Comment Submissions - Proposed Adoption of Exposures to Listed Chemicals in Coffee Posing No Significant Risk

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Comments of Steven Bayard. Ph.D. on

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 8/26/2018

Introduction

I am Steven Bayard. I reside at [redacted], MD., [redacted] I am retired (2007) from a 32 year career with the U.S. Government. Nearly thirty of those years, I was working on various areas of quantitative and scientific risk assessment of toxic chemicals, for the U.S. Consumer Product Safety Commission, the U.S. Environmental Protection Agency, or the U. S. Occupational Safety and Health Agency. At OSHA, I was Director, Office of Risk Assessment. I have a B.S. in Mathematics from Tufts University, 1965, and a Ph.D. in Biostatistics from Johns Hopkins University in 1971. I was a paid expert witness for the plaintiffs in CERT vs. Starbucks et al., but, here, I am presenting these comments on my own, without compensation of any kind.

In full disclosure, I am also a lifelong coffee drinker, consuming about two 12 ounce cups per day, more during stressful times.

The first main point I want to make in my comments is that the Proposition 65 listed carcinogen acrylamide is a component of coffee present in sufficient quantities that drinking only one cup of coffee a day for 54 years results in an increased lifetime cancer risk > 1 in 100,000. Under the Proposition 65 law and California Code, a cancer warning label on coffee should be required. In these comments I have provided a full quantitative risk assessment and all the required details to support my assertion.

The second main point that I want to make in my comments is that OEEHA, <u>without doing the necessary quantitative risk assessment for the carcinogens in coffee</u>, has proposed to exempt coffee's carcinogenic components from labeling, including some Prop 65 carcinogens. I submit that OEEHA used flawed and unsupported reasoning in proposing that:

> "exposures to Proposition 65 listed chemicals in coffee that are produced as part of, and inherent in, the processes of roasting and brewing coffee pose no significant risk of cancer." *Initial Statement of Reasons*

I submit that this proposed language is contrary to both the letter and the intent of the Proposition 65 law, as well as OEEHA's own procedures. Proposition 65 is intended to identify chemicals that cause cancer and reproductive effects at levels of increased lifetime risk > 1/100,000, and to inform consumers, so that the consumers may make an informed judgment whether they want to take those risks. Toward that end, CalEPA and OEHHA have even developed a list of Proposition 65 listed carcinogens and have codified some proscribed methods for estimating their risks. These listed carcinogens rarely exist by themselves; they almost always exist as components in products used or consumed by humans. In the case of coffee, OEHHA, in its *Initial statement of Reasons*, has identified several carcinogens in coffee, but, to my knowledge, has done no quantitative risk assessments on any of these to determine the risk to California's coffee drinkers. Instead, it has taken coffee as a complex mixture, has <u>not</u> done a hazard assessment on coffee's carcinogenicity, but, has instead relied on the hazard assessment of another respected health agency, IARC. IARC's conclusion is that <u>coffee cannot be classified as to its carcinogenicity in humans.</u> Based on this classification, if OEHHA really accepts it, I believe that it is then OEHHA's obligation to examine the increased cancer risks from the Prop 65 carcinogens in the coffee mixture[1], and to inform their public if those risks are greater than 1 per 100,000. To me, that is what the law is intended to do.

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[1] (U.S. EPA provides both Guidelines for the Risk Assessment of Complex mixtures. (U.S.EPA's. Guidelines for Health Assessment of Chemical Mixtures (1986), and U.S. EPA's supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures, EPA/630/R-00/602 (2000)). I cite EPA's Guidelines for Chemical Mixtures because, in the past, OEHHA has relied on both EPA's and IARC's carcinogenicity evaluations for some of its Prop 65 listings, and Iam not familiar with either OEHHA's or IARC's guidance for the assessment of chemical mixtures.

What does OEHHA do? It says, well if we don't know if coffee is carcinogenic then we will declare that all the Proposition 65 carcinogens produced as part of the coffee roasting or brewing process have no significant risk. What an easy solution, exempt Prop 65 carcinogens without doing any analysis! But it sounds crazy to me, and an abrogation of government responsibilities to protect the public. For, example, what if those carcinogens or other Prop 65 carcinogens are or were in the public drinking water supply or baby formula? Wouldn't we want to know about them, and if the increased cancer risks are significant? And wouldn't we want to reduce those risks if we can? Why should coffee be exempt from a similar analysis?

Coffee is, perhaps, a perfect example of a Prop 65 chemical. Lots of people drink a lot of coffee. It is habit forming, so that its daily regular use can be fairly easily computed, and historically estimated. Even though there are variations in brands and types, lots of its components in the mixture are not highly variable in quantity. And it is ingested, making it easily systemically available. With such easy access and high amounts consumed daily, I believe the public should know about what they're really consuming.

If OEHHA's proposed action is allowed to become codified, it will subject California's coffee drinkers to increased cancer risks without the notification that Proposition 65 intended. I specifically use the example of one carcinogen in coffee, acrylamide, a Proposition 65 listed carcinogen, to illustrate my case.

Acrylamide is a Prop 65 listed carcinogen, found in brewed and roasted coffee. It is not part of the fresh bean, but is both created and destroyed in the coffee roasting process. Based on my readings, light roasted coffee seems to contain more acrylamide than dark roasted coffee. Also, acrylamide is highly soluble in water, so that most of the acrylamide in the ground roasted bean will solubilize and become part of the final brew. When ingested in the coffee mixture, it is easily absorbed through the gut.

Acrylamide has been shown to be highly carcinogenic in every animal long-term bioassay in both sexes of rats and mice. However, studying the carcinogenic effects of acrylamide in coffee directly in humans would be very difficult because,

1) acrylamide is in lots of fried, baked, and roasted foods, so a non-exposed comparison population would be quite difficult to find; and 2) my estimates of increased cancer risk from the acrylamide in coffee, while > 1 per 100,000, are about 2 per 10,000 for the average consumer, who drinks about 3.1 cups per day. Under these two conditions the statistical power to study the effects of acrylamide in coffee directly in human populations is quite small. Also, to my knowledge, there are no human cancer studies of coffee in which acrylamide is studied or its risks estimated.

I want to make one related point: First, OEHHA, in its *Initial Statement of Reasons*, presents a statement that coffee contains "numerous chemicals with biological activities associated with protective, anti-carcinogenic effects," including anti-oxidants and free radical scavengers. Whether or not this is true, in order to dismiss the carcinogenic risk of acrylamide, which exerts its carcinogenicity through conversion to its active metabolite glycidamide, OEHHA must show that these chemicals could interfere with the glycidamide carcinogenic process *in vivo*, and that there is enough quantity of those chemicals in the coffee mixture to be effective at doing so. For example, there are also antioxidants and free radical scavengers in tobacco smoke.

In summary, I submit that OEHHA should follow the Proposition 65 law and California code for conducting risk assessments in discussing the risk of acrylamide and other carcinogens in coffee. I have used those codified procedures and have produced a QRA, the results of which require coffee to have a warning label as a carcinogen under the provisions of Prop 65. In addition to informing California's coffee drinkers, warning labels on coffee based on coffee's acrylamide content can have the added benefit of encouraging roasters to reduce coffee's acrylamide content to non-significant risk levels by altering the roasting process. That technology exists now. Wouldn't that be better for all?

Below is my quantitative risk assessment for Acrylamide in coffee.

Respectfully,

Steven Bayard, Ph.D. spbayard@aol.com **8/26/2018**

Quantitative Risk Assessment for the Carcinogenic Risk of Acrylamide in Coffee in California

Summary.

I have conducted a new full quantitative risk assessment, QRA, of acrylamide in coffee. I have used California code for conducting the dose-response assessment. My full QRA also includes an exposure assessment of AA in coffee and a new quantitative dose-response assessment based on a 2012 NTP Technical Report on the Carcinogenicity of acrylamide (AA) in Rats and Mice. The NTP study is of superior quality to previous studies. It is confirmative and is conclusive of AA carcinogenicity in both rats and mice of both sexes, causing multiple tumor types in each sex/species. AA animal bioassay studies previously used in quantitative risk assessments, by both USEPA (2010) and OEEHA (2005), were of lesser quality than that of the NTP. Furthermore, California code specifies that the most sensitive sex species study should be used for quantitative risk assessment, and that is the mouse in the NTP study.
To complete the QRA assessment, I then estimated coffee consumption in California adults, using coffee consumption data from the National Coffee Association and AA concentrations in coffee from measurements done by the U.S. food and Drug Administration.

The results of my QRA show that the lifetime increased risk from ingesting the AA by drinking only one cup of coffee/day for 54 years (adult, ages 17 - 70) is >1 x 10^{-5}. For the average coffee drinker who drinks about 3.1 cups/day, that increased risk is about 2 per 10,000. As part of my QRA, I did a dose-response assessment, extrapolating from the NTP mouse study to humans, again using procedures specified by California code. Based on my dose-response analysis, I have determined that the NSRL for acrylamide is **0.34 µg/day for daily exposure for 54 years** (assuming no coffee drinking below age 17), and **0.26 µg/day for daily exposure for 70 years.** Considering that coffee is drunk mostly by adults > 16 years of age, I discounted consumption during the first 16 years of life; this accounts for the different NSRL's for 54 and 70 years.

Introduction.

My purpose in this analysis below is to provide a quantitative risk analysis for the increased risk of cancer from drinking coffee, due to the acrylamide content in coffee. To estimate the cancer risk from acrylamide (AA) in coffee, we need to estimate three components:

I. The cancer potency per amount of acrylamide ingested on a daily basis;
II. The amount of acrylamide in coffee; and
III. The amount of coffee consumed on a daily basis.

This analysis develops estimates of these three components and then combines these to estimate the lifetime increased risk of cancer to the coffee drinker due to its acrylamide contaminant. Final risk estimates will be presented as both cancer risk from coffee consumption, and whether the amount of AA in coffee is above or below California's No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen AA. The results of this risk assessment will also be compared with those on AA of the Cal. EPA and the U.S. EPA

I. The cancer potency of ingested acrylamide.

First, the carcinogenic potential of AA has been studied by several government and other health agencies worldwide, and, to my knowledge, has been declared to be a presumptive human carcinogen by all those who have made formal statements on their analyses. In its most basic form the logic is that AA 1) causes cancers in multiple sites in both sexes of rats and mice in multiple lifetime bioassay tests, 2) is bioavailable from ingestion, and 3) is metabolized, in animals and humans, to a bioavailable epoxide that forms DNA adducts, and is mutagenic. Although there is little direct evidence of carcinogenicity in humans, the evidence in test animals, and other tests, provide sufficient concern that humans, too, are susceptible to cancer from ingestion of acrylamide.

Two of the lead government regulatory agencies in quantitative risk assessments are the U.S. EPA and the California EPA, and both have produced comprehensive reports on AA, including estimates of the carcinogenic potency from ingestion (U.S. EPA, 2010, Plaintiff's exhibit #48631, CERT vs. Starbucks et al); and Cal EPA, 2005, Plaintiff's Exhibit #23930). I will use results from both these reports to provide estimates of the cancer potency of ingested AA. I will also use some of their methods in my analysis. Although their methods are quite similar and they both use the same rat drinking water studies as the basis for their quantitative estimates (Johnson et al. (1986) Plaintiff's Exhibit # 23171, CERT vs. Starbucks; and Friedman et al. (Plaintiff's Exhibit #15159), there are differences that do have an effect on their final estimates. The analysis below will present and compare the results of these two reports.

A third governmental agency whose report is important to my analysis is the National Toxicology Program, (NTP, part of the U.S. National institutes of Health), which conducts much of the animal toxicology testing. Specifically, I will be using NTP's recent report on their bioassay results for AA (NTP TR 575, Plaintiff's Exhibit #48449). I will also be referring to a recent publication by some of the study's investigators (Beland et. al., (2013), Plaintiff's Exhibit #48992) which presents the major results of that study. The NTP TR 575 provides the basic data for the dose-response part of this risk assessment, specifically the multiple tumors in both rats and mice of both sexes. These NTP results have not been reported on by either the U.S. EPA or Cal EPA, although some foreign and international agencies have done analyses on these data.

As stated, both Cal. EPA and U.S. EPA use the results from two earlier studies on rats (Johnson et. al., 1986; and Friedman et al., 1995) to perform their dose-response analyses, and these analyses will not be repeated here. Instead, my analysis will use the NTP TR 575 data and I compare those results with those from the earlier analyses. These comparisons start with calculating dose-response models for the NTP data.

I.A. Dose-Response Modelling of the NTP Rat and Mouse Cancer Data for AA.

The NTP results show statistically significant dose-related tumors in multiple sites of both sexes of the tested rats and mice. As a result of their investigation, the NTP "conclude(s) that acrylamide in the drinking water caused cancer in several different tissues in male and female rats and mice (NTP, 2012, Summary page 6). More specifically, their larger statement is shown in Figure 1, below.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *clear evidence of carcinogenic activity* of acrylamide in male F344/N rats based on increased incidences of malignant mesothelioma of the epididymis and testis tunica, malignant schwannoma of the heart, and follicular cell adenoma or carcinoma of the thyroid gland. An increased incidence of pancreatic islet adenoma was also considered related to acrylamide exposure.

There was *clear evidence of carcinogenic activity* of acrylamide in female F344/N rats based on increased incidences of fibroadenoma of the mammary gland, squamous cell neoplasms (primarily papilloma) of the oral cavity (mucosa or tongue), mesenchymal neoplasms (fibroma, fibrosarcoma, or sarcoma) of the skin, and follicular cell neoplasms (adenoma or carcinoma) of the thyroid gland. Increased incidences of hepatocellular adenoma of the liver and carcinoma of the clitoral gland were also considered to be related to acrylamide exposure. The occurrence of malignant schwannoma of the heart may have been related to acrylamide exposure.

There was *clear evidence of carcinogenic activity* of acrylamide in male B6C3F1 mice based on increased incidences of neoplasms (primarily adenoma) of the harderian gland, alveolar/bronchiolar neoplasms (primarily adenoma) of the lung and squamous cell neoplasms (primarily papilloma) of the forestomach.

There was *clear evidence of carcinogenic activity* of acrylamide in female B6C3F1 mice based on increased incidences of harderian gland adenoma, alveolar/ bronchiolar adenoma of the lung, adenoacanthoma and adenocarcinoma of the mammary gland, benign granulosa cell neoplasms of the ovary, and malignant mesenchymal neoplasms of the skin. Increased incidences of squamous cell papilloma of the forestomach were also considered to be related to acrylamide exposure.

Figure 1. Statement of the NTP (2013) on the Results of their Acrylamide Bioassay

I have calculated dose-response models for most of the tumors sites for which the NTP declared either "Clear evidence of carcinogenic activity" or "considered to be related to acrylamide exposure." To do this modeling, I have used the publically available free BMDS

software used by the U.S. EPA, provided so that anyone could use the same software that it uses in its calculations. (U. S. EPA. BMDS version 2.4, and BMDS Wizard Version 1.8, available at http://www.epa.gov/ncea/bmds/. I have also used EPA's Benchmark Dose Technical Guidance. (EPA/100R-12/001. June 2012; http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf) , and specific information on reporting and their cancer example from their training modules. http://www.epa.gov/ncea/bmds/training/ . For guidance on which models and procedures to use, I also use EPA's Carcinogen Risk Assessment Guidelines. EPA/630/P-03/001F, Mar 2005.

http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF

I.B Animal Dose-Response Models for Individual Timor Sites. (All calculated using U.S. EPA's BMDS Version 2.4 Software)

The models under consideration are termed "multistage models," or "cancer-multistage models. They are basically linear (in the parameters) polynomial dose-response models of varying degree, with all the parameter values restricted to be non-negative, and the response a dichotomous "yes" or "no" cancer response. Because there are five dose groups, including the control, I allowed models with polynomials up to degree 4, plus a parameter estimate for background response. I also ran BMDS for other "best fitting" models, but this was strictly for comparing how the different models fit the data. Because of the overwhelming conclusion among so many government and health bodies, including U.S. and Cal EPA, that have considered that AA exerts its carcinogenic effects through a genotoxic mechanism of "mode of action," agencies that produce dose-response quantitative cancer risk assessments for AA would use the family of multistage models for their analysis. Often, models with only the linear term included might be considered. However, U.S. EPA's BMDS provides guidance and calculations to help choose the model that provides the "best fit" of the data from those of the multistage family. In our case, there are four models from which to choose.

For their cancer potency estimates, the U.S. EPA and the BMDS software basically use a modification of full model low-dose extrapolation called a "point of departure (POD) approach. This is all more fully explained in the BMDS training modules, but , essentially, the approach is to model the full data set, then use the best fitting model to select a lower confidence limit on the dose, $BMDL_{10}$ that will produce a 10% extra risk in cancer. From that $BMDL_{10}$, a "cancer slope factor," i.e. a linear dose-response slope, is created by taking risk/dose, or 0.1/ $BMDL_{10}$. This linear low dose model approach is used for carcinogens that are active through a genotoxic "mode of action" (MOA), which is the case for AA.

The BMDS software is used for estimating dose-response for both cancer and non-cancer risks, so it includes models not typically used in cancer modeling. However, examining some of these non-linear best fitting models can give a relative perspective on how well the multistage family fits the data.

Using the BMDS software, I fit the suite of models to the NTP tumor data for the rats and mice of both sexes. I report these results in Table 1.1 A-T. To determine the "best fitting" model(s), I relied on the BMDS Technical Guidance. The Technical Guidance suggests 3 ways to determine the best fitting model, and the statistics to evaluate these are presented in each portion of Table 1. The first is the well-known Chi square goodness of Fit test, which determines how well the model fits the data, overall at all the data points. The Guidance suggests that for the total suite of models, each model should fit with a probability, P>0.05. However, for the cancer multistage, the fit need only attain P>0.10, and that value is used here. The second criteria examines more closely the model fit at each data point, especially at the BMD_{10}; this is called the scaled residual and the suggested level of concern is the absolute value of this scaled residual is >2 . The third criterion is the Akaike information criterion, a value close to the statistical likelihood, but one that also incorporates the number of parameters estimated. The lower the Akaike score the better. If a model fits the data for these criteria, the BMDS software will declare the model "viable." Finally, the BMDS has an algorithm which will compare these models and choose one as "recommended" because it may have the "lowest Akaike score" or lowest $BMDL_{10}$. If several models provide adequate acceptance statistics, the BMDS classifies these as "alternate."

The results of my 17 individual tumor sites' modeling of the NTP rats and mice tumor data are presented in **Table I.A-U**. I was unable to obtain model results for the female rat clitoral carcinoma and female rat liver hepatocellular adenoma, and I, therefore, eliminated these from further analyses. Most of my results match those shown in Beland et al (2013), although there are a few exceptions. By far the most notable are my model choices for male and female mouse Harderian Gland tumors. Beland's results suggest either log-logistic or log-probit models for this tumor site in both male and female mice. My results suggest that a one stage model will fit the both data sets barely adequately (0.05 <P <0.10). As a result, my $BMDl_{10}$ are higher than his for the mouse, making my cancer potency slopes over 40% lower for the female mouse (See Tables 1.L and I.M, which include BMDS results of fitting the data with and without the high dose groups.

Table I.2 presents the chosen animal cancer slope factors from the results of the modeling shown in Table I. A-U.

I.C. Summing Risks from Individual Tumor Sites to Estimate Total Cancer Risks from Multiple Tumor Sites.

Since AA causes multiple site tumors in the animal bioassays, risks from total cancer must be considered. In their respective quantitative risk analyses for AA, both U.S. EPA and Cal. EPA

estimated the combined risks by summing risks for each tumor site. Although their methods were slightly different, they both included summing central estimates of individual cancer slope factors, and factoring in the standard errors of these central estimates to derive a an upper bound on the combined summed cancer potency estimate. Based on my knowledge of these methods, I conclude that they are appropriate for this assessment of AA, and, using the same central estimates and their standard errors, will give near identical results to within round-off error. To do my calculations for summed cancer risks for the NTP rat and mice data, I have used U.S. EPA's method, detailed in their assessment, Appendix D, Table D-8 and Table D-10 (Plaintiff's Exhibit #48631). My results are presented here in four separate Tables I.B.1 – i.B.4, for male and female rats, and for male and female mice. They show results based on summing risks for different combinations of sites in each separate sex-species. The final animal cancer slope factors are:

Male Rats (4 sites): 0.2617 $(mg/kg\text{-}day)^{-1}$
Female Rats (4 sites): 0.3092 $(mg/kg\text{-}day)^{-1}$
Male Mice (3 sites): 0.3813 $(mg/kg\text{-}day)^{-1}$
Female Mice (6 sites): 0.3701 $(mg/kg\text{-}day)^{-1}$

These results suggest that the AA is about 30% more potent as a carcinogen in the mice than in the rats. These results are affected by the calculated slopes for Harderian Gland tumors in both the male and female mice.

1.D. Animal-to-Human Scaling or interspecies Conversion Factors.

In extrapolating cancer risks from animals to humans, both the U.S. EPA and Cal. EPA use what is variously called an "animal-to-human scaling factor" or "interspecies scaling factor" or "interspecies conversion factor." Cal. EPA (2005) notes that "the default interspecies factor assumes that dose in amount per surface area produces the same cancer incidence in different species. The factor is described as:

Cancer potency (human) = cancer potency (animal) x interspecies factor

For Cal. EPA, its original default "interspecies conversion factor" was based on surface area scaling, i.e., (human body weight/animal body weight)$^{1/3}$ [Title, California Code of Regulation, section 12703 (a)(6)." For its interspecies conversion factors for rats-to-humans in the Friedman (1995) and Johnson (1986) drinking water bioassays, these factors (for a 70 kg human) were:

Interspecies Factor: male rat to human: $(70/0.35)^{1/3} = 5.85$
Female rat to human: $(70/0.20)^{1/3} = 7.05$

I have modified the above interspecies conversion factors that Cal EPA used in its 2005 acrylamide QRA to reflect the revision for interspecies factors based on the current California Code current California Code of Regulations 27 CCR Section 25703 on the topic "Quantitative Risk Assessment", which specifies use of the $(W_h/W_a)^{1/4}$, (25703 (a) (6), http://weblinks.westlaw.com/result/default.aspx.aspx?action=Search&cfid=1&cnt=DOC&db=C... (6/5/2013), I have concluded that, in view of the current specifications, using this ¼ power factor for the NTP rat is appropriate in this case. I have, therefore, revised the scaling factors for the rat-to-human extrapolation to reflect this change:

Interspecies Factor: male rat to human: $(70/0.35)^{1/4} = 3.76$

Female rat to human: $(70/0.20)^{1/4} = 4.33$

Also, in its AA assessment, CAL EPA (page 24) further divides this interspecies factor into pharmacokinetic (PK, differences in internal dose) and pharmacodynamic (PD, differences in response to internal dose) parts:

Cancer potency (human) = cancer potency (animal) x PK factor x PD factor

For their PK factor, Cal. EPA derived a factor of 1.2 "as the ratio of the human to rat internal dose of glycidamide, normalized by the applied dose" (see their Table 9, page 21). Then their "assessment chose to proportion equally (page 24)" the PK and PD portions. The resulting animal-to-human conversions for male and female rats were:

Cancer potency (human) = cancer potency (male rat) x 1.2 x $(5.85)^{1/2}$

Cancer potency (human) = cancer potency (Female rat) x 1.2 x $(7.05)^{1/2}$

For Cal. EPA, their final rat-to-human interspecies conversion factors are 3.19 for the female rat and 2.90 for the male rat. For my analysis of the NTP (2012) data, I substitute the NTP male rat= 418.2 gm, and female rat= 262.0 gm weights and calculate factors of 2.3 for the male rat and 2.4 for the female rat. Based on these above scaling factors I calculate the human potency estimates based on the tumor sites in the NTP rats. These results are shown in Table I.D.1.

Also shown in Table I.D.1 are my results for the Human Cancer Potency Factors for the risk assessment based on the NTP mice. For the mice, I do not have an estimate of the PK factor in mice relative to humans, and choose to use the default interspecies scaling factor, $(W_h/W_a)^{1/4}$ discussed above as well as in U.S. EPA's Publication, "Recommended Use of Default Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose." (EPA/100/R11/0001 Final) http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf EPA also

recommends use of this default animal-to-human scaling factor in its 2005 Cancer Guidelines. (http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF)

The default scaling factors for the mouse then become: male mouse = $(70/0.031)^{1/4}$ = 6.89, and for the female mouse it is $(70/0.0252)^{1/4}$ = 7.27. As can be seen in the **Table I.D.1,** the overall risk estimates based on combined tumor sites in the mouse are about three times as high as those based on the rat, but a large portion of the mouse-to-human risk estimates are due to the contribution of Harderian Gland tumors.

Finally, this section concludes with a comparison of the human cancer potency estimates for rat tumors in the Johnson (1986), Friedman (1995), and NTP (2012) AA bioassays for both sexes. Both Cal. EPA and U.S.EPA reported on the two earlier AA bioassays, but I will show the Cal. EPA factors for comparisons, because I used their interspecies conversion factors. These comparisons are shown in **Table I.D.2.** Although some of the tumor sites are different in the same sex in the different studies, the results for the combined human cancer potency estimates based on multiple tumor sites are quite close quantitatively in all three male and three female rat bioassays. Human cancer slope factors based on the NTP mouse study are about 3 times as high as those of the NTP rat. This factor is a combination of both the increased mouse cancer potency estimates, but more the animal-to-human species conversion factor that I used.

II. Acrylamide Content in Coffee

In order to estimate the risk of AA from drinking coffee, I need to know both the concentration of AA in coffee and the amount of coffee consumed per day. My estimates of AA concentration in Coffee come from the U.S. FDA survey. Dybing (2005, Plaintiff's Exhibit #23810), and Cal. EPA's "Characterization of Acrylamide Intake from Certain Foods." (2005. http://oehha.ca.gov/prop65/law/pdf_zip/acrylamideintakeReport.pdf) In 2003-2004 the FDA analyzed twenty samples of U.S. brewed coffee for acrylamide, The average concentration was 7.35 ppb or 7.35 ug/kg, standard deviation= 2.37. with a minimum of 3 ug/kg and a maximum of 13 ug/kg.

III. Amount of Coffee Consumed Per Day

The amount of coffee consumed/day will be estimated in two parts: 1) Number of cups/day, and 2) average size of a cup. Together, they will allow an estimate of the amount of coffee/day.

I estimated 1) the number of cups/day from the NCA Survey Table excel file: 0416_Age_18_Plus_banner1(Region,Gender,Age,Income,Kids).xslm I used the Table Q20, the WEST Region (column F). There were 653 (cell F858) people in the West region, of whom 428 (cell F861) replied they had drunk coffee "yesterday". The total number of cups they drank was 1318 (cell F910) for a mean number of cups = 3.08 (cell F904).

I estimated 2) the amount of ounces/cup from the same Excel file, but used Table Q21, % Drinking by Size of Cup. Again I used the West Region, Column F, summing the frequencies of those who reported drinking 3 oz. (expresso), 8 oz., 12 oz., and 16 oz., cups. – (cells F1849, F1852, F1855, and F1858). The total oz. of the 509 cups was 5,426, or 10.66 oz./cup.

IV. Estimates of Lifetime Cancer Risk from Acrylamide in Coffee.

Based on the concentration of AA in coffee (7.35 └ g/kg coffee), the amount of coffee consumed by coffee drinkers in the West, (average 3.1 cups/day, and 10.66 oz./cup), we can calculate the amount of AA per cup of coffee as:

7.35 └ g/kg x 10.66 oz./cup x 28.375 gm/oz. x 1 kg/1000 gm = 2.22 µg AA/cup.

For a 70 kg human, one cup/day yields 2.22 µg/70 kg = 0.0317 AA µg/kg-day. I use these values to estimate the lifetime cancer risk from AA in coffee based on my analyses above. I compare these results with those from both Cal EPA (2005) and U.S. EPA (2010), for daily coffee consumption of 1, 3.1, 5. 7. And 9 cups/day. All these human cancer potency factors must first be adjusted to account for little coffee drinking under the age of 18. Based on figures in the NCA Tables for coffee drinkers ages 13-17, (0416_Age_13_Plus_banner1(Region,Gender,Age,Income,Kids).xslm), I note some coffee drinkers between these ages, and I concluded that using 17 as a cut-off age for these purposes is reasonable. Thus, the results presented assume that there is no coffee drinking below age 17. (See also, Branum et. al.; 2014.) To the extent that there is, these risk estimates will be too low.

These sets of cancer increased risk estimates from AA in coffee, both from my analyses and those of the Cal. EPA and U.S. EPA are shown in **Table IV.A.1**. I use the amount of AA (2.22 µg AA/cup) from one cup per day (9th percentile of coffee drinkers) to extrapolate to amount of AA in 3.1 cups/day, the average consumption of adult coffee drinkers in the West. I also estimate the cancer risk to those who drink 5 (71st percentile), 7 (85th percentile), and 9 (91st percentile) cups per day. I note that for **all** those who drink at least one cup per day, **all** the cancer risk estimates predict greater than 1 in 100,000 increased risk of cancer. For the 20 estimates I calculated in the table, these increased risks range from a low of 1.2 x 10^{-5} for 1 cup/day to nearly 1 per 1000 for the 9 cup/day drinker.

Corresponding to cancer risk estimates, California often describes risks in terms of the **NSRL** (No Significant Risk Levels), the level of exposure below which excess

lifetime cancer risk will be less than 1 per 100000. In its March 2005 risk assessment for AA, Cal. EPA (Plaintiff's Exhibit #23930) estimated the NSRL for all sources of AA, from birth, as 1.0 µg/day. As seen above and in Table IV.A.1, this level of AA is exceeded in just ½ cup of coffee per day.

V. Estimates of Margin-Of-Exposure Ratios (MOE) From AA in Coffee.

Some European commissions and health Agencies prefer the MOE approach over dose- response and animal-to-human extrapolation procedures. (See e.g. Plaintiff's Exhibit #41795), and I have provided an MOE analysis for cancer potency in the NTP 2 year rat and mouse bioassays. The analysis, presented in **Table V.A.1**, provides the same estimates of the NTP animal cancer slope factors $BMDL_{10}$'s, amount of AA in coffee, and amount of human coffee consumption used in the quantitative risk assessment above, but it does not extrapolate down to lower levels of risk. Instead, the MOEs in the table provides ratios of the oral dose levels causing 10% extra risk of cancer in animals, to the amount of AA ingested from different levels of coffee. Note that the ratios are pure numbers, but the units are in (mg/kg –b.w.) animals/mg/kg –b.w. humans.

The estimates in Table V.A.1 show that the MOE's for the single coffee cup/day drinker (< 10% of coffee drinkers) are in the 8,000 – 12,000 range. For these 52% who drink more than the average 3.1 cups/day the MOE's vary between 900 and 3900, for a 10% excess cancer response.

VI. Conclusions and Opinion.

According to a recent National Coffee Association annual survey of 653 Western adults, the 65% who said they were coffee drinkers drank an average of 3.1 cups/day. For these drinkers, I estimated that their average excess lifetime cancer risks from the acrylamide in that coffee is between 5 and 20 per 100000, well above the California NSRL.

I believe that these are real risks. Even though the specifics of the extrapolations from animals to humans can show variations, the consistency of animal cancer responses, with multiple tumors in both sexes of all three AA rat drinking water bioassays and in the AA NTP mice bioassay, plus other positive AA cancer results in mice, provides strong evidence that AA causes cancers in humans.

I have presented four different estimates of the excess risk levels for human cancer, one each by the Cal. EPA and the U.S. EPA, and my two on the NTP (2012)

AA bioassays. They differ by as much as a factor of 3.8 - my NTP combined sex mouse based analysis vs. the U.S. EPA rat based analysis. If one specific study must be cited, I believe the higher risk NTP mouse based analysis should be used as the final estimate, because:

1) California Code of Regulations 27 CCR Section 25703 (3) states:

   "Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality."

   I note that when Cal EPA (2005) and the U.S. EPA (2010) did their quantitative risk assessments, the NTP results were not available, so the rat would have been the most sensitive species. However, in the NTP study, my analysis based on the animal cancer potency factors for combined tumor sites, Table I.D.1 shows that the mouse is 20% (for the female mouse vs. the female rat) to 45% (for the male mouse vs. the male rat) more sensitive than is the rat to the cancer effects of AA.

2) The Male and Female mouse had nearly identical combined tumor sites animal cancer slope factors of 0.381 $(mg/kg\text{-}d)^{-1}$ and 0.371 $(mg/kg\text{-}d)^{-1}$, respectively. Thus, I conclude that the male and female mice are equally sensitive.

Thus, I believe that the risks based on the pooled estimates I calculated for the NTP mice, Table IV.A.1, should be used for California's risk assessment purposes.

Additional References.

Branum A, Rossen LM, and Schoendorf KC. (2014). Trends in Caffeine Intake Among U.S. Children and Adolescents. Pediatrics. 2014; 133:386-393.

U.S. EPA. Recommended Use of Body Weight$^{3/4}$ as the Default Method in the derivation of the Oral Reference Dose. EPA/100/R11/0001 Final. http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf

Table I.1. Results of U.S.EPA's (Benchmark Dose Software) BMDS 2.4, and BMDS Wizard Version 1.8 on NTP Acrylamide 2-Year Rat and Mice Bioassay studies TR 575 (2012). Calculation of BMD_{10}, $BMDL_{10}$, and Cancer Slope Factor for all tumors sites the NTP reported as Clear or Related evidence of acrylamide carcinogenicity. Results Calculated for EPA's Cancer Dichotomous Multistage Models with Number of dose parameters from 1-4. Recommended Selection of Model to be Used for the Combined Tumor Calculations, based on Goodness-of Fit (GOF; P>.0.05) of Model to Data, Akaike Information Criteria (AIC), Scaled Residuals at Low doses, and Lowest $BMDL_{10}$ for Models meeting the Recommended Criteria.

A. Male Rat: Tumor Site: Thyroid Follicular Cell Adenoma or Carcinoma

Dose mg/kg-d	**0**	**0.33**	**0.66**	**1.32**	**2.71**
Response	**1/47**	**3/48**	**4/47**	**6/48**	**0/48**

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	**Log-Probit**
BMD_{10}	1.45	1.45	1.45	1.45	1.17
$BMDL_{10}$	0.889	0.889	0.889	0.889	0.336
Cancer Slope Factor	0.113	0.113	0.113	0.113	0.2398
AIC	146.35	146.35	146.35	146.35	147.91
P-value G.O.F	0.947	0.947	0.947	0.947	0.994
Scaled Residuals at administered doses levels: Z= Nearest BMD.					
Dose : mg/kg-day			Scaled Residuals		
0	-0.347	-0.347	-0.347	-0.347	-0.010
0.33	0.297	Z0.297	Z0.297	Z0.297	0.072
0.66	0.253	0.253	0.253	0.253	-0.053
1.32	0.134^{Z}	0.134^{Z}	0.134^{Z}	0.134^{Z}	-0.051
2.71	-0.275	-0.275	-0.275	-0.275	0.041
Recommend?	Viable/alternate	Viable/alternate	Viable/alternate	Viable/alt.	
Comment	Chosen				Low $BMDL_{10}$

B. Male Rat: Tumor Site: Heart Schwannoma

Dose mg/kg -d	0	0.33	0.66	1.32	2.71
Response	1/48	2/48	3/48	4/48	6/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	**Other: Log-Probit**
BMD_{10}	2.43	2.43	2.43	2.43	2.41
$BMDL_{10}$	1.30	1.30	1.30	1.30	1.25
Cancer Slope Factor	0.0767	0.0767	0.0767	0.0767	0.0415
AIC	116.67	116.67	116.67	116.67	116.64
P-value G.O.F	0.982	0.982	0.982	0.982	
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day Scaled Residuals					
0	-0.218	-0.218	-0.218	-0.218	-0.191
0.33	0.070	0.070	0.070	0.070	0.068
0.66	0.282	0.282	0.282	0.282	0.263
1.32	0.082	0.082	0.082	0.082	0.057
2.71	-0.183	-0.183	-0.183	-0.183	-0/172
Recommend?	Viable/alternate	Viable/alternate	Viable/alternate	Viable/alt.	Via/Recomm
Comment	Chosen				Low $BMDL_{10}$

C. Male Rat: Tumor Site: Epididymis or Testis Mesotheliomas

Dose	0	0.33	0.66	1.32	2.71
Response	2/48	2/48	1/48	5/48	8/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Probit
BMD_{10}	2.09	2.18	2.18	2.18	2.16
$BMDL_{10}$	1.21	1.29	1.29	1.29	1.60
Cancer Slope Factor	0.0826	0.0776	0.0776	0.0776	0.0625
AIC	124.49	125.88	125.88	125.88	124.00
P-value G.O.F	0.613	0.487	0.487	0.487	0.685
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day Scaled Residuals					
0	0.558	0.232	0.232	0.232	0.378
0.33	-0.090	0.080	0.080	0.080	0.030
0.66	-1.144	-0.866	-0.866	-0.866	-0.959
1.32	0.322	0.768	0.768	0.768	0.644
2.71	0.278^{Z}	$--0.193^{Z}$	$--0.193^{Z}$	$--0.193^{Z}$	-0.091^{z}
Recommended Model	Viable/alternate	Via/alt.	Via/alt.	Via/alt.	Viable/ ”Recommended”
Comment:	Chosen/lowest BMD_{10}				Lowest AIC

D. Male Rat: Tumor Site: Pancreatic Islet Adenoma

Dose	0	0.33	0.66	1.32	2.71
Response	1/46	2/48	4/48	1/48	6/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Gamma
BMD_{10}	3.37	3.093	2.92	2.84	2.77
$BMDL_{10}$	1.59	1.603	1.65	1.68	1.73
Cancer Slope Factor	0.063	0.062	0.061	0.060	0.058
AIC	107.25	109.16	108.92	106.73	106.51
P-value G.O.F	0.366	0.191	0.191	0.360	0.386
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.293	-0.472	-0.629	-0.678	-0.688
0.33	0.097	0.087	0.029	-0.002	-0.015
0.66	1.109	1.286	1.399	1.427	1.422
1.32	-1.303	-1.160	-0.966	-0.842	-0.736
2.71	0.381	0.258	0.140	0.071	0.002
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/ ”recommended”
Comment:	**Chosen/** BMD>max. dose	BMD>max. dose	BMD>maximum dose	BMD>max. dose	Lowest AIC BMD>max. dose

E. Female Rat: Thyroid Follicular cell Adenoma or CARCINOMA

Dose	0	0.44	0.86	1.84	4.02
Response	1/46	2/48	4/48	1/48	6/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Gamma
BMD_{10}	3.849	3.849	3.849	3.849	3.849
$BMDL_{10}$	2.328	2.328	2.328	2.328	2.328
Cancer Slope Factor	0.0430	0.0430	0.0430	0.0430	0.0430
AIC	70.5	70.5	70.5	70.5	70.5
P-value G.O.F	0.807	0.807	0.807	0.807	0.807
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0	0	0
0.44	-0.763	-0.763	-0.763	-0.763	-0.763
0.88	0.812	0.812	0.812	0.812	0.812
1.84	0.429	0.429	0.429	0.429	0.429
4.02	-0.429^{Z}	-0.429^{Z}	-0.429^{Z}	-0.429^{Z}	-0.429^{Z}
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/ ”recommended”
Comment:	**Chosen/** Lowest AIC ; BMD>max. dose	BMD>max. dose	BMD>maximum dose	BMD>max. dose	Lowest AIC BMD>max. dose

F. Female Rat: Mammary Gland Fibroadenoma

Dose	0	0.44	0.88	1.84	4.02
Response	16/48	18/48	24/46	22/47	31/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Dich-Hill
BMD_{10}	0.706	0.706	0.706	0.706	0.499
$BMDL_{10}$	0.441	0.441	0.441	0.441	0.0921
Cancer Slope Factor	0.227	0.227	0.227	0.227	1.086
AIC	321.59	321.59	321.59	321.59	323.48
P-value G.O.F	0.584	0.584	0.584	0.584	0.401
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.312	-0.312	-0.312	-0.312	-0.085
0.44	-0.295	-0.295	-0.295	-0.295	-0.329^{Z}
0.88	1.198^{Z}	1.198^{Z}	1.198^{Z}	1.198^{Z}	1.029
1.84	-0.571	-0.571	-0.571	-0.571	-0.786
4.02	0.001	0.001	0.001	0.001	0.184
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/ ”recommended”
Comment:	**Chosen/** Low AIC ; Good fit.				Lowest $BMDL_{10}$-

G. Female Rat: Oral Mucosa/Tongue, Sq. Cell Pappilloma or Carcinoma

Dose	0	0.44	0.88	1.84	4.02
Response	0/48	2/48	1/48	3/48	5/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Probit
BMD_{10}	3.518	3.518	3.518	3.518	4.40
$BMDL_{10}$	2.019	2.019	2.019	2.019	1.86
Cancer Slope Factor	0.0495	0.0495	0.0495	0.0495	0.0538
AIC	86.7	86.7	86.7	86.7	85.880
P-value G.O.F	0.539	0.539	0.539	0.539	0.816
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.474	-0.474	-0.474	-0.474	0
0.44	1.260	1.260	1.260	1.260	0.600
0.88	-0.391	-0.391	-0.391	-0.391	-0.733
1.84	0.133	0.133	0.133	0.133	-0.039
4.02	-0.288^{Z}	-0.288^{Z}	-0.288^{Z}	-0.288^{Z}	0.200^{Z}
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/ ”recommended”
Comment:	**Chosen/**				

H. FEMale Rat: Skin Fibroma, Fibrosarcoma or sarcoma[F]

Dose	0	0.44	0.88	1.84	4.02
Response	1/48	0/48	0/48	1/48	5/48

Results/Models	Multistage	Multistage -2	Multistage -3	Multistage -4	Other: Log-Probit
BMD_{10}	4.286				4.042
$BMDL_{10}$	3.084				3.010
Cancer Slope Factor	0.032				0.033
AIC	58.4				59.8
P-value G.O.F	0.486				0.373
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0					
0.44					
0.88					
1.84					
4.02					
Recommended Model					
Comment:	**Chosen/** Lowest AIC				Lowest $BMDL_{10}$

F. My BMD calculations for this data set failed. These are from Beland (2013).

I. Male Mouse: Harderian Gland Tumors – All Doses

Dose	0	1.04	2.2	4.11	8.93
Response	2/46	13/46	27/47	36/47	39/47

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Probit
BMD_{10}	0.386	0.386	0.386	0.386	0.383
$BMDL_{10}$	0.320	0.320	0.320	0.320	0.159
Cancer Slope Factor	0.312	0.312	0.312	0.312	0.628
AIC	240.13	240.13	240.13	240.13	237.5
P-value G.O.F	0.053	0.053	0.053	0.053	0.342
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.313	-0.313	-0.313	-0.313	
1.04	-0.075^{Z}	-0.075^{Z}	-0.075^{Z}	-0.075^{Z}	
2.20	1.284	1.284	1.284	1.284	
4.11	1.102	1.102	1.102	1.102	
8.93	-2.176	-2.176	-2.176	-2.176	
Recommended Model	Viable/Alternate				
Comment:	**Chosen/** Multistage				Lowest $BMDL_{10}$ low AIC

J. Male Mouse: Lung Alveolar/Bronchiolar Adenoma

Dose	0	1.04	2.2	4.11	8.93
Response	5/47	6/46	13/47	10/45	19/48

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Probit
BMD_{10}	2.41	2.41	2.41	2.41	1.77
$BMDL_{10}$	1.57	1.57	1.57	1.57	0.275
Cancer Slope Factor	0.0556	0.0556	0.0556	0.0556	0.3636
AIC	241.40	241.40	241.40	241.40	243.17
P-value G.O.F	0.475	0.475	0.475	0.475	0.338
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.214	-0.214	-0.214	-0.214	0.055^{Z}
1.04	-0.470	-0.470	-0.470	-0.470	-0.530
2.20	-1.367^{Z}	-1.367^{Z}	-1.367^{Z}	-1.367^{Z}	1.095
4.11	-0.599	-0.599	-0.599	-0.599	-0.812
8.93	-0.081	-0.081	-0.081	-0.081	0.168
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	"recomm."
Comment:	**Chosen/** Multistage				Lowest $BMDL_{10}$ low AIC

K. Male Mouse: Stomach (fore), Squamous Cell Papilloma

Dose	0	1.04	2.2	4.11	8.93
Response	0/46	2/45	2/46	6/47	6/44

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Dich-Hill
BMD_{10}	4.548	4.548	4.548	4.548	3.91
$BMDL_{10}$	3.094	3.094	3.094	3.094	1.10
Cancer Slope Factor	0.0323	0.0323	0.0323	0.0323	0.091
AIC	107.96	107.96	107.96	107.96	110.67
P-value G.O.F	0.667	0.667	0.667	0.667	0.647
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0.000	0.000	0.000	0.000	0
1.04	0.908	0.908	0.908	0.908	0.281
2.20	-0.194	-0.194	-0.194	-0.194	-0.670
4.11	0.879^{Z}	0.879^{Z}	0.879^{Z}	0.879^{Z}	0.559^{Z}
8.93	-0.860	-0.860	-0.860	-0.860	-0.159
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	"recomm."
Comment:	**Chosen/** near low AIC				Lowest $BMDL_{10}$

L. Female Mouse: Harderian Gland Adenoma. All Doses

Dose	0	1.10	2.23	4.65	1.96
Response	0/45	8/44	20/48	32/47	31/43

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Dich-Hill
BMD_{10}	0.567	0.567	0.567	0.567	0.808
$BMDL_{10}$	0.474	0.474	0.474	0.474	0.385
Cancer Slope Factor	0.211	0.211	0.211	0.211	0.260
AIC	226.13	226.13	226.13	226.13	222.97
P-value G.O.F	0.0867	0.0867	0.0867	0.0867	0.880
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0	0	0
1.10	-0.054^{Z}	-0.054^{Z}	-0.054^{Z}	-0.054^{Z}	0.140
2.23	1.130	1.130	1.130	1.130	-0.273
4.68	1.417	1.417	1.417	1.417	0.352
9.96	-2.202	-2.202	-2.202	-2.202	-0.192
Recommended Model	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable "recomm."
Comment:	**Chosen/** poor G.O.F.	poor G.O.F.	poor G.O.F.	poor G.O.F.	Lowest AIC

M. Female Mouse: Harderian Gland Adenoma. High dose Dropped

Dose	0	1.10	2.23	4.65	
Response	0/45	8/44	20/48	32/47	Dropped

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Logistic
BMD_{10}	0.452	0.527	0.527	0.527	0.692
$BMDL_{10}$	0.366	0.371	0.371	0.371	0.339
Cancer Slope Factor	0.273	0.270	0.270	0.270	0.295
AIC	168.42	170.09	170.09	170.09	169.82
P-value G.O.F	0.897	0.662	0.662	0.662	0.988
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0	0	0
1.10	-0.701Z	-0.359	-0.359	-0.359	-0.078Z
2.23	0.163	0.393	0.393	0.393	0.116
4.65	0.281	-0.113	-0.113	-0.113	-0.061
Dropped					
Recommended Model	Viable/ ”Recommend”	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable “recomm.”
Comment:	**Chosen Low A.I.C.**				Lowest BMDL

N. Female Mouse: Lung Alveolar Bronchiolar Adenoma.

Dose	0	1.10	2.23	4.65	9.96
Response	1/47	4/47	6/48	11/45	19/45

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Logistic
BMD_{10}	1.97	1.97	1.97	1.97	1.91
$BMDL_{10}$	1.47	1.47	1.47	1.47	0.912
Cancer Slope Factor	0.0680	0.0680	0.0680	0.0680	0.11
AIC	188.62	188.62	188.62	188.62	190.74
P-value G.O.F	0.995	0.995	0.995	0.995	.910
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.050	-0.050	-0.050	-0.050	-0.062
1.10	0.175	0.175	0.175	0.175	0.306
2.23	-0.151^{Z}	-0.151^{Z}	-0.151	-0.151^{Z}	-0.259^{Z}
4.65	0.105	0.105	0.105	0.105	-0.-096
9.96	-0.057	-0.057	-0.057	-0.057	0.119
Recommended Model	Viable/altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable "recomm."
Comment:	**Chosen Low A.I.C.**				Lowest BMDL

O. Female Mouse: Lung Alveolar Bronchiolar Adenoma.

Dose	0	1.10	2.23	4.65	9.96
Response	1/47	4/47	6/48	11/45	19/45

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Log-Logistic
BMD_{10}	1.97	1.97	1.97	1.97	1.91
$BMDL_{10}$	1.47	1.47	1.47	1.47	0.912
Cancer Slope Factor	0.0680	0.0680	0.0680	0.0680	0.11
AIC	188.62	188.62	188.62	188.62	190.74
P-value G.O.F	0.995	0.995	0.995	0.995	.910
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	-0.050	-0.050	-0.050	-0.050	-0.062
1.10	0.175	0.175	0.175	0.175	0.306
2.23	-0.151^{Z}	-0.151^{Z}	-0.151	-0.151^{Z}	-0.259^{Z}
4.65	0.105	0.105	0.105	0.105	-0.-096
9.96	-0.057	-0.057	-0.057	-0.057	0.119
Recommended Model	Viable/altern.	Viable/Altern.	Viable/Altern.	Viable/Altern.	Viable “recomm.”
Comment:	**Chosen Low A.I.C.**				Lowest BMDL

P. FEMale Mouse: Stomach (Fore) Squamous Cell Pappilloma.

Dose	0	1.10	2.23	4.65	9.96
Response					

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other:
BMD_{10}	7.66	7.62	7.62	7.62	
$BMDL_{10}$	4.29	5.05	5.05	5.05	
Cancer Slope Factor	0.0233	0.0198	0.0198	0.0198	
AIC	128.19	126.69	126.69	126.69	
P-value G.O.F	0.107	0.183	0.183	0.183	
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	1.605	1.373	1.373	1.373	
1.10	-1.633	-1.508	-1.508	-1.508	
2.23	-0.755	-0.366	-0.366	-0.366	
4.65	0.252	0.720	0.720	0.720	
9.96	0.477	-0.189	-0.189	-0.189	
Recommended Model	Viable/altern.	Viable/Recomm	Viable/Recomm	Viable/Recomm	
Comment:		**Chosen Lowest A.I.C.**			

Q. FEMale Mouse: Stomach (Fore) Squamous Cell Pappilloma.

Dose	0	1.10	2.23	4.65	9.96
Response	4/46	0/46	2/46	5/45	8/42

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other:
BMD_{10}	7.66	7.62	7.62	7.62	
$BMDL_{10}$	4.29	5.05	5.05	5.05	
Cancer Slope Factor	0.0233	0.0198	0.0198	0.0198	
AIC	128.19	126.69	126.69	126.69	
P-value G.O.F	0.107	0.183	0.183	0.183	
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	1.605	1.373	1.373	1.373	
1.10	-1.633	-1.508	-1.508	-1.508	
2.23	-0.755	-0.366	-0.366	-0.366	
4.65	0.252	0.720	0.720	0.720	
9.96	0.47^{Z}	-0.189^{Z}	-0.189^{Z}	-0.189^{Z}	
Recommended Model	Viable/altern.	Viable/Recomm	Viable/Recomm	Viable/Recomm	
Comment:		**Chosen Lowest A.I.C.**			

R. FEMale Mouse Mammary Gland Adenocanthoma or Adenocarcinoma.

Dose	0	1.10	2.23	4.65	9.96
Response	0/47	4/46	7/48	4/45	17/42

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other:
BMD_{10}	2.219	2.22	2.27	2.37	1.72
$BMDL_{10}$	1.679	1.68	1.68	1.69	0.691
Cancer Slope Factor	0.0595	0.0595	0.0595	0.0592	0.1447
AIC	158.95	158.85	160.93	160.83	161.96
P-value G.O.F	0.211	0.211	0.114	0.111	
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0	0	0
1.10	1.184	1.114	1.184	1.252	0.520
2.23	1.13^{Z}	1.046^{Z}	1.130^{Z}	1.220^{Z}	0.478^{Z}
4.65	01.788	-1.838	-1.788	-1.712	-1.973
9.96	0.265	0.375	0.265	0.132	1.096
Recommended Model	Viable/altern.	Viable/altern	Viable/altern	Viable/altern	
Comment:	Chosen				

S. FEMale Mouse Ovary Benign Granulosa Cell Tumor

Dose	0	1.10	2.23	4.65	9.96
Response	0/46	1/45	0/48	1/45	5/42

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Dichotomous-Hill
BMD_{10}	11.4	9.71	9.51	9.51	5.78
$BMDL_{10}$	6.48	6.66	6.80	6.83	4.90
Cancer Slope Factor	0.0154	0.0150	0.0147	0.0146	0.0146
AIC	55.302	56.517	58.213	58.156	58.11
P-value G.O.F	0.626	0.481	0.342	0.348	0.349
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	-0.504	-0.513	-0.452	-0.475
1.10	0.810	1.293	1.189	1.185	1.223
2.23	01.001	-0.731	-0.685	-0.721	-0.702
4.65	-0.665	-0.279	-0.000	0.019	-0.010 [Z]
9.96	0.707 [Z]	0.191 [Z]	0.023 [Z]	0.004 [Z]	0.018
Recommended Model	Viable/Recomm Lowest A.I.C.	Viable/altern	Viable/altern	Viable/altern	Viable/alt.
Comment:	Chosen				Lowest BMDL

T. FEMale Mouse Skin Fibrocarcoma, Sarcoma, Others

Dose	0	1.10	2.23	4.65	9.96
Response	0/48	0/46	3/48	10/45	6/43

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other: Dichotomous-Hill
BMD_{10}	4.09	4.09	4.09	4.09	2.34
$BMDL_{10}$	2.86	2.86	2.86	2.86	2.10
Cancer Slope Factor	0.034	0.034	0.034	0.034	.0476
AIC	115.92	115.92	115.92	115.92	
P-value G.O.F	0.0726	0.0726	0.0726	0.0726	0.799
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0	0	
1.10	-1.150	-1.150	-1.150	-1.150	
2.23	0.200	0.200	0.200	0.200	
4.65	2.315^{Z}	2.315^{Z}	2.315^{Z}	2.315^{Z}	
9.96	-1.362	-1.362	-1.362	-1.362	
Recommended Model	Questionable/ residual>2	Questionable	Questionable	Questionable	Recommended.
Comment:	Poor GOF				Lowest BMDL

U. Female Mouse Skin Fibrosarcoma, Sarcoma, Others

Dose	0	1.10	2.23	4.65	9.96
Response	0/48	0/46	3/48	10/45	Dropped

Results/Models	Multistage -1	Multistage -2	Multistage -3	Multistage -4	Other:
BMD_{10}	2.75	3.05	3.17		
$BMDL_{10}$	1.80	2.41	2.42		
Cancer Slope Factor	0.0556	0.0415	0.0413		
AIC	77.309	73.438	75.319		
P-value G.O.F	0.338	0.874	0.685		
Scaled Residuals at administered doses levels: Z= Nearest BMD. Dose : mg/kg-day: Scaled Residuals					
0	0	0	0		
1.10	-1.407	-0.797	-0.688		
2.23	-0.489^{Z}	0.235^{Z}	0.524^{Z}		
4.65	1.074	0.080	-0.097		
Dropped					
Recommended Model	Viable	Viable/Recomm Chosen	Viable		
Comment:	Lowest BMDL	Lowest A.I.C.			

Table I.2. Animal Oral Cancer Slope (Potency) Estimates for Acrylamide based on Tumor Results in the NTP (2012) Rat and Mouse 2-Year Study Bioassay. Estimates for those Tumor sites NTP judged as "Clear Evidence of Carcingenic Activity" or "Related." Estimates calculated using U.S. EPA's BMDS Version 2.4, and BMDS Wizard Ver 1.8, plus EPA's method for calculating Combined Risks.

								Animal Cancer
Sex/Species	ORGAN		Evidence	MODEL	BMD10	BMDL10	S.E. BMD	Slope factors
M/mouse	Harderian Adenoma		Clear	Multi1	0.386	0.32	0.040122	0.312500
M/mouse	Lung Adeno		Clear	Multi1	2.414	1.57	0.51307	0.063694
M/mouse	Stomach		Clear	Multi2	4.548	3.094	0.883891	0.032321
F/mouse	Harderian Adeno		clear	Multi1	0.567	0.474	0.056535	0.210970
F/mouse	Lung Adeno		clear	multi1	1.968	1.471	0.302128	0.067981
F/mouse	Stomach		related	multi2	7.623	5.045	1.567173	0.019822
F/mouse	Mammary Adcarc/acnatho		clear	multi1	2.219	1.679	0.328267	0.059559
F/mouse	Ovary granulosa		clear	Multi1	11.4	6.48	2.990881	0.015432
F/mouse	Skin fibroma/sarcoma		clear	multi2 Hi D	3.05	2.41	0.389058	0.041494
M/Rat	Thyroid Gland foll. Ad/Ca.		clear	Multi1	1.448	0.889	0.339818	0.112486
M/Rat	Heart Schwannoma		clear	Multi1	2.426	1.304	0.682067	0.076687
M/Rat	Epidy testis/mesothel.		clear	Multi1	2.09	1.21	0.534954	0.082645
M/Rat	Pancreas Islets Adeno.		related	Multi1	3.37	1.59	1.082067	0.062893
F/Rat	Thyroid Gland foll. Ad/Ca.		clear	Multi1	3.849	2.328	0.92462	0.042955
F/Rat	Mammary Fibroadenoma		clear	Multi1	0.706	0.441	0.161094	0.226757
F/Rat	Oral Mucosa/tongue		clear	Multi1	3.518	2.019	0.911246	0.049529
F/Rat	Skin fibroma/sarcoma		clear	Multi	4.286	3.084	0.730699	0.032425
F/Rat	Clitoral gland carcinoma		related	not calc..				
F/Rat	Liver Hepato Adenoma		related	not calc..				

TABLE I.B.1. Calculation of Summed Risks for tumors at Several Sites in **MALE F344 Rats** exposed to AA in Drinking Water in the NTP Bioassay (2012; Plaintiff's Exhibit 48449). Doses Groups: 0, 0.33, 0.66, 1.32, and2.71 mg/kg/day Using BMD10 and BMDL10 output from EPA's BMDS Software 2.4 and BMDS Wizard 1.8. Calculations for Combined Risks for Multiple Tumor Sites based on method in U.S. EPA Tox. Review of Acrylamide, Table D8 and Table D-10, in Appendix D. (U.S. EPA; 2010; Plaintiff's Exhibit 48631).

TUMOR SITE	**BMD10**	**BMDL10**	RAT Oral Cancer slope factor (central tendency) (per mg/kg-day)	RAT Oral Cancer slope factor (upper-bound) (per mg/kg-day)	t-statistic	s.d.	Variance
	mg/kg-day	**mg/kg-day**					
Thyroid Gland, Foll.Adeno & Carc.	**1.448**	**0.889**	0.069061	0.112486	1.645	0.02640	0.000697
Heart Schwannoma	**2.426**	**1.304**	0.04122	0.076687	1.645	0.02156	0.000465
Cumulative Variance =	0.00116						
Cumulative s.d. =	0.03408						
Sum of Central tendency Risks=	0.11028	(mg/kg-day)-1					
Upper-bound on cum risk=	**0.16635**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR TWO Combined SITES				
Thyroid Gland, a&c	**1.448**	**0.889**	0.069061	0.112486	1.645	0.026398	0.000697
Heart Schwannoma	**2.426**	**1.304**	0.04122	0.076687	1.645	0.02156	0.000465
Epididymis testis/mesothelioma	**2.09**	**1.21**	0.047847	0.082645	1.645	0.021154	0.000447
Cumulative Variance =	0.001609						
Cumulative s.d. =	0.040115						
Sum of Central tendency Risks=	0.158128						
Upper-bound on cum risk=	**0.224117**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR THREE Combined SITES				
Thyroid Gland, a&c	**1.448**	**0.889**	0.069061	0.112486	1.645	0.026398	0.000697
Heart Schwannoma	**2.426**	**1.304**	0.04122	0.076687	1.645	0.02156	0.000465
Epididymis testis/mesothelioma	**2.09**	**1.21**	0.047847	0.082645	1.645	0.021154	0.000447
Pancreatic Islets Adenoma	**3.37**	**1.59**	0.029674	0.062893	1.645	0.020194	0.000408
Cumulative Variance =	0.002017						
Cumulative s.d. =	0.044911						
Sum of Central tendency Risks=	0.187801						
Upper-bound on cum risk=	**0.261680**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR FOUR Combined SITES				

TABLE I.B.2. Calculation of Summed Risks for tumors at Several Sites in **FEMALE F344 Rats** exposed to AA in Drinking Water in the NTP Bioassay (2012; Plaintiff's Exhibit 48449). Dose Groups: 0, 0.44, 0.88, 1.84, and 4.02 mg/kg/day. Using BMD10 and BMDL10 output from EPA's BMDS Software 2.4 and BMDS Wizard 1.8. Calculations for Combined Risks for Multiple Tumor Sites based on method in U.S. EPA Tox. Review of AA, Table D-8 and Table D-10 in Appendix D. (U.S. EPA; 2010; Plaintiff's Exhibit 48631).

TUMOR SITE	**BMD10**	**BMDL10**	Oral slope factor (central tendency)	Oral slope factor (upper-bound)	t-statistic	s.d.	Variance
	mg/kg-day	**mg/kg-day**	per (mg/kg-day)	per (mg/kg-day)			
Thyroid Gland, Foll.Adeno & Carc.	**3.849**	**2.328**	0.025981	0.042955	1.645	0.010319	0.000106
Mammary Fibroadenoma	**0.706**	**0.441**	0.141643	0.226757	1.645	0.051741	0.002677
Cumulative Variance =	0.00278						
Cumulative s.d. =	0.05276						
Sum of Central tendency Risks=	0.16762	(mg/kg-day)-1					
Upperbound on cum risk=	**0.25441**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR TWO Combined SITES				
Thyroid Gland, a&c	**3.848**	**2.328**	0.025988	0.042955	1.645	0.010315	0.000106
Mammary Fibroadenoma	**0.706**	**0.441**	0.141643	0.226757	1.645	0.051741	0.002677
Oral Mucosa/Tongue	**3.518**	**2.019**	0.028425	0.049529	1.645	0.012829	0.000165
Cumulative Variance =	0.002948						
Cumulative s.d. =	0.054297						
Sum of Central tendency Risks=	0.196056						
Upperbound on cum risk=	**0.285374**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR THREECombined SITES				
Thyroid Gland, a&c	**3.848**	**2.328**	0.025988	0.042955	1.645	0.010315	0.000106
Mammary Fibroadenoma	**0.706**	**0.441**	0.141643	0.226757	1.645	0.051741	0.002677
Oral Mucosa/Tongue	**3.518**	**2.019**	0.028425	0.049529	1.645	0.012829	0.000165
Skin Fibrosar/heman/ sarc,etc	**4.286**	**3.084**	0.023332	0.032425	1.645	0.005528	3.06E-05
Cumulative Variance =	0.002979						
Cumulative s.d. =	0.054577						
Sum of Central tendency Risks=	0.219388						
Upperbound on cum risk=	**0.309168**	(mg/kg-day)-1	**CANCER SLOPE FACTOR** FOR FOUR Combined SITES				

TABLE I.B.3. Calculation of Summed Risks for tumors at Several Sites in **MALE B6C3F1 MICE** exposed to AA in Drinking Water									
	in the NTP Bioassay (2012; Plaintiff's Exhibit 48449). Dose Groups: 0, 1.04, 2.20, 4.11, and 8.93 mg/kg/day.								
	Using BMD10 and BMDL10 output from EPA's BMDS Software 2.4 and BMDS Wizard 1.8. Calculations for								
	for Combined Risks for Multiple Tumor Sites based on method in U.S. EPA Tox. Review of Acrylamide,								
	Table D8 in Appendix D. (U.S. EPA; 2010; Plaintiff's Exhibit 48631).								
TUMOR SITE	**BMD10**	**BMDL10**	MOUSE Oral Cancer		MOUSE Oral Cancer		t-statistic	s.d.	Variance
			slope factor		slope factor				
	mg/kg-day	**mg/kg-day**	(central tendency)		(upper-bound)				
			(per mg/kg-day)		(per mg/kg-day)				
Harderian Gland Adenoma	**0.386**	**0.32**	0.259067		0.3125		1.645	0.03248	0.001055071
Lung Alv./Bronch Adenoma	**2.414**	**1.57**	0.041425		0.063694		1.645	0.013538	0.000183265
Cumulative Variance =	0.00124								
Cumulative s.d. =	0.03519								
Sum of Central tendency Risks=	0.30049	(mg/kg-day)-1							
Upper-bound on cum risk=	**0.35838**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR TWO Combined SITES					
Harderian Gland Adenoma	**0.386**	**0.32**	0.259067		0.3125		1.645	0.032482	0.001055071
Lung Alv./Bronch Adenoma	**2.414**	**1.57**	0.041425		0.063694		1.645	0.013538	0.000183265
Stomach (fore) SQ. cell Pappilloma	**4.548**	**3.094**	0.021988		0.032321		1.645	0.006281	3.94562E-05
Cumulative Variance =	0.001278								
Cumulative s.d. =	0.035746								
Sum of Central tendency Risks=	0.322480								
Upper-bound on cum risk=	**0.381283**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR THREE Combined SITES					

TABLE I.B.4. Calculation of Summed Risks for tumors at Several Sites in **FEMALE B6C3F1 MICE** exposed to AA in Drinking Water in									
	the NTP Bioassay (2012; Plaintiff's Exhibit 48449). Doses Groups: 0, 1.10, 2.23, 4.65, and 9.96 mg/kg-da.								
	Using BMD10 and BMDL10 output from EPA's BMDS Software 2.4 and BMDS Wizard 1.8. Calculations								
	for Combined Risks for Multiple Tumor Sites based on method in U.S. EPA Tox. Review of Acrylamide,								
	Tables D-8 and D-10 in Appendix D. (U.S. EPA; 2010; Plaintiff's Exhibit 48631).								
TUMOR SITE	**BMD10**	**BMDL10**	MOUSE Oral Cancer		MOUSE Oral Cancer		t-statistic	s.d.	Variance
			slope factor		slope factor				
	mg/kg-day	**mg/kg-day**	(central tendency)		(upper-bound)				
			(per mg/kg-day)		(per mg/kg-day)				
Harderian Gland Adenoma	**0.568**	**0.474**	0.176056		0.21097		1.645	0.02122	0.000450475
Lung Alv./Bronch Adenoma	**1.968**	**1.471**	0.050813		0.067981		1.645	0.010436	0.000108919
Cumulative Variance =	0.00056								
Cumulative s.d. =	0.02365								
Sum of Central tendency Risks=	0.22687	(mg/kg-day)-1							
Upper-bound on cum risk=	**0.26578**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR **TWO** Combined SITES					
Harderian Gland Adenoma	**0.568**	**0.474**	0.176056		0.21097		1.645	0.021224	0.000450475
Lung Alv./Bronch Adenoma	**1.968**	**1.471**	0.050813		0.067981		1.645	0.010436	0.000108919
Mammary Adenocarc/acanth	**2.219**	**1.679**	0.045065		0.059559		1.645	0.008811	7.76318E-05
Cumulative Variance =	0.000637								
Cumulative s.d. =	0.025239								
Sum of Central tendency Risks=	0.271935								
Upper-bound on cum risk=	**0.313453**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR **THREE** Combined SITES					
Harderian Gland Adenoma	**0.568**	**0.474**	0.176056		0.21097		1.645	0.021224	0.000450475
Lung Alv./Bronch Adenoma	**1.968**	**1.471**	0.050813		0.067981		1.645	0.010436	0.000108919
Mammary Adenocarc/acanth	**2.219**	**1.679**	0.045065		0.059559		1.645	0.008811	7.76318E-05
Ovary benign Granulosa Cell Tumor	**11.4**	**6.48**	0.008772		0.015432		1.645	0.004049	1.63923E-05
Cumulative Variance =	0.000653								
Cumulative s.d. =	0.025562								
Sum of Central tendency Risks=	0.280707								
Upper-bound on cum risk=	**0.322756**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR **FOUR** Combined SITES					
Harderian Gland Adenoma	**0.568**	**0.474**	0.176056		0.21097		1.645	0.021224	0.000450475
Lung Alv./Bronch Adenoma	**1.968**	**1.471**	0.050813		0.067981		1.645	0.010436	0.000108919
Mammary Adenocarc/acanth	**2.219**	**1.679**	0.045065		0.059559		1.645	0.008811	7.76318E-05
Ovary benign Granulosa Cell Tumor	**11.4**	**6.48**	0.008772		0.015432		1.645	0.004049	1.63923E-05
Skin Fibroma/Sarcoma	**3.05**	**2.41**	0.032787		0.041494		1.645	0.005293	2.80152E-05
Cumulative Variance =	0.000681								
Cumulative s.d. =	0.026104								
Sum of Central tendency Risks=	0.313494								
Upper-bound on cum risk=	**0.356435**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR **FIVE** Combined SITES					
Harderian Gland Adenoma	**0.568**	**0.474**	0.176056		0.21097		1.645	0.021224	0.000450475
Lung Alv./Bronch Adenoma	**1.968**	**1.471**	0.050813		0.067981		1.645	0.010436	0.000108919
Mammary Adenocarc/acanth	**2.219**	**1.679**	0.045065		0.059559		1.645	0.008811	7.76318E-05
Ovary benign Granulosa Cell Tumor	**11.4**	**6.48**	0.008772		0.015432		1.645	0.004049	1.63923E-05
Skin Fibroma/Sarcoma	**3.05**	**2.41**	0.032787		0.041494		1.645	0.005293	2.80152E-05
Stomach (fore) Squam. Cell Pappil.	**7.623**	**5.045**	0.013118		0.019822		1.645	0.004075	1.66058E-05
Cumulative Variance =	0.000698								
Cumulative s.d. =	0.026420								
Sum of Central tendency Risks=	0.326612								
Upper-bound on cum risk=	**0.370073**	(mg/kg-day)-1		**CANCER SLOPE FACTOR** FOR **SIX** Combined SITES					

Table I.D.1. Animal and Human Oral Cancer Slope (Potency) Estimates for Acrylamide based on Tumor Results in the NTP (2012) Rat and Mouse 2-Year Study Bioassay. Estimates for those Tumor sites NTP judged as "Clear Evidence of Carcinogenic Activity" or "Related." Animal Cancer slopes calculated using U.S. EPA's BMDS Version 2.4, plus EPA's method for calculating Combined Risks.
Human Cancer slope factors use adaption of Cal EPA's animal-to-human scaling factors for rats, and U.S. EPA's default procedures for the mouse.

Sex/Species	ORGAN	BMDL	Animal Canc Slope factor	Scaling Factor	Human Cancer Slope Factor
M/mouse	Harderian Adenoma	0.32	0.313	6.9	**2.154**
M/mouse	Lung Adeno	1.57	0.064	6.9	**0.439**
M/mouse	Stomach	3.094	0.032	6.9	**0.223**
M/mouse	**Combined Sites**		0.381	6.9	**2.628**
F/mouse	Harderian Adeno	0.474	0.211	7.3	**1.535**
F/mouse	Lung Adeno	1.471	0.068	7.3	**0.495**
F/mouse	Stomach	5.045	0.020	7.3	**0.144**
F/mouse	Mammary Adcarc/acnatho	1.679	0.060	7.3	**0.433**
F/mouse	Ovary granulosa	6.48	0.015	7.3	**0.112**
F/mouse	Skin fibroma/sarcoma	2.41	0.041	7.3	**0.302**
F/mouse	**Combined Sites**		0.370	7.3	**2.692**
M/Rat	Thyroid Gland foll. Ad/Ca.	0.889	0.112	2.3	**0.259**
M/Rat	Heart Schwannoma	1.304	0.077	2.3	**0.176**
M/Rat	Epidy testis/mesothel.	1.21	0.083	2.3	**0.190**
M/Rat	Pancreas Islets Adeno.	1.59	0.063	2.3	**0.145**
M/Rat	**Combined Sites**		0.262	2.3	**0.602**
F/Rat	Thyroid Gland foll. Ad/Ca.	2.328	0.043	2.4	**0.104**
F/Rat	Mammary Fibroadenoma	0.441	0.227	2.4	**0.546**
F/Rat	Oral Mucosa/tongue	2.019	0.050	2.4	**0.119**
F/Rat	Skin fibroma/sarcoma	3.084	0.032	2.4	**0.078**
F/Rat	Clitoral gland carcinoma				
F/Rat	**Combined Sites**		0.309189	2.4	**0.745**

Table I.D.2. REVISED. Estimates of Human Cancer Slope Risk Factors From Daily Oral Exposure to Acrylamide in Coffee, based on Individual Tumor Sites and Summed Risks from Multiple Sites Combined for Three Rat Bioassays and One Mouse Bioassay, both Sexes separately. Estimates for NTP Rat study based on CAL EPA animal-to-human weight and dose scaling factors. TABLE REVISED 06/07/2014

	Johnson. (1986) **RATS**[A]		Friedman (1995) **Rats**[A]		NTP (2012) **RATS**		NTP (2012) **MOUSE**		
Human Cancer Potency Factors - per (mg/kg b.w.-day).									
Tumor Site Rats	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Tumor Sites Mice**	**Females**	**Males**
Mammary	1.0	--	0.4	--	0.55	--	Mammary	0.43	--
Cent. Nervous. Sys.	0.14	--	0.71	0.13	--	--	Harderian	1.53	2.15
Thyroid follicular	0.24	0.32	0.33	0.44	0.10	0.26	Fore-stomach	0.14	0.22
Testis	--	0.58	--	0.40	--	0.19	Lung alv/br. A/C	0.99	0.44
Heart Schwannoma Pancreas Islet Tumors	--	--	--	--	--	0.18 0.14	--	--	--
Oral Cavity	0.31	--	--	--	0.12	--	--	--	--
Uterus	0.15	--	--	--	--	--	Ovary	0.11	--
Clitoral Gland	0.26	--	--	--	--	--	Clitoral Gland	Not calc.	--
Skin	--	--	--		0.08		Skin	0.30	
Mult. Sites Combined.	1.5	0.75	0.69	0.77	0.75	0.60	Multi. Sties Comb.	2.69	2.63
Geo. Mean Risk Factor	0.70 (CAL/OEHHA, 2005)				0.67			2.66	

A. Human Cancer Potency Factors based on the Johnson (1986) and Friedman (1995) studies are from Cal OEHHA (2005, Exhibit #23930. Cal EPA and U.S. EPA methods for Estimating risks from Combined tumor sites judged quantitatively similar.

REVISED (6/7/2014) for both Clarification of the NSRL and use of $(W_{hum}/W_{rat})^{1/4}$ scaling factor.

Table IV.A.1 Estimates of **Lifetime Increased Risk of Cancer from consuming Acrylamide (AA) in Coffee**, based on Extrapolation of Tumor Results in the NTP Rat and Mice Bioassays, and consumption of from 1-9 Cups of Coffee/day from age 16+. Comparison of my (S.B.) Estimates with Those of the U.S. EPA (2010; Plaintiff's Exhibit #48631) and CAL. EPA (2005; Plaintiff's Exhibit #23930). All Human Cancer Slope Factors first adjusted downward (by 54/70 years) to account for little coffee drinking during < 16 years. Acrylamide amounts/day both for 54 years of coffee consumption, and for a full 70-year lifetime **(NSRL)** that will result in a 1 in 100,000 increased risk of cancer.

Human Cancer Potency Est. from:	ADJ. Human Cancer Factor	Coffee Consumption (Cups/day)[B] 1	3.1	5	7	9	Acrylamide amounts/day for a lifetime 1/100,000 increased risk[A]. Based on Study Cancer Potency Estimates.	
	$(mg/kg\text{-}day)^{-1}$	Acrylamide Content (µg/day) 2.22	6.85	11.11	15.56	20.01	For AA from 54 Years of coffee consumption	For 70 Years "**NSRL**"
Cal. EPA (2005)	0.540	1.72E-5	5.28E-5	8.58E-5	1.2E-4	1.54E-4	1.30 µg/day	1.00 µg/day [D]
U.S. EPA (2010)	0.386	1.23E-5	3.77E-5	6.13E-5	8.58E-5	1.10E-4	1.81 µg/day	1.40 µg/day
NTP RAT (S. B.)	0.517	1.64E-5	5.09E-5 1	8.20E-5	1.15E-4	1.48E-4	1.11 µg/day	0.86 µg/day
NTP MOUSE (S.B.)[C]	**2.05**	**6.52E-5**	**2.01E-4 3**	**3.26E-4**	**4.56E-4 88**	**5.86E-4**	**0.34 µg/day**	**0.26 µg/day**

A. All Estimates of the both the NSRL for AA and for AA from actual 54 years of coffee consumption are less than the amount of AA in 1 cup of coffee. Higher increased cancer risks are seen from more coffee consumption per day.

B. Estimated Percentiles based on the NCA's Survey of 428 coffee drinkers age 18+ who lived in the "West". 1 Cup: 9th %ile; 3.1 Cups: 48th %ile; 5 cups: 71st %ile; 7 cups: 85th %ile; 9 cups: 91st %ile.

C. "Most Sensitive Study." See Discussion in Section VI. Conclusions and Opinion

D. NSRL derived by Cal. EPA (2005).

Ταβλε ς.Α.1. Μαργιν–οφ–Εξποσυρε Ρατιοσ (Μ.Ο.Ε.΄σ φορ ΒΜΔΛ10 φορ Χομβινεδ Τυμορ Χανχερ Ποτενχψ Εστιματεσ ιν τηε ΝΤΠ (2012) Ρατ ανδ Μουσε 2–ψεαρ βιοασσαψσ το τηε αμουντ οφ ΑΑ ιν 1, 3.1, 5, 7, ανδ 9 χυπσ οφ χοφφεε/δαψ. ΒΜΔΛ10΄σ ανδ ΑΑ Αμουντσ/Χυπ οφ Χοφφεε Εστιματεσ αρε ιν Υνιτσ οφ μγ/κγ –β.ω. φορ Ανιμαλσ ανδ Ηυμανσ, ρεσπεχτιϖελψ.

Sex/Species	Animal Cancer slope Factor $(mg/kg\text{-}bw\text{-}d)^{-1}$	$BMDL_{10}$ µg/kg-b.w -d	Cups of Coffee Consumed/day[A] (10.7 oz./cup) 1	3.1	5	7	9
			µg/kg-b.w. Human -day				
			0.0318	0.0979	0.1588	0.2225	0.2862
			Margin-Of-Exposure Ratios				
Male Rat	0.262	383	12017	3907	2406	1718	1335
Female Rat	0.309	323	10170	3307	2036	1453	1130
Male Mouse	0.381	262	8249	2682	1652	1179	916
Female Mouse	0.370	270	8497	2762	1702	1214	944

Estimated Percentiles based on the NCA's Survey of 428 coffee drinkers age 18+ who lived in the "West". 1 Cup: 9th %ile; 3.1 Cups: 48th %ile; 5 cups 71st %ile; 7 cups: 85th %ile; 9 cups 91st %ile.