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Monet Vela
Office of Environmental Health Hazard Assessment
1001 I Street, 23rd Floor
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Sacramento, California 95812-4010

Re: Proposed Adoption of Amendments to Section 25821 (a) and (c)

Dear Ms. Vela,

I am writing in response to OEHHA's request for public comment on the Proposed Adoption of Amendments to Section 25821 (a) and (c) dated October 5, 2018 and the Initial Statement of Reasons (ISOR) Proposed Amendment to Section 25821 paragraphs (a) and (c) dated October 5, 2018 (hereafter, the "Proposal").[1] I urge OEHHA not to adopt the proposed amendment to require the use of the arithmetic mean as the only approach to determine the rate of intake or exposure for average users of consumer products in all circumstances. The proposal is scientifically inappropriate, inconsistent with generally accepted scientific principles, and it will lead to unnecessary warnings that do not advance public health.

To summarize why the Proposal is scientifically inappropriate, it is the distribution of the data – not a categorical, one-size-fits-all rule – that appropriately determines whether the arithmetic mean, geometric mean, or another measure best represents the average. In turn, the data must be analyzed using standard statistical methodology. For example, if a distribution of data follows the standard bell-shaped curve of a normal distribution, the arithmetic mean would typically be the statistically appropriate estimate of the average. In comparison, if the distribution of the data is skewed (i.e., not bell-shaped), the arithmetic mean will be more influenced by the highest (or lowest) statistical values on the distribution curve and becomes less representative of the "average" value. Therefore, for skewed data, including intake or exposure data, estimates based on the geometric mean instead of the arithmetic mean are more appropriate since the geometric mean is less influenced by the extremes.[2]

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[1] This work was supported by the American Beverage Association. A copy of my curriculum vitae is attached.

[2] Bernard Rosner (1999) *Fundamentals of Biostatistics*, 5th Edition. P. 15-16.

Notably, OEHHA itself has used the geometric mean in implementing Proposition 65. For example, it has used the geometric mean to estimate the average cancer potency from multiple studies.[3] The U.S. Environmental Protection Agency (US EPA) uses the geometric mean in deriving National Water Quality Criteria because, according to US EPA, the underlying data are more likely to be lognormally distributed (i.e., skewed) than normally distributed.[4] Outside of the Proposal, I am unaware of any regulatory agency or scientific organization that advocates using the arithmetic mean "regardless of the shape of the distribution that best describes the sampling data," as stated in the Proposal.[5]

The arithmetic mean is not "the appropriate approach" in many cases.

The Proposal is based on an unsubstantiated and scientifically incorrect assertion that the arithmetic mean is "the appropriate approach" to identify the rate of intake or exposure for average users in all situations:

> "Clarifying that the arithmetic mean of the intake of exposure level for users of a consumer product is ***the appropriate approach*** helps the responsible business to correctly determine the rate of intake or exposure for average users of the consumer product and to decide wither a warning is required for a given exposure to a reproductive toxicant."[6] [emphasis added]

The ISOR maintains that requiring businesses to use only the arithmetic mean will help businesses determine the correct exposure for average users of a food product:

> "Clarifying that the arithmetic mean of the intake or exposure level for users of a consumer product is ***the appropriate approach*** that will help businesses to determine ***the correct rate of intake or exposure for average users*** of the consumer product so they can decide whether a warning is required under Proposition 65."[7] [emphasis added]

Yet, the Proposal does not provide a clear explanation for why the arithmetic mean is the "appropriate" or "correct" approach. The Proposal seems to suggest it is the correct approach because people are more familiar with the arithmetic average than the geometric average:

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[3] OEHHA. No Significant Risk Levels (NSRLs) for the Proposition 65 Carcinogens Phenylhydrazine and Phenylhydrazine Hydrochloride (May 2001). https://oehha.ca.gov/media/downloads/crnr/phenylhydrazinensrl.pdf
OEHHA. No Significant Risk Levels (NSRLs) for the Proposition 65 Carcinogens Benzo[b]fluoranthene, Benzo[j]fluoranthene, Chrysene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, and 5-Methylchrysene by the Oral Route (May 2004). https://oehha.ca.gov/media/downloads/proposition-65/chemicals/062104clearcopy.pdf

[4] US EPA (2010) https://www.epa.gov/sites/production/files/2016-02/documents/guidelines-water-quality-criteria.pdf p. 16.

[5] OEHHA (2018) Initial Statement of Reasons, p. 7.

[6] OEHHA (2018) Initial Statement of Reasons, p. 4

[7] OEHHA (2018) Initial Statement of Reasons, p. 9.

> "The use of the familiar arithmetic mean (calculated by adding the measurements and then dividing by the number of measurements that were added together) is the appropriate metric for identifying average consumption of a product …"[8]

The decision to use a particular type of average (e.g., arithmetic, geometric) should be based on what is statistically appropriate for particular data, not on familiarity of the general population.

The Proposal offers another possible rationale, claiming that the arithmetic mean is better because it weighs all consumers equally:

> "Because Proposition 65 is intended to warn Californians of significant exposure to listed chemicals, a determination of the exposures to a chemical in a food or consumer product should be based on the full range of exposures experienced by Californians. It is appropriate to weigh all individual consumers equally for purposes of calculating intakes or exposures. The arithmetic mean accounts for consumption levels at both the low and the high end of the range, weighing the intake of each of each consumer equally. Thus, OEHHA proposes to amend the regulation so that the reasonably anticipated rate of exposure for purposes of Proposition 65 is calculated as the arithmetic mean."[9]

This rationale is highly misleading. The arithmetic mean does in fact weigh every consumer equally when the distribution curve is normal (i.e., bell-shaped and not skewed). However, this is not true for many food products because the distribution curve for many foods is skewed at the high end of consumption (i.e., there are relatively small numbers of heavy consumers that have a disproportionate impact on the arithmetic average so that not every consumer contributes equally). When this is the case, use of the arithmetic mean would result in general warnings that apply to well less than half of the population, causing unnecessary and misleading warnings.

An example of why the arithmetic average is not the best estimate of the average when data are skewed is illustrated by the recent results of the $1.537 billion mega-millions lottery. The winning ticket, worth $1.537 billion, was purchased in Simpsonville, SC. The population of Simpsonville is 22,072. Assuming the winner lives in Simpsonville, the average person in Simpsonville just won about $70,000 in the lottery, based on the arithmetic average. Unfortunately, the arithmetic average does not really tell you much about how the average resident of Simpsonville fared in the lottery. The average person in Simpsonville didn't win anything in the lottery. But, because one person out of 22,072 hit the jackpot, the arithmetic average says the average person in Simpsonville just won about $70,000. [Jay - what would geometric mean value be for this example? - not sure you need to share it, but want you to calculate it so you and I know] Using the ISOR's language and rationale, this arithmetic average weighed "all individual consumers equally" and it accounted for "both the low and the high end of the range." But, it doesn't really describe the winnings of the average person in Simpsonville.

[8] OEHHA (2018) Initial Statement of Reasons, p. 7.
[9] OEHHA (2018) Initial Statement of Reasons, p. 8-9.

While this is an extreme example of a skewed distribution curve, it illustrates why the geometric mean is scientifically more appropriate than the arithmetic mean for skewed data because it lessens the impact of the person(s) at the extreme end of the distribution curve.

And finally, the Proposal theorizes that the arithmetic mean is appropriate "[b]ecause Proposition 65 is intended to warn Californians of significant exposure to listed chemicals," and therefore, "a determination of the exposures to a chemical in a food or consumer product should be based on the full range of exposures experienced by Californians."[10] This rationale is unconvincing since both the arithmetic mean and the geometric mean take into account the full range of exposures experienced by Californians. The difference is the geometric mean provides an average value that is closer to the typical consumer than the arithmetic mean when the data are skewed, which is typically the case with exposures to food. The Proposal states: "It is appropriate to weigh all individuals equally for purposes of calculating intakes or exposures."[11] But, this statement ignores the fact that, for a skewed data set, a relatively small number of data points can have a disproportionate impact on the arithmetic mean to the point where the average no longer is representative of the typical individual. In other words, using the arithmetic mean for skewed exposure data results in warnings being driven by atypical consumers, not by average consumers.

It is important to recognize that the line between what receives a Proposition 65 warning and what does not, sometimes referred to as the maximum allowable daily level (MADL), is not the difference between safe and unsafe exposures. Under Proposition 65, the MADL is the level at which a warning is required when the reasonably anticipated rate of intake or exposure exceeds the MADL. By definition, a Proposition 65 MADL provides a high degree of protection since it represents a level of exposure which is 1000-times less than the No Observable Effect Level (NOEL) in the most sensitive study of sufficient quality. In some cases, the MADL is even more conservative than in others, particularly when the NOEL is derived from human data, not animal data. In the case of animal studies, it is customary to apply additional uncertainty factors to the NOEL in risk assessment to account for potential interspecies differences between humans and laboratory animals, such as differences in toxicokinetics and toxicodynamics. However, when the NOEL is based on human data, there is no need to adjust for interspecies differences. Yet, Proposition 65 requires that the MADL be calculated by dividing the NOEL by the 1000-fold factor, regardless of whether the NOEL is derived from humans or animals. As a result, MADLs derived from human data (e.g., lead) are expected to be more conservative in most cases than MADLs derived from animal data.

Allowing a minority of consumers at the high end of the distribution curve to have a disproportionate impact on the average will result in needless warnings and subvert the intent of the regulations and the statute. It is critical to keep in mind that over-warning can negatively impact public health. Unnecessary warnings can dilute the meaning and utility of needed warnings.

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[10] OEHHA (2018) Initial Statement of Reasons, p. 8.
[11] OEHHA (2018) Initial Statement of Reasons, p. 8.

The Proposal Misunderstands Intake and Exposure Data

The ISOR attempts to justify the Proposal as follows:

> "The geometric mean … is often used for determining the central tendency for different types of measurements. The geometric mean is often applied in the case of percentage growth values, such as annual interest rates, where amounts are compounded and use of the arithmetic mean leads to incorrect results. It is also used in estimating growth rates of populations, and generally for data that increase exponentially over time. For example, the geometric mean is used for a rating system that scores products based on two or more criteria, such as price, availability and sales data. However, the geometric mean is not typically used for identifying average consumption or usage levels of a food or consumer product. For example, the single measurement may be the amount of a food product eaten, the ounces of a consumer product used on the day it is used, or the amount of contact with a durable product used on an ongoing basis. In addition, the more variable the measurements, the more the geometric mean underestimates the expected exposure."[12]

OEHHA has cited no authority for the notion that the geometric mean is not typically used for identifying average consumption or usage levels of a food or consumer product. In my experience, this statement is simply untrue.

The ISOR implies that the geometric mean is inappropriate for calculating exposures to foods because the geometric mean has been employed for different types of data (e.g., annual interest rates, growth rates of populations) or because food consumption data uses only a single measurement. I am not aware of any distinction in statistical theory or practice between distributions based on one criterion versus distributions based on two or more criteria. Instead, the appropriate way to determine the average tendency of a distribution is to evaluate the shape of the distribution curve – for example, whether it is a normal (bell-shaped) or a skewed distribution – regardless of the number of criteria on which that distribution is based.

Nevertheless, distributions that combine two or more criteria can become more skewed by the combination of the skewed distributions that are each based on a single criterion. The existing regulation describes how to determine the "reasonably anticipated rate of intake or exposure" – i.e., based on "average users" of the consumer product. For many consumer products, including food products, data on the "rate of intake" is available in two criteria: amount consumed per eating occasion and number of eating occasions over time. Individual consumers vary in both dimensions. For example, some consumers may eat a particular food very infrequently but in relatively large quantities when they do eat it; other consumers may eat small quantities of that

[12] OEHHA (2018) Initial Statement of Reasons. p, 8.

same food every day. The "rate of intake" is therefore a combination of these two factors – the same situation that the ISOR's discussion describes as appropriate for using the geometric mean.

Furthermore, the regulation also addresses "exposure" and not just intake. For many products, including food products, the chemical at issue is a contaminant or unintended by-product of cooking or other processing that occurs at varying levels in the product. Therefore, there is at least a third factor involved in determining the "reasonably anticipated rate of … exposure" in many circumstances, making the geometric mean all the more appropriate under even the ISOR's erroneous belief that the geometric mean is only appropriate for averages based on more than one measurement. Fundamentally, it is the shape of the distribution of exposure data that must be considered in determining the "average" exposure.

The Proposal Should Not Conflate the Issue of Choosing a Measurement of Averaging with the Time Period for Averaging Exposure to a Reproductive Toxicant

The discussion in the ISOR also shows that the drafters have conflated the concept of average exposures with the issue of the appropriate averaging period for a reproductive toxicant. OEHHA justifies the arithmetic mean by stating:

> "A single consistent measurement is used to calculate the average consumption amount of a food or usage of a consumer product. In the context of a good, this would be the amount of food product eaten on the day in question."[13]
>
> "For example, the single measurement may be … the ounces of a consumer product used on the day it is used …."[14]

These statements are contrary to the Proposition 65 regulations. For a reproductive toxicant, averaging exposure over time should be determined on a chemical-by-chemical basis because it depends on consideration of multiple factors, including whether there is a narrow window of susceptibility and pharmacokinetic factors, such as the half-life. (See Section 25821(b) and (c)) OEHHA should not confuse these two issues, and it is not warranted as a matter of science or based on my analysis of the regulations to justify the arithmetic mean through use of a single day as the averaging period.

The Proposal Will Lead to Over Warning

As OEHHA correctly notes, "For food intake rates, the distribution is most often skewed to the right as discussed in OEHHA, 2012, Chapters 7 and 9. In right-skewed intake distributions, relatively smaller numbers of people consume the product at higher amounts than other consumers of that product."[15] For such distribution curves, the arithmetic mean will always be

[13] OEHHA (2018) Initial Statement of Reasons, p. 7.
[14] Id., p. 8.
[15] Id., p. 6.

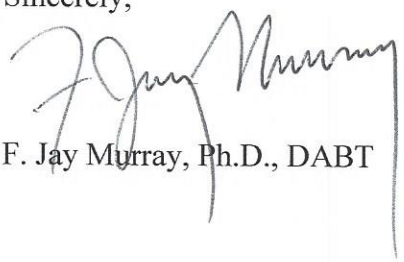
higher than the geometric mean. How much higher will depend on the shape of the distribution curve. But, because the distribution of contaminants in food products is also often quite variable and skewed, for some food products, the arithmetic mean of exposure can be at the 65th to 80th percentile. In comparison, the geometric mean is expected to be similar to the median or 50th percentile. In other words, under this scenario, 65 to 80 percent of the population may have exposures below the arithmetic mean.

When businesses elect to provide Proposition 65 warnings for a product, a warning is provided to all users of the product, and not just those who use a product above a certain rate. Obviously, providing a warning only to those who use the product above a certain rate is an impossible task. Using the geometric mean for products with skewed exposure distributions (such as most food products) leads to warnings for all users when approximately 50 percent of users are above the threshold for exposure. This amounts to over-warning for the other half of users whose exposure is below the threshold. In contrast, using the arithmetic mean for such products would lead to warnings for all users when only 20 to 35 percent of users, for example, are above the threshold level, effectively over-warning 65 to 80 percent of users. The result is bad policy, and it is unjustified from both a scientific and public health standpoint.

Conclusion

For all of the above reasons, it is scientifically inappropriate and highly misleading to use the arithmetic mean "regardless of the shape of the distribution that best describes the sampling data."[16] When the consumption data are normally distributed (i.e., bell-shaped curve), the arithmetic mean will best reflect the average consumer's exposure. However, when the consumption data are skewed (which is typically the case with food products), the geometric mean will best reflect the average consumer's exposure. I urge OEHHA not to adopt the proposal to use the arithmetic mean in every circumstance and without regard for the shape of the distribution that best describes the data.

Sincerely,



F. Jay Murray, Ph.D., DABT

[16] OEHHA (2018) Initial Statement of Reasons, p. 7.