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Dear Dr. Bowes:

I want to thank you again for asking me to be an expert reviewer of these documents. As you know, I am a native Californian with undergraduate and graduate degrees in toxicology and other areas of science from University of California campuses.

As a disclaimer, please note that although I am doing this expert review as an official part of my job at the National Institutes of Health (NIH), National Library of Medicine (NLM), the comments below are my own and do not necessarily reflect official National Institutes of Health or other Federal government opinions.

As requested, this is a review of the draft regulation, "Green Chemistry Traits," dated December 2010, and the supporting document entitled "Initial Statement of Reasons" dated December 2010. Both documents were developed by the State of California's Office of Environmental Health Hazard Assessment (OEHHA). As noted in the information provided to me, the statutory mandate for an external peer review states that the reviewer's responsibility is to determine whether the scientific portion of the proposed regulation is based on sound scientific knowledge, methods, and practices. The review that I was requested to do was to consider this relative to the issues noted below that constitute the scientific basis of the proposed regulation:

1) **Accuracy and clarity of the definitions presented (Article 1, Section 69401.2 in the proposed regulation and Section V, Article 1, Section 69401.2 in the Initial Statement of Reasons).**

   Reviewer's comments: The definitions presented are judged to be both accurate and clear in both documents. The only comment I have is that the "that negatively affects" wording could be changed to "could negatively affect." This suggested change is based on noting that an actual impact on performance or ability to respond could depend on the "reserve capacity" of the individual organism for that trait or endpoint versus the actual magnitude of the exposure and effect.

2) **Selection of the toxicological hazard traits (Articles 2 and 3 in the proposed regulation and Section V, Articles 2 and 3 in the Initial Statement of Reasons).**

   Reviewer's comments: The hazard traits provided are thorough in terms of scope. Also, the definitions presented are judged to be both accurate and clear in both documents. An exception I noted is for Article 3's Section 69403.14 on Reactivity in

Biological Systems in the proposed regulation, and also in the relevant section in the Initial Statement of Reasons. Given that the Clearinghouse seeks to provide information relevant to hazard traits associated with consumer products, the wording in these sections could consider noting the importance of consumer product-related reactivity taking place in the surroundings of an individual that could impact hazard. Examples of indoor air-related publications, including research from UC Berkeley and Lawrence Berkeley Laboratory, include (apologies for noting something that I authored; however, it is directly related to this comment and is in the Information Resources in Toxicology book as a topic):

Information Resources in Toxicology (Fourth Edition)
2009, Pages 269-279. Asish Mohapatra and Pertti J. Hakkinen. Chapter 30 - Everyday Exposures.
Excerpts: "A recent area of strong research interest is the study of indoor air chemistry, including the reactions that can occur between ozone and the chemicals used in cleaning products, air fresheners, and paint. For example, the terpenes widely used in consumer products can react with ozone under product use conditions, leading to formation of formaldehyde, hydroxyl radical, and secondary organic aerosol (very small particles that can be inhaled).

Other examples where indoor air reactivity is discussed include (please especially note the first publication on "Hazard assessment of chemical air contaminants measured in residences"):

(University of California, Berkeley and Lawrence Berkeley Laboratory)
Logue JM, McKone TE, Sherman MH, Singer BC.
Hazard assessment of chemical air contaminants measured in residences.
Indoor Air (2011) 21:92-109.
http://www.ncbi.nlm.nih.gov/pubmed/21392118 Key excerpt: "Practical implications: This analysis identifies key chemical contaminants of concern in residential indoor air using a comprehensive and consistent hazard-evaluation protocol. The identification of a succinct group of chemical hazards in indoor air will allow for successful risk ranking and mitigation prioritization for the indoor residential environment. This work also indicates some common household activities that may lead to the acute levels of pollutant exposure and identifies hazardous chemicals for priority removal from consumer products and home furnishings."

(University of California, Berkeley) Nazaroff WW and Weschler CJ. Cleaning products and air fresheners: exposure to primary and secondary air pollutants. Atmos. Environ. (2004) 38: 2841–2865.

Sarwar G, Olson DA, Corsi RL and Weschler CJ. Indoor fine particles: the role of terpene emissions from consumer products. J. Air Waste Manage. Assoc. (2004) 54: 367–377. http://www.ncbi.nlm.nih.gov/pubmed/15061618

(University of California, Berkeley and Lawrence Berkeley Laboratory)
Destaillats H, Lunden MM and Singer BC et al., Indoor secondary pollutants from household product emissions in the presence of ozone: A bench-scale Chamber study. Environ. Sci. Technol. (2006) 40: 4421–4428.
http://www.ncbi.nlm.nih.gov/pubmed/16903280

(University of California, Berkeley and Lawrence Berkeley Laboratory) Singer BC, Destaillats H, Hodgson AT and Nazaroff WW, Cleaning products and air fresheners: emissions and resulting concentrations of glycol ethers and terpenoids. Indoor Air (2006) 16: 179–191.
http://www.ncbi.nlm.nih.gov/pubmed/16683937

3) Selection of the environmental hazard traits (Article 4 in the proposed regulation and Section V, Article 4 in the Initial Statement of Reasons).

Reviewer's comments: Although this is not very much within my areas of experience and expertise, the selection of the environmental hazard traits and the definitions presented seem to be thorough and are accurately and clearly presented in both documents.

4) Selection of the exposure potential hazard traits (Article 5 in the proposed regulation and Section V, Article 5 in the Initial Statement of Reasons).

Reviewer's comments: This is not very much within my areas of experience and expertise, with the exception of the "Lactational or Transplacental Transfer" and "Particle Size or Fiber Dimension" contents. The selection of the exposure potential hazard traits and the definitions presented seem to be thorough and are accurately and clearly presented in both documents.

5) Selection of the physical hazard traits (Article 6 in the proposed regulation and Section V, Article 6 in the Initial Statement of Reasons).

Reviewer's comments: The physical hazard traits selected and described from the sources noted focus on combustion facilitation, explosivity, and flammability. The use of these traits is judged to be both quite thorough in the context of these documents, and they are clearly described in both documents. Adding mention of a publication noting and discussing a broader set of possible physical hazards that consumers and others could encounter could be considered. A possible publication about this is:

Information Resources in Toxicology (Fourth Edition)
2009, Pages 371-386. Gene Rider. **Chapter 42 - Physical Hazards**.
Excerpts: "Toxicologists have traditionally been called upon to assess the chemical and biological hazard of products. However they are increasingly required to take a more holistic approach to product hazard evaluation and consider all potential hazards – physical as well as chemical. Increasing emphasis on physical hazards can be seen, for example, in the adoption of the Physical Agents directive by the European Union in 2004, recent changes in ASTM International's Toy Safety Standard addressing magnets, strangulation, and noise, and increasing awareness that injuries are the leading cause of death to children in all developed nations. The following text addresses the wide range of physical hazards associated with products. Emphasis is placed on consumer products rather than industrial or military products, although references from the latter are cited when they have clear relevance to consumer products. References have been chosen with an eye toward eliminating hazards from products. Emphasis was placed on understanding the etiology and susceptible population groups for each hazard. This review begins with an introduction to resources and organizations concerned with physical hazards of consumer products in general. Following this, specific classes of

hazard are addressed individually. A hazard definition is provided for each of the specific hazard areas followed by a brief description of the scope of the hazard."

6) **Methodology for identifying strong evidence and suggestive evidence for toxicological and environmental hazard traits (Article 2, Sections 69402.2, 69402.4, and 69402.6, Article 3, Section 69403.16, Article 4, Section 69404.10 in the proposed regulation and Section V, Article 2, Sections 69402.2, 69402.4, and 69402.6, Article 3, Section 69403.16, and Article 4, Section 69404.10 in the Initial Statement of Reasons).**

   Reviewer's comments: The methodologies presented and described are judged to be both accurate and clear in both documents.

As a reviewer, I was also requested to contemplate a bigger picture, including:

1) **Are there any important scientific issues relevant to hazard traits that have not been addressed in the responses provided above?**

   Reviewer's comments:

   Something that seems to be missing in the mention of the development of the Toxics Information Clearinghouse in these documents is the need for early and ongoing consideration of the overall structure of this database. This is in terms of how the Clearinghouse's contents will be indexed beyond the structure shown in the tables of contents for the proposed regulation and in the Initial Statement of Response (e.g., see Article 1, Section 69401.1, in the proposed regulation). From reading other documents and Web site content, I know that the overall structure and contents of the Clearinghouse are under ongoing discussion.

   I assume that a thorough indexing structure will be considered (or will continue to be considered) during the design and development of the Clearinghouse. Also, I assume that taxonomies (systems for classifying information from multiple documents or sources) are going to be established for use by the people designing the Clearinghouse, for those preparing the information for inclusion into the Clearinghouse, and for use by people trying to search and find information. Organizations such as the National Library of Medicine with experience in indexing and development of taxonomies could be asked to provide perspective and possible help.

   Also, I trust that **"how to search"** and/or **"what to search" content** will be developed for the Clearinghouse to aid its users, including the types of information available via databases such as the National Library of Medicine's TOXNET® suite of databases (http://toxnet.nlm.nih.gov/) and the OECD's eChemPortal (http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en).

   Another comment is that an opportunity exists to note and emphasize the "read across" approach in these documents as a way to help identify and deal with hazard traits in the absence of some types of information for a substance. For example, this could have been noted and cited in the last paragraph of Page 51 of the Initial Statement of Reasons and also in Page 15's Subsection 69401.2(f) and 69401.2(g) which discuss

other relevant data including structural and mechanistic similarity. A general publication describing the read across approach that could be noted is (apologies for noting something that I authored; however, it is directly related to this comment and is in the Encyclopedia of Toxicology as a topic):

> **Encyclopedia of Toxicology** (Second Edition)
> Pages 298-299. Pertti J. Hakkinen. Toxicity Testing, 'Read Across Analysis.'
> **Excerpts:** "Testing requirements often mandate that certain sets of toxicological information have to be provided for new substances (e.g., 'base sets' or 'Screening Information Data Sets'). While the data typically come from animal studies and *in vitro* alternatives to animal testing, they can also come from use of modeling, and from human clinical or epidemiological data. A further source of information can be derived from 'read across' evaluations or analyses of the data sets available for structurally similar substances. The 'read across' approach has been accepted by some regulatory authorities, and is based on the understanding that substances with similar physicochemical property profiles will generally have similar toxicity profiles. The focus of the read across evaluation approach is on interpolation rather than extrapolation, and the rationale and data sources for the read across evaluation should be documented. For example, a read across table of data could have the related chemicals as columns, and the various types of toxicology tests and their results as the rows under each substance. Reading across the columns will highlight the amount and types of data for the group of substances. The read across evaluation will also find any gaps in the data set for a specific chemical that might be judged by the reviewer(s) to be filled by data relevant to those data gaps for the similar substances."

Other examples from the U.S. and beyond of where the **read across** approach is discussed include:

Blackburn K, Bjerke D, Daston G, Felter S, Mahony C, Naciff J, Robison S, Wu S. 2011, Case studies to test: A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. Regul Toxicol Pharmacol. 2011 Jun 1;60(1):120-35. http://www.ncbi.nlm.nih.gov/pubmed/21420459

Diderich R. Chemical categories: Filling data gaps by read-across and trend analysis, the OECD approach. Toxicology Letters (2009) 189 Supplement 1: S4

European Chemicals Agency (ECHA) content, e.g., http://echa.europa.eu/doc/press/webinars/read_across_and_categories_tatiana_netzeva_echa.pdf

Hanway RH and Evans PF. Read-across of toxicological data in the notification of new chemicals. Toxicology Letters (2000) 116 Suppl. 1: 61.

U.S. EPA's High Production Volume Web site information: http://www.epa.gov/HPV/pubs/workshop/wkshebi.htm

van Leeuwen K, Schultz TW, Henry T, Diderich B, Veith GD. Using chemical categories to fill data gaps in hazard assessment.
SAR QSAR Environ Res. (2009) 20:207-20.
http://www.ncbi.nlm.nih.gov/pubmed/19544189
(Erratum in SAR QSAR Environ Res. (2009) 20:591).

Vink SR, Mikkers J, Bouwman T, Marquart H, Kroese ED.
Use of read-across and tiered exposure assessment in risk assessment under REACH--a case study on a phase-in substance.
Regul Toxicol Pharmacol. (2010) 58: 64-71.
http://www.ncbi.nlm.nih.gov/pubmed/20394791

2) As a whole, are the proposed hazard traits, examples of environmental and toxicological endpoints and other relevant data based on sound scientific knowledge, methods, and practices?

Reviewer's comments: Yes as a whole; however, I have five additional comments for consideration:

1) Where "well-conducted scientific studies" are mentioned along with publication in the open literature (e.g., see Article 1, Section 69401.2, in the proposed regulation), it seems like the term "peer reviewed" could be added before the word "open" to indicate that the desire is to use information and publications that have undergone one or more levels of peer review.

2) Mention could be made of the use of "integrated testing strategy (or strategies)" and "intelligent testing." Examples of publications discussing these topics include:

   Ahlers J, Stock F, Werschkun B.
   Integrated testing and intelligent assessment-new challenges under REACH. Environ Sci Pollut Res Int. (2008) 15:565-72.
   http://www.ncbi.nlm.nih.gov/pubmed/18818964

   Berg N, De Wever B, Fuchs HW, Gaca M, Krul C, Roggen EL.
   Toxicology in the 21st century - Working our way towards a visionary reality. Toxicol In Vitro. (2011) 25:874-81.
   http://www.ncbi.nlm.nih.gov/pubmed/21338664

   Hulzebos E, Gunnarsdottir S, Rila JP, Dang Z, Rorije E. An Integrated Assessment Scheme for assessing the adequacy of (eco)toxicological data under REACH. Toxicol Lett. (2010) 198: 255-62.
   http://www.ncbi.nlm.nih.gov/pubmed/20633615

   An example of U.S. EPA efforts related to this topic:
   http://epa.gov/oppfead1/cb/csb_page/updates/2010/workshop-centurysci.html

3) An existing database to consider incorporating into (or linking to) the Clearinghouse when lactational or transplacental transfer information is desired (e.g., see Article 5, Section 69405.5, in the proposed regulation) is the National Library of Medicine's Drugs and Lactation Database (LactMed, fact sheet: http://www.nlm.nih.gov/pubs/factsheets/lactmedfs.html). LactMed is a part of the NLM's Toxicology Data Network (TOXNET®) suite of databases. LactMed is a database of drugs and other chemicals to which

breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. All data are derived from the scientific literature and are fully referenced, and the data are organized into substance-specific records providing a summary of the pertinent reported information and include links to other NLM databases such as the Hazardous Substances Data Bank (HSDB®, fact sheet: http://www.nlm.nih.gov/pubs/factsheets/hsdbfs.html). Users of LactMed can search by drug or chemical name, Chemical Abstracts Service Registry Number (RN), pharmacologic category, and/or subject terms. Search results can easily be viewed, printed or downloaded.

4) In addition to the mention of the Hazardous Substances Data Bank above, it is worth noting that HSDB's content could fit into (or be linked to) the Clearinghouse to help provide access to the wide range of "evidence for ____ trait" information, e.g., for carcinogenicity and developmental toxicity. Like LactMed, HSDB is a data file on the NLM's TOXNET®. The focus of HSDB is on the toxicology information available for chemicals, and the content is enhanced with information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, and related areas. All data are referenced and derived from a core set of books, government documents, technical reports and selected primary journal literature. HSDB is peer-reviewed by the HSDB's long-established Scientific Review Panel (SRP), a committee of experts in the major subject areas within the data bank's scope. HSDB is organized into individual chemical records, and contains over 5,000 records. HSDB is also part of OECD's eChemPortal suite of participating global databases (http://www.echemportal.org/echemportal/page.action?pageID=2).

5) I want to also note with regard to the Clearinghouse and its content that TOXNET's suite of databases will continue to be enhanced during 2011 and beyond to keep up with the state of the science in toxicology, e.g., the Comparative Toxicogenomics Database (CTD) was added in early 2011. (http://www.niehs.nih.gov/news/newsletter/2011/february/spotlight-database/ and http://toxnet.nlm.nih.gov/).

Thank you again for asking me to be an expert reviewer of these documents.

Sincerely,

Bert Hakkinen
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