January 12, 2009

Ms. Fran Kammerer  
Staff Counsel  
Office of Environmental Health Hazard Assessment (OEHHA)  
1001 I Street  
Sacramento, CA 95812


Dear Ms. Kammerer:

I am writing on behalf of the several clients in response to the Office of Environmental Health Hazard Assessment’s (“OEHHA” or the “Agency”) November 3, 2008 request for public input on the “Proposition 65 Regulatory Update Project, Regulatory Concepts for Exposures to Human and Plant Nutrients in Human Food” (the Regulatory Concept).¹ Thank you for the opportunity to participate in the December 12 public workshop on this topic and to provide these written comments. I appreciate all of the efforts by OEHHA to try to identify a workable solution to this particularly difficult and complex problem.

Overview

I have given this issue considerable thought since our discussion at the December 12 workshop. As I indicated at the workshop, the Regulatory Concept, while well-intentioned, will not meet the objective of avoiding misleading warnings (and undue litigation) on food products that provide beneficial nutrients. Consequently, food companies will have to decide whether to prepare to bear the costly expense of a defense afforded by this concept (and run the risk that the courts will throw it out) or to place a misleading Proposition 65 warning on their products. In many cases, they will opt for the safer, less costly option, i.e., a misleading warning. And, as

¹ http://www.oehha.ca.gov/prop65/public_meetings/Regupdate110308.html
noted in the Initial Statement of Reasons, “Providing a warning for cancer or reproductive effects for exposures to a listed chemical in a food (including dietary supplements) that is at or below the recommended level necessary for good health does not further the purpose of Proposition 65.”²

There may be no sensible way to regulate human and plant nutrients under the Proposition 65 statute – at least as it currently exists. It may take a revision of the statute itself to find a workable solution, and the resource requirements for OEHHA to attempt to amend the statute would outstrip any potential benefits. My recommendation is that OEHHA should focus its regulatory reform efforts on more productive areas and cease its regulatory reform efforts on human and plant nutrients until a viable solution is apparent.

**Background**

For over two decades, people have struggled with the issue of human and plant nutrients in the context of Proposition 65. OEHHA clearly understands the problem, as summarized in the “Necessity” section of the Initial Statement of Reasons.³ Beneficial nutrients are different from other chemicals in that they are defined by a u-shaped dose-response curve. In other words, it is possible to have too much or too little of a beneficial nutrient. For most beneficial nutrients, there is less than a 10-fold difference between too much and too little of the substance. In some cases, the difference is only a factor of two or three.

The Proposition 65 statute did not contemplate regulating beneficial nutrients. The statute is silent on the need for flexibility to account for the possibility of excessive and deficient exposures to beneficial nutrients. To the contrary, Proposition 65 has a mandatory 1000-fold factor for reproductive toxicants. OEHHA correctly recognizes, that if a 1000-fold factor were applied to beneficial nutrients, warnings would be required on necessary and beneficial exposures.

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³ Id.
To date, only one human nutrient, i.e., vitamin A, has ever been placed on the Proposition 65 list. In 1989, vitamin A was listed as “Retinol/retinyl esters, when in daily dosages in excess of 10,000 IU, or 3,000 retinol equivalents.” Obviously, the “qualified” listing of Vitamin A was designed to avoid placing Proposition 65 warnings on exposures to Vitamin A that are necessary for normal fetal development.\(^4\)

**The “naturally-occurring” exemption provides little protection against misleading warnings.**

OEHHA proposed the Regulatory Concept to address situations in which the nutrient cannot be shown to be naturally-occurring or is intentionally added to a food product. However, even in cases where a nutrient in a food is naturally-occurring, proving it can be difficult and costly. It is relatively easy for a plaintiff to demonstrate the presence of a beneficial nutrient in a food. It is much more difficult for a defendant to demonstrate in court that the nutrient is “naturally-occurring.” These enforcement actions against food companies are not rare, and I have personally been involved in several of these “naturally-occurring” lawsuits.

The reality is that the current “naturally-occurring” regulation does not work effectively. Companies must choose either to place a warning on foods even when a nutrient is “naturally-occurring” or risk being sued and mount an expensive defense. In many cases, it may be less risky and more cost-effective to place a misleading Proposition 65 warning on a healthy food product. However, for purposes of protecting public health, this is exactly the outcome that OEHHA wishes to avoid.

**The numeric limit for a human nutrient provides little protection against misleading warnings.**

The Regulatory Concept would allow a company to demonstrate that the anticipated level of exposure to the nutrient from consumption of a food does not exceed a level set by OEHHA in the future. But, it is not clear how this level would be determined. Presumably, it will be a level

\(^4\) In the case of Vitamin A, there is only about a three-fold difference between too much exposure (25,000 IU) and too little exposure (<8,000 IU).
higher than the level established by a traditional MADL that requires using the 1000-fold factor for reproductive toxicants.

I understand that the regulatory concept would be to define exposure in terms of a numeric value, which is not the same as defining a MADL. However, to many people, this will have all the appearances of an “end run” around the 1000-fold factor. It is hard to imagine that it would not be challenged in the courts as being inconsistent with the statute.

Also, demonstrating that exposure to a nutrient in a food product is below the level established by OEHHA would be complicated and costly in many cases. Obviously, if the nutrient is intentionally added to the product, it is easy to estimate the exposure by making some assumptions about serving size and frequency of consumption. However, in many cases, the nutrient is not intentionally added to the product. For products where the nutrient is naturally-occurring, the level of exposure, although well below safe levels, may vary from supplier to supplier. Even for the same supplier, the levels of a naturally-occurring nutrient may vary from season-to-season, depending on the weather and growing conditions. Given this variability, demonstrating that exposures are below the numeric limit becomes a challenging research project. So, even if the regulation and the numeric levels are not invalidated in the future, which is probably very unlikely, this is not an easy defense for a food company to make. Therefore, this approach is not an effective deterrent against misleading Proposition 65 warnings on safe food products.

**The variable numeric limit for an added plant nutrient provides little protection against meaningless warnings.**

The possible regulatory language says that a food shall not constitute an exposure to a plant nutrient to the extent that it is “naturally-occurring in the food” or “added to the soil or other growing media in an amount necessary for healthy plant development.” To prove that a plant nutrient was “added to the soil or other growing media in an amount necessary for healthy plant development” could require considerable effort. The “necessary” amount varies among plant species; some plants require more than others. Also, the existing background level of a plant

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[^1]: [http://www.oehha.ca.gov/prop65/public_meetings/Regupdate110308.html](http://www.oehha.ca.gov/prop65/public_meetings/Regupdate110308.html)
nutrient affects the amount that must be added to the soil for healthy plant development. Therefore, the numeric value will vary from farm-to-farm, season-to-season, and crop-to-crop. Plaintiff attorneys will recognize that it will be expensive and time-consuming to prove that a plant nutrient was “added to the soil or other growing media in an amount necessary for healthy plant development.” Once again, a food supplier may choose to place a misleading warning on a health food product to avoid the risk and costs of litigation.

In addition to meeting the variable numeric limit for an added plant nutrient, the possible regulatory language also requires that the exposure to the plant nutrient in the food itself does not exceed a yet-to-be-determined numeric level set by OEHHA. So, in effect, a food producer or retailer must prove that two requirements have been met. A plant nutrient in a food product must be (1) “naturally-occurring” OR (2) “added to the soil or other growing media in an amount necessary for healthy plant development; AND (3) the exposure to the plant nutrient in the food product must not exceed the yet-to-be-determined numeric limit set by OEHHA. It is not hard to imagine that many food producers and retailers would opt for a misleading Proposition 65 warnings on nutritionally beneficial food products as the lesser (and less costly) of the two evils.

**Boron and manganese both cause reproductive toxicity if exposure is too low.**
The Regulatory Concept identifies boron and manganese as two nutrients that may meet the Proposition 65 listing criteria for reproductive toxicity. Ironically, these two nutrients may be unique in that both have also been shown to cause reproductive toxicity in animals when exposure is inadequate. Requiring a Proposition 65 warning on levels of a nutrient that may be essential for normal reproductive health would be contrary to good public health and the original intent of Proposition 65.

**Manganese**
Manganese is widely distributed in the biosphere, and it is the 12th most abundant element on the surface of the earth. Manganese is both a human and a plant nutrient. The biochemical foundation for its essentiality is its role as an enzyme activator for decarboxylases, hydrolases, kinases, and transferases. In animals, the major signs of manganese deficiency are neonatal health, congenital ataxia, impaired growth, skeletal abnormalities, and defects in lipid and
carbohydrate metabolism. Thus, the predominant symptoms of manganese deficiency are endpoints of reproductive toxicity.

The National Academy of Sciences Food and Nutrition Board established an Acceptable Intake (AI) for manganese for adult men and women of 2.3 and 1.8 mg/day. An Upper Limit (UL) for manganese of 11 mg/day was set for adults. Manganese is predominantly found in foods, such as whole grains, nuts, legumes and tea. The USDA National Nutrient Database has reported the manganese content of hundreds of foods in a 24-page table.

Boron

Boron was identified as an essential element for plants nearly a century ago. There is significant evidence that boron is also a human nutrient. The National Academy of Sciences Food and Nutrition Board has reviewed the evidence of human essentiality, and declined to classify boron as an essential element in humans because it did not meet all of the current criteria for essentiality; in particular, boron’s specific mechanism of action is not known. The Food and Nutrition Board established an Upper Limit (UL) for boron of 20 mg/day for adults.

The UK Expert Group on Vitamins and Minerals 2002 concluded the following: “Boron appears to be an essential nutrient for humans, in that dietary deprivation of boron consistently results in changed biological functions that are detrimental and that can be corrected by increasing boron intake. Similar effects have been shown in animal models. However, as yet, no specific biochemical function for boron has been discovered.”

The nutritional role of boron was recently reviewed by Nielsen (2008), a leading expert on beneficial nutrients at the USDA, Grand Forks Human Nutrition Research Center. Nielsen concluded that low boron intake is a relevant nutritional concern: “Evidence from numerous laboratories using a variety of experimental models, including humans, shows that boron is a...
bioactive beneficial element. Much evidence has come from studies that did not require nutritional or environmental stressors or fastidious methods in diet preparation or environmental control. The evidence includes deprivation studies showing that boron is necessary for some higher animals to complete the life cycle, and that realistic low boron intakes result in impaired bone health, brain function, and immune response. Thus, low boron intake is a relevant nutritional concern, which diets rich in fruits, vegetables, nuts, and pulses can prevent.”  

Boron deprivation has been demonstrated to produce reproductive toxicity in animal models. Fort et al. (1999) reported that a low boron diet had a dramatic adverse effect on reproduction and development in a frog model. The frog was chosen as the experimental animal model because it is relatively easy to create boron deficiency in a freshwater aquatic environment. Frogs fed the low boron diet for 120 days produced a high proportion of necrotic eggs (54%) compared to controls. Fertilized embryos from the frogs fed a low boron diet showed a high frequency of abnormal gastrulation (26.8%), and more than 80% of the embryos died before 96 hours of development. The study authors concluded that a diet low in boron markedly impairs normal reproductive function in adult frogs.

In a later study in frogs, Fort (2002a) reported evidence of female reproductive toxicity. The results of this study suggested that boron deficiency resulted in incomplete oocyte maturation and that maturation could not be induced by administration of exogenous progesterone.

Fort et al. (2002b) summarized the results of a series of studies designed to distinguish between the female and male reproductive effects of a low boron diet. According to the study authors, reproductive effects associated with boron deficiency in female frogs included ovary atrophy, oocyte necrosis, and incomplete oocyte maturation. In males, a decrease in testis weight and sperm count was noted.

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Studies at UCLA by Rowe et al. (1998) demonstrated that low boron produced adverse reproductive effects in fish. In trout, low boron adversely affected embryonal growth. In zebrafish deprived of boron, fertilization occurred, but zygotes failed to survive when water contained less than 0.2 micromol B/L.

Attempts to study the effects of boron deprivation on rats have been unsuccessful due to the inability to create a low boron environment in rodents. It was discovered that under normal laboratory conditions, rats receive about a 60-fold greater dose of boron in their diet than do humans due to two factors: (1) rat chow is primarily plant-based and rich in boron, and (2) rats eat proportionately more food than humans on a body weight basis. It was not possible to develop a rodent model to study boron intakes less than normal human dietary intake of boron.

In summary, there is considerable evidence that boron and manganese deprivation produces reproductive toxicity in animals. OEHHA should not consider listing such nutrients until there is an effective way to avoid misleading warnings on safe and beneficial doses.

**Food is the largest source of exposure to boron; a Proposition 65 warning on foods would be harmful to public health.**

By a wide margin, the largest source of human exposure to boron is food. More than 90% of a person’s daily exposure to boron comes from food and beverages. Virtually all foods contain detectable quantities of boron. Foods with the highest concentrations of boron are fruits, vegetables, legumes and nuts. Interestingly, the top two boron contributors, coffee and milk, are low in boron, yet they make up 12% of the total boron intake by virtue of the volume consumed.

Dietary exposures to boron are well below levels of concern. As previously stated, Food and Nutrition Board established a UL for boron of 20 mg/day. In comparison, U.S. dietary intake of boron is considerably less than the UL. According to a study by Rainey et al. (1999), the weighted 5th percentile, median, mean, and 95th percentile boron dietary intakes, respectively,

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16 It should be noted that none of the rat toxicology studies takes into account the high background level of dietary exposure to boron in rat chow. In other words, none of the studies recognize that control rats receive a daily dietary dose of boron approximately 60-fold greater than typical human dietary intake.
are 0.43, 1.02, 1.17 and 2.42 mg/day for men; 0.33, 0.83, 0.96 and 1.94 mg/day for women; and 0.40, 0.86, 1.01 and 2.18 mg/day for pregnant women. For vegetarian adults, these intakes are 0.46, 1.30, 1.47 and 2.74 mg/day for men and 0.33, 1.00, 1.29 and 4.18 mg/day for women. Thus, dietary intake even at the generally higher levels of vegetarians are far below the UL and it would be counter-productive to place a Proposition 65 warning on safe foods.

**A Proposition 65 warning on non-food products containing boron would be unnecessary, misleading to consumers, and of no public health benefit.**

At the December 12th workshop, OEHHA suggested that it wished to avoid placing a Proposition 65 warning on foods that contain boron because such foods are safe and important to health. Yet, foods are the major source of human exposure to boron. If boron were eventually listed, it would potentially create a situation where a Proposition 65 warning may be required on minor sources of exposure from consumer products such as components in surfboards, but not on the major source of exposure which is from the diet. It does not make sense to consider boron as a candidate for listing when the largest source of exposure, i.e., foods, would not require a warning, but much lower sources of exposure would require a warning. This would create confusion for consumers. Companies with non-food products would be forced to defend the safety of their products by comparing the low exposure to boron from their non-food products to the greater amounts in safe food products. At best, this creates confusion; at worst, it creates the perception that fruits and vegetables are not safe to eat.

There would be no public health benefit from placing a Proposition 65 warning on food or non-food products containing boron. Boron does not pose a reproductive hazard to humans, and there is no evidence that even one person in the state of California is being harmed by boron in food or non-food products. In fact, nutritionists are concerned that Americans are not receiving enough exposure to boron. Dietary exposure to boron in the U.S. is low compared to other countries around the world because Americans tend to consume fewer fruits and vegetables and more high fat foods.

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A nutrient is a nutrient, regardless of the source of exposure.

A nutrient is a nutrient, no matter what the source of exposure. For example, boron in food is exactly the same substance as boron in a consumer product. It is not a nutrient’s presence in food that makes it a nutrient. With few exceptions, the same benefits are bestowed by a nutrient no matter what the source of exposure. While there may be economic and political reasons to distinguish between nutrients in foods vs. other products, there is no scientific basis to make such a distinction. For example, boron confers the same nutritional benefits, whether in a food, a pill, or a consumer product.

Nutrients are not simply unwanted contaminants in foods that must be tolerated because the food itself is otherwise healthy. For example, boron’s presence in fruits and vegetables provides specific health benefits attributable to boron itself. Boron is intentionally added to certain multi-vitamins (e.g., Centrum) because of its nutritional benefits.

A regulation which assumes that low doses of nutrients are safe – but only when they occur in foods – is fraught with problems. If exposures to a nutrient in foods are safe, then other products which produce even less exposure must also be safe. ¹⁸

Conclusion

In conclusion, the Regulatory Concept, while well-intentioned, will not meet the objective of avoiding misleading warnings (and undue litigation) on food products that provide beneficial nutrients. Unfortunately, there does not seem to be a way to craft a regulation that allows human and plant nutrients to be sensibly regulated under Proposition 65, given the inflexible 1000-fold factor. The Regulatory Concept will not provide the desired relief, and it has the potential to cause grave damage to public health in California. OEHHA should focus its regulatory reform efforts on more productive areas and cease its regulatory reform efforts on human and plant nutrients until a viable solution is apparent.

¹⁸ There may be a few exceptions to this rule because of pharmacokinetic differences between different routes of exposure. But, boron certainly follows the rule.
Thank for the opportunity to provide these comments. If you have any questions, please feel free to contact me at 408-239-0669.

Sincerely,

F. Jay Murray, Ph.D., DABT

cc: Dr. Joan Denton
    Ms. Carol Monahan-Cummings