developmental effects in humans and EG exposure is not biologically plausible for non-lethal doses. Consequentially, the sufficiency-of-evidence criteria identified in Section 25306(g) have not been satisfied, and EG should not be listed on Proposition 65 as a chemical known to the state to cause reproductive toxicity (developmental endpoint).

III. OEHHA Should Consider Supportive Evidence that EG Does Not Cause Reproductive Toxicity in Humans.

Recently, Environment Canada (2014) published the summary of its Ethylene Glycol Risk Assessment under the Canadian Environmental Protection Act, 1999 (CEPA 1999). This final report includes considerable additional data developed subsequent to the 2004 NTP-CERHR report. Environment Canada (2014) concludes that EG has negligible concerns for human developmental toxicity.

In 2000, Environment/Health Canada presented a first State of the Science Report on EG. At that time, they had limited information to expound on the susceptibility of humans to the developmental toxicity seen in rodents. The Report stated that "Less is known about the potential mode of induction of developmental effects, including the role of putatively toxic metabolites, although research conducted to date has focused on glycolic acid. (Carney, 1994; Carney *et al*., 1999)."

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[4] 0.5 x factor is derived from Ion Trapping and the Henderson-Hasselbach (H-H) acid-base equation, a pKa of 3.83 for GA, and the pH of human celomic fluid in first trimester which is 0.2 pH units lower than maternal blood. The H-H equation predicts the percentage of total GA in the free acid form, which is the form that can freely diffuse across membranes. [Note: The 0.5x assumes no protein binding, which is actually a conservative value as we have unpublished data showing 2-13% protein binding to human serum].

[5] Sheftel, 2000, reported human lethal dosages range of 1000 to 2000 mg/kg

In 2007, Environment/Health Canada conducted a new literature search through August 2006 and updated their 2000 State of Science Report. Several important new publications were discussed, including the development of a physiologically based pharmacokinetic model for EG and its metabolite, glycolic acid (GA), in rats and humans (Corley et al., 2005a); the MOA of GA-induced dysmorphogenesis (Corley et al., 2005b); and species differences noted in metabolism studies using liver slices from rat, rabbit, and human. Health Canada in this 2007 report concluded that human liver tissues (*in vitro*) were also more efficient in further metabolizing GA, the proximate development toxicant, and therefore, there was less chance for accumulation of GA in humans than in experimental animals.

In 2014, Environment Canada updated yet again their position on EG risk assessment based on new literature published up to January 2009.[6] In this publication, they concluded (quotes taken from this report):

- "There are no human developmental or reproductive toxicity data available on ethylene glycol."

- Under normal uses, EG does not constitute a health danger
  "Based on the information presented in this report, ethylene glycol is not entering the environment in a quantity or concentration or under conditions that may constitute a danger to human life or health. Therefore, ethylene glycol does not meet any of the criteria under section 64 of CEPA 1999", and was removed from their Priority Substance List 2 as "Toxic."

- Renal toxicity is more sensitive endpoint
  "As reported in the State of the Science Report, slight reproductive effects and developmental toxicity, including teratogenicity, have been observed in rodents exposed to ethylene glycol by the oral route <u>at doses greater</u> than those associated with renal effects." (emphasis added)

- Species differences significantly changes risk assessment
  In contrast to rats, rabbits dosed with levels of EG high enough to cause mortality did not cause developmental toxicity in the surviving rabbits. "This species difference has been recently addressed and was attributed to toxicokinetics. Glycolic acid levels in rabbit maternal blood and embryo were only 46% and 10% of the respective values in rats. This is possibly due to a slower rate of maternal metabolism and to fundamental differences in disposition of glycolic acid to the embryo (Carney *et al.* 2008)."

  "In a metabolism study, Booth et al. (2004) exposed rat, rabbit and human liver slices to ethylene glycol. <u>Liver glycolic acid levels</u> in rats were approximately 10 times higher than in rabbits and were <u>not detected in humans</u>. Human liver tissues were also more efficient in further metabolizing glycolic acid to glyoxylic acid. There is therefore less chance for glycolic acid accumulation in humans compared to rats and rabbits, clearly

[6] http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=4B7409ED-1&offset=1&toc=show

suggesting that, of the three species, humans may be less sensitive because of this difference in hepatic metabolism." (emphasis added)

- Dose rate is central to understanding the MOA
  "Maternal toxicity and fetal malformations were detected when pregnant rats were exposed to ethylene glycol through a subcutaneous (≥1000 mg/kg-bw/day) bolus injection during GD 7-15, but not when the same doses were administered at a slower rate via a subcutaneous implanted infusion pump (Carney *et al*. 2001, 2002, as cited in the OECD 2009). This difference in toxicity is considered to be due to the saturation of an intermediary step in ethylene glycol metabolism, resulting in the accumulation of glycolic acid in the bolus exposure."

- PBPK models have been developed
  "There are no human developmental or reproductive toxicity data available on ethylene glycol. However, physiologically based pharmacokinetic (PBPK) models have been developed for ethylene glycol and its metabolite, glycolic acid, in rats and humans (Corley et al. 2005a, 2005b; Corley and McMartin 2005)….These PBPK models have predicted that it is unlikely to achieve levels of human blood glycolic acid concentrations that could lead to developmental toxicity." (emphasis added)

  "These PBPK models have predicted that it is unlikely to achieve levels of human blood glycolic acid concentrations that could lead to developmental toxicity. Humans would only achieve the threshold for developmental effects determined in rats of 2 mM if they consumed bolus oral doses greater than 350 mg/kg (> 20 g ethylene glycol for a 58 kg female) during the critical window of susceptibility based on simulations of peak maximum blood concentrations of glycolic acid."[7]

OEHHA should consider this supportive evidence that EG should not be listed as causing adverse developmental toxicity.

IV. Human developmental effects from dermal or inhalation exposures are of negligible concern

In the 2004 NTP-CERHR report, which is the authoritative body report identified by OEHHA, the following statement is noted: "Toxicokinetic studies reviewed in Section 2 demonstrated that in contrast to rapid and complete absorption through the oral route, dermal exposure in rats and mice is slow and incomplete." (page II-103)

The report goes on to state: "There were no data identified that permit the evaluation of developmental toxicity in humans. Ethylene glycol was tested for developmental toxicity in mice, rats, and rabbits. There were insufficient data to determine whether ethylene glycol causes developmental toxicity by inhalation exposure in mice and rats." (page II-116)

[7] See the discussion on recent research above, which reports the GA differences between rat and man in the target organ, the embryo. Note, the estimated human threshold developmental toxicity value is greater than the minimal lethal concentration for humans.

However, NTP-CERHR 2004 report notes, "Ethylene glycol levels above 200 mg/m3 were intolerable," (page II-39) and goes on to state "Given that Wills et al. found that concentrations higher than 200 mg/m^3 were highly irritating and poorly tolerated by human volunteers, it seems that the warning properties of ethylene glycol would prevent sufficiently high inhalation exposures that result in saturating conditions." (page II-27) "The study demonstrates that exposure to an irritating concentration of ethylene glycol [which is above any current regulatory level] will likely result in a systemic dose that is well below oral doses resulting in metabolic saturation and glycolate accumulation. Therefore, the warning properties of ethylene glycol should prevent exposures resulting in metabolic saturation [necessary for a developmental toxic event]. (page II-53)

For the dermal route of exposure the NTP-CERHR 2004 report states "There were sufficient data to determine that CD-1 mice exposed to ethylene glycol by the dermal route for 6 hours/day on gd 6–15 showed no evidence of malformations, increased prenatal death, or delayed growth at doses up to 3,549 mg/kg bw/day. Maternal and fetal NOAELs were identified as 3,549 mg/kg bw/day. These findings are consistent with toxicokinetic data that indicates low absorption of ethylene glycol by the dermal route of exposure." (page II-116)

Subsequent to the NTP-CERHR 2004 report, additional scientifically valid data have been published supporting that the dermal and inhalation routes of exposure present no significant risk for human developmental toxic effects. Please refer to the Major Findings in table above Saghir (2010) and Corley (2005a), for a summary of these supporting statements, and refer to the appropriate articles for detailed discussions.

V. Conclusion

Since the 2004 NTP-CERHR report, which is the authoritative body report identified by OEHHA, eleven different studies have been published. These scientifically valid data were not available to NTP-CERHR and clearly establish that the sufficiency-of-evidence criteria for EG are not met for adverse developmental toxicity in humans because it is not biologically plausible for non-lethal doses. In addition, Environment Canada, under regulation CEPA 1999 in a 2014-updated report, states that there are no accounts of adverse human developmental effects and gives supporting evidence that EG exposures are of negligible concern for human developmental toxicity. EG should not be included on the list of chemicals known to the State to cause reproductive toxicity (developmental endpoint) under Proposition 65.

Please contact me at (202) 249-6714 or at bill_gulledge@americanchemistry.com.

Sincerely yours,

William Gulledge

William P. Gulledge
Senior Director
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