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Re: Proposed Green Chemistry Toxics Information Clearinghouse Identification of Hazard Traits, Endpoints and Other Relevant Data for Inclusion in the Toxics Information Clearinghouse

Dear Fran Kammerer:

The Dow Chemical Company (Dow) appreciates the opportunity to comment on the proposed regulation for Green Chemistry Toxics Information Clearinghouse Identification of Hazard Traits, Endpoints and Other Relevant Data for Inclusion in the Toxics Information Clearinghouse (chapter 54 to division 4.5 of Title 22).

Dow is a diversified company with a portfolio of specialty chemical, advance materials, agrosciences and plastics businesses. Dow delivers a broad range of technology-based products and solutions to customers in approximately 160 countries and in high growth sectors such as electronics, water, energy, coatings and agriculture. Dow both manufactures and imports products and raw materials that are in the scope of the proposed regulation. Dow is a leader in helping to shape chemicals management improvements across the globe. Our commitment to the Green Chemistry Initiative has been evident from the very beginning with Dow's engagement on the Science Advisory Panel and our current representation on the Green Ribbon Science Panel. Further, Dow has more presidential green chemistry challenge awards than any other company. Dow is a strong advocate for regulatory and voluntary initiatives which will enhance public health and environmental protection, promote innovation while still respecting confidential business information, and further the principles of sustainable development.

Dow has a 75 year history of maintaining a premier Toxicology and Environmental Research and Consulting (TERC) function whose vision is "*To be the most respected and valued leader in the science and practice of chemical safety assessments*". TERC's highly qualified professionals help guide the safe use of Dow products by providing Dow businesses with technical consulting, testing and research services that span more than 15 different areas of scientific expertise. Externally, TERC contributes to the science of product safety assessment by regularly publishing in peer review journals, presenting at scientific meetings, serving on Science Advisory Boards, holding academic appointments and by serving on Editorial Boards making TERC a recognized leader in the science and

practice of chemical safety assessment both within and outside The Dow Chemical Company. This body of experts has come together to also provide insight and technical review of the proposed regulation relative to hazard traits and endpoints.

General Comments

OEHHA should be complimented on its careful review and inclusion of standard guidance, definitions, criteria and practices from other authoritative bodies globally and from standard toxicology textbooks into its Green Chemistry Hazard Trait Regulation. The draft regulation is well written and technically accurate. However, significant uncertainties and deficiencies related to the Hazard Trait Framework remains that OEHHA has failed to address in its second draft of the regulation.

The proposed regulation goes beyond the authority provided for in the statute.
The enacting legislation, SB 509 (Simitian, 2008), requires "the Office of Environmental Health Hazard Assessment (OEHHA) to evaluate and specify the hazard traits and environmental and toxicological endpoints and any other relevant data that are to be included in the clearinghouse." This directive is simple and clear; however, OEHHA has proposed a new California-only system where hazard information for a given substance is classified as either "strong" or "suggestive" evidence for assigning a hazard trait. OEHHA does not have the regulatory authority to implicate a substance as having a particular hazard trait or not. This is an authority granted to DTSC as it carries out the chemical prioritization process and identifying chemicals of concern. The current framework needs to be revised and refocused to provide the basic scientific information in the Toxic Information Clearinghouse (TIC) needed by DTSC and others to quickly identify and move towards replacing chemicals of highest concern in consumer products in California.

Embedded within this effort is the need for a balanced approach that considers positive and negative data. The strength of evidence relied upon depends on looking at both. Without considering both, the format proposed by OEHHA is skewed. OEHHA's Hazard Trait Framework must provide information that will allow DTSC to implement a weight of evidence approach considering both the positive and negative evidence that may be available about substances under evaluation in the TIC.

Other overarching and recurring issue
The overarching and recurring issue seems to be focused on how the information in the draft regulation will be used. It is generally unclear and disconnected from the DTSC proposed regulations and DTSC's vision for the Toxics Information Clearinghouse (TIC). The OEHHA regulations will be a critical launching point for the safer alternatives process, in particular; therefore, scrutiny needs to be employed in the development of applicable and definable hazard traits and endpoints, including the type/format of information contained in the TIC, in order to inform the prioritization and alternative assessment process.

In the standard practice of conducting chemical safety assessments, the most sensitive toxicological endpoint, in the most sensitive test species is used as a point of departure for risk characterization and risk management. DTSC will face an added complexity in the prioritization process -- how to conduct comparative assessments between chemical hazard profiles. Under the current draft framework, all substances are likely to be identified as having one or more hazard traits. For this reason, other factors will become important to the prioritization process (i.e. the presence or absence of a hazard trait alone will not inform which hazard profiles for specific chemicals should rise to a higher level of concern over others). Thus, the TIC must contain information in a format that will inform DTSC in assessing "relative" hazards between substances.

For example, in the framework outlined by OEHHA one could imagine the following very simple scenario where the TIC reports Hazard Traits for Chemicals X, Y and Z that give the following hazard profiles:

Hazard Trait	Chemical X	Chemical Y	Chemical Z
Toxicological			
Respiratory Tox	Strong evidence		
Genotoxicity			Suggestive evidence
Environmental			
Eutrophication		Strong evidence	
Exposure Potential			
Mobility in environmental media			Strong evidence
Physical			
Flammability	Strong evidence		

Referring to the above example begs a number of important questions on how DTSC will use the information in the TIC and whether or not it provides sufficient details in the data elements needed to discriminate and prioritize one chemical hazard profile over the other. How will data within a major category be weighed in the evaluation process (e.g. is genotoxicity of higher concern than respiratory toxicity)?. How will data between the 4 major categories by weighed in the prioritization process (e.g. toxicological vs. environmental vs. exposure potential vs. physical)? Surely toxicological profiles between chemicals will vary substantially and be considerably more complex than highlighted in the above example. These differences will drive the need to consider and weigh other important supporting information in order to effectively prioritize chemicals and identify those chemicals of highest concern. The Hazard Trait framework as proposed has significant short comings that will render it inadequate for the proposed use by DTSC in the chemical prioritization process and for alternatives assessments.

Specific areas of concern, previously raised by Dow, include:

1. Clarity on the purpose of the TIC. It is impossible to design an effective database without a clear understanding of its purpose. The purpose dictates the architecture, data format and information requirements. Without a clear understanding of who will use the database and how, OEHHA is at high risk of developing an ineffective tool that in the end, may impede the regulatory process because it was inadequate to effectively prioritize chemicals of concern and identify suitable chemical alternatives. The TIC will form the foundation for the regulatory process and therefore warrants OEHHA to coordinate more closely with DTSC to develop an effective framework.

2. Process for evaluating Hazard Traits across substances. Related to the point above, a substance will likely be determined to have more than one hazard trait. Similarly, the pattern of hazard traits will vary among chemicals. How will hazard traits be ranked or prioritized in relative importance for the overall assessment process (e.g. what is the process for prioritization when one chemical is high for a human health endpoint and another is high for excotoxicity or phy/chem. properties)? OEHHA and DTSC need to consider how to evaluate the relative concern for Hazard Traits between substances and whether or not other key data elements should be built into the TIC.

3. Leveraging existing systems and information. The new California-only system is inefficient, duplicative, and will make it unnecessarily difficult to leverage existing information on chemicals. OEHHA and DTSC must coordinate more effectively to evaluate and identify opportunities to align the TIC framework to other existing frameworks in use today (e.g. OECD IUCLID). This includes re-examining the structure of the Hazard Traits and associated endpoints to conform to national and international hazard categories already in place. While it's true that many standard toxicology textbooks devote entire chapters to individual endpoints, the "systems" approach is used in textbooks because it's an effective teaching method – function follows form. Routine hazard identification does not follow a system-by-system approach. Non-standard approaches, as proposed by OEHHA, will only slow the development of the TIC database and require substantial agency effort to convert the information to the unique California system, both initially and on an ongoing basis.

4. Expansion of the information stored in the TIC to include data that support "no evidence" for a hazard trait and "no relevant information". Knowledge of negative data and/or where there is a lack of data play a critical role in determining the relative level of concern between chemicals. Additionally, thresholds for effects, routes of exposure for effects, strengths/weaknesses of the data (addressed in greater detail below) are important data elements in comparing the hazard profile of one chemical to another. The Hazard Trait Framework needs to be revised to include ALL relevant information for a hazard trait. Included in this point is the need to gather further input by DTSC and other relevant users of the TIC on what these elements might be.

5. Alternative Test Methods. The Hazard Trait regulation needs to be amended to convey the following: *Where data from multiple test methods already exist* for a chemical, the use of data derived from alternative test methods in the evaluation of a substance Hazard Trait needs to take into account its intended application. Only a

limited number of tests exist as replacement alternatives. If the alternative test method is not accepted as a fully validated replacement to an animal study then it is a preliminary screening study. In the case where the alternative test method is a preliminary screening assessment (e.g. computer-based structure-activity databases, physical property evaluations, preliminary exposure assessments, in vitro assays and short-term toxicity screens involving small numbers of animals) AND higher tiered *in vivo* animal data are available, results of data from higher-tiered *in vivo* animal studies should supersede the results from preliminary screening assessment studies.

Where data gaps are identified, it is generally accepted that the development and use of methods limiting or replacing the use of animals in some toxicity evaluations will be necessary in future hazard assessment programs. This is driven by the need to meet the demands of filling hazard data gaps while using fewer animals. We actively support the development and use of alternative test methods that are scientifically credible and acceptable as long as the limitations of the test method are clearly acknowledged (i.e. preliminary screening method). In these instances, data from these test methods alone are insufficient to conclude that the chemical has that hazard trait.

6. Data Reliability. The draft Hazard Trait regulation needs to incorporate some method for assessing the reliability of data in evaluating the hazard trait of a chemical. The quality of the study, the method, the reporting of the results, and the conclusions that are drawn, must be evaluated carefully. Reasons why existing study data may vary in quality include the use of outdated test guidelines, the failure to characterize the test substance properly (in terms of purity, physical characteristics, etc.), the use of crude techniques/procedures that have since become refined, and the fact that certain endpoint information, now recognized as being important, may have not been recorded or measured. Moreover, other reasons could be poor reporting of information and poor quality assurance.

   The use of such scoring tools, e.g. *Klimisch codes*,(described in greater detail later) allows ranking the information, and organizing it for further review. This implies focusing on the most relevant information, taking into account the endpoint being measured or estimated. The evaluation of the reliability is performed considering certain formal criteria using international standards as references. The scoring of information, e.g. according to Klimisch codes, should not exclude all unreliable data from further consideration by expert judgement because of possible pertinence of these data related to the evaluated endpoints. However, by scoring information for reliability it reduces the probability that a hazard assessment would be based solely on low-reliability or unreliable data.

Specific Comments
§ 69401.2 (e) General

Page 14 - OEHHA responded that the proposed regulation does not include provisions for addressing dose-response relationships because DTSC's regulation incorporates dose-

response information in prioritizing chemicals of concern and in alternatives analysis. Again, this is an example of where more coordination is required between DTSC and OEHHA to clarify what information will be required to be included in the TIC. Where will DTSC get dose-response information for data used in the assignment of a hazard trait if not from the TIC? Will DTSC be required to conduct a separate review of the hazard data in order to obtain this information? If so, this would be a tremendous waste of time and resources when OEHHA will be reviewing these data to assign hazard traits and could include such information at the time of its assessment.

§ 69401.2(i) General

The proposed regulation defines "well-conducted scientific studies" as studies that are published in the open literature or are unpublished but submitted to governmental or regulatory agencies. This definition is too broad and does not ensure that all studies fitting these criteria are valid for making hazard assessments. The quality of the study, the method, the reporting of the results, and the conclusions that are drawn, must be evaluated carefully.

Klimisch *et al* (1997)[1] developed a scoring system to assess the reliability of data, particularly from toxicological and ecotoxicological studies, that may be extended to physico-chemical and environmental fate and behaviour studies. This system built upon existing guidance produced by the European Commission (EU 1994[2], 1995[3]) and the considerations on the assessment of the quality of data used today in the US and OECD HPV programme (OECD 1994[4]). The system uses 4 reliability ratings:

1 = reliable without restrictions: *"studies or data [...] generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline [...] or in which all parameters described are closely related/comparable to a guideline method."*

2 = reliable with restrictions: *"studies or data [...] (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."*

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[1] H.-J. Klimisch, M. Andreae, and U. Tillmann (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicology and Pharmacology **25,** 1–5

[2] EU (1994). European Commission, Directorate—General Environment, Nuclear Safety and Civil Protection: Risk Assessment of Existing Substances, Technical Guidance Document (XI, 919/94- EN).

[3] EU (1995). European Commission: Risk Assessment of New and Existing Substances; Technical Guidance Document Draft October.

[4] OECD (1994). Revised Draft SIDS Manual (OECD Secretariat) EXCH, Manual 9405 DOC July.

3 = not reliable: *"studies or data [...] in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. unphysiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."*

4 = not assignable: *"studies or data [...] which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."*

The use of such scoring tools, e.g. the mentioned *Klimisch codes,* allows ranking the information, and organizing it for further review. This implies focusing on the most relevant information, taking into account the endpoint being measured or estimated. The evaluation of the reliability is performed considering certain formal criteria using international standards as references. The scoring of information, e.g. according to Klimisch codes, is not intended to exclude all unreliable data from further consideration by expert judgement because of possible pertinence of these data related to the evaluated endpoints. However, by scoring information for reliability it reduces the probability that a hazard assessment would be based solely on low-reliability or unreliable data.

In general, some types of data that are not reliable (i.e. those where insufficient documentation exist for making an assessment) and data for which it is not possible to assign reliability may only be used as supporting data.

For many existing substances, at least some of the available information could have been generated prior to the requirements of GLP and the standardization of testing methods. While such information may still be usable, both the data and the methodology used must be evaluated in order to determine their reliability. Such an evaluation needs evidence based decision making following established criteria and must be transparent to justify the use of a particular data set.

The following are key points that an assessor should consider when evaluating data reliability:

- The purity/impurities and origin of the test substance, as well as the reference substances, must be reported;
- The availability of the raw data from the study
- There must be an adequate description of the study e.g. a complete test report, or a sufficiently detailed description of the test procedure, which must be in accordance with generally accepted scientific standards. In these cases, the information may be considered reliable;
- When the test procedure used to generate the test data is found to differ significantly from that described by the recognized test method or generally accepted scientific standards, or the reliability of the data cannot be established fully, the assessor must decide if and how the information can be used, e.g. as supporting information where a reliable study already exists.

- The following factors, inter alia, can be used to support the view that these data may be acceptable for use in a robust hazard assessment:
    - there are other studies or calculations available on the substance, and the data under consideration are consistent with them,
    - other studies are available, for example on isomers with similar structure activity profile, homologues, relevant precursors, breakdown products or other chemical analogues, and the data under consideration are consistent with them,
    - an approximate value is sufficient for taking a decision on the endpoint of interest for the conclusion required for the hazard assessment;
- Where critical supporting information is not reported (e.g. species tested, substance identity and dosing procedure) the test data should be considered to be unreliable.

In principle, the same criteria apply to test data reported in the published literature; the extent of the information provided will provide the basis for deciding upon the reliability of the data reported. It is not appropriate to assume that peer-reviewed publications or data previously submitted to governmental agencies for regulatory purpose are reliable in all cases.

Good Laboratory Practices- OEHHA cites limitation of GLP in that the standard is not able to keep up with the evolving science and that when strictly applied; they exclude from consideration important human health data. GLP on the contrary, is a standard that is independent of the evolving science and are not intended to exclude relevant data important in the hazard assessment process. GLP is another measure that ensures the reliability and transparency of the data used to make important evaluations of a chemicals hazard to human health and the environment. It is not meant to ensure proper conduct of a study. That is the role of standard regulatory test guidelines.

Adoption of GLP does reduce the likelihood that results from a study are affected by confounding factors or unethical practices thus increasing reliability of the study results. For example, the requirement for analytical characterization of a test material provides evidence that observed adverse effects are not attributed to an unknown impurity in the test substance and allows one to be confident that from study to study the same test substance was evaluated. The requirement for dose-confirmation of the chemical in the test matrix confirms that the dose as specified was delivered in the test system. It rules out the possibility of mixing errors, stability issues, or testing of the wrong chemical. The requirement to document experimental endpoints from raw data capture through all data evaluations means that one can confirm the accuracy and validity of the results and ultimate interpretation of a study. As discussed above in the section on Klimisch codes, a study conducted according to GLP increases the reliability of the information for use in the hazard assessment. It does not exclude the use of data from other sources not conducted under GLP. As such, data conducted according to GLP should be given a higher reliability rating that those that were not.

§ 69402.3 Developmental Toxicity

Summary of Comments Relating to Developmental and Reproductive Toxicity Hazard Traits Proposed Regulations

The supplemental information section is principally sound; however, there are several opportunities for strengthening these documents that are detailed below. Overall, a significant loss of context occurred between the supplemental information and proposed regulation that inappropriately weights alternative methods of hazard identification (QSAR, cell-based assay, etc) equal to guideline studies designed to identify reproductive and developmental toxicants. Additionally, the proposed regulation provides no allowances for exposure and is based simply on hazard. Lastly, the document contains sections that will allow for developmental or reproductive toxicity labeling based on 'suspicions' of effect and in the absence of direct supporting data.

Detailed Comments Relating to Developmental and Reproductive Toxicity Hazard Traits Proposed Regulations

§ 69402.3 Developmental Toxicity

(a) The developmental toxicity hazard trait is defined as the occurrence of adverse effects on the developing organism following exposure to a chemical substance prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Developmental toxicity occurs during the postnatal period only if the developing organism shows greater quantitative or qualitative susceptibility to the chemical substance than does the adult organism.

The supplemental information cites the EPA's 1991 Developmental Toxicity guideline for risk assessment as reflecting "current basic understandings of developmental toxicity". What is missing from this information is the relevance of exposure to developmental toxicity. A recent ILSI-HESI sponsored publication by academic, government and industrial developmental toxicologists highlights the importance of considering the exposure ("agent at a stated internal dose with stated timing") leading to a permanent adverse effect (Daston et al., 2010, Birth Defects Research, Part B 89: 526-530). Furthermore, toxicokinetics should be considered, when available, in defining developmental toxicity. Several examples exist (e.g., ethylene glycol-induced rodent developmental toxicity) to demonstrate that high bolus doses can result in non-relevant modes of action causing developmental toxicity due to altered toxicokinetics.

(b) Endpoints for developmental toxicity include but are not limited to those indicating: death of the developing organism, structural abnormality, altered growth, functional deficiency or other adverse effect on the developing organism. These observations in animals or humans can be manifested at any point in the lifespan of the organism or its offspring.

The supplemental information describes variations, but does not provide examples of transient or non-adverse variations, or situations where a variation is secondary to maternal toxicity (e.g., fetal body weight or ossification delays that are secondary to

maternal body weight effects, or altered toxicokinetics). The literature on developmental toxicity effects secondary to maternal toxicity are well established and widely accepted (Carney and Kimmel, 2007, Birth Defects Research, Part B 80: 473-496). Such examples should be included to encourage providing a weight of evidence approach towards considerations of developmental toxicity.

(c) Other relevant data (insert - that may contribute to a weight of evidence evaluation for potential developmental toxicity) include, but are not limited to: mechanistic data at the molecular level such as genotoxicity or epigenetic toxicity, or at the cellular, organ, or organism level; structural or mechanistic similarity to other chemical substances with the developmental toxicity hazard trait.

Suggest addition of underlined section above in (c). There are currently no clearly established examples of "epigenetic toxicity". Reference to epigenetic toxicants seems out of place in this document and should be removed for the developmental toxicity hazard trait section.

§ 69402.4 Evidence for Developmental Toxicity Hazard Trait
(a) Each of the following constitutes strong evidence of developmental toxicity for a given chemical substance:

(1) Identification as known to the state to cause reproductive toxicity with developmental toxicity denoted as an endpoint in Title 27, California Code of Regulations, section 27001.
(2) Meeting the National Toxicology Program criteria as having clear or sufficient evidence of adverse effects for developmental toxicity, or the equivalent.
(3) Meeting the criteria for being classified as Category 1, known or presumed human reproductive toxicant based on developmental toxicity data under the United Nation's Globally Harmonized System for Classification and Labeling.
(4) Identification in the National Institute for Occupational Safety and Health's Pocket Guide to Chemical Hazards as having teratogenic or other developmental effect.
(5) Identification as a known or potential developmental toxicant or having the capacity to cause developmental toxicity, or the equivalent, in a (:any? Or a specific one?) report published by the National Academy of Sciences' National Research Council or Institute of Medicine.
(6) Identification as having sufficient evidence of carcinogenicity by the International Agency for Research on Cancer, with a clear statement that the chemical substance induces transplacental carcinogenesis noted in an IARC Monograph on the Evaluation of Carcinogenic Risks to Humans.
(7) Recognition by California, other states, the United States or other nations of the chemical substance posing a developmental toxicity hazard.

As written, most of these criteria do not take exposure into account for a risk assessment but are only hazard-based criteria supported by inclusion of a chemical on a regulatory list. Clearly, the authorities who make these designations or lists are not always well-informed of the technical relevance or reality of including substances on such regulatory

lists. OHEEA must spell out provisions for critically evaluating information and decisions derived from such lists, thereby avoiding the propagation of errors made by other "authorities".

(b) Each of the following constitutes suggestive evidence *(insert: and/or potential)* of developmental toxicity for a given chemical substance:
(1) Meeting National Toxicology Program criteria as "some evidence of adverse effects," "limited evidence of adverse effects," or the equivalent for developmental toxicity.
(2) Identification as having limited evidence of carcinogenicity by the International Agency for Research on Cancer, with a clear statement that the chemical substance may induce transplacental carcinogenesis noted in an IARC Monograph on the Evaluation of Carcinogenic Risks to Humans.
(3) Recognition as a suspected developmental toxicant, or the equivalent, by California, other states, the Federal government or other nations.
(4) Strong evidence for the Genotoxicity Hazard Trait per section 69403.5 or the Endocrine Toxicity Hazard Trait per section 69403.3 with mechanisms of genotoxicity or endocrine disruption likely to be involved in developmental toxicity.
(5) Strong indications from "supportive studies," as described by the National Toxicology Program, indicating possible developmental toxicity.
(6) Mechanistic evidence that is suggestive of developmental toxicity potential, from cell-based, tissue-based or whole organism-based assays showing perturbations of known physiological, biochemical or other pathways involved in developmental toxicity.
(7) Strong indications of developmental toxicity from structure activity relationships, (including but not):suggest taking out portion in parentheses limited to those from validated Quantitative Structure Activity Relationship models.

Many of these criteria are not based on the best available science. For example, b(3) states "recognition as a suspected developmental toxicant" without any explanation or clarification as to what or whom deemed something 'suspected'. In addition, b(4) states that genotoxicity or endocrine toxicity with a mechanism likely involved in developmental toxicity (implied as not having direct data) would mean it would receive a developmental toxicity label. These criteria are classification by association without direct evidence of developmental toxicity, are not driven by science and should be removed from the regulatory text.

Finally items #6 and 7 greatly over exaggerate the state of the science for alternative methods for correctly identifying developmental toxicants. The reality is that these tools have distinct limitations in their ability to predict developmental toxicity and should not be used **in the absence** of other clear direct data to label a molecule as a developmental toxicant.

Need to include limitations dictated in the supplemental information to clarify that at this time QSARs are not reliable for predictions of developmental toxicity. No QSAR model currently available adequately predicts developmental toxicity, owing to the complex nature of development and the multiple interrelated pathways involved. Rather QSAR

data should only be used in a weight of evidence based approach in the context of additional data.

§ 69402.5 Reproductive Toxicity

(a) The reproductive toxicity hazard trait is defined as the occurrence of adverse effects on the reproductive system or reproductive function of females or males following exposure to a chemical substance.

(b) Endpoints of reproductive toxicity include, but are not limited to, adverse alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes; adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, or lactation; developmental toxicity, premature reproductive senescence, or other modifications that compromise the integrity of the reproductive system or reproductive function in animals or humans.

(c) Other relevant data insert:that may contribute to a weight of evidence evaluation for potential reproductive toxicity include but are not limited to: data on endocrine disruption, genotoxicity, in vitro measures of the capacity of a chemical to damage the function or structure of germ cells such as sperm or oocytes or cells critical for reproductive function, such as Sertoli and Leydig cells in males; structural or mechanistic similarity to other substances exhibiting the reproductive hazard trait.

§ 69402.6 Evidence for Reproductive Toxicity Hazard Trait

(a) Each of the following constitutes strong evidence of reproductive toxicity for a given chemical substance:

(1) Identification as known to the state to cause reproductive toxicity with male or female reproductive toxicity or both denoted as an endpoint in Title 27, California Code of Regulations, section 27001.

(2) Meeting the National Toxicology Program criteria as having clear or sufficient evidence of adverse effects for reproductive toxicity, or the equivalent.

(3) Meeting the criteria for being classified as Category 1 for "known or presumed effects on human reproduction or on development" based on male or female reproductive toxicity data under the United Nations' Globally Harmonized System for Classification and Labeling of Chemicals.

(4) Identification as a known or potential male or female reproductive toxicant or both or having the capacity to cause reproductive toxicity in a report by the National Academy of Sciences' National Research Council or Institute of Medicine.

(5) Identification in the National Institute for Occupational Safety and Health ("NIOSH") Pocket Guide to Chemical Hazards with having reproductive organs as the target organ or as having sterility or other reproductive effects.

(6) The chemical substance is recognized as a male or female reproductive hazard by California, other states, the United States or other nations.

As written, most of these criteria do not take exposure into account for a risk assessment but are only hazard-based criteria.

(b) Each of the following constitutes suggestive evidence *insert:and/or potential* of reproductive toxicity for a given chemical substance:
(1) Meeting the National Toxicology Program criteria as having "some evidence of adverse effects" "limited evidence of adverse effects," or the equivalent, for reproductive toxicity.
(2) Recognition as a suspected reproductive toxicant, or the equivalent, by California, other states, the United States or other nations.
(3) Strong (insert:based upon the supplemental information the word strong should be moved to #4) evidence for the Genotoxicity Hazard Trait per section 69403.5 or the Endocrine Toxicity Hazard Trait per section 69403.3 with mechanisms of genotoxicity or endocrine disruption likely to be involved in reproductive toxicity.
(4) Supportive studies, as defined by the National Toxicology Program, indicating possible male or female reproductive toxicity.
(5) Mechanistic evidence that is suggestive of reproductive toxicity potential, from cell-based, tissue-based or whole organism-based assays showing perturbations of known physiological, biochemical or other pathways involved in reproductive toxicity.
(6) Strong indications of reproductive toxicity from structure activity relationships, (including but not):suggest taking out portion in parentheses limited to those from validated Quantitative Structure Activity Relationship models.

As before in the developmental toxicity hazard trait section, many of these examples are not based on the best available science. For example, b(2) states "recognition as a suspected reproductive toxicant" without any explanation or clarification as to what or whom deemed something 'suspected'. In addition, b(3) states that genotoxicity or endocrine toxicity with a mechanism likely involved in reproductive toxicity (implied as not having direct data) would mean it would receive a reproductive toxicity label. These criteria are classification by association without direct evidence of reproductive toxicity and not driven by science.

Finally items #5 and 6 over exaggerate the state of the science for alternative methods for correctly identifying reproductive toxicants. The reality is that these tools have distinct limitations in their ability to predict male or female reproductive toxicity and should not be used **in the absence** of other clear direct data to label a molecule as a reproductive toxicant.

Need to include limitations dictated in the supplemental information to clarify that at this time QSARs are not reliable for predictions of reproductive toxicity. No QSAR model currently available adequately predicts reproductive toxicity, owing to the complex nature of reproduction and the multiple interrelated pathways involved. Rather QSAR data should only be used in a weight of evidence based approach in the context of additional data.

§ 69403.3: Endocrine Toxicity
69403.3 (a). The endocrine toxicity hazard trait is defined as the occurrence of adverse effects following exposure to a chemical substance on the structure or function of the endocrine system, including endocrine disruption and metabolic syndrome.

In the supplemental information OEHHA states: *Subsection 69403.3(a) defines the endocrine toxicity hazard trait. The definition includes the full range of adverse effects on endocrine health that may result from chemical exposures, including endocrine disruption. The hazard trait is based on descriptions of endocrine toxicity and disruption used by the U.S. Environmental Protection Agency, the European Union[187], and in standard toxicology texts.[188]*

Currently, The Dow Chemical Company defines endocrine disruption as: *"An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function."* - European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife (Weybridge, UK; 1996). European Union Report EUR17459.

OEHHA should be complimented on including the word "adverse" in their definition of endocrine toxicity as this is omitted in most regulatory endocrine communications. However, OEHHA expands endocrine toxicity from being primarily an event that affects reproductive endpoints to also include "metabolic syndrome" or metabolic disruption. OEHHA, in this document, is attempting to link exposure of endocrine disrupting compounds (EDCs) with several disorders that include high blood pressure, insulin resistance, obesity, and increased blood levels of low density lipoprotein (bad cholesterol). The commonly accepted causes of metabolic syndrome are genetics, insulin resistance, obesity, lifestyle, and age. In the supplemental information given for section 69403.3(a) page 58, OEHHA states they used definitions of endocrine toxicity and disruption used by the U.S. Environmental Protection Agency, the European Union, and in standard toxicology texts (Chapter 21: Casarett and Doull's. 2008). In none of these references, is endocrine disruption linked with metabolic syndrome. Furthermore, evaluating synthetic chemical disruption of the endocrine system is extremely difficult and is why the US EPA has focused on the estrogen, androgen, and thyroid (EAT) hormone systems. The reference to the link between endocrine disruption and metabolic syndrome should be deleted from the regulatory text.

69403.3 (b) Endocrine toxicity endpoints include but are not limited to those indicating: adverse effects on endocrine organs; adverse perturbations of the synthesis, secretion, transport, binding, action, or elimination of natural hormones or their receptors in the body that are responsible for the maintenance of homeostasis, metabolism, reproduction, development or behavior.

In the supplemental information OEHHA states: *Subsection 69403.3(b) provides general toxicological endpoints for the endocrine toxicity hazard trait. Endocrine toxicity endpoints include observations of adverse effects on endocrine organs. The general endpoints named include those named in standard texts, which describes a variety of endpoints that would fit into this general category, for the pituitary, adrenal cortex, adrenal medulla, thyroid, parathyroid, ovary and testis. It also includes endpoints based on the definition of endocrine disruptor in the scientific literature[189] and used by U.S. Environmental Protection Agency.[190]:*

"An exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development and or behavior."

The OEHHA definition of endocrine toxicity in this section is too ubiquitous, even with the term "adverse" given to qualify the statement. For example, high doses of any chemical will lead to adverse disruption of homeostasis and metabolism. This is not necessarily due to any endocrine insult, but simply the nature of high dose overt toxicity. If such hazard data were submitted, due to the overarching and inclusive nature of this definition, it could be classified as endocrine toxicity. We recommend that OEHHA employ the US EPA strategy of using EAT endpoints to evaluate endocrine toxicity.

69403.3 (c) Other relevant data include but are not limited to: binding of a chemical substance or its metabolites to hormones or hormonal receptors or inhibition of hormone synthesis in vitro experimental models; induction of hormone metabolic enzymes; modulation of genes involved in metabolic syndrome; structural or mechanistic similarity to other chemical substances with the endocrine toxicity hazard trait.

In the supplemental information OEHHA states: *Subsection 69403.3(c) identifies other relevant data for the endocrine toxicity hazard trait. These data in and of themselves would typically not provide strong evidence of the endocrine disruption hazard trait but would support such findings and could provide suggestive evidence. (See discussion of Evidence for Toxicological Hazard Traits below at page 91). Other relevant data include results of studies on receptor binding, computational approaches and in vitro studies that are used by the U.S. Environmental Protection Agency, in academia and by various authoritative organizations to explore the potential of a chemical to cause endocrine disruption.*

This is a straight forward approach but lacks a weight of evidence evaluation. Unfortunately, EPA has yet to create a weight of evidence approach for endocrine disruption. The OEHHA document does not address whether a weak estrogen receptor binding assay result would result in a compound being evaluated as endocrine toxic. With metabolic disruption being an ill-defined and multifaceted syndrome, it is premature to evaluate its cause as being solely or even contributed to by synthetic chemicals. Againg, we suggest that all mention of metabolic syndrome and metabolic disruption be removed from this document until such time that a clear relation between it and EDCs has been established in the peer reviewed scientific literature.

§ 69403.4: Epigenetic Toxicity

69403.4 (a). The epigenetic toxicity hazard trait is defined as changes, at the cellular or organism level, in gene expression or gene function that do not involve changes in the DNA sequence, following exposure to a chemical substance.

In the supplemental information OEHHA states: *Subsection 69403.4(a) defines the epigenetic toxicity hazard trait. The definition is adapted from the definitions for epigenetics used by a number of research groups and institutes throughout the world. For example, the Epigenome Network of Excellence (NoE), a European consortium consisting of 81 research groups, defines epigenetics as:*
"The studies of heritable changes in gene function that occur without a change in the sequence of nuclear DNA and the processes involved in the unfolding development of an organism." [191]

Similarly, the Epigenomics Program at the National Institutes of Health describes epigenetics as: "An emerging frontier of science that involves the study of changes in the regulation of gene activity and expression that are not dependent on gene sequence."
For the purposes of its program, National Institutes of Health further states that:

> *"Epigenetics refers to both heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable."*[192]

The broad definition of epigenetic toxicity in the proposed regulation identifies epigenetic changes resulting from exposure to chemicals and permits flexibility in recognizing new endpoints that are emerging from ongoing dynamic research in epigenetics or epigenetic toxicology.

The definition of epigenetic toxicity needs to emphasize that epigenetic changes are a part of normal cellular function and development. Complex epigenome interactions need to be fully understood before defining an epigenetic toxicity-related change. The normal state and dynamic variation of the epigenome differs between cells, tissues, developmental stage, age, and varies over time. The current definition is too broad and needs revision because it does not distinguish toxicant-induced from normal epigenetic alterations; hence any change in the epigenome would be considered "toxicity".

69403.4 (b) Epigenetic toxicity endpoints include, but are not limited to those indicating: toxicity in humans or animals associated with epigenetic mechanisms such as chemically induced DNA methylation, histone modification, nucleosome remodeling, or non-coding RNA. Chemically induced epigenetic endpoints may be observed in an exposed individual or its offspring.

In the supplemental information OEHHA states: *Subsection 69403.4(b) provides examples of toxicological endpoints that may be used to indicate the presence of the epigenetic toxicity in an individual or its offspring, resulting from exposure to a chemical substance.*

DNA methylation, histone modification, nucleosome remodeling, or non-coding RNA, are the major epigenetic mechanisms that are currently used to identify epigenetic changes at the cellular, individual, or population level.[193] *These endpoints are included within those provided in this subsection.*

DNA methylation is an important endpoint. It is the covalent addition of a methyl group to the fifth carbon of the cytosine ring to form 5-methyl cytosine (5meC). It is actively involved in regulating cell differentiation and function. When too much or too little methylation occurs, it can often negate a gene's function and thus causes unwanted alterations in the cell and may result in disease. For example, too little DNA methylation (hypomethlation) is believed to initiate chromosome instability and activate oncogenes. Conversely, too much DNA methylation (hypermethylation) may initiate the silencing of tumor suppressor genes. In the aging process, DNA methylation in the genome decreases as cells age.[194 195]

There are a number of laboratory methods that are currently used to evaluate the status and patterns of DNA methylation in cells or tissues. In general, these methods include a combination of methylation detection strategies and identification of genes that are subject to DNA methylation[196]

Another endpoint that indicates the presence of epigenetic toxicity is histone modification. Histones are globular proteins that make up the nucleosome, the basic structural unit of chromatin. These proteins are subject to modifications including but not limited to, lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation. Histone code, or the pattern of histone modifications within a cell or DNA sequence can be analyzed by several laboratory methods. Chemical-induced histone modifications indicate abnormal changes in the epigenome.[197 198]

It is generally agreed that the current toxicity testing battery will identify adverse outcomes; epigenetic testing/screening will at best provide insight into the mechanism/mode of action for a toxicant-induced effect. As previously discussed, epigenetic alteration and modulation is a natural process that is absolutely essential to development and differentiation in multicellular eukaryotic organisms. Therefore the statement, "…identification of genes that are subject to DNA methylation…" is not appropriate and should be deleted from the regulatory text. Presumably all genes are subject to, and require, epigenetic modification. Because many different modifications influence chromosomal structure, both positively and negatively, chromosomal function (i.e., gene function) is the net effect of many different signaling pathways converging. For example, there are a number of specific examples where the hypermethylation of a specific CpG promoter for a gene does not result in transcriptional suppression, and visa versa. The bottom line is that normal variability and interaction between different epigenetic modifications needs to be fully understood before test results could be understood.

69403.4 (c) Other relevant epigenetic toxicity data include but are not limited to: in vitro or other data using biological models indicative of chemically induced epigenetic toxicity in an exposed individual or its offspring.

In the supplemental information OEHHA states: *Subsection 69403.4(c) provides general, non-exclusive categories of other relevant data that may be used to indicate the potential of epigenetic toxicity in an exposed individual or its offspring.*
Numerous studies have utilized a large variety of methods to characterize the epigenetic status in normal or abnormal cells and to evaluate the potential of environmental factors to cause epigenetic changes either in mammalian cells or in other models such as zebrafish, Drosophila, and honeybees.[199]
Including epigenetic toxicity as a hazard trait will ensure that information on chemical effects on genes produced by this emerging field in toxicology will be available to the Toxics Information Clearinghouse.

Current publications indicate that the state-of-the-science for epigenetic toxicity testing is not sufficient to support epigenetic screening (Goodman et al, Tox Sci 116:375-381, 2010; LeBaron et al, Mutat Res, 705:83-95, 2010; Rasoulpour et al, Tox Mech and Methods in press, 2010). The Goodman et al publication represents an ILSI-HESI publication that was a consensus opinion of academia, government, and industry experts that concluded testing/screening is inappropriate at this time, based on several issues including: 1) No single test is adequate to characterize epigenetic modifications (including for a single change like DNA methylation), 2) Incomplete understanding of normal methylation patterns and long term effects, 3) The need to develop a tiered screening approach. Absolutely necessary is the need to establish a direct causative relationship of chemically-induced epigenetic changes (adaptive or adverse) and adverse health outcome, which is obviously not possible without understanding normal variability.

Again normal variability and interaction between different epigenetic modifications needs to be fully understood before test results could be understood. At this time Epigentic Toxcity should be removed as a Hazard Trait and information from these assays should be considered as other relevant information.

§. *69403.5: Genotoxicity*
69403.5 (a). Genotoxicity is defined as the occurrence of a chemical substance-induced change, either direct or indirect, to the cellular genome, including DNA sequences or chromosomes.

In the supplemental information OEHHA states: *§ 69403.5 Genotoxicity*
Subsection 69403.5(a) defines the genotoxicity hazard trait. The definition is derived from the general definition of genotoxicity as the occurrence of a chemical substance-induced change to the hereditary material (cellular genome, including DNA sequences or chromosomes) that have the potential to be heritable at the cellular level, and genetic processes in living cells.[200]
Genotoxicants can potentially cause damage to all of the cells in an organism, including both germ cells (the cells that give rise to the sperm or ova of organisms that reproduce sexually) and somatic cells (all the other cells in an organism). Germ cell genotoxicity can prevent reproduction or result in deleterious heritable changes in offspring. Somatic cell genotoxicity can result in gene mutations or chromosomal damage, which are associated with increased cancer risk.[201]

A gene is a DNA sequence in a living organism that codes for a protein or a ribonucleic acid (RNA) sequence that has a function in the organism. All proteins and functional RNA chains are specified by genes. Genes code for the information needed to build and maintain cells. Genes are considered to be units of heredity in organisms, and pass genetic traits to offspring.
Damage to the genome (genes, noncoding DNA organized into chromosomes), or genotoxicity, can result in the disruption of cellular functions, which depend on protein and functional RNA chain synthesis. Genotoxicity can result in the production of partly functional or non-functional proteins and RNA chains, which in turn causes disruption of cellular function.
The definition of the genotoxicity hazard trait in the proposed regulation is meant to be sufficiently broad to cover the range of genotoxic effects that are considered adverse to human health and covered by agencies such as U.S. Environmental Protection Agency and OEHHA, and the medical community in addressing potential adverse effects. In addition, the definition is intended to encompass genotoxicity to terrestrial wildlife.

The definition of genotoxicity as given by OEHHA is straightforward and acceptable. Dow's only comment is that the genotoxicity of terrestrial wildlife needs a sufficient historical control to place data into assay context and perspective. This should be included in the regulation.

69403.5 (b). Genotoxicity endpoints include but are not limited to those indicating: DNA damage, mutations in genes, chromosomal aberrations, micronuclei, sister chromatid exchange, aneuploidy, polyploidy, DNA adduct formation, or unscheduled DNA synthesis in humans, animals, or cell lines.

In the supplemental information OEHHA states: *Subsection 69403.5(b) provides examples of genotoxicity endpoints. Genotoxicity endpoints include but are not limited to those indicating: DNA damage (such as DNA adduct formation and unscheduled DNA synthesis) mutations in genes, chromosomal aberrations, sister chromatid exchange, aneuploidy or polyploidy in humans, animals, or cell lines.*
The list in this subsection is nearly identical to that given as examples in the IARC Preamble:[202]

> *"The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy."*

The endpoints identified in this subsection can be measured in cells, animals and humans. The non-exclusive list of endpoints in the proposed regulation is intended to cover the range of genotoxicity assays, including systems named by IARC in its most recent Preamble:

> *"Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals."*

Some examples of more specific endpoints are provided here for the general genotoxicity endpoints described in the proposed regulation. DNA damage endpoints include: Alkylation; apurinic site induction; apyrimidinic site induction; base damage; bulky adduct formation; double-strand breaks; single-strand breaks; DNA-protein crosslink formation; intercalation; interstrand crosslinks; intrastrand crosslinks; phosphotriester formation; pyrimidine dimer formation; radical formation.
Some commonly used assays of DNA damage include: Alkaline elution DNA strand breakage; COMET single cell gel electrophoresis DNA strand breakage; chemical covalent DNA binding (bulky adducts); bacterial DNA damage; mammalian cell DNA repair (unscheduled DNA synthesis).

Unrepaired DNA damage can result in gene mutations or chromosomal damage.
Gene mutation endpoints include: base pair mutations, frame shift mutations or small deletions. Some common tests of gene mutation include: reverse mutation in bacteria or fungi; forward mutation in bacteria, fungi, mammalian cells in vitro, mammalian in vivo; plant gene mutation; insect sex-linked recessive lethal mutations; and fish gene mutation. Chromosomal damage classifications include structural chromosome aberrations, changes in chromosome number, and sister chromatid exchanges.

Types of chromosome aberrations include intra-chromosomal exchanges (inversions, interstitial deletions) and inter-chromosomal exchanges (dicentric chromosomes and reciprocal translocations). Common assays measure chromosome aberrations in plants, insects, fish, or mammalian (in vitro and in vivo). Sister chromatid exchanges (SCE) may be due to errors in the chromosomal replication process during the S phase of mitosis. It is common to perform mammalian evaluation of SCE in vivo or in vitro.

Aneuploidy, that is a cell has extra copies or missing chromosomes, can be induced by interference with chromosomal movement (disruption of tubulin polymerization or spindle microtubule stability) during cell division. Common assays detect aneuploidy in fungi, plant cells, and mammalian cells in in vivo and in vitro experiments.
Other common assays of chromosome damage include micronucleus evaluation in vitro or in vivo in peripheral blood or bone marrow, fungal induced recombination and fish chromosomal damage.

Chemical induction of DNA damage such as apurinic and apyrimidinic sites are often rapidly and efficiently repaired, resulting in negligible to no genotoxicity in guideline studies. This type of data should not be used to assess the genotoxicity of a material, but to indicate that further testing is required. Furthermore, additional test should use genotoxicity assays that have approved and universally accepted test guidelines.

The IARC preamble (as referenced by OEHHA earlier) states that assays using plant cells, "…suggest that genetic and related effects could occur in mammals". Any evaluation of genotoxicity in plant cells should be verified in mammalian cells when used for evaluating genotoxicity in humans.

69403.5 (c). Other relevant data include but are not limited to: data on protein-adduct formation; electrophilic potential; abasic sites; protein-DNA crosslinks; structural or mechanistic similarity to other chemical substances with the genotoxicity hazard trait.

In the supplemental information OEHHA states: *Subsection 69403.5(c) provides examples of other relevant data that can provide evidence for the genotoxicity hazard trait described in standard sources.*[203]

Assays that provide data on protein-adduct formation, electrophilic potential, abasic sites, and protein-DNA crosslinks, do not provide information on genotoxicity hazard. Data from these assays are best used to screen and identify compounds for which genotoxicity evaluation, using approved and universally accepted test guidelines, should be conducted.

§ 69403.15 Respiratory Toxicity

(a) The respiratory toxicity hazard trait is defined as an adverse change in the structure or function of the respiratory tract following exposure to a chemical substance, including respiratory tract injury or decreased ability of the lungs to function in gas exchange.

(b) Endpoints include, but are not limited to those indicating: respiratory irritation; pathological changes to the airway or other lung structures; inflammation; fibrosis; hypersensitivity pneumonitis; airways hyperresponsiveness; altered lung function; asthma; airways remodeling; increased respiratory infections; altered composition of bronchoalveolar lavage fluid.

(c) Other relevant data include but are not limited to: in vitro evidence for respiratory toxicity; particle size distribution inclusive of respirable particles; respirable fibers; long half-life in the lung; chemical reactivity; redox potential; structural or mechanistic similarity to other chemical substances with the respiratory toxicity hazard trait.

- The principal problem foreseen is the determination of **what is adverse.** A number of the functional endpoints are clearly adverse – changes in pulmonary function, airway hyperreactivity, increased respiratory infections. Some pathologic changes such as increased mucus production/storage, altered BALF composition are commonly identified but their significance or impact is difficult to determine. If these two broad classes of responses are seen as equally adverse or even indicators of an adverse effect then the ability to differentiate between truly hazardous and minimally hazardous materials may be lost.
- The impact of particle size distribution on the site of deposition was discussed but the size classification discussed in section 69405.7 refers to particles ≤ 10 microns (PM_{10}) while current ambient particle regulations are based on particles ≤ 2.5. Absent is any discussion of the fraction of particles (or gases) that are deposited and absorbed – or inhaled dose in general. The regulatory text should be expanded to discussion of the above point.
- Fibers are discussed but the usual examples of asbestos and silica are just that – examples of materials that are highly toxic due their physical and chemical

characteristics. Recognition of the inherent toxicity of the inhaled particle/fiber needs to be included in any definition of hazard – including the impact of dissolution and physical clearance on pulmonary retention and species differences in clearance rates and routes.

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§ 69403.15(a): Definition of respiratory toxicity hazard trait

"The ubiquitous nature of air pollutants impacting the lung has large measurable adverse public health impacts.[327]*"*

- The number of ambient air pollutants with measureable public health impacts is fewer than suggested by the text. They are principally ozone, SO_2, NO_2 and ambient particulate matter. These are all regulated under the NAAQS and are continually reevaluated based on experimental (laboratory animal and in vitro cultures), controlled exposure (experimental human exposures), and epidemiologic data. Each has distinct toxicological properties but the biologic responses to these pollutants overlap, as do the episodic exposure excursions, complicating interpretation of the data. The text should be modified to :

"The ubiquitous nature of air pollutants impacting the lung in some cases is known to result in adverse public health impacts.[327]*"*

"In all cases, the extent of damage is dependent on the chemical concentration to which animals or people are exposed."

- This is a simplistic and misleading statement. The text correctly points out that for particulate phase chemicals, the site of deposition is dependent on the particle size distribution and for gases, water solubility greatly impacts the site of exposure. What is missing is any link to the key exposure metric - deposited or absorbed dose, or differences in inherent toxicity of different inhaled materials, or the impact of the presence or absence of sensitive cell populations or (species – specific) metabolic enzyme systems. These elements need to be expanded on in the regulatory text.

§ 69403.15(b): Toxicological endpoints for the respiratory toxicity

"Respiratory irritation is a commonly measured endpoint in both humans and animals, and may result in stimulation of the trigeminal nerve (sensory irritation) or in tissue damage.[335]*"*

- It should be noted that measurement of sensory irritation in animals or "irritation" in human studies are all responses that occur prior to injury. They may be good data to help set occupational exposure levels but they should not be equated to chemical toxicity.

"Damage to the respiratory system from both acute and chronic chemical exposure can be measured by pathologic evaluation of the tissues of the respiratory system……"

- This is true and an essential element of understanding toxicity of inhaled materials under controlled laboratory conditions – but problematic when applied to human

population samples due to a lack of exposure-response data. These may be good data for building a case for hazard potential but hard to apply to human samples. The regulatory text should acknowledge and address shortcomings of the data for assessing human health hazards.

"Another common way to measure damage to the lung in both humans and animals that is relatively non-invasive is to evaluate the composition of bronchoalveolar lavage fluid (BALF).[339]*"*

- This is another powerful experimental tool to investigate acute and chronic responses under controlled conditions with understanding of exposure history. For humans, this may provide key information on the inflammatory status of the conducting airways and gas exchange region, but should not be used as a diagnostic aide.
- Exhaled breath analysis is actually a better endpoint for humans – assessing inflammatory/oxidative stress status of the individual. But it is non-specific except in the case of known exposure (but exposure concentration and duration are generally missing).

"Lung function testing commonly uses a spirometer to assess airway obstruction by measuring forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, forced expiratory flow rates, and peak expiratory flow rate.[341]*"*

- These endpoints are very useful in evaluating changes in the functional capacity of the lung. FEV1 and FVC correlate well between animals and humans, however, human data may be difficult to interpret due to the willingness or capability of the human subject to perform the maneuvers. Even measures of peak flow (used to monitor airway status of asthmatics) require training of the individual.

"Another type of functional impairment associated with inhaled chemicals is bronchoconstriction or airways hyperresponsiveness.[342]*"*

- At this time there are no predictive tests to determine if an inhaled material will be a respiratory sensitizer – or to distinguish a sensitizer from an irritant based on acute exposure. Provocation tests (in humans) do identify airway hyperreactivity but not the etiology of the condition; in laboratory animals, it provides useful data on exposure dependent structure/function changes in upper and lower conducting airways.

§ 69403.15(c): Other relevant data useful to evaluate chemical substances for the respiratory toxicity hazard trait.

"A number of endpoints can be measured in isolated or cultures of various types of lung cells[345] *to evaluate the effects of chemical exposure including cytotoxicity, gene expression, protein production, and metabolic changes."*

- True, but the relevance of these data are dependent on detailed characterization of test material in the test system, the dosimetry to the cells, and the relevance of the exposure route (submerged vs air/liquid interface) and cell type. Exposures using

explants can help cross species comparisons and may be more relevant because the 3D structure and cell-cell interactions are retained The text needs to be modified to reflect the relevance and reliability for using these types of data in the assessment of a hazard trait. Just because "endpoints" are measureable does not mean that they are indicative of an adverse outcome.

- The impact of particle size distribution on the site of deposition was discussed but the size classification discussed in section 69405.7 refers to particles ≤ 10 microns (PM_{10}) while current ambient particle regulations are based on particles ≤ 2.5 microns ($PM_{2.5}$). Absent is any discussion of the fraction of particles (or gases) that are deposited and absorbed – or inhaled dose in general. This should be included.
- Fibers are discussed but the usual examples of asbestos and silica are just that – examples of materials that are highly toxic due their physical and chemical characteristics. Recognition of the inherent toxicity of the inhaled particle/fiber needs to be included in any definition of hazard – including the impact of dissolution and physical clearance on pulmonary retention and species differences in clearance rates and routes.

§ 69403.14(a) Reactivity in Biological Systems

This section defines reactivity in biological systems as a hazard trait, and as one which commonly leads to toxicity.

- It should also be noted in the regulatory text that reactivity in biological systems plays a role in mitigating hazard/toxicity, and thus is not always an "adverse" hazard trait. For example, Phase II conjugations which result in rapid elimination; or reactivity of substance with water (hydrolysis) such as with isocyanates, can result in diminished or eliminated hazard properties of a parent substance.

§ 69404.1 Domesticated Animal Toxicity

Here the hazard trait of domesticated animal toxicity is defined, and points out the public value of livestock and pets.

- While the value of livestock and pets is not argued, the value of these animals should not be confused or co-mingled with intrinsic hazard. The example of melamine in cat and dog food is given as an example; however, would not the ingestion of melamine by any mammal (regardless of domestication) result in adverse effects? Consider revising the regulatory text to appropriately focus on the intrinsic hazard and avoid confusing this point with the societal factors.

§69404.10 (a)(1) Categories of findings from authoritative organizations….

There are three categories of findings presented. The third category consists of regulatory actions that identify a chemical as having a hazard trait, and the example of priority pollutants within the Clean Water Act is given.

- It should be considered that the occurrence of a substance on a contaminant list does not constitute a hazard. For example, toluenediisocyanate is included on U.S. EPA's CCL3 list of drinking water contaminants, yet this substance cannot exist as dissolved in water. Clearly, the authorities which make these designations or lists are not always well-informed of the technical relevance or reality of including substances on

such regulatory lists. OHEEA must spell out provisions for critically evaluating information and decisions derived from such lists, thereby avoiding the propagation of errors made by other "authorities".

§ 69405.6 Mobility in Environmental Media (page 22 of 24)

The qualitative evidence for this trait is given, but no specific quantitative criterion is specified- for example, based on log Pow, Koc, ionic charge density, etc. It is suggested that such quantitative criteria could be adapted from US EPA, REACh, etc and be incorporated into the current regulation.

The Dow Chemical Company appreciates the additional background OEHHA has provided for the proposed regulation since the August draft regulation was released; however, we remain highly concerned over the breadth and direction of the draft regulation; specifically as it relates to OEHHA's disconnection from the DTSC proposed regulations and DTSC's vision for the Toxics Information Clearinghouse (TIC).
For this reason, we strongly urge OEHHA to considering delaying further work on the hazard trait regulation until such time that uncertainty around the regulatory structure into which the traits must fit is resolved. In the current form there is too much uncertainty regarding both their operative impact and sufficiency.

The Dow Chemical Company respectfully submits the attached comments and concerns regarding the Proposed Green Chemistry Hazard Trait Regulation. For further information or questions regarding our comments please contact us using the contact information below.

Regards,

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