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Dear Ms. Vela,

I am providing herein, my comments to the “Notice of Proposed Rulemaking Title 27, California Regulations, Proposed Adoption of New Section under Article 7 No Significant Risk Levels Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk,” dated June 22, 2018. The basis for this proposed change has been attributed largely to the review of coffee in IARC Monograph, Volume 116<sup>1</sup> (2018), as well as risk assessment methodologies specified under Proposition 65. My knowledge and experiences that are relevant to these issues include:

- 1) 28+ years as senior toxicologist in the National Toxicology Program, NIEHS
- 2) Conducted numerous toxicology studies and evaluations on epoxide-forming chemicals
- 3) Member and chair of the NIEHS review group for NTP’s Report on Carcinogens
- 4) Member of 9 different IARC expert working groups that prepared cancer risk evaluations on nearly 100 agents
- 5) Participated in 3 IARC workshops on tumor site concordance between animals and humans and mechanisms of carcinogenesis
- 6) Served on 7 review panels of health risk assessments prepared by the US EPA
- 7) Served on the 1996 Risk Assessment Advisory Committee that reviewed California EPA’s Risk Assessment Practices, Policies, and Guidelines
- 8) Consultant and expert witness for the Attorney General of California concerning cancer risks associated with dietary exposure to acrylamide in French fries and potato chips
- 9) Consultant and expert witness for the Council for Education and Research on Toxics in the case of CERT vs. Starbucks et al. concerning cancer risk of acrylamide in coffee.

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<sup>1</sup> International Agency for Research on Cancer (IARC) 2018. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Drinking Coffee, Mate, and Very Hot Beverages. Vol. 116. Lyon, France

In my view, the rationale for the proposed change as described in the Initial Statement of Reasons Title 27 (California Code of Regulations Adoption of New Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk) lacks scientific justification and runs counter to the policies and methodologies that have been well established in 27 California Code of Regulations § 25703. The focus of my comments is on cancer risk of acrylamide in coffee.

**1) Antioxidants and other potential cancer preventive agents do not reduce the cancer risk of acrylamide (a chemical that is widely recognized as a substance of high health concern) in coffee.**

To support the proposed change in which OEHHA declares that exposures to Proposition 65 listed chemicals in coffee that are produced as part of the roasting process pose no significant risk of cancer, the Statement of Reasons makes numerous reference to coffee as a “complex mixture of carcinogens and anticarcinogens,” and in particular that coffee contains antioxidants that are “considered to have cancer chemopreventive properties” by protecting against oxidative stress. However, antioxidants in coffee have little or no impact on the mechanisms of mutagenicity and carcinogenicity of acrylamide.

Acrylamide is a very toxic chemical; it is a neurotoxin (in humans and experimental animals), it is as a reproductive toxicant, and experimental studies in laboratory animals have consistently demonstrated that acrylamide is a multi-organ site carcinogen in rats and mice. The Food and Agricultural Organization of the United Nations/World Health Organization expressed a major human health concern for carcinogenic risks from exposure to acrylamide in foods<sup>2</sup>. This concern, which is still maintained by national and international health agencies, was based on the low margin of exposure for this genotoxic carcinogen. In 2010, acrylamide was added to the European Union’s REACH candidate list of “substances of very high concern.” Coffee is the greatest source of dietary acrylamide exposure in adults. Based on the rationale for the proposed rule change presented in the Statement of Reasons, it appears that OEHHA

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<sup>2</sup> FAO/WHO. 2005. Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome, Italy.

does not share the same health concerns for human exposure to acrylamide that have been expressed by other national and international public health agencies.

Acrylamide and its primary oxidative metabolite, glycidamide – a DNA reactive epoxide – are genotoxic in most *in vitro* and *in vivo* systems, causing gene mutations and chromosomal aberrations. Acrylamide is metabolically activated in animals and humans to glycidamide by cytochrome P450 enzymes (predominantly by CYP2E1) or conjugated with glutathione catalyzed by glutathione-S-transferase isoenzymes. The finding of glycidamide-hemoglobin adducts in humans exposed to acrylamide<sup>3</sup> and the association of glycidamide-hemoglobin adducts with coffee consumption in non-smoking women<sup>4</sup> demonstrate that this DNA-reactive metabolite can be systemically distributed in coffee drinkers.

The carcinogenicity of acrylamide involves a genotoxic mechanism based on its metabolism to glycidamide and subsequent formation of glycidamide-specific DNA adducts.<sup>5 6 7</sup> Several studies show that the formation of glycidamide-DNA adducts and the genotoxicity of this epoxide do not involve oxidative stress. For example, DNA damage induced by glycidamide in male mouse germ cells and in mouse and human lymphocytes was not affected by hOGG1 (a DNA repair enzyme that excises 8-oxoguanine, a mutagenic base formed by reactive oxygen species); consequently, the authors concluded that alkylation rather than oxidation of DNA by reactive oxygen species is involved in producing DNA lesions by this DNA-reactive epoxide metabolite.<sup>8</sup> In another study, there was no increase in reactive oxygen species at concentrations of glycidamide that induced the formation of micronuclei by glycidamide in

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<sup>3</sup> Fennell TR, et al. 2005. Metabolism and hemoglobin adduct formation of acrylamide in humans. *Toxicol. Sci.* 85:447-459.

<sup>4</sup> Outzen M, et al. 2011. Dietary determinants for Hb-acrylamide and Hb-glycidamide adducts in Danish non-smoking women. *Br. J. Nutr.* 105:1381-1387.

<sup>5</sup> Bowyer JF, et al. 2008. The effects of subchronic acrylamide exposure on gene expression, neurochemistry, hormones, and histopathology in the hypothalamus-pituitary-thyroid axis of male Fischer 344 rats. *Toxicol. Appl. Pharmacol.* 230:208-215.

<sup>6</sup> Ghanayem BI, et al. 2005. Role of CYP2E1 in the epoxidation of acrylamide to glycidamide and formation of DNA and hemoglobin adducts. *Toxicol. Sci.* 88:311-318.

<sup>7</sup> Ghanayem BI, et al. 2005. Absence of acrylamide-induced genotoxicity in CYP2E1-null mice: evidence consistent with a glycidamide-mediated effect. *Mutat. Res.* 578:284-297.

<sup>8</sup> Hansen SH et al. 2010. Investigation of glycidamide-induced DNA lesions in mouse male germ cells and in mouse and human lymphocytes. *Mutat. Res.* 696:55-61.

human mammary cells, and antioxidants did not protect these cells from glycidamide-induced cytotoxicity.<sup>9</sup> The dose-dependent formation of glycidamide-specific DNA adducts and the genotoxicity of this epoxide in this study clearly did not involve oxidative stress.

Except at very high exposures to acrylamide where depletion of the cellular antioxidant glutathione might occur, oxidative stress has little to no impact on the genotoxicity or carcinogenicity of acrylamide. Consequently, the Statement of Reasons should acknowledge that the presence of antioxidants in coffee would not impact the cancer risk of acrylamide in coffee.

Two diterpenes found in coffee, cafestol and kahweol, have been suggested to be potential cancer preventing agents by inhibiting certain cytochrome P450 enzymes (but not CYP2E1) and by decreasing sulfotransferase 1A1 activity.<sup>10</sup> These effects have little bearing on acrylamide cancer risk since these agents do not inhibit CYP2E1, and sulfotransferase activity is not involved in the activation of acrylamide to glycidamide. However, furfuryl alcohol, which is also produced during the coffee roasting process, is metabolically activated by sulfate conjugation catalyzed by sulfotransferase 1A1/1A2.<sup>11</sup> Thus, cafestol and kahweol might reduce cancer risk of furfuryl alcohol, but not of acrylamide.

**2) The OEHHA proposal that exposures to Proposition 65 listed chemicals in coffee (“a complex mixture of carcinogens and anticarcinogens”) that are produced as part of the roasting process pose no significant risk of cancer requires a quantitative risk assessment and runs counter to US EPA’s view of chemical mixtures**

The California Code of Regulations § 25703 clearly requires a quantitative risk assessment for determining the NSRL, i.e., the daily exposure level that poses a cancer risk that

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<sup>9</sup> Bandarra S, et al. 2013. Mechanistic insights into the cytotoxicity and genotoxicity induced by glycidamide in human mammary cells. *Mutagenesis* 28:721-729.

<sup>10</sup> Huber WW, et al. 2008. Effects of coffee and its chemopreventive components kahweol and cafestol on cytochrome P450 and sulfotransferase in rat liver. *Food Chem. Toxicol.* 46:1230-1238.

<sup>11</sup> Sachse B, et al. 2016. Bioactivation of food genotoxicants 5-hydroxymethylfurfural and furfuryl alcohol by sulfotransferases from human, mouse and rat: a comparative study. *Arch. Toxicol.* 90:137-148.

is not greater than 1 per 10<sup>5</sup>. The current OEHHA calculated NSRL for acrylamide is 0.2 µg/day. [In 2005, OEHHA calculated a NSRL for acrylamide of 1.0 µg/day, but this value was not adopted.] The NSRL for acrylamide was based on data from the most sensitive animal bioassay studies that were considered to be of acceptable quality and design. Cancer epidemiological data on acrylamide were insufficient to perform a reliable quantitative risk assessment. As specified in the California Code of Regulations § 25703, the NSRL for this genotoxic carcinogen was calculated using a no-threshold dose-response model and body weight scaling factors to derive human cancer potency (expressed in reciprocal milligrams of chemical per kilogram of bodyweight per day) from animal cancer potency. Levels of acrylamide in a cup of coffee exceed OEHHA's NSRL [including the value calculated in 2005] for this carcinogen.

In the proposed change, acrylamide and other Proposition 65 listed chemicals in roasted coffee are simply declared as posing no significant risk. However, as specified in California Code of Regulations § 25703, "the determination of whether a level of exposure to a chemical known to the state to cause cancer poses no significant risk" .... "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer." The California Code of Regulations § 25703 also allows an exception to the 1 per 10<sup>5</sup> excess cancer risk where "sound considerations of public health" support an alternative level. One noted example for this exception is the situation in which "chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination."

However, by simply declaring no significant risk of cancer and not performing a quantitative risk assessment as required in the California Code of Regulations, OEHHA ignores their own policy (a bad precedent for future regulations) and assumes that the cancer risk level for acrylamide is zero regardless of its level in roasted coffee. Does OEHHA not realize that levels of acrylamide in coffee can vary substantially depending on numerous factors including the type of bean (Robusta vs Arabica), quality of the bean, roasting time and temperature, roasting degree (light, medium, dark), storage time and temperature? Ignoring these factors may result in coffee being served in California with much higher levels of acrylamide than are

currently present. Further, this action would discourage future efforts to reduce the levels of acrylamide in coffee.

In settling its case with the California Attorney General regarding the cancer risks of acrylamide in French fries and potato chips, the potato industry agreed to develop methods to substantially reduce levels of acrylamide in fried potato products. In contrast to the successful acrylamide mitigation effort by the potato industry, the coffee industry has avoided implementing available methods that can reduce acrylamide levels in coffee; the focus of the coffee industry has changed over the past 10 years from research on acrylamide mitigation to promoting health benefits of coffee even for effects that have not been well-established. Adoption of OEHHA's proposal will certainly lead to further abandonment of acrylamide mitigation efforts by the coffee industry. If this proposal had been passed in 2005, it is likely that the potato industry would have used that change in the regulation to argue against the need to reduce acrylamide levels in fried potato products. Because the proposal runs counter to the objective of Proposition 65 (the right of the people of California to be informed and protected from hazardous chemicals that cause cancer, birth defects and reproductive harm) OEHHA needs to address the consequence of the proposed rulemaking on future public health concerns of coffee and on the regulation of other Proposition 65-listed cancer-causing chemicals.

In contrast to the OEHHA proposal on cancer risk for the mixture of chemicals in coffee, US EPA<sup>12</sup> maintains that "environmental exposures .....to a mixture with a known carcinogenic component may pose a cancer risk in spite of negative results from a whole-mixture study." In this sense, coffee is not a unique chemical mixture. OEHHA seems to view the cancer risk of acrylamide differently when it is present in coffee compared to any other source because of the presence of "anticarcinogens." However, as explained above, the putative anticarcinogens in coffee do not impact the genotoxicity of this epoxide-forming carcinogen. Thus, there is no scientific justification for viewing acrylamide as posing no significant cancer risk only when produced in coffee as part of the roasting process. Consequently, by adopting the proposed

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<sup>12</sup> US Environmental Protection Agency. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002, Washington, D.C.

rule change, OEHHA in essence is supporting the absurd notion that the NSRL for acrylamide should also not apply for other sources, including drinking water.

### **3) A few comments on the IARC evaluation of coffee and OEHHA's reliance on that monograph to support the proposed rule change: childhood leukemia, colorectal cancer, and confounding**

a) Regarding the human data on childhood leukemia, the IARC Working Group reported “three meta-analyses of the association between maternal coffee consumption and childhood leukaemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake.” In my experience at IARC Working Group meetings, such findings would support the categorization of *limited evidence of carcinogenicity* (“a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence”). The recent finding of a positive dose-response trend ( $p=0.005$ ) and a significant elevation in the risk of child leukemia (OR=1.27, 95% CI1.09-1.43) from a pooled analysis of the data from eight case control studies on maternal consumption of coffee during pregnancy<sup>13</sup> adds further support for a causal interpretation of this association. The results for childhood leukemia indicate that the sentence in the Statement of Reasons “coffee drinking was not found to increase or probably increase any types of cancer in men or women” is a misrepresentation of the potential cancer risk of coffee consumption and consequently undermines the objectives of Proposition 65.

b) The Initial Statement of Reasons states “IARC found moderate evidence of an inverse association (risk reduction) between coffee drinking and colorectal adenoma, a precursor lesion for most colorectal cancers.” This statement is a misrepresentation of the IARC conclusion which was “There is *moderate* evidence regarding the association between coffee drinking and risk of colorectal adenomas. An inverse association between coffee drinking and risk of

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<sup>13</sup> Milne E, et al. 2018. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium. *Cancer Causes Control* 29:539-550.

colorectal adenomas was found in several studies; however, possible uncontrolled confounding and selection biases cannot be excluded.” IARC did not conclude that the Working Group found moderate evidence of an inverse association between coffee drinking and colorectal cancer!

c) Contrary to the Statement of Reasons, IARC did not “conclude[d] that drinking coffee is inversely associated with cancers of the liver and uterine endometrium.” In the final evaluation in the coffee monograph, the IARC Working Group wrote “inverse associations with drinking coffee have been observed with cancers of the liver and uterine endometrium.” The OEHHA statement extends the reported observations of inverse associations made by IARC to represent established causal relationships. To draw the conclusion that there is *evidence suggesting lack of carcinogenicity* (as IARC has done for 5 sites: pancreas, liver, female breast, uterine endometrium, and prostate) [or that inverse associations are causally related to exposures to a particular agent], certain criteria that are specified in each volume of the IARC monographs must be met: “There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up,” and “latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.” It does not appear that these criteria have been adequately met and fully characterized in the IARC monograph on coffee. In addition, the Statement of Reasons appears to blindly accept the IARC evaluations without addressing the potential impact of the above factors on the conclusion that there is *evidence suggesting lack of carcinogenicity* for 5 sites. Terms including confounding, bias, and latency are not found in OEHHA’s Statement of Reasons. This is a serious deficiency in the justification for such a major change in the policies and methodologies that were established in response to the passage of Proposition 65.

IARC’s overall evaluation was that “there is *inadequate evidence* in humans for the carcinogenicity of drinking coffee.” This does not mean that coffee is probably not carcinogenic

to humans. It is important to remember, that for 21 sites or types of cancer, IARC considered the data to be inconclusive or too sparse to evaluate, and tumor induction by acrylamide in experimental animals was observed at several of those sites (e.g., oral cavity, lung, ovary, stomach, skin, and thyroid gland). Thus, the epidemiology results do not support the dismissal of the animal cancer data for assessing the risk of cancer from acrylamide in coffee.

**4) Rather than declaring acrylamide in roasted coffee as posing no significant risk of cancer, OEHHA should support the development and implementation of methodologies that can reduce this genotoxic carcinogen to levels below its NSRL.**

Acrylamide is unique among the many chemicals produced in coffee during the roasting process. Acrylamide provides no health or organoleptic benefit to brewed coffee. In addition, the levels of acrylamide in coffee can be reduced by 90% without having a negative effect on the palatability of this popular beverage.

The discovery that acrylamide is formed in various cooked foods in 2002<sup>14</sup>, led to national and international concerns of cancer risk, as well as a burst in scientific investigations on the mechanism of acrylamide formation in heated foods, measurement of the levels of acrylamide in cooked foods under various processing conditions, mechanisms involved in its carcinogenicity, and the development of methods to prevent its formation or reduce its levels in cooked foods. The formation of acrylamide in cooked foods was shown to be due primarily to reaction of the amino acid asparagine with certain reducing sugars, fructose and/or glucose, via the Maillard reaction.<sup>15</sup> Acrylamide levels are lower in coffee brewed from Arabica beans versus Robusta beans and in dark roasted beans compared to light roasted beans. As part of my work in the case of CERT vs. Starbucks et al., I reviewed scientific publications, patents from the potato and coffee industries, and internal communications that described effective methods to mitigate the levels of acrylamide in fried potatoes and roasted coffee. In addition to optimizing

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<sup>14</sup> Tareke E. 2002. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. J. Agric. Food Chem. 50:4998-5006.

<sup>15</sup> Rydberg P. 2003. Investigations of factors that influence the acrylamide content of heated foodstuffs. J. Agric. Food Chem. 51:7012-7018.

the roasting conditions, some of the successful and promising approaches for reducing acrylamide in coffee include:

- a) Treatment with asparaginase catalyzes the hydrolysis of asparagine, a precursor for acrylamide formation. Patents awarded to Illy Caffé and to Proctor and Gamble Company showed that pretreating coffee beans with asparaginase reduced acrylamide levels in brewed coffee by 80 to 90%, and the “desired organoleptic properties remain unaltered”.<sup>16 17</sup> In Europe, more than 200 tons of asparaginase-treated beans have been processed on industrial scale and sold to the market.
- b) Heat curing of roasted coffee beans at 100<sup>0</sup>C for 16 hours reduced acrylamide levels by 66%. Plant trials of heat treated roasted coffee beans indicated that a 40-50% reduction in acrylamide was feasible while maintaining an acceptable level of quality (Kraft Foods, 2006 – presented by Dr. Melnick at trial testimony, CERT vs. Starbucks et al., 2017).
- c) Super critical CO<sub>2</sub> extraction has been used to remove caffeine from coffee beans while retaining components of aroma and taste. This technique is also effective in reducing levels of acrylamide by approximately 80% from roasted coffee beans.<sup>18</sup> This “acrylamide-mitigation strategy is expected to only slightly modify the sensory properties of coffee.” “This process offers a clean, efficient, and environmentally acceptable method of removing acrylamide from coffee”.<sup>19</sup>
- d) Extended storage of roasted and ground coffee under vacuum or nitrogen gas pressure at room temperature can lead to ~40 % reduction of acrylamide levels in brewed coffee;<sup>20</sup> acrylamide levels decrease with extended storage time due to its covalent binding to

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<sup>16</sup> Navarin L, et al. 2013. Method for reducing the content of acrylamide in a roasted coffee. International Patent Number WO 2013/005145 A1. Illy Caffè SPA.

<sup>17</sup> Dria GJ, et al. 2007. Method for reduction of acrylamide in roasted coffee beans, roasted coffee beans roasted coffee beans having reduced levels of acrylamide, and article of commerce. US Patent 7,220,440 B2. The Proctor & Gamble Company.

<sup>18</sup> Banchemo M, et al. 2013. Supercritical fluid extraction as a potential mitigation strategy for the reduction of acrylamide level in coffee. J Food Engineering 115:292-297.

<sup>19</sup> Friedman M. 2015. Acrylamide: inhibition of formation in processed food and mitigation of toxicity in cells, animals, and humans. Food Funct. 6:1752-1772.

<sup>20</sup> Baum M, (2008). Fate of <sup>14</sup>C-acrylamide in roasted and ground coffee during storage. Mol. Nutr. Food Res. 52:600-608.

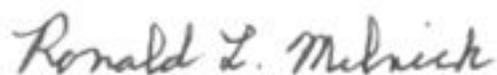
nucleophilic groups in coffee grounds. Starbucks specifies a shelf of up to 60 weeks for ground and whole bean roasted coffee, while Illy Caffé claims that due to their inert gas pressurization packaging technology, “the flavor and freshness of the unopened Illy coffee can be fully preserved for a long period of 2 years.”

e) Acrylamidase can enzymatically degrade acrylamide in roasted coffee. This enzyme can be added right after brewing from a coffee maker or it can be applied to coffee filters.<sup>21</sup> Acrylamidase treatment should not affect the organoleptic properties of brewed coffee because the activity of this enzyme is specific for acrylamide.

It is very likely that combinations of the above mitigation methods could reduce acrylamide levels in coffee by 90% or greater, without negatively affecting coffee’s important sensory properties. Thus, from a public health perspective, the appropriate future action for the State of California and the coffee industry should be to work together to further develop and implement methods that effectively reduce acrylamide levels in roasted coffee rather than simply declaring that this genotoxic carcinogen poses no significant health risk even at levels that exceed OEHHA’s NSRL in this widely-consumed beverage.

I hope my comments help OEHHA realize that the proposed change for acrylamide in coffee lacks scientific justification, runs counter to the policies and methodologies that were established for Proposition 65 listed chemicals., and is not in the best interest of public health.

Sincerely,



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<sup>21</sup> Cha M. 2013. Enzymatic control of the acrylamide level in coffee. Eur. Food Res. Technol. 236:567-571.