



Council for Responsible Nutrition

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November 17, 2014

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
P. O. Box 4010
1001 I Street
Sacramento, CA 95814
Via Email: P65Public.Comments@oehha.ca.gov

Re: Potential Regulations Workshop

Dear Ms. Vela:

On behalf of the Council for Responsible Nutrition (CRN), thank you for the opportunity to provide comments to the California Office of Environmental Health Hazard Assessment (OEHHA) regarding its Request for Public Participation on Potential Regulatory Actions, issued on September 16, 2014. CRN, founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. We represent more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our members comply with a host of federal and state requirements, including those imposed by Proposition 65 (Prop 65).

CRN supports the comments submitted to OEHHA by the California Chamber of Commerce on behalf of the Prop 65 Coalition. We also propose an additional issue for OEHHA's consideration that was not identified in the Request for Public Participation. CRN recommends that OEHHA consider the use of *in vitro* bioaccessibility data for risk assessment, based on established methods that have been reviewed and validated by international regulatory agencies, and we further request that this issue be included as an agenda item for future Prop 65 workshops. For the reasons stated below, we believe this practice would ensure realistic exposure estimates in the derivation of Prop 65 risk evaluations for foods and dietary supplements.

The study of oral bioaccessibility of metals from soil ingestion is two decades old. The concept is simple: metals such as arsenic and lead bound in different soil matrices dissolve into solution to varying degrees in the gastro-intestinal (GI) tract. Only the soluble or bioaccessible fraction of the metal in the GI tract is available for absorption into the bloodstream, thus having the potential to elicit a toxicological response in people.

Bioavailability is the fraction of a chemical which is ingested, inhaled, or applied on the skin surface that is absorbed and reaches the systemic circulation. The approach for oral bioavailability assessment of chemicals can typically be divided into four fundamental processes:

- i) oral intake;
- ii) bioaccessibility;
- iii) intestinal absorption; and,

- iv) metabolism in the liver/intestines.

Oral bioaccessibility can be defined as the fraction of a substance that is released from an exposure media, such as soil or food, upon interaction with the GI tract, thus making it soluble and available for absorption through the GI tract. In effect, this fraction represents the upper limit of bioavailability. The bioaccessible fraction is the fraction of the substance of interest that is dissolved into chyme, and represents the maximum fraction available for intestinal absorption. The dissolved substance may be absorbed and transported across the intestinal wall into the blood or the lymphatic system. Once dissolved, some of the substance may precipitate in the intestine, be bound to other substances, or undergo chemical transformation to an insoluble form. Any of these processes would lead to a portion of the substance remaining unavailable for absorption. Once distributed into the systemic circulation from the intestines or the liver, substances can ultimately start to exert systemic toxicity. Thus, assessing bioaccessibility is important because it determines the amount of a substance that will actually become bioavailable to potentially elicit effects in the body.

Toxicity data employed in most risk assessments are typically developed using a highly bioavailable chemical form (e.g., soluble inorganic salts, etc.) and delivery media (e.g., food, water, etc.) to ensure that a high dose reaches the target tissue. As such, toxicological limits do not inherently address the availability of compounds in other media, such as soils, vitamins, and herbal supplements. Therefore, it is important that the bioavailability of the compound present in a particular media, relative to bioavailability of the chemical species and delivery media used in the critical toxicological study (i.e., the study used to develop the toxicological limit), be quantitatively supported.

Traditionally, *in vivo* studies (i.e., animal studies) have been used to determine the relative bioavailability of substances; however, *in vivo* studies can have significant associated time and cost constraints. Therefore, more rapid and inexpensive *in vitro* extraction studies (designed to simulate the human stomach and intestinal system) have been developed to provide a reasonable, yet conservative, approximation of true bioavailability by assuming relative bioavailability is equal to bioaccessibility. *In vitro* extraction studies have been designed to simulate the human GI tract (e.g., pH, temperature, and chemical composition of solutions in both the stomach and small intestine, etc.) in order to assess the mobilization of compounds from soil during the digestion process.

Many different *in vitro* test methods are available to measure bioaccessibility of inorganic compounds in soil. At this time, no single *in vitro* method has been universally accepted, although the use of these methods has been accepted by regulatory agencies, including the U.S. Environmental Protection Agency, in the context of soil-related exposure. The application of these methods to other exposure media, including food and dietary supplements, has been discussed in the scientific literature.

In the context of California Prop 65, the regulation states:

- (7) When available data are of such quality that physiologic, pharmacokinetic and metabolic consideration can be taken into account with confidence, they may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations.¹

¹ Cal. Code Regs., tit. 27, § 25703(a)(7).

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On this basis, the use of *in vitro* bioaccessibility data, based on established methods that have been reviewed and validated by international regulatory agencies, should be an acceptable practice to ensure realistic exposure estimates in the derivation of Prop 65 risk evaluations for foods and dietary supplements. CRN therefore requests that OEHHA consider this concept and include this issue as an agenda item for its next workshop on potential Prop 65 regulatory actions.

Again, thank you for the opportunity to submit comments. Should you have questions, please do not hesitate to contact me at ral-mondhiry@crnusa.org or (202) 204-7672.

Sincerely,

A handwritten signature in black ink, appearing to read "Rend Al-Mondhiry". The signature is fluid and cursive, with a long horizontal stroke at the end.

Rend Al-Mondhiry, Esq.
Regulatory Counsel