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Submitted Via E-mail

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Re: OEHHA's Notice of Proposed Rulemaking Title 22, California Code of Regulations, Sections 69401 Through 69406 Green Chemistry Toxics Information Clearinghouse Identification of Hazard Traits, Endpoints and Other Relevant Data for Inclusion in the Toxics Information Clearinghouse, 12/17/10

Dear Ms. Kammerer:

The American Chemistry Council (ACC) appreciates the opportunity to provide comments on California EPA's Office of Environmental Health Hazard Assessment's (OEHHA) proposed regulatory program related to Green Chemistry Hazard Traits as part of the Toxics Information Clearinghouse (TIC).[1] ACC[2] is an active member of the Green Chemistry Alliance (GCA) and fully supports GCA's detailed comments on the proposed regulation. We are offering these additional

[1] Text of Proposed Regulations, December 2010, Division 4.5, Title 22, California Code of Regulations, Chapter 54. Green Chemistry Hazard Traits

[2] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

comments to highlight our views on several key issues that we believe the State must address to ensure a scientifically sound, efficient and effective regulatory program.

ACC questions OEHHA's proceeding with this proposed regulatory action at this time in light of Secretary Adams' announcement of December 23, 2010 that she has directed the Department of Toxic Substances Control (DTSC) to take additional time to develop regulations for the California Green Chemistry Initiative.[3] OEHHA's actions in this regard seem to fly in the face of the Secretary's decision and signal a very troubling lack of coordination in Cal/EPA among OEHHA, DTSC and the Secretary. This apparent lack of coordination with the DTSC proposed regulations and DTSC's vision for the Toxics Information Clearinghouse (TIC) signifies the need for additional time and action by the Secretary, DTSC and OEHHA to actualize the Secretary's vision of developing and implementing the very best program possible, one that is workable and addresses key policy concerns.[4]

ACC is also concerned about the resource-intensive process of creating and managing the type of program that the OEHHA describes in the proposed regulation. OEHHA is proposing to create a novel, unique-to- California hazard trait nomenclature and classification / designation system. This is an action which goes well beyond the authorization granted to OEHHA by the enabling legislation (SB 509).[5] This proposed California system of hazard trait nomenclature, for which the scientific basis has not been firmly established (or verified by external scientific peer review), would substantially increase the cost of developing and implementing the Toxics Information Clearinghouse. This is clearly an overstep of statutory authority and is contrary to the statutory direction which requires California to "operate the clearinghouse at the least possible cost to the state."[6]

Furthermore, the proposal does not recognize, and fails to provide a means to utilize, the numerous sources of information on chemicals already readily available to the public, including the Organization for Economic Cooperation and Development's (OECD) eChemPortal and its 17 participating databases.[7] These open access databases, including the National Institutes of Health's National Library of Medicine,[8] and the CDC's Agency for Toxic Substances and Disease Registry, provide access to a wealth of hazard and toxicity information already gathered and evaluated by regulatory authorities around the world and organized into resources that are readily accessible. We believe that these sources and the types of information they include are sufficient to satisfy

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[3] http://www.dtsc.ca.gov/upload/GRSP-12-23-2010.pdf
[4] ibid
[5] http://www.dtsc.ca.gov/PollutionPrevention/GreenChemistryInitiative/upload/sb_509_GCI.pdf
[6] Ibid at Section 25256.
[7] See http://webnet3.oecd.org/echemportal/. We note that eChem Portal includes publicly available information from the governments of Australia, New Zealand, the European Union, Finland, Japan, United Kingdom, and the U.S., in addition to the World Health Organization and other international bodies. eChem Portal includes several U.S. EPA databases, including the Aggregated Computational Toxicology Resource (ACTOR), the High Production Volume Information System (HPVIS), the Integrated Risk Management System (IRIS), and the Substance Registry Service (SRS) databases.
[8] See the NIH National Library of Medicine's ToxNet database at http://www.toxnet.nlm.nih.gov/; ATSDR"s ToxFAQ at http://www.atsdr.cdc.gov/toxfaqs/index.asp#bookmark01.

OEHHA's statutory obligation to "evaluate and specify the hazard traits and environmental and toxicological end-points and any other relevant data that are to be included in the clearinghouse."[9] Instead of creating a novel, California-only method of classification or designation of toxicities and endpoints that will require significant State resources to implement and manage, OEHHA could offer a far more cost efficient solution by leveraging existing data already provided to the world's governments and creating a master portal that provides easy access to existing information sources. Such an approach would be fully consistent with the enabling legislation and compatible with DTSC's vision of the TIC. DTSC has stated, "The Clearinghouse is envisioned to provide access to all of the information; and any determinations and interpretation of the data will be left to the user based on the information in the Clearinghouse."[10]

With respect to the shortcomings of scientific portions of the proposed regulation, ACC refers OEHHA to the comprehensive, section by section, comments submitted by the Green Chemistry Alliance, which we fully endorse. In addition, ACC offers detailed specific comments (see Attachment to this letter) on several key issues that we believe the State must address to ensure a scientifically sound regulatory program. These additional comments are summarized below:

- The scientific portions of the proposed regulation have not yet been subjected to independent external scientific peer review as is required by California law (Health and Safety Code section 57004). Although public comments have been solicited by OEHHA, public comment is not equivalent to independent external scientific peer review. Health and Safety Code Section 57004 requires that the scientific basis of the regulation must be thoroughly and comprehensively peer reviewed, prior to promulgation, to establish that the proposed rule is based upon sound scientific knowledge, methods, and practices.
- The definition of an "Authoritative Organization" is overly broad and lacks necessary articulation of the critical processes needed to establish an authoritative determination.
- The definition of "chemical substance" is too expansive and in fact different from the definition in DTSC's green chemistry regulatory proposal.
- The term and use of "mechanistic similarity" is imprecise in its current form and not consistent with the terms usually applied within the toxicological community.
- The definition and use of the descriptor "other relevant data" is incomplete in that it fails to include information and data on exposure or use.
- The "Evidence for Toxicological Hazard Traits" falls well short of fulfilling a scientifically-based, weight-of-evidence evaluative process. It focuses only on "positive" findings and, in doing so, fails to consider all the relevant data, and thus will fail to produce scientifically sound, causal determinations of hazard traits.
- Chemical potency is ignored in assigning hazard traits, which is in direct conflict with general principles of hazard identification and is different from, and inconsistent with, the United Nations Economic and Social Council-led Globally Harmonized System of Classification and Labelling of Chemicals.

[9] SB 509 at Section 25256.1.
[10] Toxics Information Clearinghouse Feasibility Study Report. DTSC. April 8, 2010

- Assessment of data quality and method reliability is generally lacking from the proposed regulation. Study results must be judged for reliability and quality in order to ensure that a hazard trait has a sound scientific basis.

In summary, we have serious concerns about 1) the lack of coordination among OEHHA, DTSC and the Cal/EPA Secretary; and 2) the novel approach OEHHA has proposed for hazard trait determination, which appears to be an attempt to implement a California-specific process of classifying chemicals. To develop and implement the very best program possible -- one that is firmly grounded in science, one that is workable and one that addresses key policy concerns -- will clearly require greater leadership by the Secretary of Cal/EPA to ensure the necessary coordination between OEHHA and DTSC. The novel approach OEHHA has proposed for hazard trait determination is an overstep of statutory authority. Further, in many instances the proposed approach represents scientifically questionable deviations from well established, internationally agreed upon systems for evaluating and describing chemical hazards. We strongly urge OEHHA to first undertake the necessary coordination with DTSC and the Cal/EPA Secretary and then to revise the proposed regulation to adopt a structure that allows existing chemical toxicity information and hazard trait determinations to be utilized in a scientifically rigorous manner to more quickly and cost effectively fulfill its mandate under SB509.

ACC appreciates the opportunity to comment on OEHHA's proposed regulation on the structure and content of the TIC. Please feel free to contact me or Rick Becker (Rick_Becker@americanchemistry.com) on my staff if you have any questions or require clarification on any areas of our comments.

Sincerely,

Michael P. Walls
Vice President
Regulatory and Technical Affairs

Attachment: Detailed Comments of the American Chemistry Council (ACC) on OEHHA's Text of Proposed Regulations, Division 4.5, Title 22, California Code of Regulations, Chapter 54. Green Chemistry Hazard Traits (December 17, 2010)

Attachment
(2/15/10)

Detailed Comments of the American Chemistry Council (ACC) on OEHHA's Text of Proposed Regulations, Division 4.5, Title 22, California Code of Regulations, Chapter 54. Green Chemistry Hazard Traits (December 17, 2010)

ACC is an active member of the Green Chemistry Alliance (GCA) and fully supports GCA's detailed comments on the proposed regulation. We are offering these additional comments to highlight our views on several key issues that we believe must be addressed by the State in order to have a scientifically sound, efficient and effective regulatory program.

I. Independent External Scientific Peer Review

The scientific portions of the proposed regulation have not yet been subjected to independent external scientific peer review. Although public comments have been solicited by OEHHA, the public comment process is not equivalent to scientific peer review, and does not substitute for scientific peer review.[11] Under California Health and Safety Code Section 57004 (HSC 57004), all Cal/EPA organizations, including OEHHA, are required to conduct an external scientific peer review of the scientific basis for any rule proposed for adoption, and a final regulation cannot be issued until such a scientific peer review has been completed. HSC 57004 recognizes the ramifications any science based regulations may have, and therefore imposes the general peer-review requirements which must be satisfied. OEHHA's proposed regulation would create a novel, California-only method of hazard classification or designation. Therefore, it is imperative that the scientific basis of the regulation is thoroughly and comprehensively peer reviewed by external scientific experts to establish that the proposed rule is based upon sound scientific knowledge, methods, and practices. In accordance with HSC 57004, the most appropriate body for conducting the external scientific peer review is the National Academy of Sciences (NAS), since the proposed regulation represents scientifically questionable deviations from well established, internationally agreed upon systems for evaluating and describing chemical hazards. In addition, the NAS is best suited to conduct the required external scientific peer review because of its global stature and proven track record for tackling complex toxicology and risk assessment issues. Moreover, adoption of a novel California-specific method of hazard trait identification could have global ramifications, since the California economy represents 13-14% of the US GDP and is the world's eighth largest economy. For all of these reasons, scientific peer review of the OEHHA proposal is critical to establish that the proposed rule is based upon sound scientific knowledge, methods, and practices.

[11] The differences between public comment and independent scientific per review are explained in EPA's Peer Review Handbook, 3rd Edition (2006), page 14. http://www.epa.gov/peerreview/pdfs/peer_review_handbook_2006.pdf

II. Scientific Concerns with the Hazard Trait Identification Methodology

A. § 69401.2 Definition of "Authoritative Organization"

ACC believes that the current definition of "Authoritative Organization" fails to include the necessary scientific rigor that is needed to arrive at an authoritative decision. To be considered an "Authoritative Organization," an organization must employ processes that assure comprehensive, deliberative and fully documented evaluations are employed to reach conclusions regarding chemical hazards. Although many of the bodies and organizations listed by OEHHA use such processes in order to reach conclusions that are then made public, this is not true of all the ones listed by OEHHA. For example, by listing "other states" within the definition, there is no assurance that these bodies will undergo such deliberative and transparent review. The definition should make it clear that the "Authoritative Organizations" indeed are ones that would use a thorough, deliberative and transparent review process.

B. § 69401.2 Definition of "Chemical Substance"

The proposed definition for the term "chemical substance" is overly broad and in fact different from the definition in DTSC's proposal. ACC believes that the definition must be reconciled with the definition used by the DTSC.

C. § 69401.2 Definition of "Mechanistic Similarity"

ACC believes that this term is imprecise in the current text and not consistent with the terms as usually applied within the toxicological community. It appears that what is being referenced by OEHHA is "mode of action" or "mechanism of action," two terms more commonly applied in toxicology. These more commonly used terms, however, are usually applied to understanding the basis for a specific endpoint of toxicity, such as a specific type of neurotoxicity within the broad class of neurotoxic agents. If OEHHA is attempting to group chemicals in terms of hazard traits, it would be useful to group chemicals not only by mode of action but also by 1) relevance to humans based upon a comprehensive, peer reviewed analysis in accordance with a key events dose response framework, such as that of the World Health Organization's International Programme on Chemical Safety[12] and 2) likelihood for human exposure to include consideration of the toxicokinetics of a chemical. In other words, if the goal is to group chemicals that pose similar hazard traits, it is not only the trait itself that might be important but also the relevance of such a trait to human health and the way that humans are exposed to chemicals with similar hazard traits. The current OEHHA system for hazard trait identification fails to consider human relevance and exposure which ACC believes are critical to realistic, science-based chemical hazard characterizations.

[12] 2006: Boobis et al. IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol 36:781-792; 2008: Boobis et al. IPCS framework for analyzing the relevance of a non-cancer mode of action for humans. Crit Rev Toxicol. 38:87-96.

D. § 69401.2 Definition of "Other Relevant Data"

The definition of "other relevant data" is incomplete in failing to include data such as exposure or use data. Most internationally recognized hazard classification systems (*e.g.*, GHS, WHO, etc.) link toxicity information to anticipated use and/or exposure information. ACC believes that failure by OEHHA to include some concept of exposure in the assessment of hazard is not scientifically defensible and will create tremendous potential for confusion and misuse of information in the TIC. One way to include such information would be through use of exposure and use information within the concept of "other relevant data."

E. General Comments on Article 2: Toxicological Hazard Traits – Carcinogenicity, Developmental Toxicity, and Reproductive Toxicity

ACC recognizes that the three hazard traits specified in Article 2 -- carcinogenicity, developmental toxicity, and reproductive toxicity-- are commonly used hazard traits in current hazard classification systems. These three traits are used in conjunction with acute toxicity and systemic toxicity in most internationally recognized systems (*e.g.*, GHS, WHO). However, certain key scientific principles are not acknowledged in the OEHHA Proposal. These principles include use of weight-of-the-evidence assessments to classify hazards, consideration of potency, assigning reliability indicators to available data (*i.e.*, data quality factors), and consideration of exposure and use information.

1. Weight-of-the-evidence (WOE) assessment

It is a general principle of hazard assessment that all available data must be considered and the totality of relevant and reliable information integrated in order to arrive at a scientifically defensible decision regarding chemical hazard. Since in many cases, dozens of toxicological studies will be available for review on any given chemical, the only valid scientific approach is to consider the weight of the scientific evidence. Without such an approach, the proposed regulation can be interpreted to suggest that a single study, regardless of its quality (and irrespective of other available relevant data), could be used to conclude that a chemical possesses "suggestive evidence" of a specific hazard trait. Additionally, with respect to cancer, developmental toxicity and reproductive toxicity hazards, it is likely that for many chemicals there will be multiple hazard assessments available from a variety of sources. As a result, specific discussion of how a weight-of-the-evidence assessment should be, and will be, performed is needed.

Without use of WOE, "sufficient evidence" of a hazard trait could be assigned to a chemical, for example, based on data from two poorly conducted studies even if there were several more reliable studies available that contradicted the results of those two studies. It is not scientifically valid to ignore this weight of the scientific evidence. Yet, while Section 69403.16 "Evidence for Toxicological Hazard Traits" proposes a framework for evaluating scientific results, it is not a WOE approach. Instead, OEHHA is proposing to simply count the positive studies. This proposed approach of OEHHA fails to consider all the relevant

information required for a causal determination and falls well short of the scientific standard of practice for weight of evidence evaluation in toxicity determinations.[13] A scientifically sound WOE analysis involves evaluating each study for data quality and reliability and then integrating data from all relevant studies. In contrast to a true WOE process, OEHHA's proposal makes no mention of 1) evaluating negative studies, 2) evaluating the consistency of results across different studies and over time, and 3) evaluating biological plausibility. The framework that OEHHA should employ must provide for a transparent, scientifically-based evaluation of the overall weight of evidence that there is a causal relationship between an outcome of concern and exposure to a substance.

2. Chemical Potency

Chemical potency is ignored in the current OEHHA proposal for assigning hazard traits. This is in direct conflict with general principles of hazard identification. It is a generally accepted principle of toxicology and hazard identification that the dose required to produce a toxic effect, which is a measure of the potency of the chemical to produce toxicity, is an important component of the evaluation process. For example, if a chemical only produces a certain type of toxicity at extremely high and unrealistic human exposure levels, this type of information is essential to defining the realistic hazard associated with a chemical. Without some indication of potency, every substance, whether synthetic or naturally occurring, will be labeled as toxic, even the "greenest" of substances. With respect to cancer, developmental toxicity and reproductive toxicity hazards, the issue of potency is included in most internationally recognized classification systems where it is recognized that some studies conducted at doses or routes of exposure irrelevant to human exposure must be carefully applied even in hazard identification.

3. Data Reliability Indicators

ACC believes that data included in the hazard classification process must be judged for reliability and quality in order to ensure that a hazard trait has a sound scientific basis. However, such data quality or reliability assessment is generally lacking from the OEHHA proposal, especially since WOE is not part of the current methodology. Poor quality data, or data from unvalidated study methods, should not be used to assign a hazard trait when reliable, quality data are available that do not support the assignment. Moreover, poor quality data alone should not be used to assign a hazard trait even if good quality studies are lacking. An example of this is the use of data from unvalidated *in vitro* studies to list a hazard trait when no *in vivo* data are available to support the finding, or listing a hazard trait based solely on a structure activity relationship without any verification in a biological system. In the case of cancer, developmental toxicity and reproductive hazard trait

[13] Gray, G.M., Baskin, S.I., Charnley, G., Cohen, J.T., Gold, L.S., Kerkvliet, N.I., Koenig, H.M., Lewis, S.C., McClain, R.M., et al. (2001). The Annapolis Accords on the use of toxicology in risk assessment and decision-making: an Annapolis Center workshop report. Toxicology Mechanisms and Methods 11, 225-231. Weed, D.L. (2005). Weight of evidence: a review of concept and methods. Risk Anal 25, 1545-557.

classifications under the OEHHA proposal, the discussion of "suggestive" evidence for each trait needs to incorporate the concept of data quality or reliability.

4. Exposure and Use Information

As already discussed above, exposure and use information are ignored in the current OEHHA Proposal for assigning hazard traits. This is in direct conflict with other hazard identification systems used around the world (*i.e.*, GHS, WHO, *etc.*). Since toxic effects of a chemical are a function of both inherent toxicity and the route, magnitude, frequency and duration of exposure, production processes and use patterns that influence exposure will ultimately influence the level of risk posed by any chemical. This is, in fact, the main reason that hazard identification programs worldwide have production, use, or exposure "triggers" for toxicity study data requirements. The GHS classification approach also considers anticipated levels and durations of exposure for some characteristics. Thus, ACC believes that the consideration of cancer, developmental toxicity and reproductive toxicity hazard trait discussion in Article 2 needs to incorporate the concept of exposure and/or use as well as route of exposure. It would be inappropriate to rely on theoretical hazards identified by unrealistic exposure conditions or irrelevant routes of exposures.[14]

F. General Comments on Article 3: Other Toxicological Hazard Traits

The "other" toxicological hazard traits described on pages 10-16 of the OEHHA Proposal are inconsistent with other widely recognized and implemented international categories. OEHHA has justified its position by stating that each trait was chosen in part because of listings within a textbook of toxicology, where discussions are broken out by target organ systems. Regardless of the fact that toxicology textbooks may organize information based on target organs, it is a generally accepted method for hazard identification to describe hazards in terms of either durations of exposure (*i.e.*, toxic effects seen after acute exposures, toxic effects seen after chronic exposures) or local versus systemic toxicity. Then, under the hazard trait of "systemic toxicity", the target organs would be identified (*i.e.*, liver, kidney, heart, etc.). There is no need to break out systemic toxicity or target organ toxicity by specific systems (*e.g.*, cardiovascular, gastrointestinal, liver, renal, *etc.*) when the goal is hazard identification. Instead, listing target organ effects is more than adequate to describe a chemical's hazard. This is especially true since the critical issue for chemical hazard classification should be identifying the most sensitive system(s) affected by chemical exposure, not simply a laundry list of toxicity.

In addition to the use of a system with unnecessary detail in terms of hazard trait assessment, certain key scientific principles are not acknowledged in the OEHHA proposal for "other" hazard traits. These principles are the same as the ones discussed above in association with cancer, developmental toxicity and reproductive toxicity hazards, *i.e.*, use of weight-of-the-evidence

[14] For example, as Lorentzen and Hattan point out, "assays that are meant to be screens for hazard assessment, [are] not conceived to reveal reliable information about the human dose-response …" and exposures by some routes may produce hazards that are not indicative of hazards that would could arise by another route (e.g., inhalation of water leading to hypoxia / anoxia is not relevant nor indicative of toxicity arising from over ingestion of water and resultant hyponatremia and CNS dysfunction. http://www.nature.com/nature/journal/v464/n7292/full/4641103b.html

assessments to classify hazards, consideration of potency, assigning reliability indicators to available data, and consideration of exposure and use information. The lack of consideration of each of these key scientific principles is a critical flaw in the OEHHA proposal.

Article 3 also lacks discussion of other key principles that affect the scientific basis and validity of the OEHHA Proposal. These include failure to distinguish adverse changes from adaptive changes, use of unvalidated *in vitro* studies and/or structure-activity data alone as a basis for identifying hazard trait, and use of emerging concepts in toxicology as a basis for a hazard trait regulatory decision.

1. Adaptive Versus Adverse Effects of Chemicals

An adverse effect is not any known biochemical or chemical change, or even any known or measureable precursor along a biochemical pathway that could lead to some degree of perturbation. Consideration of adversity occurs when perturbations are sufficiently large, which may depend upon susceptibility of the host. ACC believes that many of the listed effects on pages 10-16 for individual hazard traits are not adverse effects but adaptive effects. For example, a change in glucose or glycogen metabolism without some accompanying change in tissue histopathology or organ function would not be considered an adverse effect but an adaptive effect that might reverse or be accommodated by the organism. The same is true of neurotransmitter changes in the central nervous system which can adapt by up or down regulating without leading to an adverse effect on the organism. By including discussion of effects that can be adaptive only within the OEHHA proposal for certain hazard traits, OEHHA fails to distinguish between these critical concepts of toxicology. If OEHHA includes the current level of detail within endpoint lists for each hazard trait, the proposal needs to be modified to clearly define the difference between an adaptive response and an adverse effect.

2. Use of *In Vitro* and Structure-Activity Data

The conclusive identification of a toxicity hazard trait based solely on data obtained using *in vitro* methods or structural/predictive models is not scientifically justified. It is broadly recognized that the science of many *in vitro* screening assays has not advanced to the level of assuring that *in vitro* results are predictive of *in vivo* activity or can be considered to be robust measures of toxicity hazard. Just as use of *in vitro* data as a sole basis for identifying a hazard trait is not scientifically justified, the use of chemical structure-activity analysis alone should not be instituted by OEHHA. Indeed, structure-activity models themselves need to be evaluated for validity and appropriate use. The use of *in vitro or in silico* data as the *sole basis* for concluding that a chemical possesses a hazard trait is over reaching and should be removed from the OEHHA Proposal. While it is entirely appropriate to include information from *in vitro* studies and structure-activity models (as well as read across, expert judgment) in a WOE evaluation, it is not appropriate to draw conclusions about hazard from these sources alone. Results from QSAR or *in vitro* methods should only be considered for assigning hazard traits to a chemical after it has been clearly demonstrated that the specific method is scientifically valid and achieves an acceptable level

of sensitivity (false negative rate) and specificity (false positive rate). This principle is widely recognized by regulatory bodies worldwide, and is exemplified by OECD's development of internationally harmonized guidance on the validation and regulatory acceptability of QSAR models and alternative test methods.[15] Further, OEHHA needs to clearly identify how certain types of data, such as *in vitro* data, should be weighted when assessing chemical hazards, recognizing that some types of data are less reliable and less predictive of apical effects than others.

3. Emerging Concepts in Toxicology

ACC believes that it is inappropriate to include the emerging concepts of endocrine disruption and epigenetics as "other" toxicological hazard traits. Endocrine disruption is not an endpoint, but rather a mode of action. It has been standard practice in toxicology and risk assessment to describe toxic effects mediated by the endocrine system based on the apical adverse effects that are induced. Thus, a chemically-induced change on a component of the endocrine system that is of sufficient magnitude/duration/nature to cause an adverse effect on an organ system has, in practice, been evaluated as target organ toxicity (which includes assessment of reproductive toxicity or developmental toxicity). The OEHHA document fails to discuss the fact that many of the endpoints listed in this section of the proposed regulation have not been validated as unique endpoints for identifying endocrine disrupting chemicals.

As OEHHA is well aware, endocrine activity, consistent with the principles expressed in EPA's Endocrine Disruptor Screening Program (EDSP), is not a distinct toxicological hazard per se, but rather a measure of a compound's ability to interact with components of the endocrine system. Interaction with or modulation of endocrine processes may or may not give rise to adverse effects. EPA states, "The fact that a substance may interact with a hormone system, however, does not mean that when the substance is used, it will cause adverse effects in humans or ecological systems."[16] Toxicological tests that evaluate the induction of adverse effects in validated test systems (EPA's EDSP Tier 2 tests), not mechanistic screens, are to be used for hazard identification. As EPA has stated, "At this stage of the science, only after completion of Tier 2 tests will EPA be able to determine whether a particular substance may have an effect in humans that is similar to an effect produced by a naturally occurring EAT [sic; estrogen, androgen, thyroid], that is, that

[15] Guidance Document No. 69 on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models http://www.oecd.org/dataoecd/55/35/38130292.pdf Guidance Document No.34 on the Validation and International Acceptance of new or Updated Test Methods for Hazard Assessment http://www.oecd.org/officialdocuments/displaydocumentpdf?cote=env/jm/mono(2005)14&doclanguage=en

[16] EPA (2009), Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. Federal Register Volume 74, Number 71 (Wednesday, April 15, 2009), Pages 70248-70254. http://www.epa.gov/endo/pubs/revised_pandp_frn_041509.pdf

the substance is an endocrine disruptor."[17] The World Health Organization's definition of an endocrine disruptor is very similar to that of the EPA: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."[18]

Epigenetic toxicity is an even newer concept within toxicology and has been examined as the basis for identifying mechanisms of systemic toxicity. In fact, "epigenetics" is defined as a mechanism of action for potential toxic effects, not an endpoint for toxicity testing. Epigenetic changes such as DNA methylation or histone modification, as listed in the OEHHA Proposal, may not lead to stable expressions of an altered, adverse phenotype, which is what would be needed in order to identify a specific endpoint of hazard or toxicity. The changes listed in Article 3 in association with epigenetic toxicity, however, should be manifested in standard toxicity testing as endpoints of systemic toxicity and would include changes in either biological function or tissue structure (pathological or histopathological changes). If such changes do not manifest in acute or repeat dose toxicity studies, then they may be adaptive changes only and not relevant for chemical hazard assessment. OEHHA fails to provide any scientific basis for including "epigenetic toxicity" as a separate discrete hazard trait from systemic toxicity.

4. General Comments on Article 5: Exposure Potential Hazard Traits

Here again, OEHHA is proposing to establish a California-specific designation. The term "Exposure Potential Hazard Trait" is a novel construct that is not used by any other regulatory body in the US or globally, and is unnecessary. Instead, OEHHA should conform to, and take advantage of, the internationally harmonized approach developed by the OECD for reporting of Physical-Chemical Properties and Environmental Fate data elements.[19] Further, the term "Exposure Potential Hazard Trait" should be eliminated altogether, and the relevant information on Physical-Chemical Properties and Environmental Fate should be included in the "Other Relevant Information" section.

[17] EPA (1998). Endocrine Disruptor Screening Program: Statement of Policy. Federal Register Volume 63, Number 248 (Monday, December 28, 1998) page 71542.
[18] WHO/IPCS Global assessment of the state-of-the-science of endocrine disruptors. http://www.who.int/ipcs/publications/en/ch1.pdf
[19] http://www.oecd.org/dataoecd/13/18/36045056.pdf