MICHAEL P. WALLS
VICE PRESIDENT
REGULATORY & TECHNICAL AFFAIRS

September 13, 2010

BY ELECTRONIC MAIL

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

Dear Ms. Kammerer:

ACC appreciates the opportunity to provide comments on OEHHA's August 10, 2010, pre-regulatory discussion draft on the Toxics Information Clearinghouse (TIC). The short comment period provided by OEHHA required us to limit our comments almost exclusively to the toxicological hazard traits listed in the document. ACC is an active member of the Green Chemistry Alliance (GCA) and supports GCA's comments on the discussion draft. We are offering these comments to highlight our views on key issues that we believe require additional consideration.

ACC is concerned about the resource-intensive process of creating and managing the type of TIC that the OEHHA document describes. OEHHA is proposing that DTSC manage a novel California system when here are already numerous sources of information on chemicals readily available to the public, including the Organization for Economic Cooperation and Development's eChemPortal and its 17 participating databases,[1] databases from the National Institutes of Health's National Library of Medicine, and the CDC's Agency for Toxic Substances and Disease Registry.[2] Existing resources 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 OEHHA's statutory obligation to "evaluate and

[1] 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.
[2] 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.

[3] National Research Council. 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. Page 48.

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.

specify the hazard traits and toxicological endpoints and any other relevant data." Instead of creating a novel, California-only list of toxicities and endpoints that will be difficult to populate even with existing information, 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.

A summary of the detailed comments provided in the remainder of this document is as follows:

- The definition of "adverse effect" is vague and potentially at odds with modern scientific understanding of the concept.
- The description of classification systems is highly flawed and clearly oversteps the statutory authority given to OEHHA in SB 509.
- The toxicological trait list is inconsistent with well established hazard characterization systems and deviates in many cases from scientific understanding of hazard assessment.
- The approach to assigning a toxicological trait raises many questions, particularly the inappropriate use of *in vitro* methods and models as the sole evidence for making a conclusion about hazard.
- The document overreaches with regard to the use of epigenetics as a *de facto* indicator of adverse effect in many instances.
- The document fails to include exposure considerations when identifying hazard traits.
- The document fails to provide a way to list a finding of "non-toxic", even for the "greenest" of substances.
- There is no consideration of data quality or guidance for making weight-of-evidence conclusions about a chemical's hazard traits.

We have also included comments we submitted to DTSC and OEHHA on January 29, 2009, regarding implementation of the TIC. We hope that OEHHA will take this opportunity to review those comments again.

I. Comments Relating to Section 2. "Definitions"

A. Definition of "Adverse Effect"

The pre-regulatory draft document defines "adverse effect" in words that are very broad and without context in terms of how to use the definition to characterize chemicals' hazard traits. The clause in the proposed OEHHA definition of "reducing an organism's ability to respond to an additional environmental challenge" could extend the scope of effects observed in animals or humans to effects beyond commonly measured toxicity endpoints. What would be encompassed by this part of the definition is unclear. Notwithstanding the first part of the definition, we are concerned that this overly broad phrase could be interpreted such that *any* detected perturbation, even adaptive changes, could be classified as an "adverse effect." Doing so would contradict broadly accepted scientific principles. For example, in its landmark report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*, the National Research Council is clear that a perturbation and an adverse effect are not necessarily the same thing:

> *The consequences of a biologic perturbation depend on the magnitude of the perturbation, which is related to the dose, the timing and duration of the perturbation, and the susceptibility of the host. Accordingly, at low doses, many biological systems may function normally within their homeostatic limits. At somewhat higher doses, clear biological responses occur. They may be successfully handled with adaptation, although some susceptible people may respond. A more intense or persistent perturbation may*

overwhelm the capacity of the system to adapt and lead to tissue injury and possibly to adverse health effects.[3]

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. The NRC clearly indicated that consideration of adversity occurs when perturbations are sufficiently large, which may depend upon susceptibility of the host. Additional discussion of the issue of adverse effects as compared to non-adverse effects, or adaptive changes, is found below. In the absence of further clarification of intent and applicability, we recommend striking "reducing an organism's ability to respond to an additional environmental challenge" from the definition.

The proposed OEHHA definition of "adverse effects" also fails to consider threshold dose, a fundamental principle of toxicology. This principle holds that for all agents, there are doses below which no harm–no adverse effects–are expected. This is illustrated specifically in a regulatory context within U.S.EPA's *Guidelines for Developmental Toxicity Risk Assessment* which affirms that the concept of a threshold dose applies to both developmental and reproductive toxicity: "*In general, a threshold is assumed for the dose-response curve for agents that produce developmental toxicity. This is based on the known capacity of the developing organism to compensate for or to repair a certain amount of damage at the cellular, tissue, or organ level. In addition, because of the multipotency of cells at certain stages of development, multiple insults at the molecular or cellular level may be required to produce an effect on the whole organism*." [4]

Based on the lack of discussion in the current OEHHA document, OEHHA needs to more clearly define the scope of endpoints and toxicity that will be considered to be "adverse effects" within the definition provided and how chemicals that elicit adaptive, but not adverse responses, will be handled.

B. Definition of Chemical "Classes"

ACC believes that the proposed classification system should be abandoned entirely. We do not interpret SB 509 as giving OEHHA either the mandate or the authority to create a new California classification system. OEHHA's role under SB 509 is limited to defining hazard and other relevant information, not interpreting or otherwise making decisions about how that information is presented. That responsibility clearly lies with DTSC, and the proposed classification system is a significant overstep of OEHHA's authority.

Further, the proposed classification provision is unhelpful for communicating information on chemicals and thus fails to contribute to the overall goals of the California Green Chemistry Initiative. For example, there are chemicals for which the scientific data clearly demonstrates that the chemical lacks certain hazard traits, including some of the most important concerns such as carcinogenicity and reproductive and developmental toxicity.[5] However, the OEHHA proposal combines "no effect" and "lack of information" into the catch-all category "Not Classifiable." It would be impossible to identify "non-toxic" chemicals

[3] National Research Council. 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. Page 48.

[4] See *Guidelines for Developmental Toxicity Risk Assessment.* Assessment Forum, Washington, DC, EPA/600/FR-1991 at http://www.epa.gov/ncea/raf/pdfs/devtox.pdf.

[5] OECD and U.S.EPA test guidelines allow for testing chemicals at the highest feasible dose, or a "limit dose" in repeat dose toxicity studies, as well as other types of toxicity testing, where a limit dose is defined as 1000 mg chemical/kg-bw. If no adverse effects are observed at the limit dose, the substance is considered not to pose a hazard for the endpoints examined. Testing can be performed with a "limit test" design such that the only dose tested is the limit dose. When results of such testing demonstrate that the dose does not produce any observable toxic effects, the results can be used as support for decisions to not pursue further testing in larger, multi-dose studies. For example, see OECD's *Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents* and EPA's *Health Effects Test Guideline OPPTS 870.3100 90–Day Oral Toxicity in Rodents*.

using OEHHA's proposed classification scheme. Even the "greenest" of chemicals will be classified as hazardous or "unclassifiable." Clearly such a system would not be useful to any potential TIC user. In addition, the proposed system muddies the waters by lumping distinctions made in existing systems (e.g., IARC) for no apparent reason (and without providing context). This has the effect of *decreasing* the information available on chemicals because it reduces the detail available to potential TIC users.[6] Finally, it appears that a chemical is categorized as having most of the toxicities and other traits listed in the document until such time as OEHHA or DTSC determines otherwise (Section 4i). Even the "greenest" of chemicals would be held in limbo. Again, this is not helpful. It appears to contradict what was perhaps the original intent of the "Not Classifiable" category and establishes a process that is a poor use of OEHHA's and DTSC's resources.

In summary, the OEHHA classification proposal does not bring clarity to chemical information. Indeed, it increases opacity on all dimensions and should be abandoned until DTSC, the actual keeper and manager of the TIC, has sufficient time to develop a more useful system.

II. Comments Relating to Section 3. "Specific Hazard Traits, Endpoints and Other Relevant Data"

A. The Categories of "Toxicological Hazard Traits" are Inconsistent with Widely Recognized and Implemented International Categories

The categories of "toxicological hazard traits" described on pages 5-14 of the OEHHA document are inconsistent with other widely recognized and implemented international categories. For example, the United Nations, identified in the document as an "authoritative" organization, has spent a decade developing the "Globally Harmonized System" or "GHS" for understanding and communicating chemical information.[7] Similarly, the countries of the OECD have developed the Screening Information Data Set (SIDS) to understand chemical hazard, which is used broadly by OECD member states and others as a basis for developing information on and making regulatory decisions about chemicals.[8] It is not clear why OEHHA failed to incorporate any aspects of these widely used and agreed upon systems in the TIC discussion document. The GHS and OECD hazard traits are typically encountered in discussions of chemical hazard and are based on the types of data routinely gathered in toxicity testing. In contrast, the OEHHA hazard traits classification system is overly specific. There is no need to list every potentially affected organ system when the real need is to understand which system is the one critically affected by repeat-dose exposure. Instead, the use of the GHS or OECD approaches, which include information on acute and repeat-dose effects and notation of the system(s) affected, 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.[9]

A prominent omission in the OEHHA document's long list of hazard traits is a discussion of the difference between adverse effects and adaptive changes. As already discussed, the NRC Committee clearly distinguishes between adaptive and adverse effects. Further evidence for how OEHHA's inclusion of adaptive responses within the definition of an adverse effect deviates from standards of practice in the field is available from a position paper issued by the American Society for Veterinary Clinical

---

[6] In addition to the lumping of distinct and meaningful IARC classes, the inclusion of IARC 2B substances as definitive carcinogens is highly questionable and a strong example of the flawed system proposed in the document.
[7] See United Nations 2009. *Globally Harmonized System of Classification and Labeling of Chemicals (GHS)*, Third edition.
[8] See OECD Manual for the Investigation of HPV Chemicals at http://www.oecd.org/document/7/0,3343,en_2649_34379_1947463_1_1_1_1,00.html.
[9] See for example EPA IRIS program guidance at http://www.epa.gov/iris/rfd.htm; Barnes and Dourson. 1988. *Regul. Toxicol. Pharmacol*. 8:471-486; Teuschler et al. 1999. *Regul. Toxicol. Pharmacol*. 30:S19-S26.

Pathology.[10] The paper outlines the expert recommendations for the use of preclinical, clinical pathology endpoints in assessment of the potential for drug induced hepatic injury in animals and humans. In the context of that paper, preclinical studies are equivalent to the toxicological studies in laboratory animals conducted to assess potential hazards and risk from commodity chemicals. In the paper, the terms "adverse" and "no-observed adverse effect level (NOAEL)" are defined as follows:

> *"Adverse. A biochemical, morphological, or physiological change (in response to a stimuli) that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge. No observed-adverse-effect level (NOAEL). For the purpose of identifying hepatic injury in preclinical studies, we propose the following definition of NOAEL: the level of exposure within a preclinical study at which there are no adverse effects. Specifically, the NOAEL is the level of exposure at which there are no toxicologically relevant increases in the incidence or severity of effects between compound-treated and control populations. Compound-related findings must be identified as adverse to establish the NOAEL. Non-adverse changes are compound-related but of insufficient magnitude to be adverse and often consist of normal physiologic compensatory mechanisms or anticipated pharmacologic activity.*

This paper demonstrates OEHHA's failure to distinguish adverse effects from adaptive changes, which could have significant effects on the selection of hazard traits for any given chemical and will further confuse parties seeking information on chemicals.

B. Comments on the Individual Hazard Traits Listed by OEHHA

With respect to the individual toxicity hazard traits listed on pages 5-14 of the document, some of these traits warrant the following comments:

Carcinogenicity is a generally accepted hazard trait within all existing classification systems. However, OEHHA's definition appears to include consideration of data that are not relevant for evaluating risks to human health. Generally, within the scientific fields of toxicology and risk assessment, it is recognized that the mode of action of cancer induction in animal studies that results only from high dose exposures that cause extensive toxicity and stimulate cell proliferation is not a relevant mode of action for human health risk assessment at environmentally meaningful exposures. This is such a fundamental precept in toxicology that it is found in textbooks.[11] Yet, OEHHA proposes to ignore this generally accepted principle in identifying hazard traits of a carcinogen. It is not scientifically defensible to perform a cancer hazard assessment using the definition proposed by OEHHA.

ACC urges OEHHA to define carcinogenic hazard consistent with classification systems such as the GHS.[12] Additionally, the OEHHA document includes some non-standard language for defining the carcinogenicity hazard trait. For example, the listing of "epigenetic changes associated with increased

---

[10] See "Selection and Interpretation of Clinical Pathology Indicators of Hepatic Injury in Preclinical Studies" at http://www.toxpath.org/position_papers/asvcp_indicatorinjury.pdf. (Veterinary Clinical Pathology Vol. 34 / No. 3 / 2005, 182-188). Additional discussion of the definition of adverse effects in toxicological evaluations can be found in Lewis RW, Billington R, Debryune E, Gamer A, Lang B, Carpanini F. Recognition of adverse and non-adverse effects in toxicity studies. Toxicol Pathol. 2002;30:66–74 at http://tpx.sagepub.com/cgi/reprint/30/1/66.pdf.

[11] See Faustman and Omenn. 2008. Risk assessment. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons*. 7th edition. C.D. Klaassen (ed.).

[12] See United Nations 2009. *Globally Harmonized System of Classification and Labeling of Chemicals (GHS)*, Third edition.

cancer risk" is not clearly defined. The term "epigenetic changes" can include adaptive changes and such changes are not by definition 'adverse". If the document is to include a listing for "epigenetic changes associated with increased cancer risk", then OEHHA needs to provide very specific guidance that describes what epigenetic changes are valid for carcinogenicity assessment.

Cardiovascular toxicity is a common indicator of systemic toxicity. It is standard practice in toxicology and risk assessment to define cardiovascular effects within the classification of systemic toxicity, not as a unique hazard trait. This is due in part to the fact that many perturbations to other organ systems (e.g., renal effects) can lead to secondary toxicity manifested as changes in cardiovascular function. Direct toxicity on heart muscle or vascular tissue, without toxic effects on other tissues or organs, is uncommon. Therefore, toxicologists generally refer to the cardiovascular system as an organ of systemic toxicity, not as a uniquely defined hazard trait. Additionally, some of the endpoints of cardiovascular toxicity listed in the document, such as "*in vitro* cytotoxicity to isolated vascular endothelial cells" and the broad category of "adverse changes in the ability of the cardiovascular system to maintain homeostasis" have not been validated as useful for predicting either *in vivo* effects, or functional as opposed to adaptive changes. As a result, this section of the document should be significantly revised to reflect standard practices in toxicology and risk assessment and to distinguish adverse effects from effects that are adaptive.

Dermatotoxicity is not a trait commonly addressed through standard toxicity testing. Instead, various testing batteries include studies examining endpoints of dermal toxicity such as skin sensitization, phototoxicity, and dermal irritation (e.g., OECD guideline studies; EPA test guidelines). As a result, the GHS has included the specific endpoints of dermal sensitization or dermal irritation as hazard traits within its classification system. Since testing for skin sensitization and irritation, for example, are commonly included within standard toxicity testing batteries, it is unclear why OEHHA has chosen to deviate from the standard approach to identifying hazards to skin. Use of the existing system such as OECD and GHS would provide more than adequate information on the potential skin hazards of chemicals.

Developmental toxicity is a trait commonly included when defining hazard traits of chemicals. However, as already discussed with respect to the carcinogenicity hazard trait, the OEHHA document includes some non-standard language. For example, the listing of "mechanistic data at the molecular levels such as genotoxicity or epigenetic toxicity" is not clearly defined. The term "epigenetic" includes adaptive changes and such changes are not by definition "adverse." If the document is to include a listing for "epigenetic toxicity", then OEHHA needs to provide very specific guidance on what is meant to be included and that describes the validation of such changes for developmental toxicity risk assessment (i.e., adverse outcomes). It is also important to point out that some changes observed during toxicity testing in developing animals are produced only when doses exceed a maximum tolerated dose for the parental test animals and are thus not considered relevant for chemical hazard assessment. The omission of any discussion or consideration of the level of exposure when assessing the developmental toxicity hazard trait is a significant flaw in the document.

Endocrine toxicity is a new emphasis within chemical risk assessment and toxicity testing. U.S. EPA is in the process of developing an endocrine disruptor screening program. It has been standard practice in toxicology and risk assessment to describe toxic effects on endocrine organs as part of the systemic toxicity of chemicals, or as part of the hazard trait of reproductive toxicity or developmental toxicity, since toxicity to these systems is related to effects on endocrine systems. The OEHHA document fails to discuss the fact that many of the endpoints listed in their section have not been validated as unique endpoints for identifying endocrine disrupting chemicals. The listing of endocrine toxicity as a unique hazard trait is somewhat redundant when reproductive and developmental toxicity are listed.

Epigenetic toxicity as defined by OEHHA is overly broad and could include adaptive as well as adverse effects on organisms. As already discussed, the omission of a discussion of adaptive changes versus

adverse effects of chemicals is a flaw in the document that affects all steps in the process of identifying and communicating hazard traits. At page 8 of the document, the changes listed 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 apart from systemic toxicity.

Genotoxicity is a commonly used hazard trait for characterizing chemicals. However, by failing to describe the genotoxicity endpoints by exposure route (*in vitro* versus *in vivo*) or level of exposure (cytotoxic or non-cytotoxic doses), the document is inconsistent with standard practice in assessing genotoxicity hazard.[13] The definition listed on page 9 of the document needs to be revised to reflect these important considerations in genotoxicity data interpretation and hazard identification.

Immunotoxicity as defined in the document is overly broad and fails to describe how some changes in listed immune system parameters might be adaptive changes as opposed to adverse effects. Immunotoxicity is another hazard trait that is typically included under systemic toxicity, recognizing the fact that alterations in immune system parameters in toxicology studies often manifest as changes in organ function, organ pathology, or clinical signs and symptoms.

Hematotoxicity is another of the OEHHA hazard traits that is commonly defined using the term systemic toxicity. Direct toxicity on blood cells, without toxic effects on other tissues or organs, is uncommon. It is not clear why OEHHA has chosen to isolate changes in hematological endpoints as a unique hazard trait.

Hepatotoxicity and digestive system toxicity, musculoskeletal toxicity, nephrotoxicity, and respiratory toxicity are standard endpoints of systemic toxicity that would be monitored in many acute and repeat dose toxicity studies. As already discussed above for other endpoints of systemic toxicity, it is not clear why OEHHA has chosen to isolate changes in these tissues apart from systemic toxicity when all other toxicity classification systems would include these endpoints within the scope of defining chemical hazard in terms of systemic toxicity. Also as discussed above for other hazard traits, some of the endpoints listed for these traits have not been validated as indicators of more than simple adaptive changes (e.g., induction of metabolic enzymes, changes in bone mineral content, alterations in glomerular filtration rate or tubular resorption capacity, increased inflammatory cytokine expression) and as such are not properly considered adverse effects for defining hazard.

Neurotoxicity is a standard endpoint of systemic toxicity that would be monitored in most acute and repeat dose toxicity studies. As already discussed above, it is not clear why OEHHA has chosen to isolate changes in nervous system function apart from systemic toxicity when most other toxicity classification systems would include endpoints of neurotoxicity within the scope of defining chemical hazard in terms of systemic toxicity. Also as discussed above, some of the endpoints listed in the document on page 11 have not been validated as indicators of more than simple adaptive changes (e.g., altered neurochemical synthesis, storage, secretion and uptake), and as such are not properly considered adverse effects for defining hazard.

Ocular toxicity is an endpoint commonly addressed through testing for eye irritation and damage in standard acute toxicity tests. Since testing for eye irritation, for example, is commonly included within

[13] See International Conference on Harmonization. 2008. Draft consensus guideline. Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. S2(R1). March.; EPA 2007. Framework for Determining a Mutagenic Mode of Action for Carcinogens. EPA 120/R-07/002-A. DRAFT September; Plunkett et al. 2010. Regul. Toxicol. Pharmacol. In press.

standard toxicity testing batteries, it is unclear why OEHHA has chosen to deviate from the standard approach to identifying hazards to the eye.

Ototoxicity is a non-standard endpoint for animal toxicity testing. Yet, systemic toxicity testing would address the endpoint through clinical observations that are routinely made during testing, as well as through histopathological evaluation of the nervous system. It is not clear why OEHHA has proposed this as a unique hazard trait.

Reactivity in biological systems is an overly broad trait that is not useful for hazard evaluation since all chemicals could be considered to "react" with biological systems simply by being absorbed into a cell. The endpoints mentioned on page 13 of the document appear to fit more easily within other hazard trait categories as underlying mechanisms or modes of action. This trait should be dropped.

Reproductive toxicity is a generally accepted hazard trait within all current classification systems. However, some reproductive system changes observed in toxicity studies are produced only when doses exceed a maximum tolerated dose for the parental test animals and thus are not relevant for conclusively assigning the trait of reproductive toxicity for humans. The omission of any discussion or consideration of exposure or dose levels when assessing the reproductive toxicity hazard trait is a significant flaw in the document.

C. Identification of Toxicity Hazard Traits Based Solely on Data from Studies Using *In Vitro* Methods is not Scientifically Justified

The conclusive identification of a toxicity hazard trait based solely on data obtained using *in vitro* methods or structural/predictive models (e.g., as suggested for "cardiovascular toxicity" on pages 6-7 of the document) 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.[14] In recent statements regarding the *in vitro* screening assays being developed by the U.S. EPA in the ToxCast program, this same point is made with regard to the use of such data to support hazard assessment within the Endocrine Disruptor Screening Program.[15]

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 valid and appropriate use.[16] The use of *in vitro* data as the *sole basis* for concluding that a chemical possesses a hazard trait is over reaching and should be removed from the OEHHA document. While it is entirely appropriate to include information from *in vitro* studies and structure-activity models (as well as read across, expert judgement), it is not appropriate to draw conclusions about hazard from these sources alone.

---

[14] See Rusyn, I. and Daston, G.P. 2010. *Environ. Health Perspect*. 118:1047-1050.

[15] EPA 2010. Memo from R.J. Kavlock and H. Zenick, June 16, 2010 entitled "Revised ORD statement on the use of ToxCast data in EDSP".

[16] See OECD. 2004. Principles for the validation, for regulatory purposes, of (quantitative) structure–activity relationship models. http://www.oecd.org/dataoecd/33/37/37849783.pdf; OECD. 2007a. Guidance document on the validation of (Q)SAR Models. http://www.olis.oecd.org/olis/2007doc.nsf/LinkTo/NT00000D92/$FILE/JT03224782.

D. Defining Hazard Traits Based Solely on Epigenetic Effects of Chemicals is not Scientifically Defensible

Epigenetics is properly defined as a mechanism of action for potential toxic effects, not an endpoint for toxicity testing.[17] Epigenetic changes such as DNA methylation or histone modification 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. Throughout pages 5-14 of the OEHHA document, various hazard traits are discussed as being based solely on "epigenetic" changes. Defining hazard traits in this way is not scientifically defensible, since hazard traits are endpoints of toxicity, not mechanisms that underlie an observed effect.

Additionally, epigenetic effects of chemicals can include changes that are adaptive only, not adverse effects. An adverse effect is not any known biochemical or chemical change, or even any known or measureable precursor along a pathway that could lead to some degree of perturbation. Instead, an effect is adverse if it occurs when perturbations are sufficiently large (see discussion of adverse effects above). The proposed OEHHA definitions for various hazard traits are inconsistent with this concept when definitions are based solely on epigenetic effects.

III. Comments on Section 4. "Sources and Methodologies for Identifying Toxicological and Environmental Hazard Traits"

A. The Document Fails to Include Exposure Considerations

The OEHHA approach to hazard traits fails to include any assessment or consideration of exposure. This is a critical flaw in the method because chemical hazard is ultimately dependent on type, level, and duration of exposure. In fact, most internationally recognized hazard classification systems (*e.g.*, GHS, WHO [18], etc.) portray toxicity information linked to anticipated use and/or exposure information. 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.

In order to reflect hazard traits of chemicals, the document should discuss that not every chemical would need to have an animal-intensive, toxicity testing and exposure dataset in order to be adequately characterized. Chemicals differ in physical/chemical characteristics and in many other ways that influence toxicity and the hazard a chemical poses to humans. In particular, certain substances such as pesticides and pharmaceuticals are designed or developed to have biological effects, while commodity chemicals and pesticide inert ingredients, with some exceptions, generally do not possess this same kind of biological activity. Since hazard is a function of both toxicity and the potential for exposure, production processes and use patterns that influence exposure will ultimately influence the level of hazard posed by any chemical. This is, in fact, the main reason that the OECD's SIDS program, the U.S. EPA's HPV and PMN programs, and the EU's REACH requirements 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.

OEHHA needs to incorporate some aspect of chemical use or exposure into the process for assigning hazard traits. Otherwise, users may not understand that the lack of data for a particular trait is attributable to a lack of scientific justification for testing for that trait based on the known use patterns and/or exposure to the chemical. Our January 29, 2009, comments contain more comments regarding the importance of use and exposure information.

---

[17] See Berger et al. 2009. *Genes. Dev*. 23:781-783.

[18] See http://whqlibdoc.who.int/publications/2010/9789241547963_eng.pdf.

B. Failure to Include a Finding of "Not Toxic" or "Not a Hazard" for Listed Hazard Traits Is a Flaw in the OEHHA Document

As mentioned above, the classification system described in the document fails to describe the finding of "not toxic" or "not a hazard" for any of the listed hazard traits. This is a serious omission. For many chemicals with large toxicity databases, a weight-of-the-evidence assessment may find that the chemical lacks certain specific toxicities, information that is useful for consumers. The OEHHA process includes the use of weight-of-the-evidence assessments but does not include identification of "not a hazard" or "not toxic". It is likely that there will be some chemicals with adequate, reliable toxicity data that will demonstrate that certain hazard traits are indeed lacking for that chemical. Information on a lack of toxicity and a hazard trait can be just as useful as information on which hazard traits exist for any given chemical.

C. OEHHA Should Use the Most Current Information on Chemicals for Assigning Hazard Traits and Classifications for Chemicals

Throughout section 4 of the document, OEHHA states that a chemical can be given a "Class One" or "Class Two" designation if "**one** or more of the following apply" (emphasis added), and then lists the criteria for each designation. This approach is not scientifically sound for all types of chemicals, specifically chemicals where there have been repeated assessments of certain hazard traits over decades and newer data developed has altered earlier assessments. Listing "one" as an option for assigning a hazard class suggests that a chemical could be labeled as "Class One" or "Class Two" based on an outdated assessment. The OEHHA document needs to address the issue of using the highest quality data, and the most up to date data and/or regulatory assessments when attempting to identify a hazard class for a chemical. If the most recent or current information or assessment is not being used, then the reasons for this decision must also be clearly described and discussed.

D. Identification of a Hazard Trait Class Based Solely on Data from Studies Using *In Vitro* Methods is not Scientifically Justified

The identification of a chemical as having a "Class Two" hazard trait based solely on data gathered using *in vitro* methods or structural/predictive models, for example as suggested for "carcinogenicity" on page 24 of the document, is not scientifically justified. As already discussed, this is because the state of the science of many *in vitro* screening assays is 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.[19] Including a ranking for a chemical hazard trait based solely on such data is not scientifically justified. It is well recognized in existing systems that there has to be a minimum standard of evidence for making conclusions about hazard. OEHHA needs to clearly identify how certain types of data should be weighed when assessing chemical hazards, recognizing that some types of data are less reliable than others even if they are developed by government organizations. This is particularly true in this instance where OEHHA is linking specific endocrine disruption pathway effects to cancer.

E. Guidance on Conducting Weight-of-the-Evidence Assessments Should Be Included in the Document

Weight-of-the-evidence assessment is the process outlined for use in the OEHHA document. Yet, the document currently gives no guidance for conducting weight-of-the-evidence assessments. Without such guidance, the document can be interpreted to suggest that a single assessment, regardless of its quality,

[19] See Rusyn, I. and Daston, G.P. 2010. *Environ. Health Perspect*. 118:1047-1050.

could be used to conclude that a chemical possess a specific hazard trait. It is likely that for many chemicals there will be multiple assessments available from a variety of sources. Specific discussion of how a weight-of-the-evidence assessment should be, and will be, performed is needed.

IV. Additional Comments

A. Particle Size Is Not Automatically a Hazard Trait

The identification of particle size as an automatic hazard is not scientifically robust ("Particle size or fiber dimension" on page 19). While respirable particles can enter the deep lung, exposure by itself does not automatically equate to an adverse event as the OEHHA document implies. ACC recommends that the language of this section be modified to acknowledge that size and/or dimension are only important if they lead to greater toxicity above and beyond what is observed in larger physical forms. It is inappropriate for OEHHA to assume (and communicate to potential TIC users) that size automatically equates those properties with a hazard. We also question why particle size/dimension is addressed again two pages later ("Nanomaterial hazard trait" on page 21) when the language on page 19 is clearly inclusive of nanomaterials.

ACC appreciates the opportunity to comment on OEHHA's pre-regulatory discussion draft of the structure and content of the TIC. We have serious concerns about the de novo approach OEHHA has chosen, the overstep of statutory authority in the classification of chemicals, and the significant and in many cases scientifically questionable deviation from well established, internationally agreed upon systems for describing chemical hazards. We strongly urge OEHHA to recommend a structure that allows existing information on chemicals to be utilized in order to more quickly and cost effectively fulfill its mandate under SB509.

Please feel free to contact me or Jay West on my staff (Jay_West@americanchemistry.com) if you have any questions.

Sincerely,

Michael P. Walls
Vice President
Regulatory and Technical Affairs

Cc: Linda Adams, Secretary, CalEPA
Cindy Tuck, Undersecretary, CalEPA
Patty Zwarts, Deputy Secretary for Policy, CalEPA
Patrick Sullivan, CalEPA
Joan Denton, Director, OEHHA
Maziar Movassaghi, Acting Director, DTSC
John Moffatt, Office of the Governor