June 6, 2016

Karl Palmer, Chief
Safer Products and Workplaces Program
Department of Toxic Substances Control
1001 I Street, Third Floor
Sacramento, CA 95814

SUBJECT: REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

Dear Mr. Palmer:

This letter responds to the attached March 7, 2016 request for external scientific peer review for the subject noted above. The review process is described below. All steps were conducted in confidence. Reviewers' identities were not disclosed.

To begin the process for selecting reviewers, I contacted the University of California, Berkeley (University) and requested recommendations for candidates considered qualified to perform the assignment. The University was provided with the March 7, 2016 request letter to me and attachments. No additional material was asked for, nor provided. This service by the University includes interviews of each promising candidate and is supported through an Interagency Agreement co-signed by Cal/EPA and the University.

Each candidate who was both qualified and available for the review period was asked to complete a Conflict of Interest (COI) Disclosure form and send it to me for review, with Curriculum Vitae. The cover letter for the COI form describes the context for COI concerns that must be taken into consideration when completing the form. "As noted, staff will use this information to evaluate whether a reasonable member of the public would have a serious concern about [the candidate's] ability to provide a neutral and objective review of the work product."

In a subsequent letter to candidates approving them as reviewers, I provided the attached January 7, 2009 Supplement to the Cal/EPA Peer Review Guidelines, which, in part, serves two purposes: a) it provides guidance to ensure confidentiality through the course of the external review, and b) it notes reviewers are under no objection to discuss their comments with third-parties after reviews have been submitted. We recommend they do not. All outside parties are provided opportunities to address a proposed regulatory action, or potential basis for such, through a well-defined rulemaking process.

Later, I sent each reviewer the material to be reviewed and a detailed cover letter to initiate the review (attached).

Attached to the cover letter was the March 7, 2016 request for reviewers to me. Its Attachment 2 was highlighted as the focus for the review. Each reviewer was asked to address each topic, as expertise allows, in the order given. Thirty days were provided for the review. I also asked reviewers to direct enquiring third-parties to me after they have submitted their reviews.

Reviewers' names, affiliations, curriculum vitae, letters initiating the review and reviews are being sent to you now with this letter. All attachments can be electronically accessed through the bookmark icon at the left of the screen.

Approved reviewers are as follows:

1. James V. Bruckner, Ph.D.
   Professor, Pharmaceutical and Biomedical
   Sciences College of Pharmacy
   University of Georgia
   Wilson Pharmacy, Room 356
   250 W. Green Street
   Athens, GA 30602

   Telephone: 706-542-5405
   E-mail: bruckner@rx.urga.edu

2. Lisa M. Kamendulis, Ph.D.
   Associate Professor, Environmental Health
   School of Public Health
   Indiana University
   1025 E 7th, HPER C030
   Bloomington, IN 47405

   Telephone: (812) 855-8861
   E-mail: lkamendu@indiana.edu

3. Raymond S.H. Yang, Ph.D.
   Professor Emeritus
   Environmental and Radiological Health Sciences
   College of Veterinary Medicine and Biomedical Sciences
   Colorado State University
   Fort Collins, CO 80523-168

   Telephone: (970) 581-5101
   E-mail: rshyang@colostate.edu

If you have any questions, or require clarification from the reviewers, please contact me directly.

Regards,

Gerald W. Bowes, Ph.D.
Manager, Cal/EPA Scientific Peer Review Program
Office of Research, Planning and Performance
State Water Resources Control Board
1001 "I" Street, 16th Floor
Sacramento, California 95814

Telephone: (916) 341-5567
FAX: (916) 341-5284
Email: GBowes@waterboards.ca.gov

cc: Ms. Lisa Quagliaroli, Senior Environmental Scientist

Attachments (5):
(1) March 7, 2016 Request by Karl Palmer for Scientific Peer Review
(2) January 7, 2009 Supplement to Cal/EPA Peer Review Guidelines
(3) Curriculum Vitae
  (a) James V. Bruckner, Ph.D.
  (b) Lisa M. Kamendulis, Ph.D.
  (c) Raymond S.H. Yang, Ph.D.
(4) Letters to Reviewers Initiating the Review
  (a) James V. Bruckner, Ph.D.
  (b) Lisa M. Kamendulis, Ph.D.
  (c) Raymond S.H. Yang, Ph.D.
(5) Reviews
  (a) James V. Bruckner, Ph.D.
  (b) Lisa M. Kamendulis, Ph.D.
  (c) Raymond S.H. Yang, Ph.D.

Department of Toxic Substances Control

Matthew Rodriquez
Secretary for
Environmental Protection

Barbara A. Lee, Director
1001 "I" Street
P.O. Box 806
Sacramento, California 95812-0806

Edmund G. Brown Jr.
Governor

MEMORANDUM

TO: Gerald Bowes, Ph.D.
Manager, CalEPA Scientific Peer Review Program
Office of Research, Planning and Performance
State Water Resources Control Board

FROM: Karl Palmer, Chief
Safer Products and Workplaces Program
Department of Toxic Substances Control

DATE: March 7, 2016

SUBJECT: REQUEST FOR EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

The subject of this review is a proposed regulation to adopt the following product-chemical combination as a Priority Product:

Paint and Varnish Strippers Containing Methylene Chloride

The California Department of Toxic Substances Control (DTSC) is responding to the Safer Consumer Products (SCP) regulations[1] that require DTSC to identify product-chemical combinations that pose risks to people or the environment and to adopt them as Priority Products[2] in regulation. Once DTSC adopts a Priority Product in regulation, manufacturers must take one of the following actions to improve the safety of their products:

- remove or replace the chemical(s) of concern in the product, or
- remove the product from the California marketplace, or

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[1] California Code of Regulations, Title 22, sections 69503 – 69503.7

[2] "Priority Products" are consumer products that a) contain chemicals included in DTSC's Candidate Chemicals List; b) may expose people or the environment to these chemical(s) through normal use; and c) have been adopted in regulation. Candidate Chemicals exhibit hazard traits or environmental or toxicological endpoints and are included on authoritative lists established by government agencies or scientific organizations (www.dtsc.ca.gov/SCP).

- conduct an Alternatives Analysis (AA) to determine if safer alternatives exist.

In accordance with Health and Safety Code section 57004, DTSC requests external scientific peer review of the basis for proposing *Paint and Varnish Strippers Containing Methylene Chloride* as a Priority Product. As required by regulation, DTSC reviewed reliable scientific literature and concluded that this product-chemical combination meets the required regulatory criteria[3] for listing as a Priority Product for the following reasons:

- exposure to methylene chloride may contribute to or cause significant or widespread adverse impacts to people, particularly to sensitive subpopulations such as workers in the furniture stripping and remodeling industries; and
- people, particularly the sensitive subpopulation noted above, may be exposed to these chemicals through normal use or handling of products that contain methylene chloride.

For this review, DTSC recommends that reviewers have expertise in the following areas, in order of importance:

- human toxicology associated with methylene chloride or volatile organic chemicals, and/or
- human exposure assessment.

We estimate that two reviewers will be adequate to cover all of the necessary areas of expertise.

DTSC intends to initiate the formal rulemaking process by mid-2016. The documents are ready for review at any time, and the preferred period of review is 30 days. The following attachments are enclosed:

- Attachment 1: Plain English Summary of the Proposal to Adopt *Paint and Varnish Strippers Containing Methylene Chloride* as a Priority Product
- Attachment 2: Scientific Conclusions to Be Addressed by Peer Reviewers
- Attachment 3: List of Participants
    - Section A: DTSC Participants
    - Section B: External Participants

Please direct inquiries regarding this request to Lisa Quagliaroli, of my staff, at lisa.quagliaroli@dtsc.ca.gov or 916-445-3077.

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[3] Prior to proposing a product-chemical combination for adoption as a Priority Product, DTSC must ensure that the product-chemical combination meets both of the following criteria: 1) there must be potential public and/or environmental exposure to the chemical(s) in the product; and 2) there must be potential for one or more exposures to contribute to or cause significant or widespread adverse impacts (22CCR section 69503.2(a)).

Attachment 1:

Plain English Summary of the Proposal to Adopt Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product

A. Brief Statement of Conclusions[4]

DTSC identified paint and varnish strippers containing methylene chloride as a proposed Priority Product. This determination was based on a consideration of available, reliable scientific and/or authoritative information regarding the potential for exposure to methylene chloride in paint and varnish strippers and the potential for these exposures to contribute to or cause significant or widespread adverse human health impacts.

Methylene chloride has numerous recognized acute and chronic hazard traits. The use of paint and varnish strippers containing methylene chloride has led to the deaths of consumers and numerous workers due to acute methylene chloride poisoning. Methylene chloride also has the potential to significantly and adversely impact the health of certain sensitive subpopulations including pregnant women, infants and children, workers who use paint strippers on the job, and certain chronically ill individuals.

DTSC determined that there is a potential for exposure related to the use of paint and varnish strippers containing methylene chloride, and there is potential for these exposures to cause significant or widespread adverse human health impacts.

DTSC based this determination on the fact that methylene chloride is highly volatile and is likely to become airborne during the use of products that contain this chemical, and on the hazard traits of methylene chloride. The concentration of methylene chloride in paint and varnish stripping products can be very high, ranging from 16% to 100%, with the majority of products containing more than 60% methylene chloride by volume. Such high concentrations increase the potential for exposure during use. A survey of retail stores in California suggests that paint and varnish strippers containing methylene chloride are the most commonly purchased paint-stripping product, suggesting that their use is widespread.

Methylene chloride vapors are heavier than air and may concentrate in the breathing zone in the absence of adequate ventilation, further increasing the potential threat of exposure during use. Research has shown that the use of methylene chloride-based

products in home settings can potentially result in high concentrations of methylene chloride in air, in some cases approaching concentrations that are immediately dangerous to life and health. Moreover, many consumers may not be aware that the

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[4] Excerpted from the *"Summary of Technical Information and Scientific Conclusions for Designating Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product."* Section VIII, page 14.

most commonly used gloves and cartridge-type air purifying respirators do not provide adequate protection from exposure to methylene chloride.

Finally, DTSC determined that there is potential for exposure to methylene chloride for workers who use paint and varnish strippers, and that these exposures have the potential to cause or contribute to significant adverse impacts. Paint and varnish stripping products that contain methylene chloride are widely used in industrial paint stripping operations throughout California and the U.S. where workers may be exposed. Many furniture stripping firms that use methylene chloride-based stripping formulations in California have poor ventilation. Occupational Safety and Health Administration and Cal-Occupational Safety and Health Administration established a Permissible Exposure Limit (PEL) of 25 parts per million and an action level of 12.5 parts per million for methylene chloride in air. According to a 2006 study, most furniture stripping firms exceeded the PEL or the action level for methylene chloride. In addition, bathroom and kitchen remodelers and other workers may use paint and varnish strippers containing methylene chloride to strip cabinets, bathtubs, and other items for refinishing, and deaths attributed to methylene chloride poisoning have been documented among these workers. The number of remodelers and other workers who may use paint and varnish strippers containing methylene chloride is unknown.

B. Overview of the Safer Consumer Products Regulatory Program

The SCP program's primary goal is to ensure safer products and healthier lives by reducing and eliminating the use of toxic chemicals in consumer products sold in California. DTSC will advance the creation of safer substitutes for hazardous ingredients by asking manufacturers to answer two questions:

- is this chemical necessary?
- is there a safer alternative?

The SCP regulations, implemented on October 1, 2013, specify the process for identifying consumer products that contain hazardous chemicals, evaluating safer alternatives to those chemicals, and eliminating or reducing potential exposures to and adverse impacts from these products.

As required by regulation, DTSC published the initial list of proposed Priority Products on March 13, 2014, and held public workshops throughout California to solicit

stakeholder input on the selection of these products. The initial list of proposed Priority Products includes the following product-chemical combinations:

- children's foam-padded sleeping products containing tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and/or tris(2-chloroethyl) phosphate (TCEP),
- paint and varnish strippers containing methylene chloride, and
- spray polyurethane foam systems containing methylene diphenyl diisocyanates.

Prior to adopting a Priority Product in regulation, DTSC must show that each product-chemical combination meets the following regulatory criteria:

- the product contains the chemical(s) of concern to DTSC and is sold in California;
- exposure to these chemicals has the potential to contribute to or cause significant or widespread adverse impacts to people or the environment; and
- exposure to these chemicals may occur through normal use, handling, or disposal of the product.

Once DTSC adopts a Priority Product in regulation, the Department is authorized to require product manufacturers to take specific actions including:

- removing or replacing the chemical of concern in the product with a safer alternative,
- removing the product from the California marketplace, or
- conducting an Alternatives Analysis to determine if safer alternatives exist.

If the product manufacturers do not comply, DTSC is authorized to require importers, assemblers, and/or retailers to stop selling the product in California.

California's consumers have access to a variety of paint and varnish stripping products that do not contain methylene chloride. However, technical considerations, such as the type of coating to be removed and the process time required, may mean that methylene chloride cannot be removed from all paint and varnish stripping products. DTSC anticipates that some manufacturers may be able to produce methylene chloride-free products, however, most manufacturers are more likely to conduct an Alternatives Analysis to determine if there are safer alternatives that are also technically functional and feasible.

C. Overview of the Proposal to Adopt Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product

The proposed regulation defines "paint and varnish strippers containing methylene chloride" as any product that contains methylene chloride that is marketed, sold, or described as a paint or varnish stripper designed to break down paint or varnish to facilitate its removal from a surface. Such products may be designed for indoor or outdoor use and can be used to remove varnish or paint from any chosen surface.

As required by regulation, DTSC considered a number of factors including the hazard traits, toxicological endpoints, and environmental fates associated with methylene chloride, as well as potential adverse impacts to sensitive subpopulations including infants, children, pregnant women, and workers from using or handling paint and varnish strippers containing methylene chloride.

After reviewing the scientific literature and obtaining stakeholder input during several public workshops, DTSC concluded that people, particularly workers and "do it yourself" consumers, are likely to be exposed to methylene chloride from the direct use of paint or varnish stripping products that contain this chemical. This information also suggested that bystanders, including children, infants, and pregnant women, may also become exposed to methylene chloride when they are near indoor locations where these products are being used. DTSC concluded that exposure to methylene chloride, either through direct use of paint and varnish stripping products or proximity to these applications, may cause significant or widespread adverse human health impacts due to the following hazard traits and toxicological endpoints:

- acute toxicity and death directly related to poisoning from methylene chloride inhalation;
- carcinogenicity;
- neurotoxicity;
- reproductive and developmental toxicity;
- dermal toxicity; and
- ocular toxicity.

By concluding that exposures to methylene chloride through the use of paint and varnish stripping products have the potential to adversely impact human health, DTSC met the regulatory requirements to adopt this 'product-chemical' combination as a Priority Product in regulation. Once this regulation is adopted, DTSC will have the authority to require the manufacturers to determine if there are safer alternatives to this chemical.

Attachment 2:

Scientific Conclusions to Be Addressed by Peer Reviewers Regarding DTSC's Proposal to Adopt *Paint and Varnish Strippers Containing Methylene Chloride* as a Priority Product

The statutory mandate for external scientific peer review (Health and Safety Code section 57004) 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.

DTSC requests that you make this determination for each of the following conclusion statements that constitute the scientific portion of the proposed regulation. An explanatory statement is provided for each conclusion to focus this review.

The subject of this review is a proposed regulation to adopt *Paint and Varnish Strippers Containing Methylene Chloride* as a Priority Product under the Safer Consumer Products regulatory framework. This framework requires DTSC to ensure that all product-chemical combinations proposed as Priority Products meet the following criteria:

- the product contains the chemicals of concern to DTSC and is sold in California;
- exposure to these chemicals has the potential to contribute to or cause significant or widespread adverse impacts to people or the environment; and
- exposure to these chemicals may occur through normal use, handling, or disposal of the product.

Following a review of available scientific literature, DTSC concluded that the proposal to adopt *Paint and Varnish Strippers Containing Methylene Chloride* as a Priority Product meets the required regulatory criteria described above and requests that this review focus on the following conclusions:

- exposure to methylene chloride may contribute to or cause significant or widespread adverse impacts to people, particularly to infants, children, pregnant women, and workers in the furniture stripping and remodeling industries; and
- people, particularly the sensitive subpopulations noted above, may be exposed to these chemicals through normal use, handling, or disposal of paint and varnish stripping products that contain this chemical.

The results of DTSC's literature review are presented in the report, "*Summary of Technical Information and Scientific Conclusions for Designating Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product*" completed in July, 2015. **The references listed in the specific sections of this report noted below will be provided on Compact Disk(s). DTSC will provide additional references from this report upon request.**

Conclusion 1 -

The hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern to contribute to or cause significant or widespread adverse impacts to human health.

Methylene chloride is known to the State of California to cause cancer, and is suspected or anticipated to be a human carcinogen by a variety of other authoritative bodies. Exposure to this chemical is also associated with other adverse health effects including neurotoxicity, reproductive and developmental toxicity, ocular toxicity, and dermal toxicity. In addition, several deaths have been attributed to the use of methylene chloride paint strippers without adequate ventilation or respiratory protection. Methylene chloride is highly volatile suggesting a significant risk for inhalation exposure during the use of paint or varnish strippers containing methylene chloride. Its vapors are heavier than air and may accumulate in the breathing zone during use. It has been shown that the use of methylene chloride in homes can lead to significantly elevated concentrations of methylene chloride vapors in indoor air. Cartridge-type air purifying respirators and dusts masks do not provide adequate protection against exposure.

The sections of the technical report (noted above) that pertain to Conclusion 1 include:

- Section I – Executive Summary, pages 3 – 4,
- Section IV – Hazard Traits, pages 5 – 8,
- Section VI – Exposure Potential of People or Wildlife to Methylene Chloride in Paint and Varnish Strippers, pages 9 – 11, and
- Section VII – Sensitive Subpopulations with Potential for Adverse Impacts from Methylene Chloride, page 11 – 12.

References included in these sections will be provided to the reviewers on CD as part of this request.

Conclusion 2

The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to methylene chloride related to the use of paint and varnish stripping products containing this Chemical of Concern.

Methylene chloride is frequently used as the active ingredient in paint and varnish strippers, including those that are widely available for purchase by consumers in California. A recent survey suggests that the most widely used paint and varnish stripping formulations sold in California contain methylene chloride. In 2011, nearly one third of all methylene chloride manufactured worldwide was used as a solvent in paint

and varnish strippers. Between 1996 and 2006, annual U.S. imports of methylene chloride totaled between 100 million and 500 million pounds.

Methylene chloride is colorless and highly volatile. Its vapors are heavier than air and may concentrate in the breathing zone during use. Inhalation of methylene chloride vapors during the use of paint and varnish strippers is a primary route of exposure to the chemical for humans. The use of methylene chloride-based products in home settings can result in high concentrations of methylene chloride in air, often exceeding OSHA PELs. In a home simulation study of furniture stripping, methylene chloride concentrations in air exceeded 2000 parts per million when paint and varnish strippers were used indoors without local exhaust ventilation. Concentrations in air of 2,300 parts per million are considered "Immediately Dangerous to Life and Health" by the National Institute for OSHA. Methylene chloride has a penetrating, ether-like odor, but people can become desensitized to the odor. Thus, odor alone cannot be relied upon as a means to detect the presence of methylene chloride in air. Those who work frequently with methylene chloride risk becoming desensitized to methylene chloride odor and, therefore, may be at an increased risk of exposure to methylene chloride via inhalation. Many consumers may not be aware that cartridge-type air purifying respirators and dusts masks will not provide adequate protection against methylene chloride vapors.

Methylene chloride exposure may also occur by dermal contact. Many consumers may not be aware that the most commonly used types of gloves, such as latex, rubber, and acetonitrile, are easily penetrated by methylene chloride. Numerous consumer and worker deaths have been associated with the use of methylene chloride paint or varnish strippers.

The sections of the technical report (noted above) that pertain to Conclusion 2 include:

- Section I – Executive Summary, pages 3 – 4,
- Section III – Physicochemical Properties, page 5,
- Section VI – Exposure Potential of People or Wildlife to Methylene Chloride in Paint and Varnish Strippers, pages 9 – 11, and,
- Section VII – Sensitive Subpopulations with Potential for Adverse Impacts from Methylene Chloride, page 11 – 12.

References included in these sections will be provided to the reviewers on CD as part of this request.

<u>The Big Picture</u>

Reviewers are not limited to addressing only the specific issues presented above, and are asked to contemplate the following questions.

(a) In reading the staff technical reports and proposed implementation language, are there any additional scientific issues that are part of the scientific basis of

the proposed regulation not described above? If so, please comment with respect to the statutory language given above.

(b) Taken as a whole, is the scientific portion of the proposed regulation based upon sound scientific knowledge, methods, and practices?

Reviewers should also note that some proposed regulatory actions may rely significantly on professional judgment where available scientific data are not as extensive as desired to support the statutory requirement for absolute scientific rigor. In these situations, the proposed course of action is favored over no action.

The preceding guidance will ensure that reviewers have an opportunity to comment on all aspects of the scientific basis of the proposed regulation. At the same time, reviewers also should recognize that DTSC has a legal obligation to consider and respond to all feedback on the scientific portions of the proposed regulation. Because of this obligation, reviewers are encouraged to focus feedback on the scientific issues that are relevant to the central regulatory elements being proposed.

Reviewers should also note that DTSC is required to review and revise, as appropriate, the Priority Products List every three years and intends to accept

and review additional data as it becomes available for individual Priority Products. The technical report that is the basis for the proposed regulation is therefore seen as providing the best available information for program implementation at this time.

Attachment 3:

List of Participants

Section A. California Department of Toxic Substances Control Personnel

Name	Title	Program	Location
André Algazi	Senior Environmental Scientist	Safer Products and Workplaces Program	Sacramento, CA
Tracy Behrsing*	Staff Toxicologist	Human and Ecological Risk Office	Sacramento, CA
Rob Brushia	Research Scientist III	Safer Products and Workplaces Program	Sacramento, CA
Anne Cooper Doherty	Environmental Scientist	Safer Products and Workplaces Program	Sacramento, CA
Lynn Goldman	Attorney	Office of Legal Affairs	Sacramento, CA
Stephanie Hummel*	DTSC Intern	Safer Products and Workplaces Program	Sacramento, CA
Dennis Guo	Research Scientist III	Safer Products and Workplaces Program	Sacramento, CA
Patrick Kerzic	Staff Toxicologist	Human and Ecological Risk Office	Chatsworth, CA
Daphne Molin	Senior Environmental Scientist	Safer Products and Workplaces Program	Sacramento, CA
Lynn Nakayama-Wong	Associate Toxicologist	Human and Ecological Risk Office	Sacramento, CA
Karl Palmer	Environmental Program Manager I	Safer Products and Workplaces Program	Sacramento, CA
Christine Papagni	Senior Environmental Scientist	Safer Products and Workplaces Program	Chatsworth, CA
Frank Parr	Senior Industrial Hygienist	Safer Products and Workplaces Program	Chatsworth, CA
Lisa Quagliaroli	Senior Environmental Scientist	Safer Products and Workplaces Program	Sacramento, CA
Eric Sciullo	Staff Toxicologist	Human and Ecological Risk Office	Sacramento, CA
Michael Wade	Senior Toxicologist	Human and Ecological Risk Office	Sacramento, CA
Meredith Williams	Deputy Director	Safer Products and Workplaces Program	Sacramento, CA

* No longer works for DTSC

Section B. External Participants.

Name	Title	Department / Program	Location
Jeff Fowles	Staff Toxicologist	California Department of Public Health, Center for Environmental Health	Richmond, CA
David Harrington*	Health Educator Consultant III	California Department of Public Health, Occupational Health Branch	Richmond, CA
Sara Hoover	Research Scientist III	Scientific Affairs Division, Office of Environmental Health Hazard Assessment	Sacramento, CA
Gail Krowech	Staff Toxicologist	Scientific Affairs Division, Office of Environmental Health Hazard Assessment	Sacramento, CA
Melanie Marty	Deputy Director	Scientific Affairs Division, Office of Environmental Health Hazard Assessment	Sacramento, CA
Jennifer McNary	Research Scientist	California Department of Public Health, Occupational Health Branch	Richmond, CA
Claudia Polsky	Deputy Attorney General	California Department of Justice	Oakland, CA
Martha Sandy	Supervising Toxicologist	Scientific Affairs Division, Office of Environmental Health Hazard Assessment	Sacramento, CA
Eileen Sheehan	Senior Policy Advisor - Green Chemistry	U.S. Environmental Protection Agency, Region 9	San Francisco, CA
Gina Solomon	Deputy Secretary for Science and Health	California Environmental Protection Agency	Sacramento, CA
Dennis Shusterman	Professor	University of California - San Francisco, School of Medicine	San Francisco, CA

* No longer works for the listed department

January 7, 2009

Supplement to Cal/EPA External Scientific Peer Review Guidelines – "Exhibit F" in Cal/EPA Interagency Agreement with University of California Gerald W. Bowes, Ph.D.

Guidance to Staff:

1. Revisions. If you have revised any part of the initial request, please stamp "Revised" on each page where a change has been made, and the date of the change. Clearly describe the revision in the cover letter to reviewers, which transmits the material to be reviewed. The approved reviewers have seen your original request letter and attachments during the solicitation process, and must be made aware of changes.

2. Documents requiring review. All important scientific underpinnings of a proposed science-based rule must be submitted for external peer review. The underpinnings would include all publications (including conference proceedings), reports, and raw data upon which the proposal is based. If there is a question about the value of a particular document, or parts of a document, I should be contacted.

3. Documents not requiring review. The Cal/EPA External Peer Review Guidelines note that there are circumstances where external peer review of supporting scientific documents is not required. An example would be "A particular work product that has been peer reviewed with a known record by a recognized expert or expert body." I would treat this allowance with caution. If you have any doubt about the quality of such external review, or of the reviewers' independence and objectivity, that work product – which could be a component of the proposal - should be provided to the reviewers.

4. Implementation review. Publications which have a solid peer review record, such as a US EPA Criteria document, do not always include an implementation strategy. The Cal/EPA Guidelines require that the implementation of the scientific components of a proposal, or other initiative, must be submitted for external review.

5. Identity of external reviewers. External reviewers should not be informed about the identity of other external reviewers. Our goal has always been to solicit truly independent comments from each reviewer. Allowing the reviewers to know the identity of others sets up the potential for discussions between them that could devalue the independence of the reviews.

6. Panel Formation. Formation of reviewer panels is not appropriate. Panels can take on the appearance of scientific advisory committees and the external reviewers identified through the Cal/EPA process are not to be used as scientific advisors.

7. Conference calls with reviewers. Conference calls with one or more reviewers can be interpreted as seeking collaborative scientific input instead of critical review. Conference calls with reviewers are not allowed.

Guidance to Reviewers from Staff:

1. Discussion of review.

   Reviewers are not allowed to discuss the proposal with individuals who participated in development of the proposal. These individuals are listed in Attachment 3 of the review request.

   Discussions between staff and reviewers are not permitted. Reviewers may request clarification of certain aspects of the review process or the documents sent to them.

   Clarification questions and responses must be in writing. Clarification questions about reviewers' comments by staff and others affiliated with the organization requesting the review, and the responses to them, also must be in writing. These communications will become part of the administrative record.

   The organization requesting independent review should be careful that organization-reviewer communications do not become collaboration, or are perceived by others to have become so. The reviewers are not technical advisors. As such, they would be considered participants in the development of the proposal, and would not be considered by the University of California as external reviewers for future revisions of this or related proposals. The statute requiring external review of science-based rules proposed by Cal/EPA organizations prohibits participants serving as peer reviewers..

2. Disclosure of reviewer Identity and release of review comments.

   Confidentiality begins at the point a potential candidate is contacted by the University of California. Candidates who agree to complete the conflict of interest disclosure form should keep this matter confidential, and should not inform others about their possible role as reviewer.

   Reviewer identity may be kept confidential until review comments are received by the organization that requested the review. After the comments are received, reviewer identity and comments must be made available to anyone requesting them.

   Reviewers are under no obligation to disclose their identity to anyone enquiring. It is recommended reviewers keep their role confidential until after their reviews have been submitted.

3. Requests to reviewers by third parties to discuss comments.

   After they have submitted their reviews, reviewers may be approached by third parties representing special interests, the press, or by colleagues. Reviewers are under no obligation to discuss their comments with them, and we recommend that they do not.

   All outside parties are provided an opportunity to address a proposed regulatory action during the public comment period and at the Cal/EPA organization meeting where the proposal is considered for adoption. Discussions outside these provided avenues for comment could seriously impede the orderly process for vetting the proposal under consideration.

4. Reviewer contact information.

The reviewer's name and professional affiliation should accompany each review. Home address and other personal contact information are considered confidential and should not be part of the comment submittal.

January 7, 2009

Supplement to Cal/EPA External Scientific Peer Review Guidelines – "Exhibit F" in Cal/EPA Interagency Agreement with University of California Gerald W. Bowes, Ph.D.

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1. Revisions. If you have revised any part of the initial request, please stamp "Revised" on each page where a change has been made, and the date of the change. Clearly describe the revision in the cover letter to reviewers, which transmits the material to be reviewed. The approved reviewers have seen your original request letter and attachments during the solicitation process, and must be made aware of changes.

2. Documents requiring review. All important scientific underpinnings of a proposed science-based rule must be submitted for external peer review. The underpinnings would include all publications (including conference proceedings), reports, and raw data upon which the proposal is based. If there is a question about the value of a particular document, or parts of a document, I should be contacted.

3. Documents not requiring review. The Cal/EPA External Peer Review Guidelines note that there are circumstances where external peer review of supporting scientific documents is not required. An example would be "A particular work product that has been peer reviewed with a known record by a recognized expert or expert body." I would treat this allowance with caution. If you have any doubt about the quality of such external review, or of the reviewers' independence and objectivity, that work product – which could be a component of the proposal - should be provided to the reviewers.

4. Implementation review. Publications which have a solid peer review record, such as a US EPA Criteria document, do not always include an implementation strategy. The Cal/EPA Guidelines require that the implementation of the scientific components of a proposal, or other initiative, must be submitted for external review.

5. Identity of external reviewers. External reviewers should not be informed about the identity of other external reviewers. Our goal has always been to solicit truly independent comments from each reviewer. Allowing the reviewers to know the identity of others sets up the potential for discussions between them that could devalue the independence of the reviews.

6. Panel Formation. Formation of reviewer panels is not appropriate. Panels can take on the appearance of scientific advisory committees and the external reviewers identified through the Cal/EPA process are not to be used as scientific advisors.

7. Conference calls with reviewers. Conference calls with one or more reviewers can be interpreted as seeking collaborative scientific input instead of critical review. Conference calls with reviewers are not allowed.

Guidance to Reviewers from Staff:

1. Discussion of review.

   Reviewers are not allowed to discuss the proposal with individuals who participated in development of the proposal. These individuals are listed in Attachment 3 of the review request.

   Discussions between staff and reviewers are not permitted. Reviewers may request clarification of certain aspects of the review process or the documents sent to them.

   Clarification questions and responses must be in writing. Clarification questions about reviewers' comments by staff and others affiliated with the organization requesting the review, and the responses to them, also must be in writing. These communications will become part of the administrative record.

   The organization requesting independent review should be careful that organization-reviewer communications do not become collaboration, or are perceived by others to have become so. The reviewers are not technical advisors. As such, they would be considered participants in the development of the proposal, and would not be considered by the University of California as external reviewers for future revisions of this or related proposals. The statute requiring external review of science-based rules proposed by Cal/EPA organizations prohibits participants serving as peer reviewers..

2. Disclosure of reviewer Identity and release of review comments.

   Confidentiality begins at the point a potential candidate is contacted by the University of California. Candidates who agree to complete the conflict of interest disclosure form should keep this matter confidential, and should not inform others about their possible role as reviewer.

   Reviewer identity may be kept confidential until review comments are received by the organization that requested the review. After the comments are received, reviewer identity and comments must be made available to anyone requesting them.

   Reviewers are under no obligation to disclose their identity to anyone enquiring. It is recommended reviewers keep their role confidential until after their reviews have been submitted.

3. Requests to reviewers by third parties to discuss comments.

   After they have submitted their reviews, reviewers may be approached by third parties representing special interests, the press, or by colleagues. Reviewers are under no obligation to discuss their comments with them, and we recommend that they do not.

   All outside parties are provided an opportunity to address a proposed regulatory action during the public comment period and at the Cal/EPA organization meeting where the proposal is considered for adoption. Discussions outside these provided avenues for comment could seriously impede the orderly process for vetting the proposal under consideration.

4. Reviewer contact information.

The reviewer's name and professional affiliation should accompany each review. Home address and other personal contact information are considered confidential and should not be part of the comment submittal.

CURRICULUM VITAE
James V. Bruckner

Education

University of Texas, Austin, B.S., 1968, Pharmacy
University of Texas, Austin, M.S., 1971, Pharmacology and Toxicology
University of Michigan, Ann Arbor, Ph.D., 1974, Toxicology

Academic Appointments

1974-1975	Assistant Professor of Pharmacology and Toxicology, College of Pharmacy, University of Kansas.
1975-1983	Assistant Professor of Pharmacology and Toxicology, Department of Pharmacology, Division of Toxicology, The University of Texas Medical School at Houston.
1980-1983	Adjunct Assistant Professor of Toxicology, Department of Environmental Sciences, The University of Texas School of Public Health.
1983-1992	Associate Professor, College of Pharmacy, University of Georgia (UGA), Chairman of UGA Toxicology Program Steering Committee.
1987-present	Adjunct Associate Professor and Professor, Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia
1992-1997	Professor of Pharmacology and Toxicology, College of Pharmacy, Director of the Interdisciplinary Toxicology Program, University of Georgia.
1995	Acting Department Head, Department of Pharmacology and Toxicology, College of Pharmacy, University of Georgia.
1995-1996	Visiting Professor, Department of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle.
1998-present	Professor of Pharmacology and Toxicology, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia.

Recent Professional Appointments (Selected)

1997-98	Member of the Committee on the Health and Safety Consequences of Child Labor. Board on Children, Youth and Families, National Academy of Sciences.
1998-2008	Member of the Subcommittee on Acute Exposure Guideline Levels for Hazardous Substances, Board on Environmental Studies and Toxicology, National Academy of Sciences.
2001	Member of the FIFRA Scientific Advisory Panel for Evaluation of Exposure and Hazards to Children from Contact with Chromated Copper Arsenate-Treated Wood Structures, Office of Pesticide Programs, U.S.EPA.
2002	Member of the Food Quality Protection Act Science Review Board, Office of Prevention, Pesticides and Toxic Substances, U.S.EPA.
2002-2003	Member of the Committee on the Use of Third Party Pesticide Toxicity Research with Human Research Participants, Policy and Global Affairs Division, National Academy of Sciences.
2002-2012	Member of the Underwriters Laboratories Expert Review Panel for evaluation of health risks of contaminants introduced into fluids by medical and water treatment devices.
2003-2006	Member of the International Life Sciences Institute (ILSI) Working Group on Physiological Parameters for Children.
2003-2004	Expert panel for Adverse Health Effects of Dental Amalgams, National Institute of Dental and Craniofacial Research and Food and Drug Administration.
2004	National Institute for Environmental Health Sciences (NIEHS) site visit panel for evaluation of a competitive renewal for a program project application.
2006	Expert panel for review of a document entitled "A Framework for Assessing Health Risks of Environmental Exposures to Children" for the Office of Research and Development, U.S.EPA.
2008	National Institute of Environmental Health Sciences Special Emphasis Review Panel for the National Toxicology Program. Research Triangle Park, NC.

2008	Expert reviewer of a draft document entitled "Interim Safety and Risk Assessment of Melamine and Its Analogues in Food for Humans", Center for Food Safety and Applied Nutrition, U.S.FDA.
2008	Member of Federal Insecticide, Fungicide and Rodenticide Act Science Advisory Board, U.S.EPA.
2009	Member of National Institute of Environmental Health Sciences (NIEHS) scientific research panel for review of Superfund Basic Research and Training Program Project applications.
2010	Member of NIH Nephrology/Toxicology grant application review panel ZRG1 DKUS-G(11).
2011	Chair of the external review panel for Toxicological Review of 1,4-Dioxane, IRIS, U.S.EPA.
2008-2014	Member of the ACGIH Threshold Limit Value (TLV)-Chemical Substances Committee.
2004-2012	Member of the Committee on Toxicology, Board on Environmental Studies and Toxicology, National Academy of Sciences.

Recent Publications (Selected)

Fisher, J.W., Campbell, J., Muralidhara, S., Bruckner, J.V., Ferguson, D., Mumtaz, M., Harmon, B., Crofton, K., Kim, H., and Almekinder, T.L.: Effects of PCB 126 on the hepatic metabolism of thyroxine and perturbations in the hypothalamic-pituitary-thyroid axis in the rat. *Toxicol. Sci.* 90: 87-95 (2006).

Anand, S.S., Kim, K.-B., Padilla, S., Muralidhara, S., Kim, H.J., Fisher, J.W., and Bruckner, J.V.: Ontogeny of hepatic and plasma metabolism of deltamethrin *in vitro*: Role in age-dependent acute neurotoxicity. *Drug Metab. Dispos.* 34: 389-397 (2006).

Mirfazaelin, A., Kim, K-B., Anand, S.S., Kim, H.J., Bruckner, J.V., and Fisher, J.W.: Development of a physiologically based pharmacokinetic model for deltamethrin in the adult Sprague-Dawley rat. *Toxicol. Sci.* 93: 432-442 (2006).

Kim, K.-B., Anand, S.S., Muralidhara, S., Kim, H.J., and Bruckner, J.V.: Formulation-dependent toxicokinetics explains the differences in the GI absorption, bioavailability and acute neurotoxicity of deltamethrin in rats. *Toxicology* 234: 194-202 (2007).

Kim, K.-B., Anand, S.S., Kim, H.J., White, C.A., Fisher, J.W., and Bruckner, J.V.: Toxicokinetic and tissue distribution study of deltamethrin in adult Sprague-Dawley rats. *Toxicol. Sci.* 101: 197-205 (2008).

Liu, Y., Bartlett, M.G., White, C.A., Muralidhara, S., and Bruckner, J.V.: Presystemic elimination of trichloroethylene in rats following environmentally-relevant oral exposures. *Drug Metab. Dispos.* 37: 1994-1998 (2009).

Jollow, D.J., Bruckner, J.V., McMillan, D.C., Fisher, J.W., Hoel, D., and Mohr, J.C.: Trichloroethylene risk assessment: A review and commentary. *Crit. Rev. Toxicol.* 39: 782-797 (2009).

Bruckner, J.V., White, C.A., Muralidhara, S., and Dallas, C.E.: Effect of exposure route and dosage regimen on the toxicokinetics and target organ toxicity of 1,1-dichloroethylene. *J. Pharmacol. Exp. Therap.* 333: 519-527 (2010).

Kim, K.-B., Anand, S.S., Kim, H.J., White, C.A., Fisher, J.W., Tornero-Velez, R., and Bruckner, J.V.: Age- dose- and time-dependency of plasma and tissue distribution of deltamethrin in immature rats. *Toxicol Sci.* 110: 354-368 (2010).

Tornero-Velez, R., Mirfazaelian, A., Kim, K.-B., Anand, S.S., Kim, H.J., Haines, W.T., Bruckner, J.V., and Fisher, J.W.: Evaluation of deltamethrin kinetics and dosimetry in the maturing rat using a PBPK model. *Toxicol. Appl. Pharmacol.* 244: 208-217 (2010).

Bruckner, J.V., Anand, S.S., and Warren, D.A.: Toxic effects of solvents and vapors. Ch. 24 in *Casarette and Doull's Toxicology: The Basic Science of Poisons*, (Klaassen, C.D., ed.), 8th edition, McGraw-Hill, New York (2014).

Zastre, J. Dowd, C. Bruckner, J, and Popovici, A.: Lack of p-glycoprotein mediated efflux and the potential involvement of an influx transport process contributing to the intestinal uptake of deltamethrin, cis-permethrin and trans-permethrin. Toxicol. Sci. 136: 284-293 (2013).

Bruckner, J.V.: Organic Solvents, CH.11, in Mammalian Toxicology (Abou-Donia, M.B., ed.) 1st edition, Wiley and Sons, Ltd., New York (2015).

2011	Chair of external review panel for Toxicological Review of 1,4-Dioxane (With Inhalation Updated), IRIS, U.S.EPA.
2012	Elected to the Society of Toxicology Nominating Committee.
2012	Invited reviewer of the Addendum to the Toxicological Profile for Trichloroethylene for the U.S. ATSDR.
2013	Chair of symposium "Applications of PBPK Modeling in Risk Assessment of Environmental Contaminants" at the XIII International Congress of Toxicology in Seoul, Korea.
2013	Reviewer of the update of the Toxicological Profile for Trichloroethylene for the U.S. ATSDR/CDC.
2008-2014	Member of the ACGIH Threshold Limit Value (TLV)- Chemical Substances Committee
2014	External reviewer of a draft IRIS document entitled "Toxicological Review of Trimethylbenzenes", U.S. EPA.
2014	External peer reviewer of Health Effects Documents for Perfluorooctanoic Acid (PFOA) and for Perfluorooctane Sulfonate (PFOS), U.S. EPA Office of Water.
2014	External reviewer of a draft IRIS document entitled "Toxicological Review of Ethylene Oxide", U.S. EPA.
2011-17	Member of the Food Quality Protection Act (FQPA) Scientific Advisory Board (SAB), U.S. EPA.
2013-16	Fellow of the Academy of Toxicological Sciences
2013-15	Member of the Science Advisory Board Chemical Assessment Advisory Committee, U.S.EPA.
2014	Science Advisory Board assessment of IRIS Toxicological Review of Trimethyl Benzenes, U.S. EPA
2014	Science Advisory Board assessment of IRIS Toxicological Review of Inhalation Carcinogenicity of Ethylene Oxide, U.S. EPA
2013-16	Member of the Science Advisory Board Hydraulic Fracturing Advisory Panel, U.S.EPA
2015	Reviewer of the Toxicological Profile for 1-Bromopropane for the U.S. ATSDR/CDC
2016-18	Reappointed Member of the Science Advisory Board Chemical Assessment Committee, U.S. EPA

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kamendulis, Lisa M.

eRA COMMONS USER NAME (credential, e.g., agency login): lkamendu

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Massachusetts, Amherst, MA	BS	05/1989	Biology
University of New Mexico, Albuquerque, NM	PhD	05/1994	Toxicology
Indiana University, Dept of Pathology	Post-Doc	05/1995	Toxicology
Indiana University, Dept of Biochemistry and Molecular Biology	Post-Doc	05/1996	Biochemistry

A. Personal Statement

My scientific background and training is in environmental toxicology. I have extensive experience with *in vitro* and *in vivo* animal models to assess mechanisms of action for the carcinogenicity elicited by environmentally important chemicals. In addition, during my post-doctoral studies, I expanded my research to use analytical chemistry to quantify drugs and chemicals in biological systems. These skills were further refined during my employment with the Department of Toxicology for the State of Indiana, as I provided direct oversight of the Forensic Toxicology Laboratory that was responsibility for the quantitation of alcohol and drugs of abuse in cases of impaired driving for the State of Indiana. A common thread throughout my research has been the evaluation of how oxidative stress contributes to chronic disease development. My current research program utilizes analytical chemistry (LC-MS/MS) to quantify biomarkers of oxidative stress and environmental chemicals in biological specimens, and to assess at what levels environmental chemicals elicit adverse outcomes. I will provide support to this project by providing expertise in the area of toxicology

Throughout my career, I have actively engaged students in my research, both at IU-Bloomington (IUB) and previously at IU School of Medicine (IUSM). Since my initial faculty appointment in 2005, at IUSM, I served as research advisor for 2 undergraduate, 2 MS and 2 PhD students and mentored 6 additional students in laboratory-based research rotations. In addition, I served on research advisory committees for 4 MS, and 4 PhD students. While our MPH and PhD programs at IUB are in the early stages of growth and development, I have or currently serve as the academic advisor for 6 MS and 5 PhD students, and the research advisor for 2 undergraduate, 4 MS and 1 PhD student, and a member of the research advisory committees for 1 MS and 1 PhD student. Since 2005, students have served as co-authors on 14 of 23 papers that I have published, highlighting my commitment to engaging and training students in research.

B. Positions and Honors

Positions and Employment

1996 – 2001 Assistant Director, Department of Toxicology, State of Indiana
2001 – 2003 Associate Director, Department of Toxicology, State of Indiana
2003 – 2004 Deputy Director, Department of Toxicology, State of Indiana
1996 – 2004 Assistant Scientist, Department of Pharmacology and Toxicology, Indiana University School of Medicine Assistant Professor (Part-time) Department of Pharmacology and Toxicology, Indiana University School of Medicine

2005 – 2010 Assistant Professor (research track), Department of Pharmacology and Toxicology, Indiana University, School of Medicine, Indianapolis, IN
2007 – 2010 Member, Indiana University Center for Environmental Health
2010 – 2011 Assistant Professor (visiting), Department of Environmental Health, Indiana University-Bloomington
2011 – present Associate Professor, Department of Environmental Health, Indiana University- Bloomington

Honors and Awards

1994 Sigma Xi Dissertation Award, University of New Mexico
1995 – 1996 NIAAA Postdoctoral Fellowship, Dept. Biochem. And Molecular Biology
1997 Tom L.Popejoy Dissertation Award - *University of New Mexico, Outstanding Dissertation, Basic Sciences – 1994-1997*

Other Experience and Professional Memberships

1996 – present Member, Society of Toxicology
1996 – present Member, Ohio Valley Regional Chapter of the Society of Toxicology
1997 – 1998 Councilor, Ohio Valley Regional Chapter of the Society of Toxicology
1998 – 2002 Secretary/Treasurer, Ohio Valley Regional Chapter of the Society of Toxicology
2001 – 2004 Member, Career resources and Development Committee, Society of Toxicology, *Chair* (2003-2004)
2002 – 2013 Member, Carcinogenesis Specialty Section, Society of Toxicology
2004 – 2006 Councilor, Carcinogenesis Specialty Section, Society of Toxicology
2011 – present Member, Center for Pancreatic Cancer Research, Indiana University Simon Cancer Center
2012 – 2015 Member, Institutional Animal Care and Use Committee, Indiana University, Bloomington, IN
2013 – present Member, Society of Toxicology, Occupational and Public Health, Member
2014 – present Member, Editorial Board, *Nature Scientific Reports*
2015 – present Member and Chair, Institutional Animal Care and Use Committee, Indiana University, Bloomington, IN

C. Contributions to Science (*Indicates student author)

1. The majority of my research and peer-reviewed publications have been centered on characterizing the mechanism(s) of action by which environmental chemicals elicit toxicities in two major organ systems; the liver, and more recently, my research portfolio has expanded to include assessing toxicity to the pancreas. Inflammatory processes have clearly been linked to cancer development, and some of my recent work has established that Kupffer cells, the resident macrophage population in the liver, provide an inflammatory stimulus that enhances the growth of both liver cells and precancerous lesions in the liver, thus linking this cell population to the carcinogenesis process. As Kupffer cells are difficult to isolate and purify in high yields from the rodent liver, my laboratory developed and characterized a Kupffer cell line that retains many features of primary cells. I have served as the primary investigator or co-investigator in these studies.

   a) Roberts, RA, Ganey, PE, Ju, C, Kamendulis, LM, Rusyn, I, Klaunig, JE (2007).Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis.Toxicol. Sci. 96(1):2-15. (PMID: 17122412)
   b) Kamendulis LM, *Corthals SM, Klaunig JE (2010). Kupffer cells participate in 2-butoxyethanol-induced liver hemangiosarcoma. Toxicology 270: 131-136. (PMID: 20153399)
   c) *Owumi SE, *Corthals SM, Uwaifo AO, Kamendulis LM, Klaunig JE. (2012). Depletion of Kupffer cells modulates ethanol-induced hepatocyte DNA synthesis in C57Bl/6 mice. Environ Toxicol. Epub Sep 20, 2012. (PMID 22996800)
   d) *Wang, Z-Y, Burlak, C., Klaunig, JE, Kamendulis, LM (2014). Development of a Cytokine-Producing Immortalized Murine Kupffer Cell Line. Cytokine 70(2): 165-172 (PMID: 25138015)

2. Oxidative Stress and Environmental Analyses. Oxidative stress has been observed during the progression of a growing list of human diseases including various types of cancer. A critical skill needed for assessing the risk of environmental factors on human health is the ability to quantify levels of chemicals and/or biomarkers of exposure to chemicals in biological systems. A common thread throughout my research has been the evaluation of how *oxidative stress* - whether elicited by exposure to chemicals, immune cells (i.e.

Kupffer cells in the liver), or inflammatory processes – contributes to chronic disease development. I have served as the primary investigator or co-investigator in these studies.

a) Kamendulis, LM, *Zhang, H, Wang, Y, Klaunig, JE (2002). Morphological Transformation and Oxidative Stress Induced by Cyanide in Syrian Hamster Embryo (SHE) Cells. Toxicol. Sci., 68: 437-443 PMID: 12151639)
b) Klaunig JE, Kamendulis LM (2004). The Role of Oxidative Stress in Carcinogenesis. Ann. Rev. Pharmacol.Toxicol. Vol. 44: 239-267 (PMID: 14744246).
c) *Pu, X, Kamendulis, LM, Klaunig, JE (2006). Acrylonitrile Induces Oxidative DNA damage in Rat Astrocytes. Environ Mol. Mutagen., 47: 631-638 (PMID: 19546159)
d) Klaunig, J.E., Kamendulis, L.M. and Hocevar, B.A. (2010) Oxidative stress and damage in chemical carcinogenesis. Toxicological Pathology. 38: 96-109. (PMID: 20019356).

3. Collaborative Projects: Oxidative Stress Environmental Analysis. The ability to quantify oxidative stress as a biomarker of exposure in biological samples is gaining increased interest in both basic and clinical research. My laboratory uses LC-MSMS for the analysis of biomarkers of oxidative stress and for the quantitation of environmental chemicals, such as PFOA, in biological samples. In addition, a number of researchers on the IU campuses perform disease-related research in which oxidative stress and environmental influences may be contributing factors, and/or alters individual susceptibility to diseases. to address a research need in my laboratory and to assist with ongoing research efforts for other investigators on the IU campus, I created a research service laboratory facility "Oxidative Stress Environmental Analysis Core laboratory" within the Department of Environmental Health. My laboratory has provided data for several investigators at IU that have been used in extramural grant submissions and peer-reviewed publications. As a collaborator on these projects, I have served as a co-investigator on these studies.

a) Vuppalanchi, R, Juluri, R, *Bell, L, Ghabril, M, Kamendulis, L, Klaunig, JE, Saxena R, Agrawal D, Johnson, MS, Chalasani N (2011). Oxidative stress in chronic liver disease: Relationship between peripheral and hepatic measurements. Amer. J. Med. Sci. 342: 314-317 (PMID: 21691193; PMCID PMC3644215).
b) Gupta SK, Shen C, Moe SM, Kamendulis LM, Goldman M, Dubé MP (2012). Worsening Endothelial Function with Efavirenz Compared to Protease Inhibitors: A 12-Month Prospective Study. PLos ONE 7(9): e45716 (PMID 23029197).
c) *Conroy SK, McDonald BC, Smith DJ, Moser LR, West JD, Kamendulis LM, Klaunig JE, Perkins SM, Champion VL, Unverzagt FW, Saykin AJ (2013). Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res. Treatment. 137: 493-502. (PMID 23263697; PMCID PMC3543695)
d) Friedman AN, Chambers M, Kamendulis LM, Temmerman J. (2013) Short-Term Changes after a Weight Reduction Intervention in Advanced Diabetic Nephropathy. Clin J. Am. Soc. Nephrol. (PMID:23929927; PMCID PMC3817909)
e) Gupta SK, Slaven JE, Kamendulis LM, Liu Z. (2015). A randomized, controlled trial of the effect of rilpivirine versus efavirenz on cardiovascular risk in healthy volunteers. J. Antimicrob. Chemother. 70(10):2889-2893.(PMID 26169561)

4. Environmental Influences in Pancreatic Cancer. Among all cancers, pancreatic cancer is one of the most lethal forms of cancer diagnosed, and the fourth leading cause of cancer deaths in the United States, with a five year survival rate of less than 6%. Hereditary genetic predisposition accounts for only 10-20% of pancreatic cancer cases; thus as with many other chronic diseases, environmental or lifestyle exposures to carcinogens have been postulated to contribute to the development of pancreatic cancer. I have been a Co-investigator in a human study that evaluated the contribution of environmental factors and selective single nucleotide polymorphisms in relation to pancreatic cancer susceptibility. In addition, based on my training as a toxicologist and experience with animal models of disease, my research is centered on evaluating how environmental chemicals induce toxicities. Perfluorooctanoic acid (PFOA), a persistent environmental chemical, has been shown to induce pancreatic acinar cell tumors in rodents. Recently, in collaboration with Dr. Barbara Hocevar, we have shown that PFOA levels increase in the pancreas of mice following exposure, that is accompanied with increases in oxidative damage in the pancreas. I have served as the primary investigator or co-primary investigator on these studies.

a) Klaunig JE, Hocevar BA, Kamendulis LM (2012). Mode of Action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and Human Relevance. Reprod. Toxicol. 33:410-418 (PMID: 22120428)
b) Hocevar BA, Kamendulis LM, *Pu X, Perkins SM, *Wang Z-Y, Johnston EL, DeWitt JM, Li L, Loehrer PJ, Klaunig JE, Chiorean EG. (2014). Contribution of environment and genetics to pancreatic cancer susceptibility. PLoS ONE, Mar 20; 9(3): e90052. doi: 10.1371. (PMID: 24651674; PMCID PMC3961224)
c) Kamendulis, LM, *Wu, Q, Sandusky, GE, Hocevar, BA (2014). Perfluorooctanoic acid exposure triggers oxidative stress in the mouse pancreas. Toxicol. Reports 1: 513-521. (selected as Editors choice)

A complete list of published work (MyBibliography): http://www.ncbi.nlm.nih.gov/sites/myncbi/1bWW-U0yQhTA_/bibliography/48887308/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

Departmental Start-Up Grant, Indiana University 7/1/2011 – present
The purpose of this grant is to set up the PIs laboratory and fund preliminary studies needed to be competitive for extramural research support.
Role: PI
No overlap

Completed Research Support During the Last Three Years

School of Public Health – Developmental Research Grant 6/1/2014 – 5/31/2015
"Development of Analytical Measurements for Epigenetic Research"
Develop and validate an LC-MS/MS method for the quantitation of 5-mC and 5hmC as a measure of global DNA methylation status. This project will also determine whether differences in global DNA methylation exist between a population of pancreatic cancer patients and healthy control subjects.
Role: PI ($5,000 Direct Costs)

School of Public Health – Faculty Research Grant Program 1/1/2014 – 12/31/2014
"Mechanisms of PFOA mediated oxidative stress"
Studies to determine develop LC-MS/MS methods to measure biomarkers of oxidative stress produced following exposure to PFOA. The studies are designed to provide critical data needed for the resubmission of an NIH R01.
Role: Co-PI
No overlap

School of Public Health – Faculty Research Grant Program 4/1/2013 – 4/31/2014
"Role of and alcohol and nutrition in pancreatic disease"
These studies evaluated how alcohol and dietary factors altered early events that occur in the progression of pancreatic cancer development
Role: Co-PI

Indiana University Faculty Research Support Program (IU FRSP) 1/1/2013 – 12/31/2013
"Development of an *in silico* model of alcoholic liver disease"
Studies will develop an in silico model of alcoholic liver disease informed by data derived from an in vivo mouse model of alcoholic liver fibrosis
Role: Co-PI

Indiana University School of HPER: Developmental Research Grant 06/2012 – 05/2013
"Development of analytical methods for quantifying biomarkers of oxidative stress and their application to chronic human diseases"
This projects goal is to develop analytical methods for the detection and quantitation of etheno-DNA adducts, in biological matricies.
Role: PI

Children's Tumor Foundation: Neurofibromatosis Clinical Research Award. 02/2011 – 06/2012
"Biomarkers of cardiovascular disease as predictors of NF1 severity"
This study examined whether biomarkers of oxidative stress and inflammatory pathways were associated with the severity of NF-1 cardiovascular complications in human subjects.
Role: Co-PI

Indiana University School of Health, Physical Education and Recreation 05/2011 - 04/2012
Faculty Research Support Program
"Characterization of CD90+ Hepatocytes in Liver Fibrosis"
This award provided funding for the development of pilot data to isolate populations of putative stem cells from liver and to characterize general functions of the cell populations
Role: PI

RESUME

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Colorado State University
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420 Apple Blossom Lane
Fort Collins, CO 80526
Tel. 970-581-5101
Fax. 970-226-0294
Email: raymond.s.h.yang@gmail.com

EDUCATION: Cornell University, Postdoctoral Training in Environmental Toxicology 1970 - 1973
North Carolina State University, Ph.D. (1970), M.S. (1967) - Toxicology, Entomology
National Taiwan University, B.S. (1963) - Biology

EMPLOYMENT RECORD:

6/2010 – Present Professor Emeritus of Toxicology and Cancer Biology, Colorado State University
2008 – Present Principal Scientist and owner of Ray Yang Consulting, LLC
10/2007 – 9/2009 Visiting Scientist, USEPA/NCEA-Cincinnati
7/2006 – 6/2007 Visiting Professor, National Health Research Institutes (NHRI), Zhunan, Taiwan.
1983 - 1990 Chemical Manager/Senior Staff Member, NIEHS/NTP
1976 – 1983 Senior Scientist, Mellon Institute – Union Carbide Corporation
1973 - 1976 Research Associate, Assistant Professor, Institute of Comparative and Human Toxicology, Albany Medical College

SELECTED NATIONAL AND INTERNATIONAL COMMITTEE WORK:

2001-2005. Environmental Health Sciences Review Committee (Study Section for Center Grants, and Training Grants), NIEHS, NIH, DHHS.
2002-2003. USEPA Science Advisory Board, Member (Consultant), for reviewing TCE Health Risk Assessment: Synthesis and Characterization.
2003-2004. Study Section on Innovative Toxicology, NCI, NIH, DHHS.
2003-2004. USEPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel Member, for reviewing PBPK Modeling Application in Cumulative Risk Assessment of *n*-Methyl Carbamate Pesticide.
2004-2007. Board of Scientific Counselors, Agency for Toxic Substances and Disease Registry (ATSDR) and National Center for Environmental Health (NCEH), CDC, DHHS
2005-2006. Member of Committee on Human Biomonitoring for Environmental Toxins, National Research Council, National Academy of Sciences.
2006. International Workshop Panel Member on Mixture Toxicity, Society of Environmental Toxicology and Chemistry (SETAC)/NoMiracle (European Union)

SELECTED PUBLICATIONS:

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GOVERNOR

MATTHEW RODRIQUEZ
SECRETARY FOR
ENVIRONMENTAL PROTECTION

State Water Resources Control Board

April 21, 2016 **VIA ELECTRONIC MAIL**

James V. Bruckner, Ph.D.
Professor, Pharmaceutical and Biomedical
Sciences College of Pharmacy
University of Georgia
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Athens, GA 30602

SUBJECT: PEER REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

Dear Professor Bruckner,

My letter today is intended to initiate the external review.

Included with this letter are the following:

1. March 7, 2016 memorandum from Karl Palmer, Department of Toxic Substances Control (DTSC), to me, "Request for External Peer Review for the Proposed Adoption of Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product."

2. Subject of Review (Revised Title): "Summary of Technical Information and Scientific Conclusions for Designating Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product." (This is the technical report supporting the proposed regulation, not the regulation itself).

3. CD of all references listed in foregoing document.

4. January 7, 2009 Supplement to the Cal/EPA Peer Review Guidelines.

<u>Comments on the Foregoing</u>

1. You have been sent a copy of the March 7, 2016 request memorandum during the solicitation process for reviewer candidates conducted by the University of California, Berkeley Institute of the Environment.

2. <u>Attachment 2 to the request memorandum provides focus for the review</u>. I ask that you <u>address all topics, as expertise allows, in the order listed</u>.

3. The January 7, 2009 Supplement – you received this earlier when I approved you as a reviewer. I am sending it again to make certain that you have it. In part, it provides guidance to ensure the review is kept confidential through its course. The Supplement notes reviewers are under no obligation to discuss their comments with third-parties after reviews have been submitted. We recommend they do not. All outside parties are provided opportunities to address a proposed regulatory action through a well-defined regulatory process. Please direct third parties to me.

Questions about the review, or material, should be for clarification, in writing – email is fine, and addressed to me. My responses will be in writing also. DTSC should not be contacted.

Please send your reviews to me on May 21, 2016, not before. I will subsequently forward all reviews together to DTSC with reviewers' Curriculum Vitae. All this information will be posted at the appropriate DTSC program website.

Your acceptance of this review assignment is most appreciated.

Sincerely,

Gerald W. Bowes

Gerald W. Bowes, Ph.D.
Manager, Cal/EPA Scientific Peer Review Program
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April 21, 2016

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SUBJECT: PEER REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

Dear Professor Kamendulis,

My letter today is intended to initiate the external review.

Included with this letter are the following:

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May 3, 2016

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SUBJECT: PEER REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

Dear Professor Yang,

My letter today is intended to initiate the external review.

Included with this letter are the following:

1. March 7, 2016 memorandum from Karl Palmer, Department of Toxic Substances Control (DTSC), to me, "Request for External Peer Review for the Proposed Adoption of Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product."

2. Subject of Review (Revised Title): "Summary of Technical Information and Scientific Conclusions for Designating Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product." (This is the technical report supporting the proposed regulation, not the regulation itself).

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Questions about the review, or material, should be for clarification, in writing – email is fine, and addressed to me. My responses will be in writing also. DTSC should not be contacted.

Please send your reviews to me on June 1, 2016, if not before. I will subsequently forward all reviews together to DTSC with reviewers' Curriculum Vitae. All this information will be posted at the appropriate DTSC program website.

Your acceptance of this review assignment is most appreciated.

Sincerely,

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May 23, 2016

Peer Review for the Proposed Adoption of Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product

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The statutory mandate for external scientific peer review (Health and Safety Code section 57004) 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.

Conclusion 1

The hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern to contribute to or cause significant or widespread adverse impacts to human health.

The account…of the scientific basis for the assertion that DCM can contribute to or cause significant adverse health impacts…in the Summary of the current document is inadequate. Since excessive CNS depression and death are the primary concerns of excessive DCM exposure, more published accounts and details of fatalities with estimates of exposure levels are warranted. The Summary cites just one published paper and one unpublished autopsy report. Fairfax (1996) reported the deaths of two floor refinishers from exposure to an estimated >53,000 ppm. Tay et al. (1995) described a fatal case probably involving inhalation of up to 100,000 ppm DCM.

Fatalities among DCM workers have also been reported by Kim et al. (1996), Manno et al. (1992), Novak and Hain (1990), Fechner et al. (2001) and many others. Most such publications have not included measurements of DCM vapor levels, though experiments with laboratory animals are informative. Test species do not appear to vary substantially in their susceptibility to DCM. Six-hour LC_{50} values for mice and rats range from 14,000-17,000 ppm (ATSDR, 2000; NAS, 2009). Much higher vapor concentrations are required to kill animals with brief exposures (i.e., rat 15 min LC_{50} = 57,000 ppm).

It is important to recognize and cite the work of the National Academy of Sciences Subcommittee for Acute Exposure Guideline Levels (AEGLs). This panel was established in the 1990s to develop scientifically credible acute exposure limits for inhalation of hazardous substances that are accidentally or intentionally released into communities. AEGLs are vapor concentrations above which a person could experience: notable discomfort or irritation (AEGL-1); serious long-lasting health effects (AEGL-2); and life-threatening effects or death (AEGL-3).

AEGLs were determined for five exposure periods (10 and 30 min and 1, 4, and 8 hours). AEGL-3s for DCM range from 12,000-2,100 ppm (NAS, 2009).

Primary mechanisms of toxicity of DCM should be addressed, in order to demonstrate that the Priority Product designation conclusions are based on sound science. The primary cause of symptoms of acute DCM exposure is central nervous system (CNS) depression. Most all organic solvents, if inhaled in sufficient concentrations for a sufficient duration, will be readily absorbed and taken up from the blood into the brain. The lipophilic compounds accumulate in neuronal membranes and myelin sheaths. The chemicals' presence inhibits the propagation and regeneration of action potentials, though inhibition of membrane receptors is also believed to contribute to neuronal dysfunction. DCM was used in the 1920s as a surgical anesthetic. CNS effects appear to be entirely reversible, but long-term, high-level exposure to DCM and other solvents may lead to a debilitating degenerative condition known as chronic solvent encephalopathy (Bruckner et al., 2013). Thus, under extreme, chronic exposure conditions DCM may be termed a neurotoxicant (i.e., cause neurological structural and/or functional changes that persist after the parent chemical and its bioactive metabolites have been eliminated from the body). It is stated in the text of the current document's Summary that "DCM is recognized as a neurotoxicant." CDC (2012) is cited to support this statement. CDC (2012) is an account in a weekly CDC publication of deaths of bathtub refinishers due to DCM. This article should be cited instead under Acute Toxicity in the Summary. U.S. EPA (2015b) is also referenced in the Summary in support of the conclusion that DCM is a neurotoxicant. U.S. EPA (2015b) is merely a Technical Factsheet. It does not serve as scientific support for the supposition that DCM is a neurotoxicant.

The primary cause of death and other common manifestations of acute DCM exposure (e.g., dizziness, headache, confusion, memory loss, incoordination) is CNS depression (NAS, 2009). Very high concentrations of organic solvents can also induce cardiac arrhythmias by sensitizing heart muscle to catecholamines such as epinephrine (Reinhardt et al., 1973). The severity of cardiac dysfunction is exacerbated by stress and hypoxia. Decrease in cardiac output and blood/oxygen supply to tissues will potentiate the inhibitory effects on the CNS and other organ systems. Systemic accumulation of carbon monoxide (CO) formed by metabolism of DCM will further compound the degree of oxygen deficiency in tissues throughout the body.

It is accurately related in section 2.c. of the Summary that carbon monoxide (CO) formed by metabolism of DCM may differentially affect children. Although there appeared to the Summary's author to be no relevant studies, results of investigations of laboratory animals and humans exposed to CO alone have been published. Carmines and Rajendran (2008) found that CO in cigarette smoke was solely responsible for reduced fetal weight in rats. Venditti et al. (2011) reported increased fetal deaths and decreased fetal mass and litter size in mice exposed continuously to 400 ppm CO during pregnancy. Towers and Corcoran (2009) observed abnormal fetal cardiac monitor tracings for three women poisoned by CO. The irregularities disappeared upon treatment of the mothers. Such studies suggest that sufficiently high DCM exposure during pregnancy will be detrimental to the fetus, but do not tell us what the exposure intensity and

duration must be. Axelsson et al. (1984) reported a slight, but statistically insignificant increase in the spontaneous abortion rate for female laboratory workers exposed to organic solvents including DCM. Taskinen et al. (1985) reported an increased risk of spontaneous abortions of borderline significance in women exposed to DCM in the pharmaceutical industry.

Fetuses, infants and young children may be at increased risk of adverse effects of DCM due to CO. Carboxyhemoglobin (COHb) in the mother's blood reduces the amount of oxygen released to the fetus. Fetal CO levels continue to rise after the mother's peak and begin to fall, resulting in a relatively long duration of fetal CO exposure (Aubard and Magne, 2000). As related in the Summary, fetal hemoglobin has a relatively high affinity for CO. The resulting increase in COHb half-life results in reduced oxygen carrying capacity of the blood of fetuses and infants. Fetuses, infants and young children have high tissue oxygen demand because of their high intermediary metabolism rates. The CNS is particularly sensitive to hypoxia, with lipid peroxidation and other changes potentially producing long-term structural and functional deficits in the brain (Levy, 2015; Lopez et al., 2009). The latter researchers observed evidence of oxidative stress in offspring of rats exposed to just 25 ppm CO during pregnancy. A number of rodent studies reviewed by Levy (2015) have demonstrated impaired memory, learning, and behavior following prenatal and following postnatal low-level CO exposure. A 3-hour exposure of 10-day-old rat pups to 5 or 100 ppm CO inhibited developmental neuroapoptosis in the neocortex and hippocampus, dose dependently, as well as impairing memory, learning and social behavior (Cheng et al., 2012). Young children would be expected to metabolize more DCM to CO, due to their (a) relatively large liver and liver perfusion rate; and (b) high activity of hepatic microsomal cytochrome P4502E1 (Hines, 2008), the isozyme primarily responsible for oxidation of DCM.

In light of the foregoing, it is apparent that fetuses, infants, young children and pregnant women may be at increased risk of CO and DCM. Certain other groups may also be at risk, including those with compromised cardiovascular function, cerebrovascular disease, anemia, and obstructive pulmonary disease; smokers; the elderly; and people taking CNS depressant medications (Raub and Benignus, 2002). The CNS depressant effects of DCM and COHb-induced hypoxia are difficult to distinguish and likely compound one another.

Respiratory effects, dermatotoxicity and ocular toxicity are listed in the Summary of the current document. Direct exposure of the conjunctival and nictating membranes to any organic solvent in high enough concentration will cause irritation and inflammation. DCM is not unique in this regard. I anticipate that penetration of the intact stratum corneum would significantly limit skin irritation, unless DCM were placed under an occlusive patch that retarded evaporation and enhanced absorption. Inhalation of high concentrations of solvents, including DCM, will also irritate the respiratory tract, resulting in nose and throat irritation, cough, shortness of breath and difficulty breathing.

The sections of the Summary pertaining to carcinogenicity consist only of a listing of DCM's cancer classifications by regulatory and scientific bodies, and mention that fetuses, infants and children are assumed to be more susceptible to carcinogens. There should be some presentation and discussion of the scientific bases for the conclusion that DCM presents a cancer risk to immature and mature members of the community.

DCM has been found to be a relatively weak carcinogen in rodents. High, chronic exposures have produced species- and gender-specific tumors in a limited number of organs of mice or rats (ATSDR, 2000; U.S. EPA, 2011). Two-year inhalation exposures of 2,000-4,000 ppm have generally been required to cause malignant neoplasms of the salivary gland, liver and/or lung. The liver and lung tumors in mice do not appear to be associated with cytotoxicity or increased DNA synthesis and cell proliferation (Maronpot et al., 1995). The tumors are believed to be initiated by a reactive intermediate generated via the glutathione S-transferase theta (GST-T1) mediated metabolic pathway (Andersen et al., 1987). The ability of the liver of different species to metabolize DCM by the GSTT1 pathway is as follows: mouse >> rat > human high conjugators > hamster > human nonconjugators (Thier et al., 1998). DCM is metabolized primarily by GST conjugation and CYP2E1-catalyzed oxidation to formyl chloride and CO. The oxidative pathway predominates under low DCM exposure conditions found in occupational and environmental settings (Schlosser et al., 2015), but becomes saturated at high DCM concentrations, such as those used in the rodent cancer bioassays and encountered in some occupational settings.

A large body of research demonstrates there is substantial variation in the susceptibility of different species, as well as different individuals, to DCM carcinogenicity. DNA single strand breaks (SSB) are produced by a 60-fold lower concentration of DCM in mouse than in rat hepatocytes. No SSB were detected in hamster or human hepatocytes (Graves et al., 1995). GST-T1 activity is substantially higher in mouse than in rat or human hepatocytes. GST-T1 is also present in relatively high levels in mouse Clara cells and ciliated cells at alveolar/bronchiolar junctions (Mainwaring et al., 1996). Clara cells are found in much lower numbers in rat lung and are rare in humans. Interhuman variation in ability to metabolically activate DCM in the liver is associated with genetic polymorphisms in the GST-T1 allele (Haber et al., 2002; Schlosser et al., 2015). A probabilistic physiological model incorporating a Baysesian optimization to obtain posterior distributions of GST-T1 genotypes was developed and utilized to yield estimations of internal doses of GST-T1 metabolites. The model was used by the U.S. EPA (2011) in its estimation of cancer risk for the presumed most sensitive GST-T1 genotype in humans.

The Summary of the current document mentions that epidemiological data have linked DCM to cancers of the brain, liver and the biliary tract. Only Cooper et al. (2011) is cited. This reference is incomplete. It would be preferable to cite U.S. EPA (2011). It should also be noted that ATSDR (2010) published a Toxicological Profile Addendum, which contains limited information on cancer epidemiology. ACGIH (2001) gave DCM an A3 designation (Confirmed Animal Carcinogen with Unknown Relevance to Humans). Evidence of associations between DCM and specific tumors in humans is not strong, despite a substantial number of studies of

DCM-exposed employees. In just one assessment was there an elevated risk of death from liver and biliary tract cancer (Lanes et al., 1990). Blair et al. (1998) reported an elevated relative risk for breast cancer mortality in one group of female aircraft maintenance employees. Large case-control studies of women occupationally exposed to organic solvents including DCM did not show statistically significant associations (Cantor et al., 1995; Peplonska et al., 2010). There have been occasional reports of increased rates of other types of cancer, including non-Hodgkin lymphoma or multiple myeloma (Schlosser et al., 2010). In most instances the subjects were exposed to multiple solvents. The majority of investigations have revealed weak or no apparent associations between relatively high DCM inhalation exposures in industry and cancers.

Conclusion 2

The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to methylene chloride related to the use of paint and varnish stripping products containing this Chemical of Concern.

One of the basic tenets, or conclusions, in this document is that methylene, or dichloromethane chloride (DCM), may contribute to or cause significant or widespread adverse impacts to people, particularly to infants, children, pregnant women, and workers in the furniture stripping and remodeling industries. MC, when inhaled in very high concentrations, has the potential to cause adverse effects as significant/serious as myocardial dysfunction and death. There are numerous case reports in the clinical literature of fatalities due to DCM inhalation (ACGIH, 2001; ATSDR, 2000; U.S. EPA, 2011). Most fatal cases involve occupational exposure. Only two found by the NAS (2009) resulted from consumer exposure. Nevertheless, use of commercial products containing large amounts of DCM is widespread. Misuse, resulting in excessive inhalation exposure in inadequately ventilated areas, may be quite common/widespread, and result in manifestations of central nervous system (CNS) depression ranging from headache and dizziness to respiratory depression and death.

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PEER REVIEW FOR THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT

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May 21, 2016

I have reviewed all materials provided to me concerning peer review of the proposed adoption of paint and varnish strippers containing methylene chloride as a priority product, and reviewed the relevant scientific literature provided. I have addressed all topics included in the request for peer review, in the listed order.

Overview:

Methylene chloride (dichloromethane) is classified as a volatile halogenated hydrocarbon (NIOSH, 1986; ATSDR, 2000). The vapors of methylene chloride are heavier that air and may concentrate in close proximity to areas in which it is used. It is commonly used in paint and varnish stripping products, at concentrations reported between 16-100%. Due to its chemical properties and use in paint and varnish stripping products, the main route of exposure expected form use of paint and varnish strippers containing methylene chloride is inhalation exposure. Following inhalation exposure, many acute and chronic adverse health effects have been observed in animals and human studies including death, systemic effects, neurological effects, reproductive effects, developmental effects, genotoxic effects, and cancer. Based on

review of the literature concerning the adverse health effects and volume of use of methylene chloride in California, DTSC has formulated two conclusions. My specific opinions for conclusions1 and 2 are provided in the following sections. Included in my review is the evaluation of whether the proposed regulation is based on sound scientific knowledge, methods and practices.

Conclusion 1: The hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern to contribute to or cause significant or widespread adverse impacts to human health.

Methylene chloride is used widely in various industrial processes, and consumer products, including paint and varnish stripping products. Due to its widespread use and potential for human exposures (both in the general and occupational populations), numerous studies have been conducted to evaluate the acute and chronic toxicities elicited by methylene chloride. Since inhalation is the principal route of exposure to methylene chloride, many studies have evaluated adverse health effects by this route of exposure. Acute and chronic adverse health effects have been observed in animals and human studies, and include death, systemic effects, neurological effects, reproductive effects, developmental effects, and cancer.

Death: Acute exposure to methylene chloride via inhalation has resulted in death in humans (ATSDR, 2000). Numerous fatalities have been associated with the occupational use of paint and varnish stripers containing methylene chloride (CDC, 2012; OSHA, 2013). Many case reports have documented consumer deaths from use of methylene chloride-containing paint strippers, however, the exact number of consumer fatalities is not known. Exposure levels were not measured in all cases, however, it has been suggested that both high exposures and inadequate ventilation contributed to these fatalities. Death from inhalation exposure to methylene chloride is believed to result from respiratory depression secondary to narcosis.

Carbon monoxide is produced during metabolism of methylene chloride, leading to increased levels of COHb, and lowered oxygen delivery systemically. Thus, in addition to individuals with high exposures due to occupation or product use, individuals that smoke or who have underlying cardiovascular disease may be at increased risk for toxic effects from methylene chloride exposures. Similarly, carbon monoxide has a higher affinity to fetal hemoglobin, thus fetuses and infants may be a higher risk from exposures.

Respiratory Effects: Concerning human effects, a worker subjected to acute inhalation exposure of methylene chloride for one hour resulted in death by asphyxiation (Winek et al. 1981). Additional reports include that of two individuals who had been working in confined spaces with a paint remover consisting of >80% w/w methylene chloride, that presented to emergency rooms with symptoms of dyspnea, cough, and midchest tightness (Snyder et al. 1992a, 1992b).

Gastrointestinal Effects: Nausea and vomiting have been reported following acute inhalation of methylene chloride (ATSDR, 2000).

Neurological Effects: Methylene chloride has been classified as a neurotoxicant (CDC, 2012), and a number of human studies reveal that the nervous system is a common target following acute methylene chloride exposure (ATSDR, 2000). Inhalation of methylene chloride is associated with central nervous system depression, which results in headache and dizziness, as well as confusion, intoxication, incoordination, and paresthesia. In instances of high exposure or poorly ventilated spaces, unconsciousness occurred in many of these cases (ATSDR, 2000).

Cancer: Human studies have identified associations between occupational exposure to methylene chloride and increased risk for cancers of the brain, liver and biliary tract, non-Hodgkin lymphoma, and multiple myeloma (Cooper et al. 2011). Methylene chloride has been classified as likely to be carcinogenic in humans based on evidence of lung and liver cancer in

male and female B6C3F1 mice following inhalation exposure in a 2-year bioassay (reviewed in Schlosser et al., 2015).

In sum, numerous reports have documented adverse health outcomes following exposure to methylene chloride both in human populations as well as in experimental animal models. Based on these data, various exposure limits have been derived including an inhalation Minimum Risk Level (MRL) of 0.6 ppm for acute inhalation exposure (0–14 days) to methylene chloride; and an MRL of 0.3 ppm for both intermediate (15-365 days) and chronic (>365 days) inhalation exposure to methylene chloride. Further, based on animal data and human epidemiological studies, methylene chloride is classified as "Reasonably Anticipated to be a Human Carcinogen" (NTP); The International Agency for Research on Cancer (IARC) has classified methylene chloride in Group 2B, possibly causing cancer in humans; and the EPA as a "probable cancer-causing agent in humans".

Considering the information above, and that the chemical is used in occupational settings as well as in commercial products, I support the conclusion that *there is the potential for one or more exposures to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern may contribute to or cause significant or widespread adverse impacts to human health, in particular, populations such as those occupationally exposed to methylene chloride containing paint and varnish strippers, and to consumers of such products in the general population.*

Conclusion2: The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern.

According to data collected in 1996, the national average concentration of methylene chloride in outdoor air was 0.47 µg/m3 (U.S. EPA 2002). Exposures to methylene chloride indoors can result from using consumer products containing methylene chloride including paint or varnish stripping products (ATSDR, 2000). Average indoor air concentrations collected from urban, suburban, and rural residences between 1990 and 2005 ranged from 0.4 to 3.5µg/m3 (Dawson and McAlary 2009).

Methylene chloride is commonly used in paint and varnish strippers, and typically is present at concentrations between 16-100% in these products. Methylene chloride is volatile and thus, due to its chemical properties, poses a significant risk for human exposure when using products such as paint and varnish strippers that contain methylene chloride.

The report of Morris and Wolf (2006) indicates that there are at least 6 industrial facilities in California that use relatively large quantities of methylene chloride and an additional 490 that use smaller quantities, many of which are reported to have poor ventilation. OSHA has set a PEL for methylene chloride of 25ppm, and an action level of 12.5 ppm in air, which according to the report of Morris and Wolf is routinely exceeded in many of these facilities. The Morris and Wolf study does not appear to be peer-reviewed, so the enthusiasm for this information is somewhat diminished, as the methodology for the analytical quantitation for methylene chloride in those occupational settings could not be determined.

Workplace air monitoring data for methylene chloride obtained between 1968 to 1982, revealed concentrations in general work areas between 0.086 to 964.8 ppm while samples in the breathing zone of workers ranged up to 1,411 ppm (ATSDR, 2000). When appropriate ventilation systems are installed, workers' exposure to methylene chloride in the breathing

zone can be reduced from 600–1,150 ppm to 28–34 ppm (ATSDR, 2000); however, these levels remain higher than the current PEL for methylene chloride.

In home settings, the publication by MacIsaac et al. (2013) reports several cases of human fatality related to the use of methylene chloride-containing products. In this publication, blood levels of methylene chloride were reported, providing support that the individuals were exposed through the use of the commercial products. Hogson and Girman, 1987 conducted a home simulation study of furniture stripping in which they identified that the concentration of methylene chloride exceeded 2000ppm when ventilation was not used. This value is approaching the NIOSH IDLH value of 2300 ppm, providing support that proper environmental controls are essential to control ambient levels of methylene chloride in order to protect human health.

It is unclear whether workers in these industries are provided with or use the proper personal protective equipment or whether adequate engineering controls (i.e. ventilation) is in place. OSHA indicates that for any general use, individuals should be equipped with a NIOSH approved self-contained breathing apparatus (SCBA) or supplied air respirator. ESCAPE: gas mask with organic vapor canister, or escape type SCBA. Dust masks or N-95 masks are not sufficient to prevent exposure to methylene chloride. In the absence of these control measures, which is likely to occur in home use and in small volume industries, it is highly likely that the proper controls are not in place, and people are being exposed to methylene chloride by using paint and varnish strippers that contain methylene chloride. Therefore, due to concentration of methylene chloride in paint and varnish strippers, the volatility and other chemical properties of methylene chloride, I support the conclusion that *there is a potential for exposure to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern.*

Are there any additional scientific issues that are part of the scientific basis of the proposed regulation?

Proper and informative product warning labels is lacking for paint and varnish strippers that contain methylene chloride. This is a key component of safety evaluation and protection of human health. If safer alternatives are not available to replace methylene chloride containing products, at a minimum, labeling should inform consumers of the proper PPE and engineering controls that should be used when working with products containing methylene chloride. In occupational settings in which high volumes of methylene chloride strippers are used, employers should promote safe work practices (adequate ventilation, supplying proper respiratory protection and protective clothing), and provide employees with appropriate training OSHA's Methylene Chloride standard, and the Personal Protective Equipment standard.

REPORT FOR PEER REVIEW OF THE PROPOSED ADOPTION OF PAINT AND VARNISH STRIPPERS CONTAINING METHYLENE CHLORIDE AS A PRIORITY PRODUCT BY CALIFORNIA EPA

Submitted by Raymond S. H. Yang, Ph.D., Professor Emeritus, Toxicology and Cancer Biology, Department of Environmental and Radiological Health Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado 80523-1681

Submitted on May 31, 2016

A Federal Express package was delivered to me on May 04, 2016; this package was originated from Dr. Gerald W. Bowes, Manager, Cal/EPA Scientific Peer Review Program, Office of Research, Planning and Performance, State Water Resources Control Board, Sacramento, California. This Package contained the following documents/items:

1. A letter from Dr. Bowes to me initiating the External Peer Review of the "Proposed Adoption of Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product" with me as an External Peer Reviewer.

2. March 7, 2016 memorandum from Karl Palmer, Department of Toxic Substances Control (DTSC), to Dr. Gerald Bowes, "Request for External Peer Review for the Proposed Adoption of Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product" which includes three Attachments.

3. Subject of Review (Revised Title): "Summary of Technical Information and Scientific Conclusions for Designating Paint and Varnish Strippers Containing Methylene Chloride as a Priority Product." (This is the technical report supporting the proposed regulation, not the regulation itself).

4. CD of all references listed in the foregoing document.

5. January 7, 2009 Supplement to the Cal/EPA Peer Review Guidelines.

I have reviewed all the above documents (Items No. 1, 2, 3, and 5); while doing so, when necessary, I have referred to the related references provided by Dr. Bowes on a CD (Item No. 4 above). My General Comments below are based on the Instructions given to Peer Reviewers in Attachment 2 of the March 7, 2016 memorandum (Item No. 2 above). In addition, I also provided Specific Comments below regarding certain scientific issues on the "Technical Report" (Item No. 3 by DTSC).

General Comments:

Based on my review of the documents and references indicated above, I have determined that the scientific portion of the proposed regulation is indeed based on sound scientific knowledge, methods, and practices. Further elaboration is given below:

DTSC's Conclusion 1: "**The hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to methylene chloride related to the use of paint or varnish stripping products containing this Chemical of Concern to contribute to or cause significant or widespread adverse impacts to human health.**"

I support DTSC's Conclusion 1 highlighted above based on the following facts presented in the DTSC Technical Report (Item No. 3 above):

1. There were at least 13-14 reported deaths of workers in the U.S. engaging in the use of paint and varnish strippers containing Methylene Chloride by CDC and OSHA between the time period 2000 and 2013. In addition, CPSC reported a consumer death related to working with paint and varnish strippers. Also, California Department of Public Health (CDPH) reported two additional cases of deaths due to the use of paint and varnish strippers. The actual number of such fatal accidents might be even higher because of lack of information on individual consumer usage of paint and varnish strippers.

2. Many State, National, and International Agencies and Scientific Organizations have concluded that Methylene Chloride, a principal component of paint and varnish strippers, is carcinogenic to humans and animals.

3. There are sufficient evidences that Methylene Chloride also possesses neurotoxicity, dermatotoxicity, ocular toxicity.

DTSC's Conclusion 2: "The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to methylene chloride related to the use of paint and varnish stripping products containing this Chemical of Concern."

I also concur with DTSC's Conclusion 2 because it is clear to me from reviewing DTSC Technical Report (Item No. 3 above) that the potential for exposure to Methylene Chloride is high for users of paint and varnish strippers. The following facts presented in the DTSC Technical Report (Item No. 3 above) formulate the basis for my concurrence:

1. The physico-chemical properties of Methylene Chloride are such that the vapor of this chemical is easily available for inhalation exposure in not or poorly ventilated confined spaces such as a bathroom.

2. Methylene Chloride in its liquid form may be easily absorbed through the skin.

3. The protective equipment such as respirators and gloves commonly available for workers and consumers using paint and varnish strippers containing Methylene Chloride are not adequate. The average worker or consumer is usually not aware of the more specific protective equipment.

Specific Comments:

My comments in this section are related to the **"The Big Picture"** given in Attachment 2 of the March 7, 2016 memorandum from Karl Palmer to Dr. Gerald Bowes (Item No. 2 above). First, in addressing the question "…(a) In reading the staff technical reports and proposed implementation language, are there any additional scientific issues that are part of the scientific basis of the proposed regulation not described above? If so, please comment with respect to the statutory language given above…", I have the following Specific Comments:

1. Regarding "Sensitive Subpopulations", the aging population or senior citizens should be included. The declined pharmacokinetic and pharmacodynamic capabilities and the other declined physiological and biochemical capacities in the aging population are well known (see for instance Armour and Cairns, 2002). This segment of the population may very well have the hobby of refurnishing old furnitures or remodeling bathrooms. Their bodies will be in a much poorer state to handle chemicals such as Methylene Chloride. The USEPA, in their publication of Toxicological Review of Methylene Chloride (USEPA, 2010) in support of their Integrated Risk Information System (IRIS), had incorporated discussions on age-related differences covering the range of 0.5 to 80 year old male and female individuals. I would strongly urge DTSC staff members to consider adding aging population into their "Sensitive Subpopulations."

2. Co-exposure to multiple solvents in the workplace or home by workers and consumers is highly likely. Further, consideration should be given to other possible exposure to chemicals (alcohol, tobacco, drugs, cosmetics, etc.) through life style or medical necessities. Therefore, multiple chemical interactions might increase (e.g., multiple toxicological endpoints or enhancement of intoxication) or decrease (e.g., competitive inhibition of metabolic enzymes might reduce the production of reactive species) the hazard to working with paint and varnish

strippers containing Methylene Chloride. DTSC staff members are well advised to consider adding such discussions in their Technical Report.

3. There are indications of newer forms of toxicity or sensitivity to specific types of toxicity resulting from exposures, particularly from early life stage, to solvents including Methylene Chloride, in the scientific literature. I provide some examples below and I would urge DTSC staff to consider these areas in their further and continuing endeavor in the risk assessment of Methylene Chloride. In a systematic review of the scientific literature on Autism Spectrum Disorders (ASD) from environmental toxicant exposures, Rossignol et al. (2014) indicated that toxicants implicated in ASD included solvents, among a variety of other environmental toxicants. In one specific study reviewed, perinatal exposure of Methylene Chloride, as an air pollutant was significantly associated with an increased risk of ASD with OR=1.8 (95% CI, 1.2-2.7). Furthermore, these authors emphasized several unique studies in which genetic polymorphisms were reported to be more common in ASD individuals as compared to controls (Rossignol et al., 2014). Among the genes implicated were glutathione S-transferases (GSTM1and GSTT1) which were important enzymes involved in the metabolism of Methylene Chloride and similar chlorinated hydrocarbon solvents such as trichloroethylene (TCE) and tetrachloroethylene (PCE). Along this line of thinking regarding newer forms of toxicity or sensitivity to specific types of toxicity, it is of further interest that two comprehensive reviews (Guyton et al., 2014; Rusyn et al., 2014) on TCE and PCE toxicities provide the following interesting observations. Rusyn et al. (2014) indicated that human and animal studies provided strong evidence of TCE's role in autoimmune disease. Guyton et al. (2014) reported that neurotoxicity (visual changes, increased reaction time, and decrements in cognition) was among the most sensitive outcomes occurring at low exposures of PCE and that there were also reported behavioral affinity toward illicit drug use from PCE exposures.

4. In a number of places in the Technical Report, the wording "numerous" was used to describe the number of deaths due to Methylene Chloride exposure in using paint and varnish strippers. For instance, in lines 4 and 5, 2nd paragraph of the Executive Summary on page 3, there was the statement "…There have been numerous worker and consumer deaths…" According to my two dictionaries, "Numerous" means "…Amounting to a large number; many…" (The American Heritage Dictionary of the English Language 3rd Edition, 1992, Houghton Mifflin Company) or "…Consisting of many persons or items…" (Webster's II New Riverside University Dictionary, 1984, The Riverside Publishing Company). While even one worker's death is one too many, I believe that the use of this

adjective “Numerous” is over-stating it; everytime I read such a statement in the Technical Report, and there are many, it made me very uncomfortable because the number of deaths, comparing to the whole population in the U.S., is a very small fraction. My recommendation, therefore, is that since this is a scientific document, it is best to “spell out” precisely the number of death during a given period rather than using a nebulous adjective.

5. Some of the reference quotations may not be accurate. For instance, I downloaded all the references from the CD provided to me (Item 4 above). When I clicked on the reference “Stewart and Hake, 1976,pdf”, the paper of Joe et al., 2013 from California Department of Public Health showed up. Also, the reference of “Sanchez, 2012” was actually an autopsy report which was witnessed by a Notary Public as an authentic one for release in April 2012 but the original autopsy report was dated November 16, 2007, one day after the death of the individual. I urge DTSC staff to double check their quotations to make sure that they are accurate.

Second, in addressing the question “…(b) Taken as a whole, is the scientific portion of the proposed regulation based upon sound scientific knowledge, methods, and practices?...” My answer, as indicated earlier, is “Yes”!

References:

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Guyton, K. Z. et al. 2014. Human health effects of tetrachloroethylene: Key findings and scientific issues. *Environ. Health Perspect.* 122:325-334.

Rossignol, D. A. et al. 2014. Environmental toxicants and autism spectrum disorders: A systematic review. *Tranl. Psychiatry* **4**, e360; doi:10.1038/tp.2014.4.

Rusyn et al. 2014. Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. *Pharmacol Ther.* 141(1): . doi:10.1016/j.pharmthera. 2013.08.004.

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