September 9, 2016

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

SUBJECT: EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF SPRAY POLYURETHANE FOAM SYSTEMS WITH METHYLENE DIPHENYL DIISOCYANATES AS A PRIORITY PRODUCT

Dear Mr. Palmer:

This letter responds to the attached March 25, 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 25, 2016 request letter to me and attachments. No additional material was asked for. This service by the University includes interviews of each promising candidate and is supported through an Interagency Agreement co-signed by CalEPA 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 subsequent letters to candidates approved as reviewers, I provided the attached January 7, 2009 Supplement to the CalEPA 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. <u>We recommend they do not</u>. 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).

Also, attached to the cover letter was the March 25, 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, 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. Ian Kimber, Ph.D.
   Professor, Faculty of Life Sciences
   The University of Manchester
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   Oxford Road
   Manchester, M13 9PT, UK

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2. James Lockey, MD, MS
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   University of Cincinnati College of Medicine
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   G251 Medical Science Building
   Cincinnati, OH 45267

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3. Benoit Nemery, MD, Ph.D.
   Professor, Toxicology and Occupational Medicine
   Department of Public Health and Primary Care
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   B-3000 Leuven – Belgium

   Telephone: +36 16 330801
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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
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FAX: (916) 341-5284
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Attachments:

(1) March 25, 2016 Request by Karl Palmer for Scientific Peer Review
(2) Letters to Reviewers Initiating the Review
  (a) Ian Kimber, Ph.D.
  (b) James Lockey, MD, MS
  (c) Benoit Nemery, MD, Ph.D.
(3) January 7, 2009 Supplement to Cal/EPA Peer Review Guidelines
(4) Curriculum Vitae
  (a) Ian Kimber, Ph.D.
  (b) James Lockey, MD, MS
  (c) Benoit Nemery, MD, Ph.D.
(5) Reviews
  (a) Ian Kimber, Ph.D.
  (b) James Lockey, MD, MS
  (c) Benoit Nemery, MD, Ph.D.

ATTACHMENT 1

Department of Toxic Substances Control

Matthew Rodriquez
Secretary for
Environmental Protection

Barbara A. Lee, Director
1001 "I" Street
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Sacramento, California 95812-0806

Edmund G. Brown Jr.
Governor

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 25, 2016

SUBJECT: REQUEST FOR EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF SPRAY POLYURETHANE FOAM SYSTEMS WITH METHYLENE DIPHENYL DIISOCYANATES AS A PRIORITY PRODUCT

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

Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates.

The Safer Consumer Product (SCP) regulations[1] that require the California Department of Toxic Substances Control (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
- conduct an Alternatives Analysis to determine if safer alternatives exist.

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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).

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In accordance with Health and Safety Code section 57004, DTSC requests external scientific peer review of the basis for proposing *Spray Polyurethane Foam Systems (SPF) with Methylene Diphenyl Diisocyanates (MDI)* 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 unreacted MDI may contribute to or cause significant or widespread adverse impacts to people, particularly to unprotected workers and consumers who do their own insulation improvement work; and
- people, particularly those subpopulations noted above, may be exposed to these chemicals during application of spray foam through 2-component systems; normal cleaning and maintenance of application equipment; and disposal of unused products that contain unreacted MDI.

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

- human toxicology, particularly with respect to isocyanates, and/or
- human exposure assessment or industrial hygiene.

We estimate that two to three reviewers will be adequate to cover all needed 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 *Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates* 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 Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product

A. Brief Statement of Conclusions[4]

DTSC identified high-pressure and low-pressure SPF systems containing unreacted MDI as a proposed Priority Product. Following a review of available scientific data, including peer-reviewed journal articles, government reports, and industry-generated information, DTSC concluded that applicators, including workers, contractors, consumers, and bystanders, may be exposed to unreacted MDI through the use of high- and low-pressure systems in both commercial and do-it-yourself project sites. Exposure to unreacted MDI has resulted in respiratory and dermal sensitization, chronic asthma, and other bodily injuries.

The scientific and public health communities generally consider isocyanates, including MDI, asthmagens, and isocyanates are the cause of some documented cases of work-related asthma. Isocyanates bind with proteins, such as albumin or glutathione, and may cause respiratory sensitization that can lead to an elicitation of asthma in subsequent exposures to isocyanates, including MDI. People who have become sensitized to isocyanates may experience life-threatening asthma attacks when subsequently exposed to extremely low levels of isocyanates. Exposure to airborne MDI can also lead to other adverse human health impacts including hypersensitivity pneumonitis, respiratory irritation, pulmonary inflammation, and contact dermatitis.

Measurable concentrations of MDI have been detected in applicators' breathing zones during their work shifts. In some cases, particularly with high-pressure SPF systems, work-shift concentrations exceeded the OSHA PEL of 200 $\mu g/m^3$, a national regulatory standard. Although airborne concentrations of MDI are generally greater during the use of high-pressure systems, respirable particles containing MDI are present in the applicators' breathing zones during the use of low-pressure SPF systems as well. Studies and documented consumer complaints also suggest that bystanders and building occupants have the potential to be exposed to MDI if they re-enter treated areas without adequate protection.

Businesses that own and operate high-pressure systems generally follow State and federal worker safety standards to train, supervise, and provide employees who apply SPF products

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[4] From the "*Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product*". Section VIII, page 21.

with appropriate personal protection equipment (PPE) and engineering controls, such as ventilation. In some cases, employees who apply SPF through high-pressure systems also participate in industry-sponsored certification programs and are aware of industry safety recommendations. By contrast, low-pressure systems are readily available and widely used by smaller contracting businesses and individual consumers. Small businesses with few or no employees and individual consumers are not generally required to comply with State or federal worker safety standards. They are also unlikely to be aware of industry-sponsored training programs or the need to protect themselves by following product safety data sheet (SDS) or using appropriate PPE and engineering controls.

PPE and engineering controls are considered the lowest tiers in the hierarchy of controls against occupational exposure to hazards because any user-error or malfunction can result in exposure to the hazard. Applicators who do not know how to wear PPE properly or who have been provided with ill fitting, poorly maintained, or improper PPE are at the greatest risk of exposure to MDI. Those who understand the hazards associated with applying SPF and protect themselves through the proper use of PPE and engineering controls still risk exposure to airborne MDI if these controls malfunction or fail. Because SPF applications produce measurable concentrations of airborne MDI in the breathing zone, any person involved in, or near, the application risks exposure to MDI even when protective measured are used. Any applicator who does not use PPE or engineering controls, through choice or ignorance, is being exposed to potentially high concentrations of respirable MDI.

Therefore, DTSC concluded that workers, helpers, consumers, and bystanders could be exposed to MDI using either high-pressure or low-pressure SPF systems that contain MDI. These exposures have the potential to contribute to or cause significant or widespread adverse impacts on the health of a considerable number of people in the State of California.

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 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 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.

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, or
- 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.

C. Overview of the Proposal to Adopt Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product

The proposed regulation defines "SPF systems containing MDI" as two-component high- or low-pressure systems composed of two separate liquid chemical mixtures that are mixed together and sprayed to form polyurethane foam used for insulation or roofing or for sealing and filling voids and gaps. "Side A" of the system consists of unreacted methylene diphenyl diisocyanates and "Side B" consists of a mixture of polyols and other ingredients including catalysts, blowing agents, flame retardants, and surfactants.

The following products are specifically excluded from this regulatory proposal:

- Polyurethane products that are not applied by spraying (e.g., rolled- or painted-on coatings);
- One-component foams sold in hand-held cans;
- Flexible polyurethane foam;
- Installed or pre-fabricated rigid polyurethane foam; and
- Assembled products containing polyurethane foam.

As required by regulation, DTSC considered a number of factors including the hazard traits, toxicological endpoints, and environmental fate associated with MDI as well as potential adverse impacts to subpopulations including workers and consumers who use or handle SPF products that contain unreacted MDI.

After reviewing the scientific literature and obtaining stakeholder input during public workshops, DTSC concluded that people, particularly workers, helpers, and bystanders at commercial foam spraying job site and individual consumers who purchase two-component foam kits, are likely to be exposed to MDI from spraying, handling of SPF products and cleaning and maintenance of equipment during and right after spraying. These exposures may contribute to or cause significant or widespread adverse impacts to those exposed due to the following hazard traits and toxicological endpoints:

- MDI is a respiratory sensitizer and generally considered as an asthmagen associated with work-related asthma. Once sensitized, re-exposure to even low concentrations of MDI (<1 ppb) may trigger severe asthma attacks in some people.
- In addition to respiratory sensitization, exposure to MDI in the workplace can cause adverse respiratory effects including inflammation and irritation, and dermatotoxic effects such as allergic contact dermatitis.

By concluding that exposures to MDI through the use of SPF products have the potential to adversely affect human health, DTSC has met the regulatory requirements to adopt this 'product-chemical' combination as 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 these chemicals.

Attachment 2:

Scientific Conclusions to Be Addressed by Peer Reviewers Regarding DTSC's Proposal to Adopt Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates 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 *Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates* as a Priority Product under the SCP 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 may 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 SPF Systems with Methylene Diphenyl Diisocyanates as a Priority Product meets the required regulatory criteria described above and requests that this review focus on the following conclusions:

- exposure to MDI may contribute to or cause significant or widespread adverse impacts to people, particularly to professional applicators and helpers, bystanders, and non-professional consumers; and
- people, particularly the sensitive subpopulations noted above, may be exposed to MDI through the normal use, handling, or disposal of low- and high-pressure two-component SPF systems.

The results of DTSC's scientific literature review are presented in the report, "*Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product with*

Chemicals of Concern" completed in November 2015, and subsequently updated in January 2016. The references listed in the specific sections of this report noted below will be provided on CD(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 MDI related to the use of SPF Systems containing these Chemicals of Concern to contribute to or cause significant or widespread adverse impacts to human health.

Isocyanates are low molecular weight chemicals that act as haptens. In vivo, haptens bind with larger proteins such as albumin or glutathione and thereby may elicit an immune response. This process is known as sensitization. Respiratory sensitization can lead to an elicitation of asthma in subsequent exposures to diisocyanates. Therefore, it is generally accepted that diisocyanates, including MDI, are asthmagens and are associated with work-related asthma. According to the California Work-Related Asthma Prevention Program surveillance data from 1993-2008, there were 23 reported cases of work-related asthma due to exposure to the class of chemicals known as diisocyanates. Exposure to isocyanates is recognized as one of the most frequently reported causes of occupational asthma. The National Institute for Occupational Safety and Health, Centers for Disease (NIOSH) has repeatedly issued hazard summaries and alerts warning of asthma and deaths resulting from occupational exposure to isocyanates. Scientific evidence also suggests that exposure to MDI in the workplace can cause immuno-, respiratory, dermato-, and musculoskeletal toxicities. Scientific studies suggest that both workers and by-standers may be at risk during spray operations if they are not protected against MDI exposure. Studies have found that levels of MDI in the air, within 10 to 20 feet from the applicator, may be elevated for a period of time after spraying, and these levels may exceed both the American Conference of Governmental Industrial Hygienists Threshold Limit Values and the Occupational Safety and Health Administration Permissible Exposure Level.

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

- Section I – Executive Summary, pages 3 – 6,
- Section IV – Hazard Traits of MDI, pages 11 – 14,
- Section VI – Exposure Potential of Humans to MDI in SPF Systems, pages 16 – 19, and
- Section VII – Sensitive Subpopulations with Potential for Adverse Impacts from MDI, page 19 – 21.

References included in these sections will be provided to the reviewers on CD or DVD 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 MDI related to the use of SPF products containing these Chemicals of Concern.

MDI is a member of a highly reactive group of compounds called isocyanates commonly used in spray polyurethane foam (SPF) systems. SPF systems containing MDI are heated during mixing and application and may result in MDI molecules becoming airborne during spraying. Inhalation of airborne MDI is a common route of exposure to MDI although dermal contact is also an exposure pathway. Scientific studies, including those conducted by the polyurethane foam industry, suggest that both workers and by-standers may be at risk during spray operations if they are not protected against MDI exposure. In addition to highly specialized professional workers, SPF systems are readily available to both independent contractors and consumers. While some professional workers receive training and certification from the SPF industry on industry-recommended safety guidelines, consumers and other applicators may not have access to adequate information or training or use PPE when using SPF systems. The SPF industry is rapidly expanding due to financial incentives for energy upgrades offered by various government organizations. The rapid increase in the use of SPF materials may result in increased risk of exposure for workers and consumers involved in using SPF systems.

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

- Section I – Executive Summary, pages 3 – 6,
- Section III – Physicochemical Properties of MDI, pages 10 – 11,
- Section V – Environmental Fate of MDI, pages 14 – 16,
- Section VI – Exposure Potential of Humans to MDI in SPF Systems, pages 16 – 19, and
- Section VII – Sensitive Subpopulations with Potential for Adverse Impacts from MDI, pages 19 – 21.

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

The Big Picture

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 might 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 currently-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
Valerie Hanley	Staff Toxicologist	Human and Ecological Risk Office	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	Environmental Scientist	Safer Products and Workplaces Program	Sacramento, CA
Lynn Nakayama Wong	Staff 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

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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

Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern

July 2016

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Safer Products and Workplaces Program

Department of Toxic Substances Control

California Environmental Protection Agency

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I. Executive Summary

The purpose of this document is to illustrate how the Department of Toxic Substances Control (DTSC) identified and prioritized spray polyurethane foam (SPF) systems containing unreacted methylene diphenyl diisocyanates (MDI)[1] for listing as a Priority Product. DTSC conducted an extensive literature review on the associated hazard traits and exposure potential of MDI and the potential for these chemicals in SPF products to contribute to or cause significant or widespread adverse impacts. This report summarizes the technical information evaluated and presents the conclusions of this evaluation.

Isocyanates are low molecular weight chemicals that act as haptens (Bernstein 1982). *In vivo*, haptens bind with larger proteins such as albumin or glutathione and may elicit an immune response known as respiratory sensitization (Janeway et al. 2001). Respiratory sensitization can lead to an elicitation of asthma in subsequent exposures to isocyanates, even when exposures are very low (< 1ppb) (OEHHA 2016). Therefore, it is generally accepted that isocyanates, including MDI, are asthmagens (AOEC 2014) and are associated with work-related asthma (CDPH 2013).

Work-related asthma is defined by the California Department of Public Health (CDPH) as asthma that is caused or aggravated by conditions or substances in the workplace. In order to qualify as work-related asthma, the asthma needs to be diagnosed by a physician and shown to have started after the possible workplace exposure began. The California Work-Related Asthma Prevention Program recorded 23 cases of work-related asthma associated with isocyanate exposure from 1993 to 2008 (CDPH 2013).

In addition to respiratory sensitization, scientific evidence suggests that exposure to MDI in the workplace can cause immuno-, respiratory, and dermato- toxicities, which is summarized in more detail under “Section IV” of this document. MDI-induced fatalities have been documented for workers using spray polyurethane paints (NIOSH 1996a; NIOSH 2006).

Inhalation of airborne MDI is a common route of exposure to MDI during and soon after application of SPF products (ACC 2014d) and is of particular concern to DTSC.

[1] The term “unreacted MDI” refers to MDI monomers and oligomers that are typically present in technical-grade MDI mixtures used in SPF manufacturing. Studies by authoritative bodies and the SPF industry have detected unreacted MDI in air during and after spraying. The purpose of using this term is to differentiate airborne MDI from spraying from polymerized MDI in finished SPF products. Polymerized MDI in finished SPF is beyond the scope of this document.

Applicators may also be exposed to MDI through dermal contact during handling activities (ACC 2014d; Bello 2007; HSDB 2011; Liljelind et al. 2010; Lockey et al. 2015).

Human exposure to isocyanates may occur with either high- or low-pressure systems including home use SPF kits. High-pressure SPF systems are distributed in unpressurized drums and totes, which are preheated prior to spraying and pressurized at about 1,200 pounds per square inch (psi) during mixing and spraying (ACC 2015). Low-pressure fillable systems and one-time use kits are sold pressurized at about 250 psi and passively mixed through the spray gun (ACC 2015). During spraying, inhalable materials containing MDI, including vapors, aerosols, dusts, and respirable particles, become airborne.

Studies, including some from the SPF industry, suggest that workers and bystanders may be exposed to MDI during spraying, especially when they do not use any protective measures.[2] During 13 separate indoor applications, MDI has been detected in the applicators' breathing zones at concentrations that ranged from 12 to 570 $\mu g/m^3$ (Crespo and Galan 1999). Other studies detected measurable levels of airborne MDI up to 20 feet from the applicators' breathing zones for a considerable amount of time after spraying (ACC 2015; ACC 2012; Lesage et al. 2007; Roberge 2009; Wood 2013). A recent review found that airborne MDI concentrations ranged from 0.1 to 1,320 $\mu g/m^3$ in European and US monitoring studies (Environment Canada 2014b). In some of the studies, airborne MDI levels exceeded 51 $\mu g/m^3$, which is both the Threshold Limit Values (8-hour Time Weighted Average) set by the American Conference of Governmental Industrial Hygienists (ACGIH 2015) and the Permissible Exposure Limits (PEL) of the California Division of Occupational Safety and Health (Cal/OSHA) (Cal/OSHA 2015). [3] In other studies, MDI exceeded 200 $\mu g/m^3$, which is the Occupational Safety and Health Administration (OSHA) PEL (ceiling) (NIOSH 2010).

Occupational exposures to harmful substances such as MDI in SPF materials should be addressed via well-documented hazard control methodology widely accepted by the industrial hygiene profession and safety organizations, such as OSHA. Following this approach, hazards are controlled via a "hierarchy" of potential solutions (CDC 2015). This hierarchy, in order of preference, is: 1) elimination of the hazard; 2) substitution

[2] DTSC is primarily concerned about potential human exposure to unreacted MDI during the process of spraying. DTSC is aware of ongoing studies and reports on exposure scenarios where individuals entering or residing at locations after SPF application could be exposed to chemical hazards; however, these exposure scenarios are not the focus of this document.

[3] The PEL is the maximum concentration of a chemical that workers may be exposed to for a certain period, typically 8 hours. Workers may be exposed to concentrations that exceed the PEL provided they do not exceed the time-weighted average specific to that PEL or any applicable excursion limits.

with a different chemical; 3) engineering controls, including processes and systems such as exhaust ventilation, which are designed to remove the hazard at the source, before it comes in contact with the worker; 4) administrative controls, including the implementation of policies, procedures, and employee training; and 5) the use of personal protective equipment (PPE) (CDC 2015).

Eliminating the chemical hazard entirely, or substituting a less hazardous chemical, is the most effective means of minimizing potential occupational exposures to workers. Engineering controls can be effective, especially when their use is combined with the use of administrative controls and PPE. Administrative controls and PPE are considered to be the least desirable approaches to control potential occupational exposure (CDC 2015). This is largely because the original hazard is still present in the workplace. The level of workers' training, experience, and supervision, as well as a range of physical and environmental variables, may reduce the effectiveness of administrative controls and PPE (Parr 2015). Worker exposure that can lead to injuries or illness is often a consequence of improper use of PPE or failure to follow administrative controls. Even when worn properly, PPE may place workers at risk due to reduced dexterity, visual acuity, and mobility. It may also increase the likelihood of trip, slip and fall accidents as well as developing heat-related illness (Parr 2015).

Of the two categories of SPF systems, workers who operate high-pressure systems are more likely to be required to complete industry-recommended training and certification programs follow employer-developed safety procedures, and to be provided with PPE. However, as stated above, engineering and administrative controls and use of PPE are at the bottom of the hierarchy of control methods, and therefore are the least effective in protecting workers from exposures to occupational hazards. DTSC has determined that industry recommended engineering and administrative controls and use of PPE reduces the likelihood of exposure, but they cannot eliminate worker exposure to MDI during spraying of high-pressure systems.

Depending on the size of the job, workers may work continuously for typical shifts lasting more than four- to six-hours. High-pressure SPF products are heated and pressurized and, as a result, atomization of these materials occur during spraying (ACC 2015). Regardless of the curing time and level of ventilation, if any at all, SPF aerosols and particles containing MDI will be present in the workers' breathing zone during the entire work shift of spraying. In addition to handling-related exposures, workers may also be exposed to MDI through accidental spills or leaks, cleaning and maintenance of the equipment (Lockey et al. 2015), failure to use (Kavanaugh 2016), improper use, imperfect fit or malfunction of PPE.

Low-pressure systems including home use SPF kits are not heated and operate under lower pressures than high-pressure systems (ACC 2015). In addition to use by commercial applicators (ACC 2015), low-pressure systems are also commonly used by workers employed by businesses that are exempt from OSHA requirements and non-commercial users undertaking “do-it-yourself” projects (Environment Canada 2014a; Levinson et al. 2014; Lockey et al. 2015; U.S. EPA 2011a). A consumer can purchase low-pressure kits from the Internet and home improvement centers (Levinson et al. 2014). Limited data from the industry suggested that spraying of low-pressure systems generates less airborne MDI than spraying of high-pressure systems, but in several studies, measurable MDI was detected around applicators’ breathing zones during application (ACC 2015; Bloom 2012; Levinson et al. 2014; Wood 2013). Workers increase their risk of exposure to MDI when they assume low-pressure systems are safer than high-pressure systems, and do not use engineering controls such as local exhaust ventilation and PPE that are otherwise available to them. The SPF industry has occasionally identified and sanctioned contractors who failed to use PPE while publicly demonstrating the use of SPF (Kavanaugh 2016). Workers who are not covered by OSHA regulations, self-employed contractors, and consumers are of particular concern. These groups are unlikely to invest in engineering controls and PPE, nor industry recommended administrative controls (Environment Canada 2014a; Lockey et al. 2015; U.S. EPA 2011a)(.

Based on the information presented above, DTSC determined that spraying of both high- and low-pressure SPF systems including home use SPF kits has the potential to cause significant and widespread adverse impacts to human health. The Priority Product has the potential to harm not only workers of highly specialized commercial operations; it also can harm workers who are not fully protected against MDI exposure such as self-employed contractors and individual consumers in California.

II. Identification of the Priority Product and Chemicals of Concern

DTSC has identified as a Priority Product SPF systems containing unreacted methylene diphenyl diisocyanates (MDI). These systems are typically used for insulating, roofing, sealing, and filling of voids and gaps.

An SPF system is composed of two liquid chemical mixtures that are sold or distributed together, and intended to be mixed and sprayed, at which point they react to form polyurethane foam. The liquid chemical mixtures are referred to as “sides,” with “Side A” of the system consisting of unreacted MDI, and “Side B” consisting of a mixture of polyols and other ingredients, which may include catalysts, blowing agents, flame retardants, and surfactants (U.S. EPA 2013a).

The designated Priority Product excludes (a) polyurethane foam materials that do not involve mixing and spraying, (b) finished (cured) foam, and (c) one-component, premixed (prereacted) foam materials.

These products may be packaged under either high- or low-pressure (Table 1). High-pressure SPF systems require considerable investment in equipment and are typically marketed for use by highly specialized commercial applicators (ACC 2014d). Low-pressure SPF systems require less investment in the use of specialized equipment and may be purchased by highly specialized commercial applicators, commercial contractors, and non-commercial users such as individual consumers for indoor or outdoor applications (Table 1).

Table 1. Overview of SPF systems (U.S. EPA 2013c) †

	High-Pressure	Low-Pressure
SPF Types	• Open-Cell (low density, half lb.) • Closed-Cell (medium density, 2 lb.) • Closed-Cell (high density, 3 lb.)	
Uses	• Larger insulation applications • Air sealant in hybrid insulation • Installation with fiberglass or other insulation materials • Roofing applications (Closed-Cell, high density, 3 lb.)	• Air sealant adhesive • Smaller insulation applications • Weatherization activities
Applicator	• Professional installer	• Professional installer • Weatherization worker • Do-it-yourselfers
Container size	• 55 gallon drum containers	• Typically three to five gallons per container from the system house, but can be purchased in larger containers over the internet or in some retail markets
Chemical Exposure Potential	***Chemical exposures may occur***: • During application • After application • During heat-generating processes such as drilling, welding, or sanding • During fires ***Through***: • Aerosols • Vapors • Dust that may contain unreacted chemicals	

Hazards	• Sensitization • Asthma • Lung damage • Other respiratory and breathing problems • Skin and eye irritation
Re-Entry	Some manufacturers estimate that it can take 23 to 72 hours for the foam to fully cure after this type of application, but curing rates can vary.

† Adopted with slight format and language modifications.

The Chemicals of Concern are members of a highly reactive group of compounds called isocyanates. An isocyanate is any chemical that contains in its structure at least one isocyanate group (i.e., –N=C=O). A chemical containing two such isocyanate groups is referred to as a diisocyanate (3M Australia 2008). The term 'isocyanates' is more general and will be used in this document for simplicity.

The names and Chemical Abstract Service Registry Numbers (CAS #) of the Chemicals of Concern include:

- 4,4′-Methylene diphenyl diisocyanate (4,4′-MDI), CAS #: 101-68-8
- Generic methylene diphenyl diisocyanate (generic MDI), mixed isomers, CAS #: 26447-40-5

For the purpose of this document, the Chemicals of Concern are collectively referred to as MDI, which includes isocyanates that are referred to as 4,4′-MDI or pure MDI (ACC 2001), generic MDI, and technical grade MDI (sometimes called polymeric MDI (PMDI)), all of which contain 4,4′-MDI (CAS # 101-68-8). This approach is based on the rationale described below:

- MDI molecules can be produced in a relatively pure form [4,4′-MDI isomer (CAS #: 101-68-8)], and they may be referred to as "pure MDI" (ACC 2001). The term "MDI" is often used for pure MDI (ACC 2014d).

- MDI molecules (monomers) generally can exist in more than one isomeric form, and can be produced as a mixture of isomers; this mixture may be referred to as "generic MDI" (ACC 2001), which contains 4,4′-MDI (CAS # 101-68-8).

- The technical grade of MDI also contains 4,4′-MDI isomer as well as other isomers, and is commonly known as “polymeric MDI” (ACC 2014d). However, use of the term, “polymeric MDI,” in the literature is a misnomer as this material is not a polymer, but a liquid mixture of MDI and higher molecular weight oligomers of MDI (ACC 2014d). “Polymeric MDI" contains 30 to 80 % w/w 4,4′-MDI; the rest consists of MDI oligomers and MDI homologues (Wiley-VCH 2012).

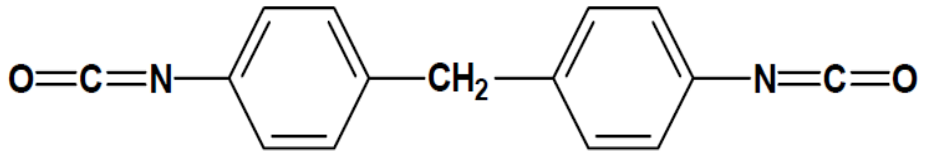
- According to one authoritative body, the CAS #: 26447-40-5 for “generic MDI” includes the isomeric mixtures as well as all other specific isomers, including those with unique CAS numbers (U.S. NLM 2015).

- “Generic MDI” was also referred to as polymeric MDI (IARC 1987).

Additional information on the Chemicals of Concern:

- Molecular formula for both 4,4′-MDI (IARC, 1987) and generic MDI (U.S. NLM 2015):
  - $C_{15}H_{10}N_2O_2$
- Chemical Abstract Names (ACC 2001; IARC 1987):
  - CAS # 101-68-8: benzene, 1,1’-methylenebis(4-isocyanato)
    - Short Name: 4,4′-MDI
  - CAS # 26447-40-5: benzene, 1,1′-methylenebis(4-isocyanato)
    - Short Name: generic MDI
- IUPAC Systematic Names:
  - CAS # 101-68-8: 1-isocyanato-4-(4-isocyanatobenzyl)benzene (ACC 2001), Isocyanic acid, methylenedi-paraphenylene ester (IARC 1987)
  - CAS # 26447-40-5: No IUPAC name for mixtures (ACC 2001)

- Chemical structures (HSDB 2011; IARC 1987):



MDI, CAS # 101-68-8

- 4,4’-MDI Common synonyms or trade names (ACC 2001)

MDI
Pure MDI
Monomeric MDI
Bis-(p-isocyanatophenyl)methane
Bis-(4-isocyanatophenyl)methane
Di-(4-isocyanatophenyl)methane
Diphenylmethane-4,4′-diisocyanate
Isocyanic acid, methylenedi-p-phenylene ester
Methylenebis(p-phenyl isocyanate)
Methylenebis(p-phenylene isocyanate)
Methylenebis(4-phenyl isocyanate)
Methylenebis(4-phenylene isocyanate)
4,4′-Diisocyanatodiphenylmethane
4,4′-Diphenylmethane diisocyanate
4,4′-Methylenebis(phenyl isocyanate)
4,4′-Methylenediphenyl diisocyanate
4,4′-Methylenediphenylene isocyanate

- Generic MDI common synonyms or trade names (ACC 2001)

  Methylene diphenyl diisocyanate
  Diisocyanatodiphenylmethane
  Methylenediphenylene diisocyanate
  Diphenylmethane diisocyanate
  Diphenyl methane diisocyanate
  Di-(isocyanato phenyl)methane
  Methylenebis(phenylisocyanate)
  Diphenylmethyl diisocyanate

MDI meets the conditions specified in California Code of Regulations, title 22, section 69503.6(a) in that it appears on one or more of the authoritative lists in California Code of Regulations, title 22, section 69502.2(a)(1) and is a chemical listed in California Code of Regulations, title 22, section 69502.2(a)(2):

- MDI is listed on the Air Toxics Hot Spots list of chemicals whose emissions must be quantified and the Office of Environmental Health Hazard Assessment (OEHHA) has inhalation Reference Exposure Levels for respiratory toxicity.
- MDI is classified by the European Commission as a respiratory sensitizer.

- MDI is identified by the California Air Resources Board as a Toxic Air Contaminant.

III. Physicochemical Properties of MDI

For MDI with CAS # 101-68-8:

- Color: White to light yellow (NIOSH 2010)
- Molecular weight: 250.25 g/mol (Haynes 2010)
- Density: 1.197 g/mL at 70 °C (Haynes 2010)
- Specific gravity: 1.23 (solid at 25 ^{o}C); 1.19 (Liquid at 50 ^{o}C)(NIOSH 1997)
- Melting point: 37 °C (Haynes 2010)
- Boiling point: 196 °C at 5 mm Hg (Haynes 2010)
- Log K_{ow}: 5.22 (est.) (U.S. EPA 2011b)
- Water solubility: 1.51 mg/L at 25°C, estimated (U.S. EPA 2011b)Vapor pressure: 5.0 x 10^{-6} mmHg at 25 °C (NIOSH 1997)

IV. Hazard Traits of MDI

MDI is a respiratory sensitizer and generally considered as an asthmagen (AOEC 2014) associated with work-related asthma (CDPH 2013). Once sensitized, re-exposure to even low concentrations of MDI (<1 ppb) may trigger severe asthma attacks in some people (OEHHA 2016). In addition to respiratory sensitization, exposure to MDI in the workplace can cause adverse respiratory effects including inflammation and irritation, and dermatotoxic effects such as allergic contact dermatitis.

1. Immunotoxicity

a. Allergic Sensitization

A number of studies in animals have demonstrated that isocyanates, including MDI, are respiratory sensitizers. Several animal models of asthma have been developed for both respiratory and dermal sensitization to MDI or PMDI (Pauluhn and Poole 2011; Pauluhn et al. 2000; Rattray et al. 1994; Wisnewski et al. 2011). In mice and guinea pigs with previous MDI skin exposure (≥1% MDI in solution) significant airway inflammatory responses to respiratory MDI challenge have been demonstrated (Rattray et al. 1994; Wisnewski et al. 2011). Both high acute exposures and lower level exposures may induce sensitization (OEHHA 2016).

- Short duration, high concentration (1,000 mg PMDI/m^3 for 10 minutes) repeated inhalation exposure in rats followed by PMDI inhalation challenge (40 mg/m^3) resulted in increased neutrophils in bronchoalveolar

lavage fluid (BALF) and delayed-onset respiratory changes (Pauluhn and Poole 2011).

- Topical application of polymeric MDI to rats followed by inhalation of MDI resulted in increased neutrophils in BALF and a delayed respiratory response (as determined by breathing patterns; enhanced pause [Penh]). During the dermal sensitization phase, rats were dosed contralaterally two times, seven days apart. Two weeks after the second dermal dose, rats underwent four inhalation challenges, in two week intervals. The first three inhalation challenges were ~38 mg MDI/m^3 and the fourth challenge was either 8, 18, or 39 mg/m^3. Rats were lavaged and sacrificed one day after the fourth inhalation challenge. The degree of respiratory response was more dependent on the inhaled dose during elicitation, than the dose applied topically during induction/sensitization (Pauluhn 2008).
- Topical skin application of MDI on mice resulted in systemic sensitization with increased total antibody production of IgE and MDI-specific antibodies (IgE, IgG1, and IgG2a). MDI skin exposed mice (>1% MDI weight/volume administered on days 0 and 7) and challenged seven days later via intranasal droplet (days 14, 15, 18, and 19) with MDI-albumin adducts had significant increases of inflammatory cells (eosinophils and lymphocytes) in the BALF. These observations suggest that dermal sensitization may result in respiratory inflammation (Wisnewski et al. 2011).

2. Respiratory Toxicity

Many studies in both animals and humans demonstrate respiratory toxicity of MDI. The toxicological endpoints include the following:

a. Respiratory irritation
   - Inhalation of aerosolized MDI for four hours by mice resulted in decreased respiratory rate (as determined by plethysmography) and increased lung weight. In contrast to toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI), MDI acted primarily as a pulmonary irritant rather than a sensory irritant. Decreased respiratory rate was also observed in mice exposed to MDI aerosol via tracheal cannuation, which bypasses the trigeminal nerve and therefore sensory irritation. This study demonstrates the stimulation of lower respiratory tract receptors rather than the trigeminal nerve (Weyel and Schaffer 1985).

b. Pulmonary Inflammation
   - An acute six hour inhalation exposure of PMDI (10, 30, or 100 mg/m^3) to rats resulted in concentration-related increases of inflammatory cells

(neutrophils and alveolar macrophages), total protein, and enzyme activities (lactate dehydrogenase, alkaline phosphatase, and N-Acetyl glucosaminidase) in BALF at post-exposure days 1 and 3. Complete recovery was observed by post-exposure day 30 (Kilgour et al. 2002).

c. Pathology and Fibrosis
   - Chronic inhalation exposure to MDI in rats induced a dose dependent interstitial and peribronchiolar fibrosis (i.e., narrowing and fibrotic wall thickening of small airways) that was significantly increased in all treatment groups in comparison to controls (Ernst et al. 1998; Hoymann et al. 1998).
   - Chronic inhalation exposure to high concentrations of polymeric MDI in rats resulted in focal fibrosis around accumulations of alveolar macrophages after one year. After two years, high concentrations resulted in collagen synthesis and basement membrane thickening (Reuzel 1994).
   - Chronic inhalation exposure to high concentrations of polymeric MDI in rats resulted in increased basal cell hyperplasia of nasal olfactory epithelium (Reuzel 1994).

d. Airways hypersensitivity and Asthma
   - In a prospective study of the respiratory effects of MDI exposure, a study evaluated the respiratory health of workers in a new wood products manufacturing plant in which MDI resin was used as a binder. Fifteen of 56 workers with high exposure had new onset of asthma after 2 years vs. 0 of 43 workers with low exposure.(Petsonk et al. 2000)
   - Eleven foundry workers exposed to MDI and formaldehyde had bronchial hyperreactivity and respiratory symptoms compatible with asthma. MDI-induced asthma was confirmed in six workers after specific inhalation challenge (SIC) to MDI (12 ppb over 60 minutes) resulted in ≥20% decrease in forced expiratory volume in one second (FEV_1). These six workers did not react after SIC to formaldehyde (2.5 ppm for 30 minutes. One patient reacted to both MDI and formaldehyde, but the bronchoconstriction was attributed as an irritant response rather than sensitization (Zammit-Tabona et al. 1983).
   - A foundry worker, frequently exposed to MDI with no previously reported respiratory symptoms, was diagnosed with reactive airways dysfunction syndrome (RADS) after an acute high-level inhalation exposure to MDI produced by an accidental spill in his work area. Symptoms included headache, sore throat, cough, and chest tightness. After the incident, chest symptoms worsened at work with increased wheeze and chest tightness. A spirometric test revealed moderate airflow obstruction with FEV_1 of 2.5 L (83% predicted) and forced vital capacity (FVC) of 4.5 L

(121% predicted). Occupational asthma was confirmed after a inhalation challenge with MDI (15 ppb for 60 minutes) resulted in a 22% fall in FEV_1 seven hours post exposure (Leroyer et al. 1998).

e. Hypersensitivity pneumonitis
   - In a review of company physician's case histories of 1,780 isocyanate workers, fourteen patients were suspected of having isocyanate-induced hypersensitivity pneumonitis following isocyanate exposure with work-related symptoms of dyspnea, fever, and malaise. Nine of these patients were exposed to MDI only (the other patients were exposed to TDI, HDI, or a combination with MDI). Diagnosis was based on chest x-ray films, levels of IgE and IgG antibodies to isocyanate-human serum albumin, lung function tests, and analysis of lymphocytes in BALF. Hypersensitivity pneumonitis symptoms were also confirmed in five subjects who underwent inhalation challenge with MDI, symptoms occurred after a latency period of two to eight hours (Baur 1995).
   - Eight subjects who worked in a woodchip board manufacturing plant that used PMDI resin as a binding agent developed hypersensitivity pneumonitis with symptoms of chest tightness, cough, and shortness of breath associated with myalgia, chills, headaches, and nausea. Three to seven hours following inhalation challenge with MDI vapor, subjects experienced systemic symptoms and significant falls in both FEV_1 and FVC, hypoxia, increased blood neutrophils, increased neutrophils and lymphocytes in BALF, and significant levels of IgG and IgE antibodies to MDI-human serum albumin (Vandenplas et al. 1993).

3. Dermatotoxicity

Dermal sensitization to MDI exposed skin can result in allergic contact dermatitis.

a. Allergic contact dermatitis
   - Fifty-four patients underwent patch testing for dermal sensitization to MDI, TDI, HDI, isophorone diisocyanate, and methylenedianiline (MDA), the metabolite/reaction product of MDI (U.S. EPA 1998). Twelve patients reacted to MDI and forty-four patients reacted to MDA. MDA is an important marker of MDI hypersensitivity (Aalto-Korte et al. 2012).
   - Seventeen workers exposed to MDI-based polyurethane foam in a vehicle equipment factory had work related skin symptoms, which appeared from three days to six months after their first occupational exposure. Symptoms included itchy, stinging and/or burning skin lesions, localized on the exposed, bare skin areas. Diagnosis of allergic contact dermatitis for seven subjects was based on dermal sensitization patch test results

where responses to MDA, but not MDI, were positive (Kieć-Świerczyńska 2014).

V. Environmental Fate of MDI

MDI may be released to the environment via either accidental discharge or normal use of the Priority Product, which may contribute to airborne MDI, deposition to soil and/or surface waters in the vincinity where releases occur.

1. Air

MDI can exist in both vapor and particulate phases in the atmosphere as indicated by a vapor pressure of 5.0 x 10^{-6} mmHg at 25 ^{o}C. Airborne MDI does not readily react with water vapors in the atmosphere (Tury et al. 2003). Atomospheric MDI tends to form aerosols by condensing onto airborne particulates and water (Environment Canada 2014b). MDI has been detected in air with concentrations ranging from 0.1 to 1,320 µg/m^3 (Environment Canada 2014b). Vapor-phase MDI is degraded in the atmosphere via reaction with photochemically-produced hydroxyl radicals with a reaction half-life estimated to be between 11 (HSDB 2011) and less than 24 hours (Tury et al. 2003).

Particulate-phase MDI will be removed from the atmosphere by wet or dry deposition (HSDB 2011) onto soil and water particles, structures, and equipment (Environment Canada 2014b).

MDI is not expected to be susceptible to direct photolysis by sunlight (European Chemicals Bureau 2005; HSDB 2011).

Once SPF is installed and cured, airborne concentrations of MDI are expected to be negligible. Most isocyanates will remain bound in the matrix as part of a rigid material under normal ambient conditions. However, it can undergo thermal degradation and release toxic chemicals (ACC 2014c; U.S. EPA 2013b). Thermal degradation may be caused by fires and other heat-generating processes such as welding, soldering, grinding, sawing on or near SPF insulation, which may generate a range of airborne degradation chemicals including isocyanates, hydrogen cyanide, and others (ACC 2014c; Blomqvist 2005; Blomqvist et al. 2003; U.S. EPA 2013b).

2. Water

Although MDI is hydrophobic (Environment Canada 2014b; Gilbert International Limited 2005), it reacts with water to form predominantly insoluble polyureas and carbon dioxide (Gilbert International Limited 2005). Studies suggest that the

heterogeneous hydrolysis reaction occurs slowly at the MDI-water interface and can last for a considerable amount of time (Yakabe et al. 1999). This is due to the fact that the major product of such a reaction is polyurea, which tends to form quickly, starting on the outside and forming a crust that may restrict ingress of water and egress of amines such as methylene dianiline (MDA) and urea (Gilbert International Limited 2005; Heimbach et al. 1996; Yakabe et al. 1999). The amines (e.g., MDA) are expected to bond with soil and sediments and biodegrade (Cowen et al. 1998). Hydrolysis reaction rates of MDI and reaction byproducts are dependent on many factors such as the starting concentration of MDI and aquatic temperatures (Environment Canada 2014b). Although there is little data describing degradation of MDI in various aquatic environments, it is generally presumed that MDI will not accumulate in aquatic systems or the food chain (Environment Canada 2014b; HSDB 2011).

3. Soil

Depending on soil temperature, particle size, and density, MDI released to or deposited onto the soil may be transported from the soil to adjacent waters, air, or freeze before reacting with moisture and slowly forming polyureas and small amounts of amines (e.g., MDA) (Environment Canada 2014b; Gilbert International Limited 2005; Sendijarevic et al. 2004). Although degradation data in various soil media are not available, MDI is presumed not to leach or adsorb to solids, volatilize, or bioconcentrate due to hydrolysis of MDI in the soil in the presence of water (HSDB 2011).

VI. Exposure Potential of Humans to MDI in SPF Systems

1. Market Presence

a. The global market for building insulation (fiberglass, SPF, and others) is projected to grow from $18.5 billion in 2011 to $24 billion by 2016 (Markets and Markets 2014a). The global market for plastic insulation foams will have a compound annual growth rate (CAGR) of 5.8% from 2011 to 2016, and is projected to reach $10 billion by 2016 (Markets and Markets 2014a).
b. In 2015, the SPF industry reported between 460 and 490 million pounds of SPF were used for roofing and insulation in the U.S. and Canada, and reached the milestone of $1 billion market (Kavanaugh 2016).
c. Demand for SPF for residential construction and updating grew about 15% per year from 2013 to 2015 (Kavanaugh 2016).
d. Within the global polyurethane industry, the SPF sector is currently estimated to be worth $800 million, and is projected to grow to $1.1 billion by 2015. Global demand for SPF is projected to grow 13% per year from 2013 to 2015

(Business Wire 2013).

e. In North America, the polyurethane foam market revenue was $203 million in 2009, and is projected to reach $273 million by 2016, with a CAGR of 4.2% (Markets and Markets 2014b).
f. In California, approximately 83 polyurethane-related facilities, including those producing polyurethane foam, reported a total of $616.6 million in sales in 2011 (C. Barnes & Co. 2010).
g. The Spray Polyurethane Foam Alliance (SPFA) currently lists 38 California SPF contractors among its members (SPFA 2015).
h. The Center for the Polyurethane Industry (CPI) estimated that two-component SPF market in California to be $55-60 million (ACC 2016)
i. In California, the use of SPF materials is rapidly expanding due to their effectiveness as insulation materials, and financial incentives for energy upgrades offered by both government agencies and non-government organizations. These incentives are generally offered as tax breaks or monetary offers through contractors and utilities to increase energy efficiency in residential and commercial establishments (Energy Upgrade California 2016). The number of businesses and individual consumers that are trying to conserve energy through upgrades is also growing due to awareness of government incentives and educational outreach by governments, non-profit organizations, and advocacy groups. In Northern California, for example, new construction homes are being insulated entirely with SPF in Placer County (Bozorgchami 2013).

2. Worker Exposure Routes

a. Exposure to isocyanates via inhalation or dermal contact can occur in the following ways (NIOSH 2006; Petsonk et al. 2000; Rundman 2013; U.S. EPA 2013b; U.S. EPA 2013c; U.S. EPA 2014):
   - Via inhalation of vapors, aerosols, and particles generated when a product is sprayed. Inhalation exposures during spray foam insulation were found to exceed OSHA occupational exposure limits (ACC 2012; Lesage et al. 2007), and require skin, eye, and respiratory protection.
   - Via inhalation and dermal contact with degradation products, including isocyanates, from heat-generating processes such as drilling, welding, soldering, grinding, sawing, or sanding on or near foam insulation.
   - Via inhalation and dermal contact with isocyanates and other toxic chemicals released during fires (ACC 2014c; Blomqvist 2005; Blomqvist et al. 2003).
b. When neither engineering controls nor PPE are used, workers of small businesses and self-employed contractors in the construction and

weatherizing industries, and individual consumers using SPF kits for do-it-yourself projects can be at risk for exposure to MDI. The SPF industry has occasionally identified and sanctioned contractors who failed to use protection during spraying of SPF products (Kavanaugh 2016)

c. Many factors, including worker's physical characteristics, training, experience, and supervision as well as physical and environmental variables, can reduce the effectiveness of PPE (Parr 2015). These factors are included in the inspection procedures of the OSHA NEP as potential causes of occupational exposures to isocyanates (Rundman 2013). The OSHA NEP runs from June 2013 to May 2016, which requires three inspections per year per area office and covers all sources of isocyanates including SPF materials. Investigations are made only when a complaint/referral is received, or an OSHA Certified Safety & Health Official observes an activity where potential isocyanate exposures are suspected (Rundman 2013).

3. MDI-Induced Worker Fatalities

a. A maintenance worker developed isocyanate-induced hypersensitivity pneumonitis and died after repairing an MDI foaming system at a facility that made artificial plants with polyurethane foam bases (NIOSH 1994a).
b. A 45-year old worker died due to an acute asthma attack after 12 months on the job spraying MDI-based bed liners onto the floor and sides of cargo vans (NIOSH 2006).

4. MDI-induced Occupational Asthma

Exposures to isocyanates have been identified as an attributable cause of work-related asthma for some exposed workers (Creely et al. 2006; Mapp 1988; OEHHA 2016; U.S. EPA 1998; U.S. EPA 2011a). NIOSH has issued multiple hazard summaries and alerts warning of asthma and deaths resulting from occupational exposure to isocyanates (NIOSH 1996a; NIOSH 2004; NIOSH 2006). Harmful or fatal incidents involved workers spray-painting cars, applying spray-on truck bed liners, installing foam, or exposed to MDI-based adhesives used in coal mining.

a. Ten workers with no preexisting asthma developed MDI-induced asthma after 1-8 months on the job at an engineered wood products plant. All 10 workers reported respiratory symptoms when they were in areas where MDI was used (NIOSH 1996b).
b. Nine spray-paint workers in a large airplane assembly plant developed asthma (Seguin et al. 1987). MDI in aerosols was one of the attributable isocyanates identified in this study.
c. A 29-year-old male working for a company that installed spray-on truck bed

liners developed isocyanate-induced asthma (Bonauto and Lofgren 2004).

d. Isocyanate-induced asthma was reported in a 30-year old man who worked for a truck bed lining company (Bonauto and Lofgren 2004; NIOSH 2006).
e. A 22-year-old worker developed isocyanate-induced asthma after working in the truck bed lining industry for 18 months (Bonauto and Lofgren 2004; NIOSH 2006).
f. Coal miners complained of respiratory difficulties, asthma, and shortness of breath, dizziness, headache, sore throat, fatigue, and contact dermatitis after exposure to MDI-based polyurethane rock glues. Company medical records showed nine reports of health problems attributed to rock glue exposure (NIOSH 1994b).
g. As noted earlier, several studies in the published literature have found associations between exposure to MDI in the workplace and induction of asthma (OEHHA 2016).

5. Non-Occupational Exposure Potential

a. The number of products and systems containing MDIs has been increasing rapidly and is widely available to the consumer. The Household Products Database lists 55 consumer products containing MDI (Household Products Database 2015).
b. Unlike employees of large commercial operations who have access to hazard information, training, engineering controls, and PPE, consumers are not generally aware of the potential hazards of SPF systems containing MDI and other isocyanates, and are unlikely to have the training or proper equipment to protect themselves (U.S. EPA 2011a).
c. A 1998 NIOSH report concluded that application of roofing material with MDI in a school could have contributed to the increased prevalence of asthma among school employees (Kullman et al. 1998).
d. Large quantities of polyurethane foam and isocyanate coating material applied to a school roof may have caused 34 staff members to experience asthmatic symptoms (NIOSH 1994c).
e. There are anecdotal reports of strong odors and physiological reactions (headaches, dyspnea) following installation of insulation in various settings (Green Building Advisor 2010) and documentation of alleged injuries to occupants of SPF-insulated housing units (U.S. CPSC 2011a; U.S. CPSC 2011b; U.S. CPSC 2011c; U.S. CPSC 2012a; U.S. CPSC 2012b; U.S. CPSC 2012c; U.S. CPSC 2012d; U.S. CPSC 2013a; U.S. CPSC 2013b; U.S. CPSC 2014).

VII. Sensitive Subpopulations with Potential for Adverse Impacts from MDI

DTSC is concerned about all users and the public who may come into contact with, or in close proximity to, SPF materials containing unreacted MDI. The populations of greatest concern to DTSC are commercial operators using high- and/or low-pressure SPF systems employing only lower tiers of protection, unprotected workers in small businesses, and individual consumers who purchase SPF system for various do-it-yourself projects. The latter two groups generally use little or no protective measures against hazards associated with SPF materials.

a. Workers who work with or around isocyanates may be susceptible to both acute and chronic exposure to MDI via the inhalation and dermal routes. Inhalation exposures to isocyanates including MDI in excess of the OSHA PEL have been documented among workers during spray-on applications of foam roofs and insulation foam (ACC 2012; Crespo and Galan 1999; Hosein and Farkas 1981; Lesage et al. 2007; NIOSH 2005; NIOSH 2006; U.S. EPA 2011a). During spray foam applications, approximately 20% of the spray foam aerosol was found to be in the respirable size range (Lesage et al. 2007). Inhalation exposures have been documented after thermal degradation (welding or grinding) of isocyanate-containing products (OEHHA 2016; U.S. EPA 2011a). Both inhalation and dermal exposures to isocyanates are thought to contribute to the development of isocyanate-induced asthma (Bello 2007; Liljelind et al. 2010).
b. Exposure to isocyanates is recognized as a cause of occupational asthma (Bakerly et al. 2008; Bello et al. 2004; U.S. EPA 1998; Vandenplas 2011). Asthmatic symptoms may occur immediately upon exposure, be delayed for several hours after exposure, or consist of both an immediate and delayed reaction.
c. The polyurethane industry, through the SPFA and American Chemistry Council, has developed industry training and certification programs for SPF workers and contractors. These stewardship programs address medical monitoring, recommendations, practices, training materials, and health and safety guidance for workers (ACC 2014a; ACC 2014b; CPI 2014) to mitigate hazards associated with SPF products containing unreacted MDI. Large commercial operations may be willing and able to invest in training, and purchasing of equipment for engineering controls and personal protection for their workers. There is little evidence that workers exempt from or unregulated by OSHA such as small contractors are receiving industry recommended training and certification. Further, smaller, non-regulated businesses typically do not invest in engineering controls, or hire industrial hygienists. Individual consumers may not have any

knowledge or training before they purchase and apply SPF kits for do-it-yourself projects, nor do they invest or use any PPE. To date, California businesses' participation rates in the industry's training certification program remain unknown to DTSC.

d. Despite industry's certification program for some employees who work with SPF systems (SPFA 2013), accidental spills, leaks, cleaning and maintenance of equipment create situations where exposure to isocyanates can occur (Lockey et al. 2015).
e. The SPF industry sanctioned at least one contractor who was found on a Youtube video spraying SPF products without protection (Kavanaugh 2016).
f. Despite industry guidelines and access to personal protective equipment and engineering controls, safety violations may occur (Rundman 2013).
g. Individual consumers can purchase low-pressure kits either online or from suppliers of SPF systems (Levinson et al. 2014). These consumers are of particular concern (Environment Canada 2014a; Lockey et al. 2015; U.S. EPA 2011a; U.S. EPA 2014) because these kits are typically sold without a Safety Data Sheet or the necessary PPE (ACC 2015). Most consumers may not fully understand the potential hazards associated with SPF products, and do not utilize engineering controls or PPE (U.S. EPA 2011a).
h. OSHA recognized the potential harm associated with isocyanates, and developed a national emphasis program specifically designed for protecting workers from exposure to isocyanates in June 2013. However, the OSHA Isocyanates National Emphasis Program (NEP) is a limited, temporary enforcement action, which will expire in May 2016. Each OSHA Area Office is required to make only three (3) inspections per year (Rundman 2013). Despite multiple attempts, DTSC could not find any further information on program implementation and the number of inspections in the State of California. These inspections are specific only to the use of isocyanates, not SPF. Thus, OSHA inspections specific to SPF may or may not be conducted. The NEP does not cover individual consumers.

VIII. Conclusions

DTSC identified high-pressure and low-pressure SPF systems containing unreacted MDI as a proposed Priority Product. Following a review of available scientific data, including peer-reviewed journal articles, government reports, and industry-generated information, DTSC concluded that applicators, including workers, contractors, and consumers, may be exposed to unreacted MDI through the use of high- and low-pressure systems in both commercial and do-it-yourself project sites. Exposure to

unreacted MDI has resulted in respiratory and dermal sensitization, chronic asthma, and other bodily injuries.

The scientific and public health communities generally consider isocyanates, including MDI, asthmagens, and isocyanates are the cause of some documented cases of work-related asthma. Isocyanates bind with proteins, such as albumin or glutathione, and may cause respiratory sensitization that can lead to an elicitation of asthma in subsequent exposures to isocyanates, including MDI. People who have become sensitized to isocyanates may experience life-threatening asthma attacks when subsequently exposed to extremely low levels of isocyanates. Exposure to airborne MDI can also lead to other adverse human health impacts including hypersensitivity pneumonitis, respiratory irritation, pulmonary inflammation, and contact dermatitis.

Measurable concentrations of MDI have been detected in applicators' breathing zones during their work shifts. In some cases, particularly with high-pressure SPF systems, work-shift concentrations exceeded the OSHA PEL of 200 $\mu g/m^3$, a national regulatory standard. Although airborne concentrations of MDI are generally greater during the use of high-pressure systems, respirable particles containing MDI are present in the applicators' breathing zones during the use of low-pressure SPF systems as well. Studies and documented consumer complaints also suggest that bystanders and building occupants have the potential to be exposed to MDI if they re-enter treated areas without adequate protection.

Businesses that own and operate high-pressure systems generally follow State and federal worker safety standards to train, supervise, and provide employees who apply SPF products with appropriate PPE and engineering controls, such as ventilation. In some cases, employees who apply SPF through high-pressure systems also participate in industry-sponsored certification programs and are aware of industry safety recommendations. By contrast, low-pressure systems are readily available to and widely used by smaller contracting businesses and individual consumers. Small businesses with few or no employees and individual consumers are not generally required to comply with State or federal worker safety standards. They are also unlikely to be aware of industry-sponsored training programs or the need to protect themselves by following product SDS or using appropriate PPE and engineering controls.

PPE and engineering controls are considered the lowest tiers in the hierarchy of controls against occupational exposure to hazards because any user-error or malfunction can result in exposure to the hazard. Applicators who do not know how to wear PPE properly or who have been provided with ill fitting, poorly maintained, or improper PPE are at the greatest risk of exposure to MDI. Those who understand the

hazards associated with applying SPF and protect themselves through the proper use of PPE and engineering controls still risk exposure to airborne MDI if these controls malfunction or fail. Because SPF applications produce measurable concentrations of airborne MDI in the breathing zone, any person involved in, or near, the application risks exposure to MDI even when protective measures are used. Any applicator who does not use PPE or engineering controls, through choice or ignorance, is being exposed to potentially high concentrations of respirable MDI.

Therefore, DTSC concluded that workers, consumers, and bystanders could be exposed to MDI during the use of either high-pressure or low-pressure SPF systems that contain MDI. These exposures have the potential to contribute to or cause significant or widespread adverse impacts on the health of a considerable number of people in the State of California.

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APPENDIX A. Glossary and Abbreviated Terms

ACC: American Chemistry Council
ACGIH: American Conference of Governmental Industrial Hygienists
BALF: Bronchoalveolar lavage fluid
CARB: California Air Resources Board
Cal/OSHA: Division of Occupational Safety and Health, California Department of Industry Relations
CAS #: Chemical Abstract Service Registry Numbers
Cal/OSHA: California Division of Occupational Safety and Health (DOSH, commonly referred to as Cal/OSHA)
CDPH: California Department of Public Health
Diisocyanates: Isocyanates (see definition below) that have two isocyanate (–N=C=O) groups
DTSC: Department of Toxic Substances Control, State of California
FEV_1: Forced expiratory volume in one second
FVC: Forced vital capacity
HDI: Hexamethylene diisocyanate
HSDB: Hazardous Substances Data Bank maintained by the U.S. National Library of Medicine of the National Institutes of Health and Prevention, U.S. Department of Health & Human Services
IARC: International Agency for Research on Cancer
Isocyanates: Organic compounds that contains an isocyanate group (–N=C=O) with the general formula R–N=C=O.
MDA: Methylenedianiline
MDI: Methylene diphenyl diisocyanate
NIOSH: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health & Human Services
NEP: National Emphasis Program
OEHHA: Office of Environmental Health Hazard Assessment, State of California
OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limits
PMDI: Polymeric methylene diphenyl diisocyanate
Polyurethane: A polymer composed of a chain of organic units joined by carbamate (urethane) links. Polyurethane polymers are formed by reacting an isocyanate with a polyol. Both the isocyanates and polyols used to make polyurethanes contain on average two or more functional groups per molecule
PPE: Personal protective equipment
PSI: Pounds per square inch
RADS: Reactive airways dysfunction syndrome

SIC: Specific inhalation challenge
SPF: Spray polyurethane foam
SPFA: Spray Polyurethane Foam Alliance
TDI: Toluene diisocyanate
U.S. EPA: United States Environmental Protection Agency

ATTACHMENT 2

June 30, 2016 **VIA EMAIL ONLY**

Ian Kimber, Ph.D.
Faculty of Life Sciences
The University of Manchester
D4414 Michael Smith Building, Oxford Road
Manchester, M13 9PT, UK

SUBJECT: EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF SPRAY POLYURETHANE FOAM SYSTEMS WITH METHYLENE DIPHENYL DIISOCYANATES AS A PRIORITY PRODUCT

Dear Professor Kimber,

My letter today is intended to initiate the next phase of the external review.

The California Department of Toxic Substances Control will receive reviewers' comments and curriculum vitae from me after the review has concluded, and not be a party to the process.

Documents for review are being provided through a secure FTP site. Sections I and II below give instructions for accessing the FTP site and list the documents on the site.

You can access this site through the one month period of review. The URL, username and password are as follows:

I. https://ftp.waterboards.ca.gov/

Username : PRFTP
Password : 0xyqSb

II. List of Documents at FTP site:

A. **March 25, 2016 memorandum signed by Karl Palmer: "Request for External Peer Review for the Proposed Adoption of Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product."** **(**Three attachments are included in the memorandum)

Attachment 1: Plain English Summary of the Proposal to Adopt Spray Polyurethane Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product.

Attachment 2: Scientific Conclusions to Be Addressed by Peer Reviewers Regarding DTSC's Proposal to Adopt Spray Polyurethane

Foam Systems with Methylene Diphenyl Diisocyanates as a Priority Product**.**

Attachment 3: Individuals Involved in the Development of Documents and Reference List:
Section A: California Department of Toxic Substances Control Personnel
Section B: External Participants.

B. Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern; and

C. List of all references contained in the forgoing document.

Return your comments directly to me, on August 8, 2016, and not before to ensure I receive all reviews on the same day. Questions about the review should be for clarification, in writing – email is fine, and addressed to me. My responses will be in writing also. I subsequently will forward all reviews together to Karl Palmer with reviewers' Curriculum Vitae. All this information will be posted at the appropriate California Department of Toxic Substances Control program web site.

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
Office of Research, Planning and Performance
State Water Resources Control Board
1001 "I" Street, MS-16B
Sacramento, California 95814

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

June 27, 2016 **VIA EMAIL ONLY**

James Lockey, M.D.
Professor Emeritus
Department of Environmental Health
University of Cincinnati College of Medicine
231 Albert Sabin Way
G251 Medical Science Building
Cincinnati, OH 45267

SUBJECT: EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF SPRAY POLYURETHANE FOAM SYSTEMS WITH METHYLENE DIPHENYL DIISOCYANATES AS A PRIORITY PRODUCT

Dear Dr. Lockey,

My letter today is intended to initiate the next phase of the external review.

The California Department of Toxic Substances Control will receive reviewers' comments and curriculum vitae from me after the review has concluded, and not be a party to the process.

Documents for review are being provided through a secure FTP site. Sections I and II below give instructions for accessing the FTP site and list the documents on the site.

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C. List of all references contained in the forgoing document.

Return your comments directly to me, on July 27, 2016, and not before to ensure I receive all reviews on the same day. Questions about the review should be for clarification, in writing – email is fine, and addressed to me. My responses will be in writing also. I subsequently will forward all reviews together to Karl Palmer with reviewers' Curriculum Vitae. All this information will be posted at the appropriate California Department of Toxic Substances Control program web site.

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
Office of Research, Planning and Performance
State Water Resources Control Board
1001 "I" Street, MS-16B
Sacramento, California 95814

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

June 27, 2016 **VIA EMAIL ONLY**

Benoit Nemery, MD, PhD
Professor, Toxicology and Occupational Medicine
Department of Public Health and Primary Care
Faculty of Medicine, KU Leuven
Herestraat 49 (O&N 706)
B-3000 Leuven – Belgium

SUBJECT: EXTERNAL PEER REVIEW FOR THE PROPOSED ADOPTION OF SPRAY POLYURETHANE FOAM SYSTEMS WITH METHYLENE DIPHENYL DIISOCYANATES AS A PRIORITY PRODUCT

Dear Dr. Nemery,

My letter today is intended to initiate the next phase of the external review.

The California Department of Toxic Substances Control will receive reviewers' comments and curriculum vitae from me after the review has concluded, and not be a party to the process.

Documents for review are being provided through a secure FTP site. Sections I and II below give instructions for accessing the FTP site and list the documents on the site.

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Manager, Cal/EPA Scientific Peer Review Program
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ATTACHMENT 3

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.

ATTACHMENT 4

May 19, 2016

Professor Ian Kimber

Ian Kimber is currently Professor of Toxicology and Associate Dean for Business Development in the Faculty of Life Sciences at the University of Manchester.

He has broad research interests at the interface between toxicology and immunology, with a particular focus on allergy and inflammation.

Professor Kimber holds, and has held, a variety of positions on national and international expert and scientific advisory committees. Currently these include the following: Member UK Medicines and Healthcare products Regulatory Agency (MHRA) Devices Expert Advisory Committee, Programme Advisor Food Standards Agency Food Allergy and Intolerance Research Programme, member Scientific Advisory Board National Institute for Biological Standards and Control, and member MRC Translational Research Group. Professor Kimber was previously President of the British Toxicology Society (2012-2014), and Chairman of the Board of the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (2008-2013).

He has published over 625 research papers, review articles and book chapters, and serves currently on the editorial boards of toxicology, immunology, dermatology and pathology journals.

Professor Kimber has received a number of awards and prizes. These include: the SmithKline Beecham Laboratory Animal Welfare Prize (2000) (jointly with David Basketter and Frank Gerberick), the 9th Robert A Scala Award in Toxicology (2001), the Doerenkamp-Zbinden Foundation Prize for Realistic Animal Protection in Biomedical Research (2001), Society of Toxicology Enhancement of Animal Welfare Award (2003) (jointly with Frank Gerberick), and Society of Toxicology Immunotoxicology Career Achievement Award (2005).

In 2010 Professor Kimber received the Eurotox Bo Holmstedt Memorial Fellowship Award and Lecture at the International Congress of Toxicology.

In 2015 Professor Kimber received the Society of Toxicology Distinguished Toxicology Scholar Award.

In 2015 he was awarded the Barnes Prize Lecture by the British Toxicology Society.

In 2011 Professor Kimber was awarded an OBE in the Queen's Birthday Honours list for services to science.

BIOGRAPHICAL SKETCH

NAME James Edward Lockey	POSITION TITLE Professor Emeritus - Environmental Health and Internal Medicine (Pulmonary)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Kenyon College, Gambier, Ohio	BA	1968	Biology
Temple University, Philadelphia, PA	MD	1972	Medicine
University of Cincinnati, Cincinnati, OH	MS	1985	Environmental Health

Dr. Lockey's primary research focus for more than 30 years has involved occupational and environmental exposures and adverse human health outcomes. Dr. Lockey's research includes ongoing studies of the health impact from exposure to asbestiform mineral fibers found in vermiculite ore; studies investigating the relationship of diesel exhaust exposure and the risk for developing allergic rhinitis and asthma; a follow-up study of workers exposed to asbestiform contaminated vermiculite ore; the erionite fiber exposure study of North Dakota residents; studies on food flavoring agents and obstructive lung disease; exposure characterization of firefighters in collaboration with Underwriters Laboratories; and the development of an environmental sensor for personal exposure assessment of PM1.0 in collaboration with Mechanical, Industrial and Nuclear Engineering at the University of Cincinnati. Dr. Lockey has a patent to measure ultrafine particle exposure using a personal and wearable sensor. Dr. Lockey served as the primary investigator or co-investigator in all of these studies. The results from Dr. Lockey's research have helped derive proposed guidelines for various occupational and environmental exposures on a national and international basis.

Dr. Lockey has advised many MD, MS, and medical students in occupational and environmental medicine and epidemiology/clinical studies, and is committed to the graduate studies program at the University of Cincinnati. He has served on more than 60 MS and PhD committees. Dr. Lockey has also enjoyed an extensive career in teaching and advising medical students, pre and post doctoral students, and junior faculty. He has trained physician residents during his clinical activities in occupational and environmental related pulmonary disorders. He continues to be involved on student thesis committees, teaching medical students and physician residents within the graduate school, and continues to serve as a resource to faculty in the College of Medicine. He will continue to serve on the College of Medicine PSTP Promotion Board Committee, the Occupational and Environmental Medicine Residency Advisory Committee, the National Advisory Board on Radiation and Worker Health, and the Defense Health Board Public Health Subcommittee.

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2) **Lockey JE**, Levin LS, Lemasters GK, McKay RT, Rice CH, Hansen KR, Papes DM, Simpson S, Medvedovic M. Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. Am J Resp Crit Care Med 1998; 157:1226-1233.
3) Lemasters GK, **Lockey JE,** Levin LS, McKay RT, Rice CH, Horvath EP, Papes DM, Lu JW, Feldman DJ. An industry-wide pulmonary study of men and women manufacturing refractory ceramic fiber. Am J Epidemiol 1998; 148(9):910-919.
4) **Lockey JE,** Lemasters GK, Levin L, Rice C, Yiin J, Reutman S, et al. A longitudinal study of chest radiographic changes of workers in the refractory ceramic fiber industry. Chest 2002; 121(6):2044-2051.
5) LeMasters GK, **Lockey JE**, Yiin JH, Hilbert TJ, Levin LS, Rice CH. Mortality of workers occupationally exposed to refractory ceramic fibers. J Occup Environ Med 2003; 45(4):440-450.

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Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1jsN5k9FY7nQ_/bibliography/48778710/public/?sort=date&direction=ascending

D**. Research Support**

HTIW Coalition (Lockey, PI) 07/01/2011 - 12/31/2015 2.64 calendar months
HTIW (contract) $312,253
Pulmonary Surveillance of RCF Manufacturing Facilities
This is an ongoing morbidity and mortality study of workers involved with refractory ceramic fiber production (asbestos substitute) as related to pulmonary health.

T42 OH008432-08 (Rice, PI) 07/01/2005 - 06/30/2016 0.54 calendar months
CDC/NIOSH $1,216,970
Education and Research Center (ERC-Cincinnati)
The objectives are to conduct interdisciplinary graduate education and research, continuing education and outreach in environmental and industrial hygiene, occupational and environmental medicine, occupational health nursing and occupational safety and ergonomics; and to operate pilot research project program including several other academic institutions including two historically black colleges and two agricultural colleges.

CURRICULUM VITAE OF B. NEMERY (December 2015)

ADMINISTRATIVE DATA

- Name: Benoit NEMERY de BELLEVAUX
- Born: 10 September 1953, Fataki (Congo)
- Belgian citizenship
- Married (with Danielle PIETTE), 2 children, 3 grandchildren

DEGREES

- "***Doctor in de Genees-, Heel- en Verloskunde***" (Doctor in Medicine), K. U. Leuven, 1977
- ***"Diploma in de Tropische Geneeskunde***" (Diploma in Tropical Medicine), I.T.G. Antwerpen, 1977
- "***Licence en Médecine du Travail***" (Master in Occupational Medicine), U. C. Louvain, 1980
- ***Master of Science*** (M.Sc.) in Toxicology, University of Surrey, Guildford, 1982
- ***Doctor of Philosophy*** (Ph.D.) in Toxicology, Medical Research Council Toxicology Unit, Carshalton, Surrey & Council for National Academic Awards, U.K., 1986

PAST AFFILIATIONS

- 1977-81: Research assistant in cardio-pulmonary laboratory, U. C. Louvain
- 1981-85: Training in toxicology in Great-Britain at University of Surrey and at MRC Toxicology Unit, as Ph.D. student.
- 1985-86: Assistant in Unit of Industrial Toxicology and Occupational Medicine of U. C. Louvain

PRESENT AFFILIATION

- Since 1987, affiliated with Katholieke Universiteit Leuven, Faculty of Medicine
- Head of Research Unit of Lung Toxicology (joint venture between Divisions of Occupational Medicine and of Pneumology), now integrated within “Centre for Environment and Health” (within Department of Public Health and Primary Care)
- "***Gewoon Hoogleraar***" (Full Professor) since 1998
- Chair of the Department of Public Health (2005-2011)
- Member of the Research Council of the KU Leuven (2012-).

CURRENT WORK

- Research

Head of Research Unit of Lung Toxicology (2 senior scientists, 1 scientist, 1-2 post-doctoral fellows, 6-8 doctoral students or visiting researchers).

Research funded mainly by KU Leuven, regional or national research agencies (FWO-Vlaanderen, Belspo), international programmes (EU) and some private sources.

Main current research areas:

<u>1. Mechanisms of toxicity</u>
- In vivo and mainly in vitro studies (using isolated pulmonary epithelial cells from animals and humans) to investigate the mechanisms of pulmonary toxicity (including biotransformation, oxidant stress, cell injury and production of mediators of inflammation) caused by various agents, such as metallic compounds, therapeutic drugs, pesticides, industrial chemicals and polymers, air pollutants, nanomaterials.
- Development of a mouse model of chemical-induced asthma; influence of prior dermal sensitization to low molecular weight agents on immune-mediated respiratory effects.
- Mechanisms of the cardiovascular effects of pollutant particles.
<u>2. Clinical and epidemiological research</u> in occupational and environmental health
- Occupational asthma
- Cardiopulmonary effects of urban air pollution
- Adverse health effects of asbestos
- Health effects of green and blue spaces
- Health effects of occupational and environmental pollution by metals, especially in Katanga (D.R. Congo).

- Teaching

- Toxicology for post-graduate degrees in Occupational Medicine and in Environmental Sciences
- Environmental and Occupational Health in Medical School and for post-graduate degree in Occupational Medicine
- Supervision of master’s dissertations, mainly in Occupational Medicine
- Promoter or co-promoter of doctoral theses (21 completed)
- Various lectures and seminars, mainly at post-graduate level and continuous professional education: *approximately 200 invited lectures for international audiences at congresses or courses*

- Clinical activities

Staff member of Division of Pneumology within University Hospital Gasthuisberg

- out-patient clinic for occupational and environmental (respiratory) disease
- advice on toxicological problems for in-patients
- expert witness in compensation claims.

PUBLICATIONS

Author or co-author of

- 197 original articles,
- 48 case reports or letters to the editor,
- 108 reviews, editorials or commentaries
  (284 entries as author in Pubmed; >6000 citations; h-index 45 according to Web of Sciences)
- 48 chapters or contributions in textbooks

OFFICIAL APPOINTMENTS

- Past member of the "Technical Council" of the Belgian Fund for Occupational Diseases
- Member of the "Hoge Gezondheidsraad" (Health Council) of the Belgian Ministry of Health and Environment (1992-2013), now expert.
- Member of the WHO-CISAT Scientific Committee for the Toxic Oil Syndrome (1995-2008)
- Member of the "Agence Française de Sécurité Sanitaire de l'Environnement et du Travail" (AFSSET) (2006-2007)
- Member of the "Koninklijke Academie voor Geneeskunde van België" (Royal Academy of Medicine of Belgium) (2006-present)
- Member of SCOEL, the [EU] Scientific Committee on Occupational Exposure Limits (2015-)

MEMBERSHIP OF SCIENTIFIC SOCIETIES

- Belgian Society of Pneumology
- Belgian Society of Toxicology – BELTOX (founding member)
- Belgian Societies of Occupational Medicine (VWVA, SSST)
- British Association for Lung Research
- European Respiratory Society – ERS (head of "Epidemiology and Occupation Assembly" 2002-2005; chair of the Scientific Committee 2006-2009)
- American Thoracic Society – ATS (chair Program Committee of "Environmental & Occupational Health Assembly" 1999-2000)
- International Commission on Occupational Health – ICOH
- Collegium Ramazzini

MEMBERSHIP OF EDITORIAL BOARD OF SCIENTIFIC JOURNALS

- Occupational and Environmental Medicine (1994-2003)
- European Respiratory Journal (1995-1999)
- Inhalation Toxicology (2004-2007)
- American Journal of Respiratory and Critical Care Medicine (associate editor) (2004-2009)
- Journal of Occupational Medicine and Toxicology
- African Journal of Respiratory Medicine

MEMBERSHIP OF SCIENTIFIC COMMITTEES (selection)

- Member of the External Scientific Council of Vall d'Hebron Institut de Recerca (VHIR), Barcelona (December 2010-present)
- Member of the 3^{d} five-year review of the National Health Research Institutes of Taiwan (1-2 April 2012).

AWARDS

- ***Derscheid prize 1980*** from the Belgian Society of Pneumology for thesis in Occupational Medicine
- ***Boehringer-Ingelheim prize 1986*** from the Belgian Society of Pneumology for Ph.D. thesis
- Holder of the ***Belgian Francqui Chair 2007*** at University of Gent [http://www.francquifoundation.be/ang/chaires_histo_en.htm]
- Recipient of 2007-2008 Visiting Pulmonary Fellow Program [jointly organized by various academic/research institutions in North Carolina]
- ***Val Vallyathan Senior Investigator Award 2013*** from the Environmental and Occupational Health Assembly of the American Thoracic Society "in recognition of outstanding contributions to basic or translational science in environmental or occupational respiratory diseases"

ATTACHMENT 5

California Environmental Protection Agency

Department of Toxic Substances Control

Designation of Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern

Peer review performed by:

Professor Ian Kimber

University of Manchester

August 2016

Introduction

The subject of this review is the proposed adoption of Spray Polyurethane Foam (SPF) systems with Methylene Diphenyl Diisocyanates (MDI) as a priority product under the Safer Consumer Product (SCP) regulations.

The review that follows is based on a scientific paper (dated July 2016) produced by The Department of Toxic Substances Control (DTSC) entitled:

Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern

The main (but not only) concern is the potential of MDI to induce allergic sensitization of the respiratory tract associated with work-related asthma.

The emphasis on *unreacted* MDI is important. It is unreacted MDI that has the potential following exposure to form stable associations with proteins. It is such chemical (hapten)-protein conjugates that are required to drive immune responses resulting in allergic sensitization.

The product of concern is an SPF system that is comprised of 2 separate chemical components (one containing MDI, the other a mixture of polyols and other ingredients) that are sold together. These chemical components are intended to be mixed and sprayed, at which point they interact to form polyurethane foam.

In this case the Priority Product excludes those that do not contain unreacted MDI such as: polyurethane foam materials that do not involve mixing and spraying, finished (cured) foam, or one-component premixed, pre-reacted foam materials. Such products do not contain unreacted MDI, and therefore are not able to induce sensitization of the respiratory tract

Background to chemical respiratory allergy

Chemical respiratory allergy associated with occupational asthma is an important health issue, and one that can be associated with significant morbidity.

Several chemical classes have been associated with allergic sensitization of the respiratory tract, and these include acid anhydrides, certain chloroplatinate salts, some reactive dyes, and diisocyanates (Baur, 2013; Baur and Bakehe).

In considerations of risk assessment and occupational health it important to appreciate that the acquisition of sensitization of the respiratory tract to a chemical allergen does not necessarily require inhalation exposure to the material. There is increasing evidence that skin exposure to a chemical respiratory allergen is able to induce an immune response capable of causing respiratory sensitization (Rattray et al., 1994; Kimber and Dearman, 2002; Bello et al., 2007; Redlich, 2010; Liljelind et al., 2010; Lockey et al., 2015).

In general terms, exposure to a chemical respiratory allergen via an appropriate route (inhalation or skin contact) will, if the level of exposure is sufficient, provoke in susceptible individuals an immune response that results in sensitization of the respiratory tract. If subsequently a sensitized subject is exposed again, via inhalation, to the same chemical then a more vigorous secondary immune response will be elicited in the respiratory tract that, in turn, provokes a hypersensitivity reaction.

There remains considerable uncertainty about the precise immunological mechanisms through which sensitization of the respiratory tract is acquired. In particular, it is not clear what role – if any – is played by IgE antibody responses (Kimber and Dearman, 2002; 2005; Kimber et al., 1998; Kimber et al., 2014a). Nevertheless, there is more general agreement that respiratory sensitization to chemical allergens is commonly characterized by a Th2-type immune response, and recently an adverse outcome pathway has been described that attempts to identify the key events associated with sensitization of the respiratory tract to chemicals (Kimber et al., 2014b).

Scientific conclusions to be considered

The subject of the review is the proposed regulation to adopt SPF with MDI as a Priority Product under the Safer Consumer Product (SCP) regulatory framework.

Following review of the relevant data, DTSC has concluded that the proposal to adopt SPF systems with MDI as a Priority Product meets required regulatory criteria. The following conclusions were drawn:

- exposure to MDI may contribute to or cause significant or widespread adverse impacts to people, particularly to professional applicators and helpers, bystanders, and non-professional consumers
- people, particularly sensitive subpopulations, may be exposed to MDI through the normal use, handling or disposal of low-pressure and high pressure 2-component SPF systems

Against that background, the purpose is to determine whether:

- *the hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to MDI related to the use of SPF systems containing these Chemicals of Concern to contribute to or cause significant or widespread adverse impacts to human health*
- *the information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to MDI related to the use of SPF products containing these Chemicals of Concern*

Responses

Question 1

*Is the hazard information the DTSC relied upon sufficient to conclude that there is the **potential** for one or more exposures to MDI related to the use of SPF systems containing these Chemicals of Concern to contribute to or cause significant or widespread adverse impacts to human health?*

There is no doubt that diisocyanates, including MDI, have the potential to cause allergic sensitization of the respiratory tract, and they have all the properties required to induce sensitization, including the ability (of unreacted MDI) to form stable associations with proteins and create immunogenic hapten-protein conjugates (Bernstein, 1982; Lalko et al., 2012).

Although there are as yet no fully validated or widely accepted methods for the identification and characterization of chemical respiratory allergens, in those animal models that have been described MDI elicits a positive response (Rattray et al., 1994; Dearman et al., 1996; Pauluhn, 2008; Pauluhn and Poole, 2011).

All of the above is consistent with the fact that MDI – in common with other diisocyanates - is a confirmed cause of respiratory sensitization and occupational asthma in humans (Zammit-Tabona et al., 1983; Mapp et al., 1988; Kimber and Dearman, 1997; Petsonk et al., 2000; Creely et al., 2006; Bakerly et al., 2008).

In addition, MDI has been associated with other manifestations of respiratory hypersensitivity and respiratory toxicity, including hypersensitivity pneumonitis/extrinsic allergic alveolitis and reactive airways dysfunction syndrome (RADS) (Vandenplas et al., 1993; Leroyer et al., 1998).

For completeness, MDI has been implicated as a cause of allergic contact dermatitis (ACD) (Hamada et al., 2012). However, it is not a common contact allergen, and ACD is not the major health hazard associated with MDI.

Taken together the available data provide compelling evidence that MDI has a clear potential to induce allergic sensitization of the respiratory tract and to elicit respiratory hypersensitivity and occupational asthma. That is, there is a clear potential health hazard.

It is important to appreciate also that although the elicitation of respiratory hypersensitivity reactions will require inhalation exposure of sensitized subjects to MDI, both inhalation and skin contact has the potential to induce sensitization to MDI.

In the context of Question 1 it can be concluded that there is sufficient information to confirm that one or more exposures to MDI (related to the use of SPF systems containing unreacted MDI) has the potential to cause significant adverse health effects.

Question 2

Is the information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a ***potential*** *for exposure to MDI related to the use of SPF products containing these Chemicals of Concern?*

It has been estimated that the 2-component SPF market in California is valued currently at over $55M, and that the use of SPF materials is expanding rapidly.

As discussed above, the relevant route of exposure for the elicitation of a respiratory hypersensitivity reaction in a subject already sensitized to MDI is via inhalation. However, there is a growing appreciation that sensitization of the respiratory tract to chemical respiratory allergens (including diisocyanates) can be acquired by either skin or inhalation exposure to sufficient quantities of the chemical (Rattray et al., 1994; Kimber and Dearman, 2002; Bello et al., 2007; Redlich et al., 2010; Liljelind et al., 2010; Lockey et al.,2015). Therefore, when evaluating opportunities for exposure both routes should be considered.

The extent to which there may be opportunity for occupational exposure to unreacted MDI in 2-component SPF systems will vary according to a number of factors, including: the expertise, experience and training of individual workers, the workplace environment and culture, and the effective use of personal protective equipment (PPE).

However, it is important to recognize that, in addition to their use in a conventional workplace environment, individual consumers using SPF kits for home improvement purposes are also at risk of exposure to unreacted MDI. Such consumers are of particular concern because they will not have received appropriate training and supervision, and may not have access to suitable PPE.

It has been found that workers in certain occupational settings may be exposed to airborne levels of MDI that exceed the permissible exposure limit (PEL) prescribed by the Occupational Safety and Health Administration (OSHA) (200µg/m^3), and that when using spray foam applications a significant fraction of the aerosol generated was in the respirable size range (Crespo and Galen, 1999; Lesage et al., 2007).

It seems clear that the levels of MDI found in the breathing zone of users of both high-pressure, and to a lesser extent low-pressure, SPF systems can exceed permissible limits. These levels are probably adequate to induce sensitization, or to elicit a respiratory reaction in previously sensitized subjects.

Taken together, the data indicate that there will be opportunity among some of the workforce when using SPF systems to be exposed to levels of unreacted MDI sufficient to induce and elicit respiratory hypersensitivity and occupational asthma.

Although it may be possible to limit exposure to MDI by the use of appropriate training, effective supervision and high quality PPE, there will nevertheless be a risk of exposure to biologically relevant levels of MDI due to accidents, spillages, failure of engineering controls, and poorly fitting or functioning PPE etc. Moreover, it is clear that those at greatest risk of exposure will be workers in small businesses and individual consumers using SPF systems for home improvement purposes.

The conclusion drawn is that, in practice, it will not be possible to prevent exposure of all those using SPF systems containing unreacted MDI to concentrations of the chemical sufficient to induce sensitization of the respiratory tract, or to elicit a respiratory reaction, in susceptible subjects. At particular risk are those workers employed in small commercial operations where standards may be insufficient to contain exposure, and individual consumers undertaking home improvement work.

In the context of Question 2 it can be concluded that there is sufficient information to confirm that there is a potential for exposure to unreacted MDI resulting from the use of SPF products.

Comment

The DTSC Report: *Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisoccyanates as Priority Product with Chemicals of Concern(July 2016)* is generally very well written and well structured.

My only comment is that there is some information in the Executive Summary (exposure levels of isocyanates required to elicit a pulmonary reactions, and the ACGIH TLV value for MDI) that appear not to be in the main body of the report.

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Hamada H, Isaksson M, Bruze M, Engfeldt M, Liljelind I, Axelsson S, Jonsson B, Tinnerberg H, Zimerson E (2012) Dermal uptake study with 4,4'-diphenylmethane diisocyanate led to active sensitization. Contact Derm 66, 101-115.

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Kimber I, Dearman RJ, Basketter DA (2014a) Diisocyanates, IgE antibody and occupational asthma: implications for hazard characterization. J Appl Toxicol 34, 1073-1077.

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Lockey JE, Redlich CA, Streicher R, Pfahles-Hutchens A, Hakkinen PB, Ellison GL, Harber P, Utell M, Holland J, Comai A, White M (2015) Isocyanates and human health: multistakeholder information needs and research priorities. J Occup Environ Med 57, 44-51.

Mapp CE, Boschetto L, Dal Vecchio P, Maestrelli P, Fabbri LM (1988) Occupational asthma due to diisocyanates. Eur Respir J 1, 273-279.

Pauluhn J (2008) Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): analysis of the elicitation dose-response relationship. Toxicol Sci 104, 320-331.

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Zammit-Tabona M, Sherkin M, Kijek K, Chan H, Chan-Yeung M (1983) Asthma caused by diphenylmethane diisocyanate in foundry workers. Clinical, bronchial provocation, and immunologic studies. Am Rev Respir Dis 128, 226-230.

DTSC document entitled “Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern” dated July 2016.

Review By
James E. Lockey, MD, MS, Professor Emeritus
Departments of Environmental Health and Internal Medicine
University of Cincinnati College of Medicine

Submitted: August 8, 2016

Scientific conclusions to be addressed by peer reviewers regarding DTSC's proposal to adopt spray polyurethane foam systems with methylene diphenyl diisocyanates as a Priority Product:

Conclusion #1:

The hazard information that DTSC relied upon is sufficient to conclude that there is the potential for one or more exposures to MDI related to the use of SPF Systems containing these Chemicals of Concern to contribute to or cause significant or widespread adverse impacts to human health.

It is this reviewer's opinion that the scientific portion of the proposed regulation from which conclusion #1 is derived is based on sound scientific knowledge, methods, and practices.

It has been documented within the medical literature that exposure to diisocyanates, including the known sensitizer MDI, can cause various respiratory disorders in susceptible working population. Adverse outcomes include allergic conjunctivitis and rhinitis, asthma including chronic airway obstruction, and less commonly hypersensitivity pneumonitis. Contact dermatitis has also been associated with isocyanate sensitization. The host risk factors that account for increased susceptibility in subpopulations have not been identified.

The majority of human health data related to isocyanate exposure is based on industrial and commercial applications. Human health data from potential MDI exposure regarding use of spray polyurethane foam systems are more limited and inadequate. These limitations include health data related to commercial applications using high and low pressure systems, consumers using low pressure systems and SPF products, and by-standers potential exposure with building re-entry after application of spray polyurethane foam. The potential for MDI exposure using SPF products has been demonstrated, but more comprehensive and informative exposure data from commercial to consumer applications under various environmental conditions is needed. Just as critical is the lack

of health surveillance data of MDI SPF system workers combined with workplace MDI exposure assessment. The inadequacy of exposure and health data from workers and consumers who use MDI SPF systems is sufficient justification for adopting SPF systems with MDI as a Priority Product.

Specific Comments on Explanatory Statement listed under conclusion #1**:**

- State that isocyanate exposure is the most common form of occupational asthma;
- For 23 reported cases of work-related asthma from 1993-2008, how many were related to MDI within SPF Systems?
- Remove musculoskeletal toxicities as a result of MDI exposure. Not documented and not within the Summary of Technical Information.

Conclusion #2:

The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a potential for exposure to MDI related to the use of SPF products containing these Chemicals of Concern.

It is this reviewer's opinion that the scientific portion of the proposed regulation and from which conclusion #2 is derived is based on sound scientific knowledge, methods and practices.

There are data that indicates a potential for MDI exposure during application of SPF products. The problem is the paucity of these data under the various circumstances this product is utilized particularly by small contractors and consumers and the increasing use of SPF products particularly as energy-conservation measures.

The lack of adequate exposure monitoring data combined with inadequate isocyanate sampling analytic methodologies is problematic when trying to determine what represents adequate engineering, industrial hygiene controls and the current adequacy of personal protection equipment for lung and dermal protection. As stated previously, the inability to link exposure data to medical surveillance data from current and former workers is

very problematic in terms of whether or not current work practices for handling MDI SPF systems and products are sufficiently protective.

Specific Comments on Explanatory Statement listed under conclusion #2:

- Would comment on the lack of data on potential exposed populations and how this lack of data supports this proposal to adopt SPF systems with MDI as a Priority Product.

Additional Comments: These comments address additional scientific issues that are part of the scientific basis of the proposed regulation and the proposed implementation language.

- There is a paucity of data that documents whether or not MDI SPF systems can be safely utilized under current commercial and consumer work practice situations. Problems range from sampling methodologies for air and dermal, inadequate isocyanate analytical methodologies, lack of comprehension industrial hygiene air sampling across the broad spectrum of SPF products, and lack of health surveillance data on current and former MDI SPF system workers and consumers. This paucity of data regarding this potent sensitizer that can cause asthma including asthma with long-term chronic airway obstruction should be a component of the Technical Document.
- The document covers the various parameters usually involved with the toxicological review of a chemical or physical agent but can be better organized. For example, human health data are covered under Respiratory Toxicity (IV.1) and again under MDI-induced occupational asthma (V1.4), entitled Exposure potential of humans to MDI in SPF Systems. Justification for putting these under separate headings is not clear and confusing. For example, were the studies under IV.1 related to MDI exposure as a general category and the latter (V1.4) related to MDI based polyurethane foam? However, this does not appear to be the case based on my review of these sections.

- Within the main body of the document there is a paucity of information regarding measured exposure levels during application of SPF products. This issue is covered in some detail in the executive summary. A brief summarization within the executive summary and inclusion and expansion of measured exposure levels within the main text of the document is recommended.
- Place animal and human health data under one heading (Health Hazards of MDI). One potential format could be as follows:
    A. Animal data
        1) Immunotoxicity
        2) Respiratory inflammation and irritation
        3) Pathology
    B. Human Data (would include brief discussion of high variability of isocyanate induced occupational asthma across the industry)
        1) Airway disease and asthma
            a) Case report (include isocyanate type if available) (morbidity and mortality)
            b) Case series
            c) Cohort studies
        2) Hypersensitivity pneumonitis
            a) Case reports
            b) Case series
            c) Cohort studies
        3) Contact dermatitis
            a) Case reports
            b) Case series
            c) Cohort studies
        4) Other potential adverse health effects (odors and physiologic impact)
- As mentioned within the document, there is an industry-recommended training and certification program for workers who operate high pressure SPF systems. This program represents an opportunity to fill the data gaps at least in regard to

the commercial application of high pressure SPF systems as well as worker and by-stander exposure risk, especially if linked to current and former worker medical surveillance programs. This issue could be mentioned as a possible path forward to help fill some of the exposure and health data gaps regarding MDI SPF systems.

- For completeness, the document authors may want to cite the following test: International Isocyanate Institute supported text entitled “MDI and TDI, Safety, Health and the Environment”. A Source Book and Practical Guide. Editors: Allport DC, Gilbert DS, Outterside SM. John Wiley and Sons, Ltd., England (2003).

Review of documents related to “DTSC’s proposal to adopt spray polyurethane foam systems with methylene diphenyl diisocyanates as a priority product” (August 25, 2016)

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General introductory comments

I have concentrated my efforts on reviewing the scientific document *“Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern”* authored by Dennis Fengmao Guo, Lynn Nakayama Wong, Valerie Hanley, and Jesse Schenell. I have also read the documents *“Attachment 1”* and *“Attachment 2”*. I also accessed the references provided on the FTP site, but I did not read all of them and I gave preference to (peer-reviewed) scientific articles above reports from governmental agencies or industry, and I selected the ones that I did not know or that I thought would be the most relevant to check some of the claims made in the document.

Based on my expertise as an occupational physician and toxicologist, I have focused on the human health aspects, rather than on engineering or exposure aspects, although I have also considered the latter issues to the best of my ability.

Overall, I consider the document *“Summary of Technical Information and Scientific Conclusions for Designating Spray Polyurethane Foam Systems with Unreacted Methylene Diphenyl Diisocyanates as a Priority Product with Chemicals of Concern”*, as being based on sound scientific knowledge, methods, and practices. However, I do have some issues with the overall structure of the document, as explained below.

In this review, I shall provide comments to the different sections of the document in their order of appearance. In other words, the sequence of my comments does not reflect their relative importance.

Specific comments

I. Executive summary

This executive summary gives a good and concise overview of the state-of-knowledge, major points of concern and conclusions.

Second paragraph: I suggest to rephrase slightly as follows: “Isocyanates are low molecular weight chemicals that are generally considered to act as haptens. In vivo, haptens bind with proteins [no need to specify which proteins] and this may lead to immune responses that, in some people, consist of (allergic) sensitization. Individuals who have thus been sensitized will exhibit an exaggerated (“allergic”) response when they are exposed again to the hapten, even in very low amounts. Depending on the route of exposure, responses elicited by subsequent exposures may consist of dermal reactions (allergic contact dermatitis) or

respiratory reactions (asthma or hypersensitivity pneumonitis). It is generally accepted … " (the wording of first paragraph of section IV is more appropriate)

Third paragraph: it might be advisable to indicate that the 23 cases of isocyanate-related asthma recorded over 15 years (i.e. fewer than two cases per year) likely represent only a fraction of the real number of cases, in view of the well-known fact that work-related conditions tend to be underdiagnosed and underreported by clinicians.

Sixth paragraph: last sentence is vague and not entirely correct (an aerosol is made up of particles and vapors/gases; dusts are composed of respirable and other particles, …).

Ninth paragraph: "administrative controls and PPE are considered to be the least desirable approaches" although I understand the meaning of this claim, it would be prudent to qualify this statement by adding "if they are the only measures taken"

Eleventh paragraph, line 3: typo: occurs; end of third sentence: consider adding "and possibly beyond."

Last paragraph: "significant and widespread" ; I am not sure these terms are entirely appropriate in the absence of a clear definition of what is to be considered "significant" (serious? – some purists argue that one should restrict the use of "significant" to its statistical meaning, i.e. "unlikely due to chance", and then also specify what degree of significance is accepted, e.g. $p<0.05$) and "widespread" (some could argue that "only" 23 cases of occupational asthma over a period of 15 years in a population of several millions does not represent a widespread occurrence of disease); are these terms really necessary/mandatory? The review confirms that MDI is a hazardous agent (this was well known) and documents further that exposure to MDI during spraying polyurethane foam can seriously harm (not just annoy) operators, especially casual workers and even consumers or bystanders (i.e. a more vulnerable fraction of the population).

II. Identification

The multiple names given to "MDI" have always given rise to some confusion. So, it is appropriate to devote a detailed section to this issue. This section is generally clearly written.

The rationale for using the plural "methylene diphenyl diisocyanates" could be made explicit upfront and the various possible isomers could be listed or shown.

The composition (and toxicity) of the ingredients other than MDI in the SPF systems could be briefly mentioned (e.g. in a table).

Note that PMDI is used further in the text, but this abbreviation is not explained in this section.

III. Physicochemical properties

Boiling point: I did not check (Haynes 2010), but internet sources state boiling point is above 300°C at atmospheric pressure, which is more relevant than at 5 mm Hg (almost vacuum!).

Water solubility is only notional, because MDI degrades in water.

Add bullet before "vapor pressure".

I advise to put these properties in perspective using plain English text such as: pure MDI is a solid at room temperature, but MDI (i.e. polymeric MDI) used for SPF is always in a liquid

form (hence, present in drums); at normal temperatures, MDI does not evaporate to a large extent (in contrast to, e.g., TDI) but it may do so at high temperature; although MDI does not evaporate easily, MDI may nevertheless be airborne (as droplets) as a result of nebulization or other forms of (intentional) aerosolization as occurs with spray guns.

IV. Hazard traits

In general, the content of this section is OK, but its structure is confusing because of the artificial distinction that is made between immunotoxicity, respiratory toxicity, and dermatotoxicity. I suggest to classify the hazard traits into either a mechanism-based classification (irritation/toxicity, immune-mediated effects, mutagenicity/carcinogenicity), or an organ-based classification (skin, respiratory tract, other systems). Alternatively, experimental studies and human clinical or epidemiological studies could be discussed separately.

1. Immunotoxicity. a. allergic sensitization. (note there is no corresponding b.).

   The most relevant notion, in my opinion, is that diisocyanates, including MDI, can induce sensitization (by virtue of the high chemical reactivity of the -NCO groups towards proteins). In experimental animals (and presumably also in humans) sensitization may be obtained either by dermal contact ("dermal sensitization") or by "respiratory sensitization", i.e. contact with the respiratory mucosa (either in a single high amount, or in repeated low amounts). Once animals (or humans) have been sensitized to MDI, respiratory reactions can be elicited by aerial exposure to low amounts of MDI (probably regardless of the initial sensitization route). This is why MDI (and similar agents) are called "respiratory sensitizers" but, in my opinion, this term is a misnomer, because it suggests that the sensitization (necessarily) occurs via the respiratory route, which is clearly not the case, as demonstrated in experimental animals and to some extent also in humans. (This does not imply that the route of sensitization plays no role in the pathophysiology of MDI-induced asthma). Hence, the term "asthmogen" (or "asthmagen") is preferable to that of "respiratory sensitizer." However, as indicated below, MDI can also cause hypersensitivity pneumonitis (also called "extrinsic allergic alveolitis"), which is also a form of respiratory immunotoxicity, however this condition is different from asthma in its mechanisms and clinical expression. In addition, MDI can also cause allergic contact dermatitis (eczema). In sum, MDI is a sensitizer that can lead to adverse reactions in the respiratory tract or the skin when it is administered to previously sensitized individuals.

   The choice of experimental studies that are described in the document is appropriate, but some critical details (exact route and mode, as well as timing of exposure) must be reported. The last sentence needs to be completed by "after an airway challenge with the sensitizer".

   An "immunotoxicity" issue, that could have been addressed in the document, is that of the possible occurrence of cross-reactivity between different diisocyanates. This is not only of theoretical importance, but also of practical importance for the prevention of elicitation of dangerous reactions in MDI-sensitized subjects. This issue is not entirely settled (see: Pollaris et al. Toluene diisocyanate and methylene diphenyl diisocyanate: asthmatic response and cross-reactivity in a mouse model. *Archives of Toxicology*, 2015, 90, 1709-17).

2. Respiratory toxicity. Sections a, b and c deal with animal studies and sections d and e deal with human studies.
   The choice of studies is adequate, and the description and interpretation of the observations are sound. However, it should be recognized that none of these studies deal with MDI-based SPF.

3. Dermatotoxicity. a. Allergic contact dermatitis. OK. (note there is no corresponding b).

Why are other toxicity issues (mutagenicity, carcinogenicity, developmental toxicity) of MDI not addressed in the document? Admittedly, these do not appear to be of great concern, but this fact could be mentioned.

In conclusion #1, it is also stated that exposure to MDI in the workplace can cause […] musculoskeletal toxicit[y]. The review does not address this, and I don't think there is evidence for such a toxicity (although workers involved in SPF activities may, of course, suffer from musculoskeletal disorders).

V. Environmental fate of MDI.

I did not scrutinize the data in this section, but this looks OK.
The first sentence of the 1. Air section is unclear (and not entirely logical, in my view).
Note typo in Atemospheric.

VI. Exposure potential of humans to MDI in SPF systems

This section is very important, but sections 3 and 4 do not really deal with "exposure potential" and could have been included in section IV.2

1. Market presence: not checked

2. Worker exposure routes
   In my view this section should provide more details and figures about the concentrations (and their time course and spatial distribution) that were actually measured in various occupational circumstances, especially when using SPF systems. These data are at least as relevant – if not more relevant – than the exposure data provided when describing the animal experiments in the previous sections. An aspect worth mentioning with regard to exposure is the fact that SPF is often applied in "confined spaces", such as attics or crawling spaces, hence in environments with poor ventilation leading to potentially high exposures to MDI (and other harmful agents).

3. MDI-induced worker fatalities.
   I know of at least one other published case report of a fatality in the workplace (Carino et al. *Respiration* 1997, 64, 111-3).

4. MDI-induced occupational asthma.
   It would be appropriate to indicate that no systematic review on MDI-related occupational asthma has been published in the biomedical literature.

The choice of sources quoted to provide evidence for the existence of MDI-induced occupational asthma is somewhat strange and unbalanced. In view of the very extensive database on the subject it is appropriate to cite reviews and reports from NIOSH or other agencies. However, the three cases described by Bonauto and Lofgren (2004) (presumably non-peer-reviewed) appear anecdotal

5. Non-occupational exposure potential
   Again this section is important, but one should acknowledge that the "evidence" reported in c, d and e is weak with regard to a causal role of MDI. The language used in e (anecdotal, physiological reactions, alleged) does suggest that the evidence is poor (or even non-existent), but I recommend that our ignorance (or skepticism) about these effects among occupants of insulated buildings be acknowledged more candidly.

VII. Sensitive subpopulations …

Overall, this section gives a good summary of the evidence and rationale for the conclusions.

One additional issue to consider is that people who become sensitized to an agent through their work (or otherwise) remain sensitized for ever. This implies that workers or consumers who would become sensitized to MDI via the use of SPF systems remain at risk of adverse reactions to MDI in other exposure scenarios, e.g. when using MDI-based glues or when treated with an MDI-based plaster (Donnelly et al. Occupational asthma after exposure to plaster casts containing methylene diphenyl diisocyanate*. Occup Med (Lond).* 2004 Sep;54(6):432-4. Suojalehto et al. Occupational asthma related to low levels of airborne methylene diphenyl diisocyanate (MDI) in orthopedic casting work. *Am J Ind Med*. 2011 Dec;54(12):906-10. Review).

VIII. Conclusions

Again, I generally agree with the content of this section, although, as argued above, I would query the use of "significant and widespread" in the last sentence.

Final conclusions

I agree with Conclusion #1 (Attachment 2, pg.8) that **"The hazard information that DTSC relied upon is sufficient to conclude that there is the *potential* for one or more exposures to MDI related to the use of SPF Systems containing these Chemicals of Concern to contribute to or cause significant or widespread adverse impacts to human health."** However, as indicated above, I have some reservations about the use of the (poorly defined terms) "significant" and "widespread." I also suggest to be more explicit (providing actual data) about our knowledge regarding the exposure scenarios in SPF operations. I suggest to delete 'musculoskeletal' from the list of conditions potentially caused by MDI exposure.

I agree with Conclusion #2 (Attachment 2, pg.9) that **"The information that DTSC relied upon to evaluate exposures is sufficient to conclude that there is a *potential* for**

exposure to MDI related to the use of SPF products containing these Chemicals of Concern."

With regard to Attachment 1 (Plain English summary), I consider this to be generally adequate, but I suggest to incorporate some of the comments made above.