To: Jeff Wong, Ph.D.
Office of the Chief Scientist
Department of Toxic Substances Control

From: William H. Farland, Ph.D., ATS
Scientific Peer Reviewer

Date: September 16, 2012

Subject: Scientific Peer Review for Safer Consumer Products Regulations

Thank you for the opportunity to serve as a scientific peer reviewer on the latest version of the above referenced subject. I have completed my review which is structured around the scientific issues and peer review points that you provided. My detailed comments are attached.

My detailed comments notwithstanding, I am of the opinion that the proposed rule is based upon sound scientific knowledge, methods and practices. The regulations rely heavily on the work of others who have constructed lists of potentially hazardous substances which, for the most part, have relied on public processes and scientific peer review in their construction. This provides firm ground for starting the process of safer alternatives determinations. The Department should address how it will deal with a decision to differ in its determination of potential hazard compared to the original source list. For instance, one might ask the question of how much new information will be required to move away from a hazard decision made by another authoritative body? It is my understanding that the Department's position will be to accept those original determinations of hazard in order to be protective of health and the environment and to avoid "paralysis by analysis" but it should be clear that the Department will use the best available science and judgments in its decision-making. This point leads into a second issue that is the subject of some of my detailed comments below. That is that the paradigm for identifying chemical hazards is changing. This will require re-thinking the interpretation of existing data and the development of new and different types of information for decision-making. While this perspective should not delay the current approach to regulation, it should be acknowledged explicitly. The scientific credibility of the regulations and of the decisions based on them will ultimately depend on embracing these scientific advances.

Thank you again for the opportunity to participate in the scientific peer review of these proposed regulations. Feel free to contact me if you have questions regarding the attached detailed comments.

Review Topic: The use of the chemicals lists developed by the sources named in the regulations identifies chemicals with hazard traits that have public health and environmental concerns to produce an initial Chemicals of Concern (CoC) list.

Comment:

The use of chemical lists developed by "authoritative bodies" in California as well as elsewhere in the US and internationally is a scientifically defensible approach. Each of the lists was the product of a rigorous process for determining criteria for inclusion and all have undergone independent peer review at the process level if not at the individual listing step. This point is well made in the "Initial Statement of Reasons" (ISOR) document where individual lists, their processes and scientific integrity are described. While each list will have its own criteria and listing thresholds, in the aggregate, they produce a list of "Chemicals of Concern" that embody the hazard traits or chemical characteristics described in the regulation. The chemical types identified in subsection (a)(2) are identified as Chemicals of Concern (COCs) in order to address or prevent chemical contamination in environmental media, such as air and water and the exposures that may cause adverse impacts to public health or environment. Other chemicals that are identified for biomonitoring in humans are included to identify whether chemical exposure is occurring in humans. All of these chemicals are identified to inform public health agencies in policy and risk management decisions. Because these chemicals were identified for a specific purpose (monitoring or reducing exposure/contamination), the Department is relying on the authoritative organization's determination regarding chemicals exhibiting a hazard trait. These chemicals lists do not have the basis for identifying individual chemical hazards included with the list and it is noted that these data and findings, at times, are not easily accessible. It is DTSC's intent to verify the hazard trait or environmental or toxicological endpoint associated with the specific chemical before the Department's informational list of COCs is posted on DTSC's website The individual lists on the list of lists seem to meet the specified criteria of providing "value" by not being overly redundant. Given the COC list to be generated through this process, it is quite likely that the list will meet the objective of not having to be updated in the early years of implementation of the regulation. However, the regulation provides for the opportunity to add (or remove?) chemicals to the list as new information relating to hazard traits becomes available. This may be important for some future listing decisions because of the infrequency of updating of individual lists mentioned in the regulations and the evolution of the testing and assessment process mentioned in comments below.

Review Topic: Use of the initial product prioritization criteria in the chemical and product prioritization process in Article 3 are sufficient to identify all types of consumer products with CoCs as potential Priority Products. Use of the key prioritization criteria considers those critical factors which identify the potential Priority Products during the initial phase as high priority.

Comment:

The regulation has provided a scientifically sound approach to using the product prioritization criteria to identify all types of consumer products with COCs as potential Priority Products, and DTSC has explained its rationale fully in its ISOR. The regulation is explicit in its desire to use both hazard (potential for adverse outcomes) and exposure in its decisions making. In addition,

it will use availability of information as a criterion. More, and more specific, available information on the COCs in the context of the product leads to a higher priority for listing. Also, the degree to which other state or federal regulatory programs would mitigate the concerns raised by the criteria discussed above would affect product priorities.

As stated in the ISOR, the regulations need to allow consideration of information from both Chemicals of Concern and consumer products. Evaluating and examining the information from both, based on the information available, will allow for flexible decision-making regarding which of the products that contain a Chemical of Concern should be listed as Priority Products. Because the decision-making process to designate a product as "high priority" is based on a variety of information and a narrative approach, DTSC has continued to use a narrative approach to describing its priority setting decisions rather than a quantitative weighting scheme. This seems like a sound decision given the typical available information and the differences one would see from product to product. The DTSC will "begin the product evaluation and identification process, specified in section 69503.2, by using available information to consider and evaluate the adverse impact and exposure factors specified in section 69503.2(a)(1), along with the extent of available information as specified in section 69503.2(a)(2)." Given the broad range of characteristics related to adverse impact and exposure parameters specified for evaluation over the lifecycle of the product within the regulation, this approach should be applicable to a wide range of products.

Engineering and administrative controls such as precautionary measures or have warning labels regarding limiting or reducing exposures will be taken into consideration when assessing exposures. The ISOR is particularly helpful in illustrating the range of information to be considered and how it will affect priority setting. I could not think of an example where this would not be effective in identifying products of a higher priority. The Department has expressed the intent to consider whether there is a readily available safer alternative that is "functionally acceptable and technically and economically feasible" to further adjust the prioritization prior to listing a product as a Priority Product. While this process detail is praiseworthy, the implementation of this aspect of the process will be particularly difficult. The data required to demonstrate functional and technical equivalence is unlikely to be readily available for a head-to-head comparison and the ability of the Department to make the hypothetical case in the absence of such information will be limited. Practically speaking, unless the Department can demonstrate its ability to carry out such analyses, it might be prudent to indicate that this process would infrequently come into play in priority setting. Alternatively, if the Department has some examples where the availability of safer alternatives meets these criteria for products, they should be included in the ISOR.

I was also gratified to see the "internal consistency" step included in the priority setting process. The ability to look across products potentially considered priorities for consistency in the risk analysis process should proof instructive and increase the scientific credibility of the priority setting process. This point also applies to the intent to allow the public and other interested parties to comment on the Priority Product decisions prior to them being finalized. As indicated in the ISOR, "the public comment process related to Priority Products listing will provide transparency to stakeholders and will provide an opportunity to review and comment on setting the concentration for the AA Threshold exemption, among other issues." This issue, in

particular, is likely to be contentious, depending on how the Department's stated criteria are applied. The Department has indicated that will not specify the AA Threshold at the time it proposes the Priority Product List, but will request that recommendations with supporting rationale and information be submitted at the time of the public workshops and the public notice. It will be incumbent on the Department to evaluate this information and publish the AA Threshold when it posts the final Priority Product List. While the Department is explicit about its intent to separate this from a determination of *de minimus* risk, it is likely to find that stakeholders will not see, or respect, this distinction when providing their comments. This issue is likely to increase the confusion around Department's decision-making unless it is handled carefully.

Review topic: The principles outlined in the proposed regulations that will allow the department to develop Alternatives Analysis Threshold based on best available technologies is scientifically understood.

Comment:

The DTSC has stipulated in the regulation that " a responsible entity is exempt from the requirements of article 5 with respect to a product that is listed as a Priority Product and that meets the criteria for an alternatives analysis threshold (AA Threshold) exemption specified in ARTICLE 3, SECTION 69503.5, subsection (b), if one of the responsible entities for the product submits a complete and timely Alternatives Analysis Threshold Exemption Notification to the Department under section 69503.6, unless subsection (d) or (e) of section 69503.6 applies." It will be incumbent on the Department to evaluate this information and publish the AA Threshold(s) when it posts the final Priority Product List. To be eligible for an alternatives analysis threshold exemption, the concentration in the product of each Chemical of Concern that is/are the basis for the product being listed as a Priority Product must not exceed the applicable AA Threshold specified. If subsection (d) applies, the total concentration of all Chemicals of Concern to which the AA Threshold applies must not exceed that threshold. In order to develop these thresholds, the Department must take into account a broad range of information relating to the potential for low dose risk as well as understanding the current state of the science regarding analytical limits. While the Department has articulated its intent to take into account the eight principles of risk assessment listed in ARTICLE 3, SECTION 69503.5, subsection (c) (3) as well as the source characteristics of the COCs and their analytical challenges, this is easier said than done.

The Department proposes to set the AA Threshold level on the bases of the availability of reliable information that demonstrates that the concentration of the Chemical of Concern is protective of public health and/or the environment at concentration levels above the limit of detection. In making this determination, it will take into account the eight principles mentioned above. A variety of difficulties will be inherent in this endeavor. For the most part, potential difficulties with applying these eight principles are not discussed in the ISOR and should be in the spirit of full disclosure. For instance, in discussing ***The inherent potency of the Chemical of Concern***, it should be mentioned that such a determination will be dependent on the extent of available test data for a variety of toxicological endpoints as well as applicability of various statistical treatments of those data. Comparative potency determinations for individual endpoints like cancer in animals has been fraught with difficulty and these issues cannot be ignored.

Likewise, the discussion of ***The presence or absence of a threshold dose response*** is rather simplistic. Issues such as dose-dependent transitions in response to exposure to toxic substances are now recognized. These may or may not equate to a threshold for toxicity. Additivity to background concentrations of both exogenous and endogenous concentrations of COCs must be considered. Most of the scientific community would argue with a default position that all carcinogens and mutagens will demonstrate thresholds. Similarly, the treatment of ***Cumulative exposures to other Chemicals of Concern that exhibit the same hazard trait*** leaves much scientific complexity unstated. Suggesting that cumulative exposures can be defined when they exhibit the same hazard trait and /or environmental or toxicological endpoint. This approach has been used in screening assessments but it ignores the fact that we understand modes of toxic action for substances which challenge the notion that things which exhibit the same toxicological endpoint will likely be additive in their toxicity. These are three examples that illustrate the concern that the listing of the principals in the regulation and the limited discussion in the ISOR will compromise the Departments credibility to carry out the AA Threshold assessment that they will be required to do and undermines the public and stakeholders confidence that the best available science will be used in the process.

With regard to the source characteristics, the Department can give consideration to those situations when it is not technically or economically feasible to remove the contaminants which are unavoidable and beyond the control of the responsible entity. This seems like a reasonable accommodation to consider and should be feasible given information received from the responsible entity.

A further factor that the Department must consider is the minimum concentration of the COC(s) that can be detected in the Priority Product with available laboratory analytical methodology. In the ISOR, the Department is clear that it is proposing to use a limit of detection with a low probability of false positive detections (less than 1%) and is not relying on a limit of quantification. Their rationale is to set a low analytical limit that is likely to be closer to some of the health based criteria discussed above. Limit essentially becomes the default AA Threshold if the COC is present as an intentionally added ingredient. While this approach to setting the AA Threshold is a reasonable approach to take, it is essentially a policy- rather than a science-based decision.

Review Topic: The definitions of the various "adverse" impacts and general usage of the term "adverse" impacts is used throughout the regulations. Within the context of the definitional and general use of the term "adverse" impacts in the regulations and when scientific information is available, a qualitative or quantitative determination of adverse impact can be made, and is adequately protective of public health and the environment.

Comment:

The regulation is clear in its intent to protect consumers from the hazardous components of consumer products. In this context, avoiding "adverse" impacts is easily understandable. In the scientific or toxicological definition of adverse, it is less clear. Certain endpoints from toxicological testing which are used to characterize the hazards associated with exposure to chemicals are the subject scientific debate as to whether these constitute "adverse" effects in the

context of human hazard. Issues discussed in this regard have to do with what constitutes an "adverse" versus and "adaptive" response to the exposure. The National Academy of Sciences National Research Council's (NRC) 2007 report, ***Toxicity Testing in the 21st Century***, focuses on this issue. According to the press release from the NRC, "Recent advances in systems biology, testing in cells and tissues, and related scientific fields offer the potential to fundamentally change the way chemicals are tested for risks they may pose to humans, says a new report from the National Research Council. The report outlines a new approach that would rely less heavily on animal studies and instead focus on in vitro methods that evaluate chemicals' effects on biological processes using cells, cell lines, or cellular components, preferably of human origin. The new approach would generate more-relevant data to evaluate risks people face, expand the number of chemicals that could be scrutinized, and reduce the time, money, and animals involved in testing, said the committee that wrote the report." Issues addressed in this report include the use of high doses in animal tests to predict low dose hazards for humans, the relationship between the biology of the test species and the heterogeneous human population, co-exposures to chemicals, and the use of a "systems" approach to integrate information and inform human hazard and risk. All of these issues are ones with strong relevance to these regulations and how we address the likelihood of adverse impacts from chemical exposures.

This report has spawned a large number of publications in the scientific literature that provide perspective around this changing paradigm for testing and assessment. For example, a recent article that I co-authored (Keller DA, Juberg DR, Catlin N, Farland WH, Hess FG, Wolf DC, and Doerrer NG. "Identification and Characterization of Adverse Effects in 21st Century Toxicology." *Toxicol Sci* 126, no. 2 (Apr 2012): 291-7.) reported the outcomes of a Health and Environmental Sciences Institute (HESI) committee May 2011 workshop to discuss approaches to identifying adverse effects in the context of the NRC report. In this article we reported how scientists from industry, government, academia, and NGOs discussed two case studies and explored how information from new, high data content assays developed for screening can be used to differentiate adverse effects from adaptive responses. The terms "adverse effect" and "adaptive response" were defined, as well as two new terms, the relevant pathways of toxicological concern (RPTCs) and relevant responses for regulation (RRRs). RPTCs are biochemical pathways associated with adverse events and need to be elucidated before they are used in regulatory decision making. RRRs are endpoints that are the basis for risk assessment and may or may not be at the level of pathways. Workshop participants discussed the criteria for determining whether, at the RPTC level, an effect is potentially adverse or potentially indicative of adaptability, and how the use of prototypical, data-rich compounds could lead to a greater understanding of RPTCs and their use as RRRs. Also discussed was the use of RPTCs in a weight-of-evidence approach to risk assessment. Inclusion of data at this level could decrease uncertainty in risk assessments but will require the use of detailed dosimetry and consideration of exposure context and the time and dose continuum to yield scientifically based decisions. Discussion of this type of thinking should be presented, at least in the ISOR, so that the public recognizes that the State's flexible approach to assessing safer alternative chemicals will evolve with the evolving science to be fully protective of human health and the environment.