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Legal, Government, Public Affairs

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Fran Kammerer
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1001 I Street
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RE: Green Chemistry Hazard Traits, Endpoints, and other Relevant Data, Pre-Regulatory Draft, August 10, 2010.

Dear Ms. Kammerer:

On behalf of Koch Industries, Inc. (KII) and its affiliate companies, we appreciate this opportunity to comment on OEHHA's Green Chemistry Hazard Traits, Endpoints, and other Relevant Data, Pre-Regulatory Draft, August 10, 2010 ("Draft"). KII owns a diverse group of companies involved in refining and chemicals; process and pollution control equipment and technologies; minerals; fertilizers; polymers and fibers; commodity trading and services; and forest and consumer products. Koch companies have a presence in nearly 60 countries with approximately 70,000 employees – over 1,400 of which are in California.

The Draft appears to be disconnected from the DTSC proposed safer alternatives regulations ("SAR"). The OEHHA regulations will be a critical launching point for the safer alternatives process, therefore, scrutiny needs to be employed in the development of applicable and definable hazard traits and endpoints in order to inform the SAR prioritization process. Below we list some of the overall concerns with the Draft. In addition, we have attached a document outlining technical concerns and suggestions related to specific Draft sections.

- The Draft lacks a prioritization process and therefore the regulations lack usefulness. The standard paradigm for usefulness is the grading of endpoints - both for environmental and human health. A guideline for ranking tests and support for endpoints is needed to make any type of evaluation of hazards useful; this important prioritization step is lost in the Draft. A weight-of-evidence approach must be incorporated into the draft. Weight-of-evidence will allow stakeholders to be confident in the studies and data relied upon in the complex DTSC safer alternatives process.
- Generally, it is unclear in the draft how the information described will be used. The stated objective of the draft is to evaluate and specify the hazard traits and environmental and toxicological end-points. However, there is no evaluation in the Draft and the hazard

traits and endpoints listed are not formally accepted/generally accepted by toxicologists as hazard traits or endpoints. Rather, much of what is listed in the draft are preludes in multiple-step pathways that may or may not lead to disease or an adverse outcome (i.e., these are actually mechanisms and not endpoints; examples include epigenetic adverse perturbations and electrophilic potential.). This will not further the Green Chemistry goals or provide the certainty necessary to make prioritization decisions or weigh chemical alternatives. SB 509 calls on OEHHA to “evaluate and specify the hazard traits and environmental and toxicological end-points ...that are to be included in the clearinghouse.” H&S Code §25256.1. The Department is required to establish the TIC to “provide a decentralized, Web-based system for the collection, maintenance, and distribution of specific chemical hazard trait and environmental and toxicological end-point data.” H&S Code §25256. The Draft does not indicate whether OEHHA has evaluated the various hazard traits and end-points and lacks specification necessary for DTSC to accomplish the goal of identifying “specific” hazard traits and end-point data necessary for the SAR prioritization process.

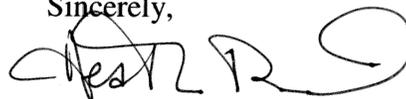
- Open scientific literature, as described in the Draft, may include research mainly conducted by a graduate student. Such studies and publications are generally small, may lack appropriate statistical rigor (e.g., n is small) and are not stringent enough to establish policy (e.g., lack of GLP guidelines). (Example: even articles in respected journals like Science have been retracted due to malfeasance.) Rather an *a priori* approach should be taken with more weight given to studies conducted by a well-qualified contract research organization (CRO) under GLP conditions. Examples of accepted study protocols include OECD and GLP. These reflect good evaluation work to determine data adequacies.
- *In silico* (computer simulation) QSAR is still in its infancy and has not been validated, therefore *in silico* should not be relied upon. All testing methods in the Draft should require validated methods. A priority for *in vivo* rather than *in vitro* should be established in the regulation.
- The draft does not address exposure potential. Rather, the draft lists *cause célèbre*. These are reports where the data supporting the effect is equivocal with regard to actually proving the affect using weight of evidence to people, animals, or plants. (Examples include: neurosensitization, mood disorders, lactational or transplacental transfer, particle size or fiber dimension, stratospheric ozone depletion potential, toxic environmental transformation.) Guidance for exposure potential is needed in the Draft in order to inform the DTSC process.
- As mentioned above, the Draft regulation generally fails to list priority for the different traits and endpoints. This is not consistent with current scientific practices in this area and results in a lack of utility in identifying the chemicals of highest concern.
 - For example, there is no discussion of endpoints that are relevant only to unique strains or strain/gender effects.

- A second example is the eco-risk section. The general paradigm for eco-risk is to look at increasing complexity of the biological assemblage as being of higher priority (individual < species < population < communities). Biology is quite variable and alternative cause is frequently observed. Interpretation of data must be pursued cautiously and seeming effect on an individual may result in no change in a population. This is even more the case at the biochemical level including hormones and specific lipo-proteins such as vitellogenin.
- Computational toxicology should not be so heavily relied upon in the draft. Computational toxicology eliminates dose all together from the analysis. This type of analysis results in "guilty by association" determinations, rather than on sound science.

The regulations fail to provide the basis for the Toxic Information Clearinghouse envisioned by SB 509. All that the regulations attempt to do is outline the different types of endpoints, hazard traits and precursors to hazard traits and endpoints. Due to this overly broad approach, every chemical would end up being listed in the database. This would thereby dilute the efforts of industry to use the database to select alternatives and would fail to achieve the goal of informing the public due to an overload of information without qualification or differentiation based on risk. This merely would be another database and redundant with other existing databases as outlined in the Green Chemistry Alliance comment letter. SB 509 intended DTSC and OEHHA to work together to establish a consumer friendly clearinghouse of information on chemicals to assist consumers and manufacturers with decision making. For the consumer, the clearinghouse must be easy to use and not require a science degree to decipher the information. It would be unwise and potentially negligent to simply dump information into the database intended to inform consumers without proper qualification of how to use the information as well as outlining the limitations of the information.

We respectfully submit these comments and look forward to working with OEHHA to develop regulations that result in useable data and a clearinghouse that will be useful and informative for California consumers.

Sincerely,



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Green Chemistry Hazard Traits, Endpoints, and other Relevant Data
Pre-Regulatory Draft, August 10, 2010
Specific Comments

Definitions

2.a. “Adverse effect.” An adverse effect should not include the ability to reduce an organism’s ability to respond to an additional environmental challenge. This can be influenced by a large number of factors, especially sleep, diet, and physical activity. Example: running or low-carbohydrate diets can cause a decrease in detoxifying enzymes, but running and diets are not considered to cause adverse effects.

2.c. “Authoritative Organization.” KII supports the proposal by the Green Chemistry Alliance in defining “authoritative organization”.

2.e. & f. “Class One” and Class Two”. The purpose or desired outcome for categorizing should be given.

2.j “Exposure Potential Characteristic.” The definition refers to significant human or environmental exposure. ‘Significant’ should be defined to provide clarity.

2.q. “Well Conducted Scientific Studies.” The definition refers to those studies “published in the open literature or accepted by a local, state, national or international government agency.” ‘Open literature’ may include research mainly conducted by a graduate student. Such studies and publications are generally small, may lack appropriate statistical rigor (e.g., n is small) and are not stringent enough to establish policy (e.g., lack of GLP guidelines). These studies should not be relied upon for setting policy because they are not conducted under stringent enough quality control standards. Rather an *a priori* approach should be taken with more weight given to studies conducted by a well-qualified contract research organization (CRO) under GLP conditions. Examples of accepted study protocols include OECD and OPPTS guidelines (EPA methodology). These reflect good evaluation work to determine data adequacies.

Specific Hazard Traits, and Endpoints and Other Relevant Data

3.a.i.2. Carcinogenicity. Benign neoplasia are by definition benign and should not be considered a hazard trait for purposes of the draft regulation.

3.a.i.3. Carcinogenicity – Other Relevant Data. It is unclear how the information listed in this section will be used. Will a weight-of-evidence approach be used? Also, some of what are listed are not toxic endpoints, but rather one step in a multiple-step pathway that may or may not result in an adverse effect (i.e., these are actually mechanisms and not endpoints).

3.a.ii.2. Cardiovascular Toxicity Endpoints. It is also unclear how the listed endpoints in this subsection will be used. Will a weight-of-evidence approach be used? Also, some of what are listed are not toxic endpoints, but rather one step in a multiple-step pathway that may or may not result in an adverse effect (i.e., these are actually mechanisms and not endpoints).

3.a.v.1. Endocrine Toxicity. Metabolic syndrome is a name for a group of risk factors that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes. Therefore, endocrine toxicity is a trigger, not an endpoint. These risk factors are due to poor diet (obesity) and lack of physical activity rather than anthropogenic chemical exposure. Thus, metabolic syndrome should be excluded from the list of endpoints for this hazard trait.

3.a.v.2. Endocrine Toxicity. The list of endpoints for this hazard trait includes adverse perturbations. It is unclear how OEHHA plans to use this term. Generally, adverse perturbations are defined as “an alteration of the function of a biological system, induced by external or internal mechanisms.” Perturbations are a preliminary step that may or may not lead to an adverse effect or toxic outcome. It is not an endpoint. The same analysis is applicable to all of the other steps listed in this subsection: “secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, metabolism, reproduction, development or behavior, and other interactions with hormone receptors or receptor processes to mimic, enhance or inhibit action of a natural hormone on the target organ system”.

3.a.vi. Epigenetic Toxicity. Epigenetic refers to mechanisms of control of gene activity during the development of complex organisms and is not an endpoint. All of the items listed in 1-3 are steps in a long pathway that may or may not lead to disease. Moreover, these events are normal and occur throughout the day, they do not often result in disease (i.e., adverse outcome or toxic endpoint).

3.a.vi.2. Epigenetic Toxicity. Our toxicologists have only seen these effects (toxicity in humans or animals associated with epigenetic mechanisms such as chemically induced DNA methylation) occur *in vitro*. Only *in vivo* data should be used for the purpose of evaluating the risks associated with chemicals.

3.a.vii. Genotoxicity. A weight-of-evidence approach should be taken. The two-year animal carcinogenicity study is considered the industry standard for evaluating this end point and should weigh more than an Ames assay. However, human data may weigh more than the animal studies.

3.a.vii.3 Genotoxicity. Electrophilic potential is basic chemistry, basically assigning a functional group as being toxic. Electrophilic potential should not be an endpoint.

3.a.viii.2. Immunotoxicity. “Changes in specific immunoglobulins with no obvious explanation” is not a toxic endpoint and should not be listed.

3.a.viii.3. Immunotoxicity. “Neurosensitization” syndrome is a syndrome of subjective discomfort and objective functional disability. It is not a diagnosis established by the medical community; rather it is hypothetical and may be psychiatric in cause.

3.a.x.3. Hepatotoxicity and digestive system toxicity. It is unclear how the information listed in this section will be used. Will a weight-of-evidence approach be used? Also, some of what are listed are not toxic endpoints, but rather one step in a multiple-step pathway that may or may not result in an adverse effect (i.e., these are actually mechanisms and not endpoints).

3.a.xi.2. Musculoskeletal toxicity. Fibromyalgia has not been demonstrated to be attributed to an anthropogenic chemical exposure and should not be included in the draft regulation.

3.a.xiii.2. Neurotoxicity. Altered neurochemical synthesis, storage, secretion, and uptake are not endpoints but rather part of a cascade of events that may or may not lead to an unfavorable outcome. This may also be affected by diet, exercise, sleep, etc. Furthermore, mood disorders are difficult to differentiate from an epidemiological association versus causation.

3.a.xvi. Reactivity in biological systems. This is a broad term covering a variety of mechanisms of action that may or may not lead to an adverse effect. This is a mechanism by which a toxic endpoint may be achieved.

3.a.xvii.2. Reproductive toxicity. Chemicals have not been proven to cause reproductive toxicity in humans by acting on the endocrine system at environmentally-relevant concentrations. Furthermore, “endocrine disruption” and “premature reproductive senescence” are mechanisms, and not endpoints.

3.a.xviii. Respiratory toxicity. Are the relevant data mentioned obtained from validated methods? OEHHA should consider following established testing guidelines (e.g., OECD) where testing is applicable.

3.a.xviii.3 Respiratory toxicity. Although this discussion is helpful, we note that fibrous nature of and by itself should not be considered toxic.

3.b. Environmental Hazard Traits. We are concerned with the lack of priority in this section and throughout the regulation. The current draft regulation’s listing of traits is not consistent with current prioritization practices and results in a lack of utility in identifying chemicals of highest concern. The regulation does not provide a discussion of endpoints that are relevant only to unique strains or strain/gender effects. As an example, for ecological-risk the general paradigm is to look at

increasing complexity of the biological assemblage as being of higher priority. Consequently, that leaves the priority at: individual < species < population < communities. Biology is quite variable and alternative cause is frequently seen. Interpretation of data must be pursued cautiously and seemingly effects on an individual may result in no change in a population. This is even more the case at the biochemical level including hormones and specific lipo-proteins such as vitellogenin.

3.b.i.1. Wildlife Survival Impairment. The definition of wildlife survival impairment refers to chemicals that "...significantly decreases the potential..." From a scientific perspective, it is better to measure survival, which is an endpoint, rather than what has been proposed which is not an endpoint.

3.b.i.2. Wildlife Survival Impairment. The endpoints listed for wildlife survival impairment should not include the same endpoints that were listed for humans. What is meant by "non-specific toxicity"? Are "behavioral impacts" toxic endpoints?

3.b.ii.2. Wildlife Reproductive Impairment. The "endpoints" listed in this subsection are mechanisms and not endpoints. Furthermore, many factors can affect wildlife reproductive impairment such as seasonal temperature variations. Caution should be taken with field studies to differentiate between association and causation. Furthermore, a weight-of-evidence approach should be taken with more weight given to controlled lab studies than field studies.

3.b.vi. Loss of Genetic Diversity, Including Biodiversity. Loss of genetic diversity and biodiversity is due to other endpoints and is not sensitive enough to be protective. This is more of a biological trait requiring extensive field study, rather than a hazard trait. It is unclear how to focus the impact on biodiversity of a single particular chemical.

3.b.vii. Eutrophication. Eutrophication is the result of excessive nitrogen or phosphorous loads to a water supply. Examples of sources of eutrophication include, but are not limited to, inadequate waste water treatment, agricultural use of fertilizer, etc. In the case of agriculture, the chemicals used in fertilizers are good for plants; it is the subsequent runoff that can cause concerns. Education to users of fertilizers and waste water treatment facilities as to safe practices to avoid eutrophication is needed, not regulation under this Draft as an endpoint to be evaluated for specific chemicals.

3.c Exposure Potential Hazard Traits. For the most part, the "endpoints" listed in this section are not actual exposure potential elements, but rather *cause célèbre*. These are hypothetical or academic and have not been proven to be occurring by chemical exposure or to negatively affect people, animals, or plants. We suggest listing actual exposure potential traits rather than these unproven elements.

3.c.iv. Global Warming Potential. Human-caused global warming is the subject of increasing scientific debate and, given the complexities regarding any correlation between a particular chemical that may be contained in a consumer product and any

proven impact on climate, is not an appropriate factor for OEHHA to consider at this time. Global warming potential does not equate to exposure and is not an end-point.

3.c.v. Lactational or Transplacental Transfer. Basically, any lipophilic chemical has the ability of a chemical substance to transfer from the mother's tissues into breast milk or across the placenta. However, this does not necessarily mean that such transfer is bad. Determining whether there is a concern with the transfer is a matter of dose. If OEHHA feels that this trait should remain, a standard or limit would have to be set for each chemical.

3.c.vi. Mobility in Environmental Media. Mobility in the environment is not necessarily of concern, in fact at times, mobility is a positive aspect of a chemical. This "hazard trait" is basically the contradiction to chemicals that exhibit higher bio-accumulation as a function of higher distribution (Kd) kinetics.

3.c.vi.2. Mobility in Environmental Media. Since even normal soil contains a certain amount of radioactive elements or isotopes, there needs to be a cutoff limit below which is acceptable.

3.c.vii Particle Size or Fiber Dimension Section. Size of and by itself should not be a factor for determining toxicity. The size of a particle or fiber may naturally be considered non-toxic by employing natural repair and protective mechanisms. This should not be considered a hazard trait.

3.c.viii.2. Persistence in Biota. How was 0.1% of their lifespan chosen for the half-life for species other than humans? OEHHA's consideration of the half-lives should be made transparent in order for stakeholders to understand why OEHHA selected this number.

3.c.ix. Stratospheric Ozone Depletion Potential. This is hypothetical and not ready for use in setting public policy.

Physical Hazard Traits

3.d.i. Explosivity. This hazard trait being used to prioritize chemicals would potentially have the effect of precluding fuels. OEHHA must provide some guidance as to what the intent is of listing these characteristics as hazard traits or endpoints.

4. **Sources and methodologies for identifying toxicological and environmental hazard traits.** OEHHA and DTSC should not rely upon open literature which was primarily conducted by students. Rather, OEHHA and DTSC should rely upon studies conducted by CROs under GLP conditions. We note that even articles in respected journals like *Science* have been retracted due to malfeasance. This section outlines Class One, Class Two, and Not Classifiable. There is currently no category that would accept a "safe" chemical. This should be added. *In silico* methods are still being developed and

not considered by the scientific community as being accurate. Furthermore, the methods have not been validated. The draft should require validated methods.

4.c Class One Hazard Trait. The bodies listed should not be the sole determinate as to whether a chemical should be listed as Class One.

- Proposition 65 listings have not been vetted for prioritization.
- The NIOSH Pocket Guide should not be used to prioritize chemicals because it is really a guidance document and is not designed for prioritization purposes.