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SECRETARY FOR
ENVIRONMENTAL PROTECTION

State Water Resources Control Board

July 14, 2021

Shelley DuTeaux, Ph.D., MPH, Chief
Human Health Assessment Branch
1001 I Street
P.O. Box 4015
Sacramento, California 95812

SUBJECT: INTERIM RESPONSE TO REQUEST FOR EXTERNAL PEER REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

Dear Dr. DuTeaux,

This letter responds to the attached April 29, 2021, 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, my colleague contacted the University of California, Berkeley (University) and requested recommendations for candidates considered qualified to perform the assignment. This service is supported through an Interagency Agreement co-signed by CalEPA and the University. The University was provided with the request letter and attachments. No additional material was asked for, nor provided. The University interviews each promising candidate.

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 my colleague for review, with their 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."

For each candidate judged to be free of conflict, my colleague approved that person as reviewer, affirmed by an approval letter. Reference was made to specific parts of the completed COI form and CV. The approval letter also asked the approved candidate which of the conclusions that person would be able to address "with confidence, based on expertise and experience."

Later, my colleague sent letters to reviewers to initiate the review. These letters provided access instructions to a secure FTP site where all material to be reviewed was placed. Confirmation was requested that the reviewer could access the site and all documents that had been uploaded to it. Each reviewer was asked to address each conclusion to which he or she had previously agreed, and these were identified in the letter. Thirty days were provided for the review, unless a reviewer requested additional time. Reviewers were also asked to direct enquiring third parties to me after they submitted their reviews.

Guidance was provided a) to ensure confidentiality through the review process; and b) for format presentation to meet "accessibility" requirements.

Reviewers' names, affiliations, curriculum vitae, initiating letters and reviews are being sent to you now with this letter. This information can be accessed easily through the bookmarks listed on the left of the screen, or by scrolling down.

Approved reviewers:

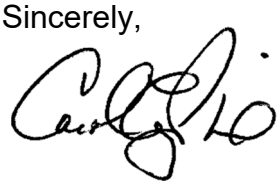
1. Alison Elder, Ph.D., Associate Professor
   Dept. of Environmental Medicine
   School of Medicine and Dentistry
   University of Rochester Medical Center
   601 Elmwood Ave., Box EHSC
   Rochester, NY 14642

2. Judith T. Zelikoff, Ph.D., Professor
   Dept. of Environmental Medicine
   NYU Grossman School of Medicine
   341 E. 25th Street
   New York, NY 10010

3. Thomas O. Spicer, Ph.D.
   Professor and Maurice Barker Chair in Chemical Engineering
   Ralph E. Martin Department of Chemical Engineering
   University of Arkansas
   Fayetteville, AR 72701

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

Sincerely,



Carol Perkins
Manager, CalEPA External Scientific Peer Review Program
Office of Research, Planning, and Performance
State Water Resources Control Board
1001 "I" Street, 13th Floor Sacramento, California 95814
Carol.Perkins@waterboards.ca.gov

Attachments:

(1) April 29, 2021, Request by Shelley DuTeaux, for Scientific Peer Review
(2) Letters to Reviewers Initiating the Review
    (1) Alison Elder, Ph.D.
    (2) Judith T. Zelikoff, Ph.D.
    (3) Thomas O. Spicer, Ph.D.
(3) Curriculum Vitae
    (1) Alison Elder, Ph.D.
    (2) Judith T. Zelikoff, Ph.D.
    (3) Thomas O. Spicer, Ph.D.
(4) Reviews
    (1) Alison Elder, Ph.D.
    (2) Judith T. Zelikoff, Ph.D.
    (3) Thomas O. Spicer, Ph.D.

cc: Karen Morrison, Ph.D., DPR Assistant Director
Department of Pesticide Regulation
Karen.Morrison@CDPR.ca.gov

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Andrew L. Rubin, Ph.D., DABT
Primary State Toxicologist
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Department of Pesticide Regulation

Gavin Newsom
Governor

Jared Blumenfeld
Secretary for Environmental Protection

Val Dolcini
Director

MEMORANDUM

TO: Gerald W. Bowes, PhD
Manager Cal/EPA Scientific Review Panel
Office of Research, Planning and Performance
State Water Resources Control Board
1001 I Street, MS 16B
Sacramento, California 95814

FROM: Shelley DuTeaux, PhD MPH, Chief
Human Health Assessment Branch

DATE: April 29, 2021

SUBJECT: REQUEST FOR AN EXTERNAL SCIENTIFIC REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

In accordance with Health and Safety Code section 57004, the California Department of Pesticide Regulation (DPR) requests external peer review of its draft risk and exposure assessment document entitled "Draft Allyl Isothiocyanate Risk Characterization Document: Occupational and Bystander Exposures." The intent of the external peer review of the human health assessment of allyl isothiocyanate (AITC) is to review the science that will serve as the basis of the designation of this specific pesticide active ingredient as a restricted material, and in particular, the toxicological evaluation that resulted in the recommendation of a 14 parts per billion (14 ppb) reference concentration for acute exposures. The documents requested for external scientific review may also provide scientific basis for permit conditions, mitigation of any potential exposures, and regulation development relative to AITC applications.

It is suggested that the reviewers have expertise in the following areas, in order of importance:

1. **Human Health Risk Assessment** (Charge Questions 3, 4, 8, 9)

   This expert would have a professional and applied experience in the practice of human health risk assessment, preferably in the regulatory sector, and be able to apply his or her knowledge in the process of estimating the nature and probability of adverse health effects in humans.

2. **Inhalation Toxicology** (Charge Questions 1, 2, 3, 7)

   This expert would have a practiced understanding of mammalian respiratory systems and the impacts of inhaled toxicants on localized and systemic effects. Especially helpful would be experience in evaluating inhaled fumigants and the establishment of regulatory target for acute inhalation exposures to workers and sensitive subpopulations.

3. **Exposure Assessment and Air Dispersion Modeling** (Charge Questions 5, 6, 8, 9)

   This expert would be a specialist in airborne contamination modeling used to predict breathing zone concentrations and the associated mathematical formulations used to characterize atmospheric dispersion. This expert would be well-versed in the practices of exposure assessment especially for inhalation exposures in workers and sensitive subpopulations.

Three reviewers will be adequate to cover all needed areas of expertise. The preferred period of review is 30 days from the reviewer's receipt of the documents, and ideally the reviews would be completed by **June 30, 2021**.

The following attachments are enclosed:

Attachment 1: Plain English summary of the Draft Risk Characterization Document developed for evaluating occupational and bystander exposures to Allyl Isothiocyanate

Attachment 2: Description of scientific assumptions, findings, and conclusions to be addressed by the peer reviewers

Attachment 3: Bibliography

Attachment 4: List of Participants

If you have any questions regarding this request, please contact Marilyn Palmer-Townsend at <Marilyn.Palmer-Townsend@cdpr.ca.gov>. Thank you for your time and consideration of this request.

Attachments

cc: Karen Morrison, PhD, DPR Assistant Director
Svetlana Koshlukova, PhD, Senior Toxicologist, Risk Assessment Section
Eric S. Kwok, PhD DABT, Senior Toxicologist, Exposure Assessment Section
Peter N. Lohstroh, PhD, Senior Toxicologist, Toxicology & Dose Response Section
Andrew L. Rubin, PhD DABT, Primary State Toxicologist

Attachment 1

Plain English summary of the Draft Risk Characterization Document developed for evaluating occupational and bystander exposures to Allyl Isothiocyanate

Allyl isothiocyanate (AITC) is a naturally occurring plant compound produced by mustard, horseradish, wasabi, and other cruciferous vegetables. AITC is federally registered as a biopesticide for use on food and non-food crops to control microbial pathogens, nematodes, and weeds. AITC was previously registered in California as an animal repellent in formulations containing less than 5% AITC. There are no current registrations of AITC in California.

In 2017, Isagro USA Inc. submitted a registration application to the California Department of Pesticide Regulation (DPR) for the use of AITC (96.3% by volume) as a pre-plant soil fumigant for food and non-food crops and as a post-plant crop termination applications. DPR has a policy of conducting comprehensive pre-registrational human health risk assessment for all fumigants under consideration for use in California. DPR initiated the human health risk assessment process for AITC in 2018. The result was a July 2020 draft Risk Characterization Document (RCD) which focused on inhalation toxicity to align with AITC's proposed use as a chemical fumigant.

The draft RCD and its appendices reviewed all available toxicology data for hazard identification and presents reference concentrations (e.g., air concentrations that are likely to be without appreciable risk of deleterious effects) and risks to humans calculated as margins of exposure. Risks were estimated for workers handling and applying the fumigant, for other workers in nearby fields (e.g., occupational bystanders), and for downwind populations, including vulnerable receptors and subpopulations (e.g., residential bystanders) if this fumigant was to be registered for use in California.

The inhalation toxicity database for AITC is very limited, consisting of three studies in rats (two acute and one subchronic). A number of oral toxicity studies in laboratory animals were available and used to evaluate toxicokinetics, developmental and reproductive toxicity, and oncogenicity, with the acknowledgement that the oral route of exposure is unlikely with an agricultural fumigant. The toxicological evaluation resulted in the recommendation of a reference concentration of 14 parts per billion (14 ppb) for acute exposures. While the studies that provided the basis for this recommendation were well designed, the overall confidence in the calculated risk estimates is impacted by the database limitations. Likewise, because there are limited in-field use data for this fumigant, evaluation of the exposure potential relied upon chemical surrogates and air dispersion modeling to develop potential emission scenarios on which to base exposure assumptions.

The intent of this external scientific review is the review the science that will serve as the scientific basis of the designation of AITC as a restricted material, and any resulting permit conditions, exposure mitigation, and regulation development.

Attachment 2

Description of Scientific Assumptions, Findings, and Conclusions to be addressed by the Peer Reviewers

Reviewers are asked to determine whether the scientific work product is based upon sound scientific knowledge, methods, and practices. As such this request is that the external reviewers make this determine for each of the following issues.

For those work products which are not proposed rules, as is the case here, reviewers must evaluate the quality of the product using the same exacting standard as if it was subject to Health and Safety Code 57004, which requires highly-qualified experts to perform impartial peer reviews. This is intended to ensure that proposed rulemaking by the California Environmental Protection Agency (CalEPA) and its boards, departments, and office meet accepted standards of the relevant scientific disciplines and to prevent any influence on rulemaking stemming from irrelevant findings, unwarranted claims, unacceptable interpretations, and personal views.

The assumptions and conclusions used to calculate the acute reference concentration (RfC) for allyl isothiocyanate (AITC) are discussed in accompanying draft Risk Characterization Document and it appendices. These include the rationale for selection of the critical points of departure (PODs), the approaches for derivation of human equivalent concentrations (HECs), the choice of appropriate uncertainty factors (UFs), and the approach of the exposure assessment. Reviewers are requested to review the entire document and make determinations on the scientific approaches used to determine each of the following:

1. **A default 10x extrapolation factor was used to establish the critical acute point of departure (POD) of 2.5 ppm.** [Addressed in sections C.2, D.1.1, and E.1.2 of the Risk Characterization Document.]

The critical study was a whole body inhalation toxicity study in rats exposed for 4 hours to vaporized AITC. This study did not include a no observed effect level (NOEL). The effects at the lowest tested dose (LOEL of 25 ppm) included decreased rearing counts and decreased motor activity. A benchmark dose (BMD) modeling approach was not used to establish the acute POD for AITC because the high variability in the data for the critical endpoints was not conducive to such modeling. Instead, a default dose extrapolation factor of 10 was used to establish the critical POD.

2. **The critical chronic inhalation POD was estimated from the subchronic critical POD by applying a default duration extrapolation factor of 10. This was necessitated by the lack of chronic inhalation studies.** [Addressed in sections C.6, D.1.3, and E.1.4 of the Risk Characterization Document.]

The critical chronic inhalation POD of 0.5 ppm was derived from the subchronic critical POD of 5 ppm. The latter was established from a 13-week inhalation toxicity study in rats. The effects at the LOEL of 10 ppm resulted from both portal of entry (metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium) and systemic (decreased motor activity) delivery to the target sites. When a 13-week subchronic study is used for duration extrapolation, a factor of 3 may be considered because the study covers substantial portion (about 13%) of the 2-year rat lifetime. However, we applied the full default value due to the limited inhalation database.

3. **PODs from oral studies were not used to establish critical PODs.** [Addressed in sections C. D.1, E.1 and Appendix 4 of the Risk Characterization Document.]

All critical points of departure (PODs) for this risk assessment were established from inhalation studies in rats. These studies were well designed and provided crucial information on multiple toxicologically relevant parameters, including motor activity, functional observational battery behaviors, and organ and tissue histopathology. However, the AITC inhalation toxicity database was limited, consisting of only three inhalation studies in rats (two acute and one subchronic). In addition, no human inhalation studies for derivation of PODs were identified by systematic review and no inhalation studies were available to determine toxicokinetics, reproductive or developmental toxicity, chronic toxicity or oncogenicity.

A number of oral toxicity studies in laboratory animals were available and were used to inform AITC's toxicokinetics, oncogenicity, and developmental toxicity. Effects seen in oral studies of short-term, subchronic, and chronic durations in laboratory animals included hyperplasia of the stomach and urinary bladder epithelium, and cataracts in rats. Importantly, these effects were not observed in the acute and subchronic inhalation studies in rats. Therefore, oral PODs were not used to establish critical inhalation PODs due to concerns about route specificity of observed effects.

However, when we converted the oral PODs to inhalation PODs using duration adjusted default rat breathing rates, we determined that the equivalent external air concentrations derived from the oral studies showed effects at concentrations similar to those in the inhalation studies. For example, the subchronic oral NOEL of 6.6 mg/kg/day for urinary bladder hyperplasia in rats established in a 13-week drinking water study produced an equivalent external air concentration of 9.5 ppm. This value was similar to the estimated critical subchronic inhalation POD of 5 ppm in rats for motor activity decrements. The same route extrapolation was performed on the chronic oral POD of 0.6 mg/kg/day for urinary bladder hyperplasia in rats exposed for 2 years by drinking water. The resultant chronic equivalent external air concentration of 0.9 ppm was similar to the estimated critical chronic inhalation POD of 0.5 ppm for motor activity decrements. Because urinary bladder hyperplasia was the most sensitive systemic endpoint in the oral studies, this analysis showed that the critical inhalation PODs would be protective of any systemic toxicity induced by AITC.

4. **This RCD did not include a cancer risk estimate for AITC.** [Addressed in sections C.6, D.1, E.1, E.4 and Appendix 4 of the Risk Characterization Document.]

Chronic inhalation studies were not available to indicate if AITC has the potential to cause tumors by the inhalation route. However, orally administered AITC appeared to increase the incidence of three types of tumors in rats: undifferentiated leukemia, fibrosarcoma, and urinary papilloma.

Undifferentiated leukemia: This tumor was observed in one oral oncogenicity bioassay. However, there was compelling evidence that the observations were artifacts of the study design and the selected rat stain (F344/N) rather than the AITC treatment.

Fibrosarcomas: This tumor was observed in a two year oral gavage study using rats. A role for AITC in fibrosarcoma induction was plausible. However, cancer potency analysis was precluded by the fact that the apparent effect occurred only at the high dose.

Urinary bladder tumors: This tumor was observed in two oral oncogenicity bioassays in rats. However, AITC by the inhalation route did not induce urinary bladder hyperplasia after 13 weeks of exposure. This observation suggested that bladder effects were relevant to oral, but not inhalation exposures. Consequently, urinary bladder epithelial hyperplasia and bladder tumors induced by chronic oral exposure were unlikely to result from inhalation exposure. Furthermore, weight of evidence analysis of mode of action for urinary bladder tumors indicated a threshold dose response with urinary bladder hyperplasia as the pre-requisite key event. As a result, bladder tumor data were not used to calculate a cancer potency value.

5. **Due to a lack of AITC exposure monitoring data, worker exposures to AITC were estimated using exposure monitoring data from 1,3-D and chloropicrin.** [Addressed in Appendix 1, Human Exposure Assessment for Allyl Isothiocyanate, sections V.A – V.C.]

As described in Tables 7 through 18 of the Exposure Assessment Document (see Appendix 1 of the Risk Characterization Document), worker exposures to AITC were assessed for three application methods (shallow shank, deep shank and drip). DPR used worker exposure monitoring data from chloropicrin to assess AITC worker exposures for all exposure scenarios except for loaders, which used 1,3-dichloropropene (1,3-D) data as there is no chloropicrin exposure monitoring data available (see pp. 14 – 22 of Appendix 1). The chloropicrin or 1,3-D air concentrations measured at the worker breathing zone were corrected for recoveries and adjusted to the maximum AITC application rates for different application methods (shallow shank, deep shank and drip (see pp. 25 – 26 of Appendix 1). Due to the lack of AITC data, the adjusted 1,3-D or chloropicrin air concentrations were used as a conservative measure to estimate worker exposures to AITC. The underlying assumptions and rationales are discussed in detail in Section VI. Exposure Appraisal (see pp. 25 – 28 of Appendix 1).

6. **DPR estimated bystander exposures to AITC using an air dispersion model (AERMOD). Occupational bystander exposures were estimated at the field edge, and residential**

bystander exposures were estimated at 25 and 100 ft from the field edge. [Addressed in Appendix 1, Human Exposure Assessment for Allyl Isothiocyanate, section V.D.]

The AERMOD model employs hourly soil emission rates of a fumigant to estimate air concentrations at different distances from a treated field. DPR conducted AERMOD modeling for five different application and tarp methods, two of which used AITC-specific soil emission data. For the other three methods without AITC data, 1,3-D and chloropicrin data was used as surrogates. The complete review of 1,3-D and chloropicrin emission data is appended to Appendix 1 of the Risk Characterization Document, which discusses the rationales of selecting 1,3-D and chloropicrin data as a conservative measure when AITC data were not available (see pp. 50, 51, 55 – 57 of Appendix 1). As AITC is not registered for use in California, DPR conducted AERMOD modeling in 5 regions where soil fumigants are currently applied (central valley, central coast, south coast, inland empire and the northern region), and used meteorological data from 6 weather stations (Merced, Kern, Santa Cruz, Ventura, Riverside, Siskiyou) within these five regions. Details on the modeling methodologies and rationales of choosing these specific model inputs are also appended to Appendix 1 of the Risk Characterization Document (see p. 66 of Appendix 1).

7. **Dosimetric adjustments of air concentrations to account for pharmacokinetic differences between laboratory animals and humans were used to calculate reference calculations (RfCs) and risk targets (i.e., target Margins of Exposure).** [Addressed in sections D and E, of the Risk Characterization Document.]

The critical PODs from the selected animal studies were converted to human equivalent concentrations (HEC or POD_{HEC}) using dosimetric adjustment factors based on reference concentration (RfC) methodologies developed by the US EPA. For RfCs calculated from HECs, the conventional interspecies uncertainty factor of 10 was reduced to 3 because the interspecies pharmacokinetic differences were considered resolved by the HEC conversion, regardless of whether the effects were portal of entry or systemic. The remaining default interspecies pharmacodynamic uncertainty factor (UF) of 3x was retained because data relating to tissue level interactions were insufficient to quantitatively resolve potential animal-to-human differences. The full 10-fold intraspecies (UF_H) factor was also retained to reflect the range of sensitivity within the human population. The target MOE for AITC was equivalent to the UF_{TOTAL} of 30. This target MOE was considered adequate to protect human health for all potentially exposed populations (handlers, re-entry workers, occupational bystanders, and residential bystanders).

8. **Risks to workers were estimated for acute (short term), subchronic (seasonal) and chronic (annual, lifetime) exposures.** [Addressed in sections D.2, D.3, E, and Appendix 1 of the Risk Characterization Document.]

Under short-term, seasonal, and annual exposure conditions, worker MOEs for many scenarios were lower than the target of 30.

9. **Risk to occupational and residential bystanders were estimated for acute exposures.** [Addressed in sections D.2, D.3, E, and Appendix 1 of the Risk Characterization Document.]

Under short-term exposure conditions, all occupational and residential bystander MOEs were lower than the target of 30.

The Big Picture

Reviewers are not limited to addressing only the specific charges presented above, and are asked to consider the following questions:

- Are there any scientific issues not mentioned above that are part of the scientific basis of the draft Risk Characterization Document for AITC? If so, please comment on whether these are based on sound scientific knowledge, methods, and practices.

- Taken as a whole, is the proposal to establish 14 ppb as the acute reference concentration for AITC based upon sound scientific knowledge, methods, and practices?

In addition, for the reviewers' convenience we are providing a link to the recent peer review of the AITC Risk Characterization Document provided by the Office of Environmental Health Hazard Assessment (OEHHA).
https://oehha.ca.gov/media/downloads/pesticides/document/commentsaitc110320.pdf

Attachment 3: Bibliography

The references included in this bibliography include the technical document and associated appendices under review and documents referenced in support of the findings and conclusions described in Attachment 1.

1. DPR, 2020. Allyl Isothiocyanate: Draft Risk Characterization Document Occupational and Bystander Exposures (including appendices). Attached.
2. Herberth, M. T. 2017. Acute Inhalation Neurotoxicity Study of IR9804 in Sprague-Dawley Rats. Product Safety Labs, Dayton, New Jersey (5940): Isagro USA, Inc. (DPR Vol. No. 50544-0025, Record No. 298558) 1400.
3. Lowe, C. 2012. Acute Inhalation Toxicity Study in Rats. Product Safety Labs, Dayton, New Jersey (5940): Isagro USA, Inc. MRID 48824105. (DPR Vol. No. 50544-0009, Record No. 279508) 60.
4. Randazzo, J. 2017. A 13-Week Whole-Body Inhalation Combined Subchronic Neurotoxicity/Toxicity Study of IR9804 in Sprague-Dawley Rats. Product Safety Labs, Dayton, New Jersey (5940): Isagro USA, Inc. (DPR Vol. No. 50544-0026, Record No. 298559) 2597.

NOTE: The references highlighted in green are available only upon request. To request those references, please fill out the "Acknowledgment of Data Handling Responsibilities" form and email it to Marilyn Palmer-Townsend at <marilyn.palmer-townsend@cdpr.ca.gov>. Be sure to include the DPR data volume number inthe list of references you provide. By law, the requestor will need to sign either a confidentiality form or a confirmation of status form before the documents can be provided.

Attachment 4: List of Participants

All individuals involved in the risk or exposure assessment for AITC are listed alphabetically below.

California Department of Pesticide Regulation Staff

Risk Assessment Team

Brandon Brown, PhD, Associate Toxicologist
Puttappa Dodmane, PhD DABT, Staff Toxicologist
Qiaoxiang Dong, PhD, Staff Toxicologist
Mitra Geier, PhD, Associate Toxicologist
Svetlana Koshlukova, PhD, Senior Toxicologist
Peter N. Lohstroh, PhD, Senior Toxicologist
Stephen Rinkus, PhD, Staff Toxicologist
Andrew L. Rubin, PhD DABT, Primary State Toxicologist
Kim Truong, PhD, Associate Toxicologist

Exposure Assessment Team

Christopher DeMars, Senior Environmental Scientist
Weiying Jiang, PhD, Staff Toxicologist
Eric S. Kwok, PhD DABT, Senior Toxicologist
Ian Reeve, PhD, Staff Toxicologist

Senior Management Reviewers

Shelley DuTeaux, PhD MPH, Branch Chief
Karen Morison, PhD, Assistant Director

Contributors and Additional Reviewers

Charles Aldous, PhD DABT, Staff Toxicologist (retired)
Lucia Graham, PhD, Research Scientist III (Epidemiology/Biostatistics)
Harry Green, Senior Environmental Scientist (retired)
Peter Leung, PhD DABT, Senior Toxicologist
Thomas Moore, PhD, Staff Toxicologist
Michel Oriel, Senior Environmental Scientist (Supervisory)
Ruiqin Pan, MS, Research Scientist III (Chemical Sciences)
Neelima Verma, PhD DABT, Senior Toxicologist

Other Reviewers (Office of Environmental Health Hazard Assessment):

Rima Woods, PhD, Staff Toxicologist
James Nakashima, PhD, Staff Toxicologist
Jing Tao, PhD, Research Scientist III (Chemical Sciences)
Katherine Sutherland-Ashley, PhD, Senior Toxicologist
Ouahiba Laribi, PhD, Senior Toxicologist
David Ting, PhD, Branch Chief
Vincent Cogliano, PhD, Deputy Director of Scientific Affairs
Allan Hirsch, Chief Deputy Director (retired)
Lauren Zeise, PhD, Director

State Water Resources Control Board

June 7, 2021

Alison Elder, Ph.D., Associate Professor
Dept. of Environmental Medicine
School of Medicine and Dentistry
University of Rochester Medical Center
601 Elmwood Ave., Box EHSC
Rochester, NY 14642

SUBJECT: INITIATION OF REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

Dear Professor Elder,

I recently approved you to be a peer reviewer. The purpose of this letter is to initiate the external peer review.

Components of the review:

1. Request for External Scientific Peer Review, with the following attachments:
    - Attachment 1: Plain English Summary.
    - Attachment 2: Scientific Assumptions, Findings, and Conclusions to Review.
    - Attachment 3: Individuals who Participated in the Development of the Proposal.
    - Attachment 4: References Cited.
2. Document(s) for review.
3. Electronic copies of references cited.
4. Guidance for reviewers, as described after my signature. (Please pay particular attention to the section titled, "The review.")

All components of the review are posted at a secure FTP site, or addressed in this letter:

- https://ftp.waterboards.ca.gov
- username: gbowes-ftp30
- password: kWWhmn

The findings, assumptions, and conclusions that need review are listed in Attachment 2 of the review request. Please address the subjects you noted you would cover with confidence, in your June 7, 2021 email to me: You will address conclusions 1 and 2 from that perspective, and to a lesser extent conclusions 7 and 8.

I will help with any questions you have. To ensure a clear record of our communication, all of our communications should be in writing (email is preferred).

Please email your reviews to me by Tuesday June 22, 2021. I will subsequently forward all reviews and the curricula vitae of all reviewers to the Department of Pesticide Regulation. All of this information will be posted at the Department of Pesticide's program website.

The organization requesting the review may require clarification or additional information on a specific subject. If this occurs, I will contact you to supplement your review to address those comments.

Your acceptance of this review assignment is most appreciated.

Sincerely,

Gerald W. Bowes, Ph.D.
Manager, CalEPA External Scientific Peer Review Program
Office of Research, Planning, and Performance
State Water Resources Control Board
1001 "I" Street, 13th Floor Sacramento, California 95814
Gerald.Bowes@waterboards.ca.gov

Guidance for Reviewers

Communication with the Peer Review Program. As noted above**,** to ensure a clear record of our communication, all of our communications should be in writing (email is preferred).

Confidentiality. You are required to help maintain the confidentiality of this review process.

- Confidentiality began at the point you were contacted by the University of California, Berkeley.
- You should not inform others about your role as reviewer.
- You will not know the names of other reviewers until all reviews are complete and the organization decides to release reviews.
- You not allowed to discuss the proposal with employees of the requesting organization or individuals who participated in development of the proposal.

- The individuals who participated in development are listed in Attachment 3 of the review request.

Independence. If you learn what you are reviewing was developed by someone with whom you share a common supervisor or have or had a working relationship, you must let us know so that we can determine whether to seek another peer reviewer. For example, if the CalEPA organization asking for the review contracted with someone in your department or organization to help develop the material you were asked to review, you have a potential conflict of interest.

The review. The statutory mandate for external scientific peer review (California Health and Safety Code Section 57004) states that the reviewer's responsibility is to determine whether "the scientific portion of the proposed rule is based upon sound scientific knowledge, methods, and practices." Your task is to make this determination for the assumptions, findings, or conclusions that the CalEPA External Scientific Peer Review Program has determined you can address with confidence, based on expertise and experience. (If you decide to address other assumptions, findings, or conclusions, identify the expertise and experience you are relying on to do so.) We also invite you to address these questions:

- Are there any scientific subjects that are part of the scientific basis of the proposal that are not described above?
- Taken as a whole, is the proposal based upon sound scientific knowledge, methods, and practices?

You may have been asked to review the implementation or application of established work. In some cases, there is a clear, previously-reviewed scientific basis for what you are reviewing but the scientific basis of the specific implementation of it still must be reviewed. For example, a United States Environmental Protection Agency criterion may have a solid peer review record, but you might determine that the proposed implementation or application of the criterion is not based upon sound scientific knowledge, methods, or practices.

You may ask for clarification or for additional specific supporting documents. We will provide what we can to you and all reviewers. Send clarification questions to Dr. Yoram Rubin (rubin@ce.berkeley.edu).

Text to include in your review:

- Your name, professional affiliation, and the date.
- The name of the item you are reviewing.
- Begin your review with, “Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence:” and list them by number, as they are referred to in Attachment 2 of the review request.

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State Water Resources Control Board

June 3 2021

Judith T. Zelikoff, Ph.D., Professor
Dept. of Environmental Medicine
NYU Grossman School of Medicine
341 E. 25th Street
New York, NY 10010

SUBJECT: INITIATION OF REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

Dear Professor Zelikoff,

I recently approved you to be a peer reviewer. The purpose of this letter is to initiate the external peer review.

Components of the review:

1. Request for External Scientific Peer Review, with the following attachments:
    - Attachment 1: Plain English Summary.
    - Attachment 2: Scientific Assumptions, Findings, and Conclusions to Review.
    - Attachment 3: Individuals who Participated in the Development of the Proposal.
    - Attachment 4: References Cited.
2. Document(s) for review.
3. Electronic copies of references cited.
4. Guidance for reviewers, as described after my signature. (Please pay particular attention to the section titled, "The review.")

All components of the review are posted at a secure FTP site, or addressed in this letter:

- https://ftp.waterboards.ca.gov
- username: gbowes-ftp30
- password: kWWhmn

The findings, assumptions, and conclusions that need review are listed in Attachment 2 of the review request. Please address the subjects you noted you would cover with confidence, in your June 3, 2021 email to me: You will address inhalation toxicology in conclusions 1, 2, 3, and 7.

I will help with any questions you have. To ensure a clear record of our communication, all of our communications should be in writing (email is preferred).

Please email your reviews to me by Tuesday June 22, 2021. I will subsequently forward all reviews and the curricula vitae of all reviewers to the Department of Pesticide Regulation. All of this information will be posted at the Department of Pesticide's program website.

The organization requesting the review may require clarification or additional information on a specific subject. If this occurs, I will contact you to supplement your review to address those comments.

Your acceptance of this review assignment is most appreciated.

Sincerely,

Gerald W. Bowes, Ph.D.
Manager, CalEPA External Scientific Peer Review Program
Office of Research, Planning, and Performance
State Water Resources Control Board
1001 "I" Street, 13th Floor Sacramento, California 95814
Gerald.Bowes@waterboards.ca.gov

Guidance for Reviewers

Communication with the Peer Review Program. As noted above**,** to ensure a clear record of our communication, all of our communications should be in writing (email is preferred).

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- You not allowed to discuss the proposal with employees of the requesting organization or individuals who participated in development of the proposal.

- The individuals who participated in development are listed in Attachment 3 of the review request.

Independence. If you learn what you are reviewing was developed by someone with whom you share a common supervisor or have or had a working relationship, you must let us know so that we can determine whether to seek another peer reviewer. For example, if the CalEPA organization asking for the review contracted with someone in your department or organization to help develop the material you were asked to review, you have a potential conflict of interest.

The review. The statutory mandate for external scientific peer review (California Health and Safety Code Section 57004) states that the reviewer's responsibility is to determine whether "the scientific portion of the proposed rule is based upon sound scientific knowledge, methods, and practices." Your task is to make this determination for the assumptions, findings, or conclusions that the CalEPA External Scientific Peer Review Program has determined you can address with confidence, based on expertise and experience. (If you decide to address other assumptions, findings, or conclusions, identify the expertise and experience you are relying on to do so.) We also invite you to address these questions:

- Are there any scientific subjects that are part of the scientific basis of the proposal that are not described above?
- Taken as a whole, is the proposal based upon sound scientific knowledge, methods, and practices?

You may have been asked to review the implementation or application of established work. In some cases, there is a clear, previously-reviewed scientific basis for what you are reviewing but the scientific basis of the specific implementation of it still must be reviewed. For example, a United States Environmental Protection Agency criterion may have a solid peer review record, but you might determine that the proposed implementation or application of the criterion is not based upon sound scientific knowledge, methods, or practices.

You may ask for clarification or for additional specific supporting documents. We will provide what we can to you and all reviewers. Send clarification questions to Dr. Yoram Rubin (rubin@ce.berkeley.edu).

Text to include in your review:

- Your name, professional affiliation, and the date.
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State Water Resources Control Board

June 4 2021

Thomas O. Spicer, Ph.D.
Professor and Maurice Barker Chair in Chemical Engineering
Ralph E. Martin Department of Chemical Engineering
University of Arkansas
Fayetteville, AR 72701

SUBJECT: INITIATION OF REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

Dear Professor Spicer,

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4. Guidance for reviewers, as described after my signature. (Please pay particular attention to the section titled, "The review.")

All components of the review are posted at a secure FTP site, or addressed in this letter:

- https://ftp.waterboards.ca.gov
- username: gbowes-ftp30
- password: kWWhmn

The findings, assumptions, and conclusions that need review are listed in Attachment 2 of the review request. Please address the subjects you noted you would cover with confidence, in your June 4, 2021 email to me: You will address conclusions 6 and 9.

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BIOGRAPHICAL SKETCH

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

NAME: Elder, Alison

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

POSITION TITLE: Associate Professor

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Chatham College, Pittsburgh, PA	B.S.	1992	Chemistry
University of CA, Irvine, Irvine, CA	Ph.D.	1997	Environmental Toxicology
University of Rochester	Postdoc.	1997-2000	Inhalation Toxicology

A. Personal Statement

I am an Associate Professor of Toxicology in the Department of Environmental Medicine and an inhalation toxicologist. My training was focused on inorganic analytical chemistry, environmental toxicology, and pulmonary and cardiovascular toxicology. I served as the deputy director of the Toxicology Training Program from 2014-2017 and now direct the Program. I also serve as the director of the Rochester Environmental Health Sciences Center inhalation exposure facility.

Research: The goal of my research as an inhalation toxicologist is to understand the fate and effects of inhaled engineered nanoparticles and ambient air pollutant aerosols. Using a combination of acellular, in vitro, and in vivo systems, my laboratory examines the relationships between the physicochemical properties of particles and respiratory tract deposition, translocation to extrapulmonary organs, cellular uptake, particulate oxidative capacity, and effects at the cellular and tissue levels. My studies are broadly focused on oxidative stress and inflammation and the mechanisms of these responses in the respiratory tract and in the cardiovascular and central nervous systems. My early training was focused on the respiratory tract effects of oxidant gases and particulates and I have published on the toxicological interactions between these pollutants in the lungs and age as a determinant of response. As the air pollution health effects field evolved, it became clear that the cardiovascular system was also a target with respect to adverse health outcomes; my studies in susceptible animal models, in particular those that used real-world exposure models, have contributed significantly to this body of work. I became interested in the CNS as a target organ through biokinetics studies that showed accumulation of ultrafine/nanosized particles in the brain, studies which also provided evidence that accumulation was associated over time with CNS inflammatory cell activation and increased expression of proinflammatory mediators. Recent literature that establishes the link between oxidative stress, inflammation, and neurodegeneration led to the hypotheses that are being tested in a current project on the impact of traffic-related ambient ultrafine particle-enriched aerosols on inflammation, cell activation, course of pathology, and learning/memory behavior in a mouse model of Alzheimer's disease. I also continue projects focused on the lung effects from nanoparticle exposures of concern in occupational settings. My research is and has been supported through NIH, EPA, DoD, and departmental grants on which I have served as PI and co-investigator, as well as industry and NY State funding.

Mentoring and teaching: My roles in the Toxicology Training Program include director, primary research mentor, committee member, and teacher. I have been the primary mentor for 4 pre-doctoral students, 1 postdoctoral fellow, and 2 undergraduate students and co-mentored a PhD student from the Chemical Engineering doctoral program. I have hosted 12 rotation students and served on 18 thesis committees at the Masters and Doctoral levels, including for two students at other institutions. Publications with these trainees

are underlined below. I teach in the second-year core class for the toxicology students, specifically in the pulmonary and cardiovascular toxicology section, and also direct this course. I also lecture in two undergraduate courses (Public Health, Environmental Science). In addition, I worked in 2014-2015 with a team of other faculty members to create a new biostatistics course for non-clinicians that is now required for the students in the toxicology training and other programs at the School of Medicine and Dentistry.

Role in this program: Center Member, Inhalation Exposure Facility Director, Mentor, Training Grant PI

B. Positions and Honors.

Academic Positions

2000-2007	Research Assistant Professor Department of Environmental Medicine University of Rochester, Rochester, NY
2007-2010	Assistant Professor Department of Environmental Medicine University of Rochester, Rochester, NY
2010-present	Associate Professor (tenure, 2014) Department of Environmental Medicine University of Rochester, Rochester, NY
2017-present	Director, Toxicology PhD Training Program University of Rochester, Rochester, NY
2018-present	Director, EHSC Inhalation Exposure Facility University of Rochester, Rochester, NY

Honors and Awards

Cornerstone Award in Environmental Medicine, 2007 (Chatham University, Pittsburgh, PA)
Young Investigator Award, 2009 (Inhalation & Respiratory Specialty Section, Society of Toxicology)
Vice president-elect (2011-2012), Vice president (2012-2013), President (2013-2014), Past President (2014-2015), Nanotoxicology Specialty Section, Society of Toxicology
Specialty Section Collaboration and Communications Group, Society of Toxicology (2013-2015)
Nominating committee, Society of Toxicology (2012-2015)
Co-Chair, 8th International Nanotoxicology Congress (2016)
Current Concepts in Toxicology Committee, Society of Toxicology (2015-2018)
National Nanotechnology Initiative Women's History Month Celebrating Women in Nanotechnology (2019)

Other Experience and Professional Memberships

Professional Memberships: Society of Toxicology (1992-present), American Thoracic Society (2001-present), American Conference of Governmental Industrial Hygienists TLV-CS committee (2008-present), International Alliance for NanoEHS Harmonization (2008). *Review Committees (Ad hoc)*: EPA, review panel for Airborne Particulate Matter Health Effects, 2001; NIOSH, review panel for National Occupation Research Agenda (NORA) program projects, 2005; EPA, review panel for Nanomaterials Health Effects, 2006; NIOSH Nanotechnology Research Center intramural program, June, 2009; HEI pilot project review, May, 2010; Helmholtz Association Virtual Institute, outside reviewer, April, 2011; NSF panel review, Toxicology of Nanomaterials, April, 2012; NIOSH Nanotechnology Research Center (NTRC) intramural program, Sept./Dec., 2012; Update of the 2009 Environmental Protection Agency Integrated Science Assessment for Particulate Matter (Particle Translocation; Factors Modifying Clearance), 2012; NIH Nano Study Section, panel review, January, 2013; FutureNanoNeeds (FP7) project ethics advisor, 2013-2016; FDA CORES proposal evaluations, March, 2013; NIH Neurodegenerative Application Review Special Emphasis Panel, March, 2014; NSF EHSNano Nanotox Panel, April, 2014; Peer Reviewed Medical Research Program (PRMRP) pre-application review, Department of Defense Congressionally Directed Medical Research Programs, July-Aug., 2014; NIOSH Health Effects Laboratory Division, Nanotoxicology proposal review panel, Aug., 2014; NIH Nano Study Section, panel review, February, 2015; Update of the 2009 Environmental Protection Agency Integrated Science Assessment for Particulate Matter (Particle Translocation; Factors Modifying Translocation), 2015; NIH Nano Study Section, panel review, February, 2016; Health Canada, Chemicals Management Plan Research and Monitoring and Surveillance Program, March, 2017; NIH SIEE Study Section, panel review, June, 2017; NIH P51 Study Section review, November, 2017; NIH SEP panel IAM reviews, 2017, 2019; NIH

P51 Study Section review, 2107; NIH K award review panel, 2019; DoD Military Operational Medicine grant review panel, 2019; NIEHS P42 review panel, 2019; NIEHS R25 review panels, 2019, 2020; DoD CDMRP review panel, 2020; *Continuing Education:* Seventh IUTOX Summer School on Risk Assessment of Chemicals (RASS VII), Toftagården, Sweden, August 22-30, 1998. *Journal Reviews: American Journal of Physiology, American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Cell and Molecular Biology, Chemical Research in Toxicology, Environmental Research, Journal of Aerosol Medicine, Journal of Aerosol Science, Journal of Toxicology and Environmental Health, Toxicological Sciences, Toxicology and Applied Pharmacology, Toxicology Letters, Nature Nanotechnology, Journal of Hazardous Materials, Environmental Health Perspectives, ACS Nano, Neurotoxicology, Cardiovascular Toxicology, Particle and Fibre Toxicology (editorial board member), Critical Reviews in Toxicology (editorial board member), Inhalation Toxicology (editorial board member), Nanotoxicology (Interim editor-in-chief, Jan-Aug, 2010; Dep. EIC, Aug. 2010-present), Current Research in Toxicology (editorial board member, associate editor)*

C. Contributions to Science (up to 5 contributions with 4 citations each; trainees underlined)

The physicochemical properties of engineered nanoparticles and the method of exposure are key determinants of toxicological outcomes: The relatively nascent field of nanotoxicology is a highly interdisciplinary one and requires combined expertise in material characterization, exposure characterization, detailed dose-response analyses, and mechanistic investigations. We have contributed to this field in terms of methodology related to in vivo exposures, material characterization, and to deeper understanding of the dose-response relationships, building on previous experience with occupationally-relevant and ambient particles. Specifically, our body of work has demonstrated the critical importance of the delivered dose rate on poorly-soluble nanoparticle retention, inflammatory responses, and the mechanisms of these responses. These findings have important ramifications in terms of how existing and future data sets should be interpreted for the purpose of hazard characterization and risk assessment of engineered nanomaterials. We have also demonstrated the central importance of inherent oxidant capacity and biosolubility of nanoparticles, contributing to predictive frameworks for grouping nanomaterials for potential health risks in the absence of abundant toxicological data.

1. Keller, J.G., U. Graham, J.M. Koltermann-Jülly, R. Gelein, L. Ma-Hock, R. Landsiedel, M. Wiemann, G. Oberdörster, **A. Elder***, W. Wohlleben*. Predicting dissolution and transformation of inhaled nanoparticles in the lung using abiotic flow cells: The case of barium sulfate. *Sci. Reports*. 2020. **shared senior authorship*
2. Shi, M., K.L.D. Bentley, H. Mattoussi, **A. Elder**, H. Yang. Cytotoxicity of copper nanoparticles: Effects of surface chemistry, dissolution, and delivered dose. *Nanoscale* 9: 4739-4750, 2017. PMCID:PMC5482280
3. Guttenberg, M., L. Bezerra, N.M. Neu-Baker, M. del Pilar Sosa Peña, **A. Elder**, G. Oberdörster, S.A. Brenner. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy. J. Biophotonics 9(10): 987-993, 2016. PMCID:PMC5291524
4. Lerner, C.A., P. Rutagarama, T. Ahmad, I.K. Sundar, **A. Elder**, I. Rahman. Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation. Biochem. Biophys. Res. Comm. 477(4): 620-625, 2016. PMCID:PMC4967027
5. Lerner, C.A., I.K. Sundar, R.M. Watson, **A. Elder**, R. Jones, D. Done, R. Kurtzman, D.J. Ossip, R. Robinson, S. McIntosh, I. Rahman. Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols. *Environ. Poll.* 198: 100-107, 2015. PMCID:PMC4323666
6. Sotiriou, G.A., C. Watson, K.M. Murdaugh, T.H. Darrah, G. Pyrgiotakis, **A. Elder**, J.D. Brain, P. Demokritou. Engineering safer-by-design, transparent, silica-coated ZnO nanorods with reduced DNA damage potential. *Environ. Sci.: Nano*. 1: 144-153, 2014. PMCID:PMC4060637
7. Baisch, B.L., N.M. Corson, P. Wade-Mercer, R. Gelein, A.J. Kennell, G. Oberdörster, **A. Elder**. Equivalent titanium dioxide nanoparticle deposition by intratracheal instillation and whole body inhalation: The effect of dose rate on acute respiratory tract inflammation. *Part. Fibre Toxicol*. 11(1): 5, 2014. PMCID:PMC3905288
8. Doudrick, K., N. Corson, G. Oberdörster, **A. Elder**, P. Herckes, R.U. Halden, P. Westerhoff. Extraction and quantification of carbon nanotubes in biological matrices with application to rat lung tissue. *ACS Nano*. 7(10): 8849-56, 2013. PMCID:PMC3908926
9. Bonner, J.C., R.M. Silva, A.J. Taylor, J.M. Brown, S.C. Hilderbrand, V. Castranova, D. Porter, **A. Elder**, G. Oberdörster, J. Harkema, L. Bramble, T.J. Kavanagh, D. Botta, A. Nel, K.E. Pinkerton. Interlaboratory Evaluation of Rodent Pulmonary Responses to Engineered Nanomaterials. *Environ. Health Perspect*. 121(6): 676-82, 2013. PMCID:PMC3672912

10. Xia, T., R.F. Hamilton, Jr., J.C. Bonner, E.D. Crandall, **A. Elder**, F. Fazlollahi, T.A. Girtsman, K. Kim, S. Mitra, S.A. Ntim, G. Orr, N. Tagmount, A.J. Taylor, D. Telesca, A. Tolic, C. Vulpe, A. Walker, X. Wang, F.A. Witzmann, N. Wu, Y. Xie, A. Nel, A. Holian. Inter-laboratory comparison of in vitro nanotoxicological assays from the NIEHS NanoGo Consortium. *Environ. Health Perspect*. 121(6): 683-90, 2013. PMCID:PMC3672931
11. Shi, M., H. S. Kwon, Z. Peng, **A. Elder**, H. Yang. Effects of surface chemistry on the generation of reactive oxygen species by copper nanoparticles. *ACS Nano*. 6(3): 2157-64, 2012. PMCID:PMC3314088
12. Han, X., N. Corson, P. Wade-Mercer, R. Gelein, J. Jiang, M. Sahu, P. Biswas, J.N. Finkelstein, **A. Elder**, G. Oberdörster. Assessing the relevance of in vitro studies in nanotoxicology by examining the correlations between in vitro and in vivo data. *Toxicol*. 297(1-3): 1-9, 2012. PMCID:PMC3350601
13. Han X, R Gelein, N Corson, P Wade-Mercer, J Jiang, P Biswas, JN Finkelstein, **A Elder**, G Oberdörster. Validation of an LDH assay for assessing nanoparticle toxicity. Toxicol. 287(1-3): 99-104, 2011. PMCID:PMC4070602
14. Gillespie, P.A., G.S. Kang, **A. Elder**, R. Gelein, L. Chen, A.L. Moreira, J. Koberstein, K.M. Tchou-Wang, T. Gordon, L.C. Chen. Pulmonary response after exposure to inhaled nickel hydroxide nanoparticles: short and long-term studies in mice. *Nanotoxicol*. 4(1): 106-119, 2010. PMCID:PMC2922767
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Ultrafine or nanoscale particles translocate to extrapulmonary tissues, including the brain: It has long been recognized that ambient particulate matter causes adverse pulmonary health effects. The more recent studies have focused on effects in extrapulmonary organ systems and their underlying mechanisms. There are three main mechanisms that can explain the extrapulmonary effects of inhaled ambient particulate matter that have been noted in epidemiological studies, namely the activation of inflammatory responses in the lung that then spill over into the systemic circulation, the delivery of dose directly to the target tissue via translocation, or the activation of the autonomic nervous system. We showed that exposures to laboratory-generated model ultrafine/nanoparticles resulted in the accumulation of chemical signatures for the particles in tissues like liver, heart, and brain. Using manganese oxide ultrafine particles – as a model of welding fume – we also demonstrated that accumulation in brain was due in part to olfactory neuronal transport.

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Extrapulmonary effects of inhaled ultrafine particles: inflammatory changes in cardiovascular and central nervous systems: It has long been recognized that ambient particulate matter causes adverse pulmonary health effects. As the epidemiological evidence grew regarding air pollution health effects, it was discovered that adverse cardiovascular outcomes were also occurring, particularly in individuals with pre-existing disease. We were among the earliest groups to examine the effects of inhaled ambient and model pollutant aerosols in the cardiovascular system using rodent models, focusing on inflammation and disease susceptibility. Through our earlier work with inhaled manganese oxide nanoparticles, we demonstrated that the accumulation of manganese in the various brain regions was also associated with increased inflammatory and oxidative stress responses. These studies were the catalyst for our keen interest in the neurodegenerative, inflammatory, and behavioral effects of inhaled ambient ultrafine particles. Our studies have shown that exposure to ambient ultrafine particles causes deficits in learning and memory behavior, as well as increased tau phosphorylation in a rodent model of Alzheimer's disease.

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Ambient ultrafine particles cause alterations in autonomic control of heart rate: The third main mechanism that can explain the extrapulmonary effects of inhaled ambient particulate matter is the activation of the

autonomic nervous system. In a series of studies conducted in rat models, we developed methods for quantitating the impact of exposure on the autonomic nervous system through the study of heart rate variability using radiotelemetry. Using these methods, we showed that exposures to freshly-generated traffic-related ultrafine particles caused a short-term decrease in heart rate that was mediated through activation of parasympathetic pathways, as well as an alteration in vagosympathetic balance.

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Particle surface area is a determinant of effects in the lung: It is known that poorly-soluble particles with low cytotoxicity can accumulate in the lungs and, if this happens at a high enough dose and for long periods of time, pathology can develop, with female rats being particularly sensitive. We conducted a series of multi-species subchronic inhalation studies with industrially-relevant carbon blacks of two different sizes that differed by their surface area, hypothesizing that this parameter would be a determinant of response. We showed that the retention of particles in the lungs was prolonged and that the inflammatory and epithelial proliferative responses were of greater magnitude for high-surface area versus low-surface area carbon black and that the rat was more sensitive than mouse or hamster. These data contributed to 1) the definition of particle surface area being an important dose metric when considering particles of varying sizes of the same composition and 2) the development of occupational exposure guidelines for poorly-soluble particles, e.g., ACGIH, NIOSH.

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Effects of inhaled air pollutant mixtures: Air pollution is a complex mixture of particulate- and gas-phase components that exhibits spatial and temporal variability in composition. Aside from the use of systems that are capable of concentrating some of these components and conducting natural experiments, much of our knowledge about health effects derives from the use of model aerosols. Our interest is in ultrafine particles (UFP, <100 nm in diameter) due to their high number concentrations and their ability to penetrate to the gas-exchange regions of the lung. In the studies described below, we learned more about the independent effects of UFP and their effects when combined with other pollutant components, namely ozone (ubiquitous oxidant gas) and endotoxin (as a model of acute respiratory tract inflammation). We showed that carbonaceous UFP have statistically significant and independent effects in terms of generating acute inflammatory and oxidative stress responses in the lung and that there are demonstrable interactions with other pollutants, e.g., endotoxin primes the lung for response to UFP. These studies also demonstrated that the aged versus young rodents have different responses to pollutant mixtures, probably as a result of different baseline antioxidant defenses. We also showed that endotoxin, when administered repeatedly, has a protective effect with respect to challenge exposures and that this effect is blunted in senescent mice and rats.

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Resident alveolar macrophages are key regulators of response to particulates and lung injury: Using a model of alveolar macrophage depletion (aerosolized liposome-encapsulated clodronate), we and our colleagues demonstrated the key regulatory role that these cells play in determining the course of the inflammatory response following various lung insults like endotoxin inhalation challenge, instilled crystalline silica particles, and thoracic radiation. We showed that – depending on the nature of the initial insult – macrophages and the lung epithelium communicate in such a way to coordinate the initial response and recovery from exposure.

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Pro-inflammatory effects of ozone: My earliest research was directed toward better-understanding the mechanisms of the inflammatory events in the lung following exposure to inhaled ozone, a ubiquitous urban air pollutant. Our results showed that single, acute exposures to ozone at levels ~10 times higher than the *current* National Ambient Air Quality Standards cause inflammation and changes in the adhesive interactions between alveolar macrophages and the lung epithelium.

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D. **Ongoing Research Support.**

American Chemistry Council 12/20-12/21
PI A. Elder
Analysis of airborne microplastics in indoor environments
This project will generate better understanding of the quantity, size distribution, inhalability, and chemical composition of plastic particles that are found in the indoor environment, focusing on distinguishing between airborne and surface sources of contamination.

NIH R21 HL142507 (subcontract) 3/20-3/21
MPIs J. Zelikoff, G. Grunig (NYU)
Subcontract PI, Inhalation Exposures
Electronic cigarette cardiotoxicity varies by flavors: Lessons learned from mice

The overarching aim of the parent project is to test the hypothesis that flavoring chemicals in electronic cigarette aerosols are responsible for lung damage that predisposes mice to the development of pulmonary hypertension. Rochester's Inhalation Exposure Facility was engaged to conduct subchronic inhalation exposures for this project.

Lung Biology and Disease Program Pilot Award 6/19-6/20 (NCE)
PIs C. Yan (contact), A. Elder
Phosphodiesterase 4 and Phosphodiesterase 10A synergistically regulate ozone-induced lung inflammation and resolution
This project explores the hypothesis that combined phosphodiesterase inhibition will promote the resolution of environmentally-induced lung inflammation by regulating macrophage polarization.

NIH P30 ES001247 04/95-03/20 (NCE)
PI B.P. Lawrence
Role: Director of Inhalation Exposure Facility, effective June 2018
Environmental Agents as Modulators of Disease Processes
This Center provides core services that support and integrate research across the environmental health sciences.

Training Program support.

NIH T32 ES007026-41 8/18-6/23
PI A. Elder (since 2/19)
Training in Environmental Toxicology
This training grant provides support for state-of-the-art pre-doctoral and post-doctoral training in cellular and molecular toxicology. The major goal is to prepare our graduates to assume significant leadership positions in academia, government, industry and other occupations related to environmental health and public policy.

Research Projects completed within the past 3 years.

NIH/NIEHS (R01 ES020332) 9/13-5/19 (NCE)
PIs A. Elder (contact), M.K. O'Banion
Impact of Ambient Nanoparticulate Exposures on Alzheimer's Disease Progression
This project focuses on the impact of ambient ultrafine particle-containing air pollution on disease severity and progression in a mouse model of Alzheimer's disease with the aim of finding therapeutic or other interventions that can improve the quality of life

Pilot Project (EHSC) 11/18-10/19
PI B. Berk
Phosphodiesterase 10A is a Key Mediator of Air Pollution-Induced Cardiovascular Events
This pilot project will explore the hypothesis that pollutant exposure-related systemic inflammation is mediated by PDE10A and that interruption of this pathway can prevent atherosclerotic plaque rupture.

Pilot Project (EHSC) 12/17-11/18
PI C. Ackert-Bicknell/A. Elder
*Establishment of a gene by ambient air pollution (G*E) interaction: impact on bone mass*
This pilot study explores the hypothesis that an inhaled ambient air pollutant mixture can induce systemic inflammation that impacts bone mass and that interactions between genetic background and responsiveness to air pollution can be found such that susceptible populations can be identified and/or therapeutic interventions developed.

IHSFC Minipilot 10/16-4/18
PI A. Elder
Seasonal Variability in the Physicochemical Characteristics of HUCAPS Aerosols: Building a Database for Correlation with Health Outcomes
These pilot funds are being used for elemental and organic carbon and metals analyses of filter samples collected at different time points throughout the year from ambient air and from our ultrafine particle concentrator.

FDA R13 FD005696-01 6/16-5/17
PI A. Elder
2016 International Nanotoxicology Congress
This conference support will be used to pay for audiovisual and poster display equipment and a conference secretary.

NIH/NIEHS R13 ES027345-01 6/16-5/17
PI A. Elder
International Nanotoxicology Congress: Nanotox 2016
This conference support will be used to cover in part the travel expenses of trainees and junior scientists from underrepresented groups and underdeveloped nations.

NSF CBET-1638437 6/16-5/17
PI A. Elder
8th International Nanotoxicology Congress
This conference support will be used to cover in part the travel expenses of trainees and for an evening scientific session, the "Young Investigator's Colloquium", that includes light refreshments.

Pilot Project (EHSC) 7/15-6/16
PI M. O'Reilly
Developmental Effects of Oxygen and Ambient Ultrafine Particulate Matter on the Adult Lung and Brain
This pilot study examines the hypothesis that exposure to UFP in neonates that are born into hyperoxia will alter lung and CNS inflammation, lung function, and behavior as measured in adults.

Pilot Project (EHSC) 1/15-12/15
PI S. Georas
Developing a Mouse Model of PM and RSV Interactions
This pilot study focuses on diesel particulate matter effects following inhalation exposures in neonatal mice that impact responses to subsequent viral infection to develop a better understanding of susceptibility in children.

Pending.

NIH/NIEHS R01 (submitted 10/20)
PIs I. Rahman (contact), A. Elder, K. Kannan
Particulate matter and heat stress induced health effects: Epidemiological, clinical, and biomarker studies
This project proposes complimentary studies in humans and a pre-clinical mouse model to examine physiological and toxicological interactions between air pollutant exposures and extreme heat and the mechanisms of these interactions.

NIH/NIEHS R21 (submitted 2/19)
PI S. Georas
Role: Investigator
Early Life Diesel Exhaust Particle Exposure: Developing a Mouse Model of Sustained Epithelial Barrier Dysfunction
This project will explore the function of tricellulin in maintaining lung epithelial barrier structure and function following environmental insult, namely inhalation exposure to diesel exhaust particles.

Planned.

NIH/NIEHS R21 or R03
PI N. Aich (SUNY Buffalo)
Role: subaward PI
Transformation and Pulmonary Toxicity of 2D and 3D Hierarchical Nanohybrids
The goal of this exploratory project will be to generate basic knowledge regarding the in vivo additivity of 2D and 3D nanohybrid components so that a larger project can be launched that thoroughly examines the interactions of the hybrids and their constituents at the cell, tissue, and organ level upon inhalation exposure.

BIOGRAPHICAL SKETCH

Judith T. Zelikoff, Ph.D
Professor
Department of Environmental Medicine 341 E. 25th Street Telephone: (646)751-9451
New York University Grossman School of Medicine. NY, NY 10010. Email: Judith.zelikoff@nyumc.org

a. Professional Preparation

1969-1973 B.S. Biology, Upsala College, East Orange, NJ
1973-1976 M.S. Microbiology, Farleigh Dickinson University, Teaneck, NJ/University of Medicine & Dentistry (UMDNJ), Newark, NJ.
1976-1982 Ph.D. Experimental Pathology, UMDNJ (Currently, Rutgers Med School), Newark, NJ
1982-1984 NIH Post-doctoral Trainee, NYU School of Medicine, Dept. Environmental Medicine, NY, NY

b. Appointments

2005-Present Tenured Professor; NYUGSoM, Dept. Environ. Medicine
1995-2005 Associate Professor; NYUGSoM, Dept. Environ. Med (tenured, 1997)
1989-1995 Assistant Professor; NYUGSoM, Dept. Environ. Med
1986-1989 Research Assistant Professor; NYUGSoM, Dept. Environ. Med.
1984-1986 Associate Res. Scientist; NYUGSoM, Dept. Environ. Med.
1982-1984 NIH Post-doctoral Trainee; NYUGSoM, Dept. Environ. Med.
1977-1978 Research Scientist; Pfizer Pharmaceuticals, Dept. Genetic Toxicology
1974-1975 Assistant Scientist; VA Hospital/UMDNJ, Dept. of Neuroscience
1979-1994 Adjunct Professor; William Paterson College, Biology Dept.
1979-1984 Adjunct Professor; Rockland Community College, Biology Dept.
1979-1982 Adjunct Professor; Seton Hall University, Biology Dept.

c. Awards and Honors

2020: Garfield, NJ Community Outreach & Engagement Award for Public Health
2018: Society of Toxicology (SOT), Education Award
2015: SOT, Women in Toxicology Mentorship Award
2013 West African SOT (WASOT), Distinguished Recognition
2012 – 2014: SOT, Distinguished Service as SOT Secretary
2013 SOT, Global Senior Scholar Host Award
2012 SOT, Career Achievement Award in Immunotoxicology

d. Publications (Out of 160)

(i) **Five pertinent publications**

1. Potter N., Awada C., Blackman T., Avenbaun O., **Zelikoff JT**. Ambient Particulate Matter and Associated Metals: Impacts on Brain Health. *Atmosphere*. 12 (4), 425. 2021.
2. Avenbaun O., **Zelikoff JT**. Woodsmoke and emerging issues. Curr. Opinions in Toxicol. Vol. 22: Pages 12-18, August, 2020.
3. Klocke C., Allen JL., Sobolewski M., Blum JL., **Zelikoff JT**., Cory-Slechta DA. Exposure to fine and ultrafine particulate matter during gestation alters postnatal oligodendrocyte maturation, proliferation capacity, and myelination. *Neurotoxicol*. 65:196-206. 2018.
4. Blum J.L., Chen L-C., **Zelikoff J.T***. Exposure to ambient particulate matter during specific gestational periods produces adverse obstetric consequences in mice. Environ. Health Perspect. *Environ Health Perspect*; 125(7). 2017.
5. Naher, L.P., K.R. Smith, M. Brauer, C. Simpson, J.Q, Koenig, M. Lipsett, **J.T Zelikoff.** Woodsmoke Health Effects: A Review. *Inhal. Toxicol*. 19:67-106 2007.

(ii) **Five other publications**

1. Blum J.L., Chen L-C., **Zelikoff J.T***. Exposure to ambient particulate matter during specific gestational periods produces adverse obstetric consequences in mice. Environ. Health Perspect. *Environ Health Perspect*; 125(7). 2017.
2. Blum J.L., Rosenblum L.K., Grunig G., Beasley M.B., Xiong J.Q., and **J.T. Zelikoff**. Short-term inhalation of cadmium oxide nanoparticles alters pulmonary dynamics associated with lung injury, inflammation, and repair in a mouse model *Inhal. Toxicol. 26(1):48-58* (2014).
3. **Zelikoff, J.T**. Other environmental health issues: Inhaled woodsmoke. In: *Encyclopedia of Environmental Health*. J. Nriagu (Ed.). Elsevier, UK. Pages 310-330. 2010.
4. Iba, M.M., J. Fung, Chung, L., J. Zhao, B. Winnik, B. Buckley, L.C. Chen, **J.T. Zelikoff,** Y. Kou. Differential inducibility of rat pulmonary CYP1A1 by cigarette smoke and wood smoke. *Mutat. Res*. 606:1-11. 2006.
5. Lippmann, M., Frampton, M., Schwartz, J., Dockery, D., Schlesinger, R., Koutrakis, P., Froines, J., Nel, A., Finkelstein, J., Godleski, J., Kaufman, J., Koenig, J., Larson, T., Luchtel, D., Liu L.J., Oberdorster, G., Peters, A., Sarnat, J., Sioutas C., Suh, H., Sullivan, J., Utell, M., Wichmann, E., and **Zelikoff, J.T**. The U.S. Environmental Protection Agency particulate matter health effects Research Centers Program: A midcourse report of status, progress, and plans. *Environ. Health Perspect.* 111:1073-1092. 2003.

e. Synergistic Activities

(i) March 2021. Symposia organizer/speaker**.** Marginalized populations and chemical contamination through a toxicology lens. **Society of Toxicology**.

(ii) January 2018: Speaker What's safer for the unborn child: electronic cigarettes or air pollution? **Mt. Holyoke College.** MA.

(iii) February 2014: Speaker**.** Air pollution in developing nations. ***West African Society of Toxicology*** – Lagos, Nigeria.

(iv) March 2012:– Organizer/speaker. Toxicological implications for domestic burning. ***Biomass Symposium***. U of PA.

(v) Sept. 2011: *Plenary Lecturer***:** The toxicology of biomass combustion emissions. Satellite Workshop on Biomass Combustion. ***European Aerosol Conference –*** Manchester, England.

(vi) Editorial Boards: *Environmental Health Perspectives; J of Inhalation Toxicol; J of Immunotoxicology;*

Thomas O. Spicer, III

Ralph E. Martin Department of Chemical Engineering, University of Arkansas
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Education

PhD, Engineering, University of Arkansas, 1985
Dissertation: Mathematical Modeling and Experimental Investigation of Heavier-Than-Air Gas Dispersion in the Atmosphere
MS, Chemical Engineering, University of Arkansas, 1983
BS, Chemical Engineering, University of Arkansas, 1981

Recent Professional Experience

Professor, Ralph E. Martin Department of Chemical Engineering, University of Arkansas
Professional Engineer, Arkansas State Board of Licensure for Professional Engineers and Professional Surveyors
Consulting Chemical Engineer, clients including U.S. Department of Homeland Security, U.S. Defense Threat Reduction Agency Reachback, and others

Areas of Expertise and Research Interests

Atmospheric dispersion of toxic and flammable air-borne contaminants, particularly those that are denser-than-air.
Flashing two-phase flow of materials released to the atmosphere including the rate of release and potential for aerosol formation.
Computational modeling of combined phase and chemical equilibria.
Fire and explosion hazard assessment.
Chemical process safety education.

SELECTED HONORS AND AWARDS

Norton H. Walton - Russell L. Miller Award, Safety and Health Division, American Institute of Chemical Engineers, 2018.
Maurice E. Barker Chair in Chemical Engineering, Ralph E. Martin Department of Chemical Engineering, University of Arkansas, 2013 to 2021.
Fellow, American Institute of Chemical Engineers, 2012.

Selected Publications, Reports, and Courses

1. Spicer, T., and D. Miller, "Quantifying the Mass Discharge Rate of Flashing Two Phase Releases through Simple Holes to the Atmosphere," *Process Safety Progress*, https://doi.org/10.1002/prs.11964, 2018.
2. Spicer, T.O., "Atmospheric Dispersion," *Perry's Chemical Engineers' Handbook*, D. Green (ed.), 9th ed., 2018.
3. Spicer, T., and K. Koslan, "SAChE Certificate Program – Atmospheric Dispersion," AIChE Academy,

https://www.aiche.org/academy/courses/ela967/sacher-certificate-program-atmospheric-dispersion, 2019.

4. Spicer, T., A. Feuvrier, and S. Fox, "Transient Large-Scale Chlorine Releases in the Jack Rabbit II Field Tests: Rainout Source Data Analysis from Video Records," *Journal of Loss Prevention in the Process Industries*, Vol 59, 2019.
5. Spicer, T. And S.B. Fox, "Chlorine Reactivity with Environmental Materials in Atmospheric Dispersion Models," Report CSAC 20-011, U.S. Department of Homeland Security Science and Technology Directorate, Chemical Security Analysis Center, Aberdeen Proving Ground, 2020.
6. Sun, C., S. Haider, and T. Spicer, "HABIT 2.2: Description of Models and Methods," U.S. Nuclear Regulatory Commission Report, January 2021.
7. Spicer, T., and G. Tickle, "Simplified Source Description for Atmospheric Dispersion Model Comparison of the Jack Rabbit II Chlorine Field Experiments," *Atmospheric Environment*, Vol 244, 117866, 2021.
8. Mazzola, T., S. Hanna, J. Chang, S. Bradley, R. Meris, S. Simpson, S. Minor, S. Gant, J. Weil, M. Harper, J. Nikmo, J. Kukkonen, J.-M. Lacome, M. Nibart, O. Bjornham, S. Khajehnajafi, K. Habib, P. Armand, T. Bauer, L. Fabbri, T. Spicer, and N. Ek, "Results of comparisons of the predictions of 17 dense gas dispersion models with observations from the Jack Rabbit II chlorine field experiment," *Atmospheric Environment*, Vol 244, 117887, 2021.
9. Spicer, T., S.B. Fox, and B.B. Hicks, "Preliminary Assessment of Chlorine Reactivity with Environmental Materials Accounting for Boundary Layer and Maximum Deposition Effects," *Atmospheric Environment*, 2021.
10. Spicer, T., and C.T. Smith, "Jack Rabbit II Mock Urban Environment Trials: Wind Tunnel Model Investigation and Validation," submitted to U.S. Department of Homeland Security Science and Technology Directorate, Chemical Security Analysis Center, Aberdeen Proving Ground, 2021.

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June 25, 2021

Gerald W. Bowes, PhD
Manager, Cal/EPA Scientific Peer Review Program
Office of Research, Planning and Performance
State Water Resources Control Board
1001 I Street
Sacramento, CA 95814

RE: **Evaluation of the Risk Characterization Document for Allyl Isothiocyanate**

Dear Dr. Bowes,

I was asked to provide comments about the findings, assumptions, and conclusions that are presented in the risk characterization document for allyl isothiocyanate (AITC) with a particular focus on conclusions 1, 2, 7, and 8 as described in Attachment 2 of the request to review. My comments for each one of these conclusions appears below, as well as some additional general comments that follow:

Conclusion #1: A default 10x extrapolation factor was used to establish the critical acute point of departure (POD) of 2.5 ppm.

The document describes an approach where the rodent lowest-observed-effect-level (LOEL) of 25 ppm AITC was adjusted by a factor of 10 to derive a POD of 2.5 ppm. This ***may be too stringent*** given the findings of Goto et al. (2010). While the study was not peer-reviewed, it is in the 'right species' and can provide a guidepost for the POD considerations. Specifically, the study showed that people could be awoken 'with less discomfort' when AITC concentrations were kept below 15 ppm than when they were higher, suggesting that 15 ppm could be a LOEL. AITC has decent warning properties in that the odor threshold is lower than the concentration at which sensory irritant responses begin and these responses would likely lead to exposure avoidance behavior. Indeed, the decreased motor activity and irregular respiration that was observed in animals upon two-week exposures for several hours a day could be indicative of sensory irritant responses mediated via the TRPA receptor system. The main reason for raising this point is that it seems odd to promote reference concentrations (RfC) for acute exposures (Summary Table 1) that are similar to or lower than those for subchronic and chronic exposures. If the Goto study findings are considered, then a smaller adjustment factor could be used given that the interspecies component would no longer be needed, resulting in a POD that is somewhat higher than 2.5 ppm AITC as the starting point for deriving estimates for bystander and occupational acute exposures. This would also obviate the need for further adjustment related to interspecies variability when calculating the RfC.

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Conclusion #2: The critical chronic inhalation POD was estimated from the subchronic critical POD by applying a default duration extrapolation factor of 10. This was necessitated by the lack of chronic inhalation studies.

Because no chronic inhalation exposure studies were available for review, the document describes the findings from a single subchronic inhalation study to serve as a starting point for considering risks from longer-duration exposures. The reported NOEL from Randazzo (2017) was 5 ppm AITC. Responses at higher concentrations included degenerative and metaplastic changes in the nasal epithelium, as well as decreased motor activity. Subchronic oral studies showed effects related to preneoplastic changes in the urinary bladder; while these effects were not reported upon inhalation exposure, it is likely that systemic absorption would occur via this route and, so, the findings should not be completely discounted. Nevertheless, dosimetric extrapolation suggests that the proposed POD from inhalation exposure is likely to be protective with respect to the documented responses following oral exposures (see below). Accounting for differences in exposure duration, as well as the points regarding oral exposures and the fact that only a single subchronic inhalation exposure was available, ***the factor of 10 to derive the chronic exposure POD of 0.5 ppm AITC is warranted***.

Conclusion #7: Dosimetric adjustments of air concentrations to account for pharmacokinetic differences between laboratory animals and humans were used to calculate reference calculations *[sic]* (RfCs) and risk targets (i.e., target Margins of Exposure).

In general, the approach that is described in the document is sensible. It aligns with the US EPA's approach and assumes that interspecies differences are minimized based on an assumption of similar respiratory tract absorption rates (thus reducing the UF_A from 10 to 3). The RfCs that were derived for subchronic and chronic exposure scenarios for workers should be amply protective. As mentioned above, though, ***the acute exposure RfCs are somewhat out of alignment with those for longer-duration exposures***. Specifically, they are an order of magnitude lower than the subchronic RfC, which is odd. It is acknowledged that the single human study (Goto et al., 2010) was limited, but further consideration could be helpful in reducing uncertainties related to species-specificity and response threshold, thus producing both a less stringent POD and further reducing the UF_A from 3 to 1.

Conclusion #8: Risks to workers were estimated for acute (short term), subchronic (seasonal), and chronic (annual, lifetime) exposures.

The risk appraisal involved comparisons of the acute, subchronic, and chronic PODs with AITC exposures in 88 different modeled conditions to derive margins of exposure (MOEs). The target MOE was defined to be equivalent to the total uncertainty factor of 30 that was used in the RfC calculations for different exposure categories. For many of the 88 scenarios, the MOEs were lower than the target of 30, suggesting risks for adverse health outcomes. The exposures were all modeled due to the lack of data regarding real-world applications with AITC. My expertise is not related to exposure modeling, but it was curious that bystander exposures were often modeled to be much higher than occupational ones. Another consideration, as mentioned above, is that the POD for acute exposures may be too low, which would impact the MOE for this category of exposure. ***Nonetheless, in the absence of information, additional precautions are***

sensible. The document does not describe how the findings regarding the MOEs would change practices, if at all, with respect to AITC application in agricultural settings. As pointed out, applicators are instructed to wear respirators, for example. The use of respirators by other types of workers may be considered.

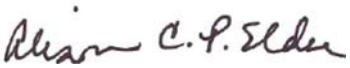
Additional comments:

1. Table 3 reporting of the Goto et al. (2010) study could be modified to include a description of the findings regarding responses around a threshold of 15 ppm.
2. The study by Herberth (2017) was said to have been done via whole-body inhalation of AITC vapors, which could have interacted with structures throughout the entire respiratory tract. The Lowe study (2012) was done via nose-only inhalation exposure to an atomized mist (respirable droplets). With the data available, it seems that the aerosol deposition patterns and, therefore, the dosimetry may have been very different in these two studies, possibly explaining the differences in outcomes. The nose-only exposure method of Lowe may have also contributed to more severe outcomes given the significant stress to the animals (no mention of adaptation phase prior to start of study), thus producing higher ventilation rates. These points could be added for clarity to help the reader understand the differences in findings between the two studies.
3. Agree with the conclusion that the 25 ppm level is appropriately interpreted as being the acute exposure LOEL from rat inhalation studies. The main critical effects in these studies related to motor and ambulatory behavior. The reductions in respiratory rates at the higher concentrations are consistent with the sensory irritation potential of AITC.
4. Agree with the conclusion that the 5 ppm level is appropriately interpreted as being the 13-week study NOEL in male and female rats that were exposed via whole-body inhalation to AITC. The main critical effects in these studies (at higher airborne AITC concentrations) included degeneration of the olfactory and respiratory epithelium in the nose, changes in motor activity, and losses in body weight. Interestingly, there were no reported changes in urinary bladder histology in this study, even at the highest concentration of 25 ppm in air.
5. The report is largely dominated by findings from oral exposures, i.e., drinking water, corn oil gavage, and feeding studies in rats and mice over various time frames using either AITC itself or horseradish extract, which contains a large fraction of AITC. Many of these studies are consistent in their reporting of urinary bladder epithelial preneoplastic (hyperplasia) or neoplastic changes (papilloma). There is also some evidence of other lesions such as cytoplasmic vacuolization of liver, cataract formation, and subcutaneous fibrosarcoma. AITC may also function as a tumor promoter in the urinary bladder, as evidenced by increased incidence of neoplastic changes, tumor volumes, and acceleration of pathology in rats that were pretreated with a nitrosamine. I performed my own calculations using a slightly different approach than the one described in the report in section D.1.2 to estimate the airborne concentrations to which humans would have to be exposed to reach similar whole-body doses (assuming 100% absorption via the respiratory tract) as those described for oral exposures. The airborne concentrations that I derived from these calculations were of a similar order as the NOEL of 5 ppm from the 13-week inhalation study (range of 2-18 ppm depending on exposure duration).

6. While the oral studies contribute to a more thorough understanding of AITC toxicity, they are limited by the failure to define NOELs, as pointed out in the document, making it difficult to consider adjustments to the overall NOEL. The findings via the oral route also contradict those from the subchronic inhalation studies, where no urinary bladder pathological changes were found. This may suggest that the biodistribution and/or metabolism of AITC differ(s) as a function of route of exposure or that the means of delivery is a confounding factor (i.e., bolus). This analysis points to a suggested revision of the draft document, specifically the summary of findings from the chronic oral exposure studies as presented in Table 14 on page 49. Here, the conclusion from the NTP study in rats is incomplete, in that there was a finding of a positive association between exposure and urinary bladder papilloma incidence (conclusion included at the top of page 45, data presented in Table 11).
7. The route to route extrapolation that is presented on page 54 may need to be modified. First, there is an error, I believe, in the AITC milligram per cubic meter to ppm conversion factor. By my calculation, 1 mg/m^3 AITC is equivalent to 0.25 ppm AITC (mg/m^3 x 24.45/molecular weight). Also, the rationale for including an adjustment for weekly intake does not make sense when the starting value of 6.6 mg/kg/day represents daily intake. These things do not affect the interpretation regarding the utility of the oral exposures at all, so the comment is made for the sake of clarity and completeness. Showing more detail for the calculations in their entirety may be helpful.
8. It is unclear as to why the 2-week oral gavage studies from NTP (1982) and Hasamura et al. (2011) are included in Table 6 with subchronic studies, as opposed to being grouped with other 2-week studies in Table 3 (a 2-week exposure is typically considered to be acute in nature).

Thank you for giving me this opportunity to participate in the review process for AITC. If I can be of further assistance or answer any questions about the comments above, please do not hesitate to contact me.

Sincerely,



Alison C.P. Elder, PhD
Associate Professor, Toxicology

SUBJECT: REQUEST FOR AN EXTERNAL SCIENTIFIC REVIEW OF THE DEPARTMENTOF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR ALLYL ISOTHIOCYANATE (AITC)

Review Prepared by:
Professor, Judith T. Zelikoff
Department of Environmental Medicine
New York University Grossman School of Medicine
341 E. 25th Street
New York, New York 10010
June 22, 2021

Selection of Conclusions for Evaluation:

Inhalation Toxicology (Charge Questions 1, 2, 3, 7)

Conclusion 1: A default 10x extrapolation factor was used to establish the critical acute point of departure (POD) of 2.5 ppm.

Reviewer's Comments:

- For the risk determination of Allyl isothiocyanate (AITC), only three papers were available for review by the DPR that utilized inhalation as the exposure scenario. Two studies were carried out in rats and submitted as FIFRA guideline studies and the other one a human patent study that tested an alarm device for aerosolized AITC in a contained room. The two rodent studies utilized a well-thought out design that evaluated the neurotoxic potential of AITC in rats following either a single 4-hour whole-body vapor or nose-only aerosol inhalation exposure. Both studies used valid and measurable health outcomes for setting the POD value, and excluded the point-of-contact endpoints such as nasal discharge, which were less valid for determining risk.
- I agree with the DPR that the use of decreased motor activity and neuromuscular performance were excellent endpoints from which to derive the LOEL of 25 ppm. I also agree that: NOEL values could not be established from the aforementioned rodent studies; the two rat inhalation studies are valid for use in setting short term guidelines; and an uncertainty factor of 10 was a conservative UF to be used in this case.
- There were different outcomes between the two inhalation studies as was mentioned in the Draft Risk Characterization Document which were most likely due to AITC vapor vs. aerosol and nose-only vs. whole body exposure. Nose-only is likely to lead to a higher tissue both locally and systemically tissues than whole body and could have led to the increased mortality seen with nose-only exposure. Also, more information should be provided in the document regarding the chemicals that may

differ between AITC vapor and the gas/particle aerosol, particularly since the vapor was selected for POD.

- Selection of inhalation endpoints for setting the POD should be one that is positive for both sexes, as was selected for the acute rodent studies by relying on ambulatory activity and total motor activity. If a LOEL or NOEL is only established in a single sex then it is my belief that two different PODs could be used for each sex. Alternatively, the lowest value observed between the two sexes for a given endpoint could be used as the POD, but this choice should be thoroughly explained in the Document.
- I agree with the selection of the critical study for this Risk Assessment Document being the whole body inhalation toxicity study in rats exposed for 4 hours to vaporized AITC. The nose-only exposure experiment should be discounted due to the high rate of mortality. The effects at the lowest tested dose (LOEL of 25 ppm) for both sexes included decreased ambulatory and decreased motor activity in both sexes. I also agree that a benchmark dose (BMD) modeling approach should not be used to establish the acute POD for AITC because of the high variability in the data. I also agree that a default dose extrapolation factor of 10 was appropriate and concervative for setting the POD, in this case.
- As the most relevant route of exposure for assessing risk for AITC are via inhalation, it makes perfect sense to me to use the DPR-selected whole-body exposure to set the POD, rather than dermal or drinking water studies.
- This study also revealed concentration dependent effects which goes towards weight-of-evidence for the selection of the whole-body AITC inhalation study.

Conclusion 2. The critical chronic inhalation POD was estimated from the subchronic critical POD by applying a default duration extrapolation factor of 10. This was necessitated by the lack of chronic inhalation studies.

Reviewer's Comments:

- No studies evaluating the toxicity of AITC via the inhalation route were available, as the DPR points out. That being said, two long-term studies were reviewed in mice and rats exposed orally by gavage with either AITC or AITC-rich substances (horseradish extract (HRE) for 103-wk, and evaluated for chronic toxicity in this risk assessment. The third oral study was focused on the ability of AITC to serve as a promoter for NNK-mediated carcinogenesis.
- I concur with the DPR's decision not to use the urinary oncology studies to derive the POD, because: the study design uses an historical basis for the control values; and the sex differential effects.
- I agree with the DPR that the three rodent studies using an oral exposure paradigm should not be used to set a POD, as they differ substantially by exposure

route which will likely result in different effects than by inhalation, and because of study design weaknesses in the NTP studies, including the low survival rate (58 – 74%) in the controls and possible infection in the mouse studies which will/could skew the outcomes.

- As the subchronic LOEL of 10 ppm included degenerative lesions in the olfactory epithelium and metaplasia of the respiratory epithelium and systemic effects at the same concentration (i.e., activity decrements), I agree with the use of the 13-wk inhalation study to derive the POD of 0.5 ppm from the subchronic POD of 5 ppm and using the full default value of 10, rather than 3 due to the limited inhalation database.

Conclusion 3: PODs from oral studies were not used to establish critical PODs.

Reviewer's Comments:

- I agree with the DPR's conclusion that all critical points of departure (PODs) for this risk assessment are established from inhalation studies in rats. These studies were well designed and provided crucial information on multiple toxicologically relevant parameters, including motor activity, functional observational battery behaviors, and organ and tissue histopathology.
- My agreement for using the inhalation studies rather than the acute, sub-chronic or chronic oral studies are primarily based on the observed differences in physiological outcomes between oral and inhalation exposures and the fact that outcomes in oral studies are more inclined to be due to exposure route rather than treatment-specific.
- Sex differentials for ADME are important and should be discussed in the Risk Characterization Document, along with the fact that different amounts of urine are stored/excreted between the sexes and could account for differentially-observed effects.
- Use of oral studies that employ extracts from horseradish or other cruciferous vegetables are not appropriate to set PODs for AITC inhalation exposure as they contain small amounts of other ingredients that could also be playing a role in observed toxicity, depending on the toxic potential of these minor ingredients.
- More information regarding the differences between nose-only and whole body, as well as between vapor and aerosols should be described in the Risk Assessment Document in greater detail as the differences observed in the studies may be due to these exposure variables.
- In the Lowe study (2012) description in the Draft Risk Document, the Standard deviation of the AITC particles, as well as the MMAD should be provided.
- Due to loss of body weight and changes in eating patterns, some oral study-induced effects may be due to dehydration, nutritional deficit and/or body weight loss, and thus confirm that results should not be used for setting PODs.
- More information should be provided in the Risk Document for the nose-only study regarding the high incidence of mortality in the controls.

Conclusion 4: This RCD did not include a cancer risk estimate for AITC.
While this conclusion was not assigned to me, based on my expertise and publications in rodent tumor challenge studies, I feel qualified to address this question.

Reviewer's Comments:

- Chronic inhalation studies using AITC were not available for assessing a cancer risk estimate in humans or rodents. However, several long-term oral studies in rodents were available for review, but were not considered by DPR as they were thought to be either species-specific or associated only with the oral exposure route. Thus, these studies were deemed inappropriate for basing an inhalation POD.
- I disagree with the statement/conclusion that because no carcinogenic effects were observed after a 13-wk inhalation exposure, the idea of urinary bladder tumors by inhalation was completely ruled out. The fact that bladder cancers did not appear after a 13-wk inhalation exposure is of no surprise given the extensive exposure time (i.e., 1 year) required for chemical exposures to produce cancers in exposed mice or rats. This, however, does not rule out using the 13-wk inhalation study as a POD, but the aforementioned statement is not accurate and at best uncertain and should be removed.
- Given the study design shortcomings identified above in the chronic drinking studies performed by NTP, these rodent studies are not reliable for use to set a cancer risk estimate for AITC, not the least of which is the low survival rates of the control rats and the report of an infection in the chronically-exposed mice which can impact such factors as nutrition, behavior and immune response which is critical for tumor surveillance, all of which can lead to unreliable outcomes.
- The whole-body inhalation exposure of AITC in the chambers appeared to be uneven which could have erroneously accounted for any observed effects including the observed formation of cataracts. It is my contention that based on the chamber variables and uneven distribution of AITC in the chambers, the LOEL for non-neoplastic effects should not be based on cataract data.
- Cytoplasmic vacuolization is considered by many human pathologists as a "morphological phenomenon" that can be transient and form as a general response that can occur with infections and/or a variety of natural and artificial low molecular weight compounds, and therefore not recognized as a specific pathologic endpoint. For these reasons, cataracts should not be considered an endpoint for POD consideration.

Conclusion 7: Dosimetric adjustments of air concentrations to account for pharmacokinetic differences between laboratory animals and humans were used to calculate referencecalculations (RfCs) and risk targets (i.e., target Margins of Exposure).

Reviewer's Comments:

- *As this is not an area that I am confident in reviewing and have not published in this scientific area, I prefer not to comment.*

Thomas O. Spicer, III, Ph.D., P.E.
Professor
Ralph E. Martin Department of Chemical Engineering
University of Arkansas
Fayetteville, AR 72701

Review of
Assumption 6 and Conclusion 9 of the May 27, 2021 request for review by the Department of Pesticide Regulation for Allyl Isothiocyanate (AITC)

to

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Assumption 6. DPR estimated bystander exposures to AITC using an air dispersion model (AERMOD). Occupational bystander exposures were estimated at the field edge, and residential bystander exposures were estimated at 25 and 100 ft from the field edge.

This charge question is stated as an assumption, and the basis for the assessment of the validity of this assumption was obtained from the report by Weiying Jiang titled "Human Exposure Assessment for Allyl Isothiocyanate as Soil Fumigant" which is included in the main report as Appendix 1. Appendix 1 includes two memoranda from Weiying Jiang to Shelley DuTeaux (via Eric Kwok) outlining the method used to estimate the soil emissions of allyl isothiocyanate (AITC) and the method used to estimate air concentrations of AITC. Both memoranda are included in Appendix 1 of "Human Exposure Assessment for Allyl Isothiocyanate as Soil Fumigant."

The memorandum titled "Using Allyl Isothiocyanate-Specific and Surrogate Data to Determine AITC Soil Emissions for Residential and Occupational Bystander Exposure Assessments" dated February 18, 2020 (Emission Memorandum) outlines the methods used to estimate soil emissions of AITC which is a necessary pre-requisite for estimating airborne concentrations of AITC for occupational and residential bystanders. This memorandum addresses the soil emission estimates depending on the method of AITC application including shallow shank injection (with and without post-treatment tarp coverage), deep shank injection (without post-treatment tarp coverage), drip chemigation (with post-treatment tarp coverage), and deep drip chemigation (without post-treatment tarp coverage). Data for all of these emission scenarios are unavailable for AITC, so surrogate data was used in these cases based on emission estimates for 1,3-dichloropropene (1,3-D) and chloropicrin (Pic). The calculated maximum soil emissions for three different averaging periods (4, 8, and 24 hr) were subsequently used to estimate airborne AITC concentrations.

In the Emission Memorandum, A review of AITC emission study data was summarized, and previously identified issues were resolved satisfactorily so that this data was used (after normalization to the maximum AITC application rate) in the summarized emission rates. The normalization process uses different rates which makes direct comparison of the reported values difficult (e.g., Table 5 is normalized to 340 lb/ac for drip and shallow shank application methods, but Table E1. normalizes drip to 245 lb/ac and 340 lb/ac for shallow shank). Furthermore, the differences between Table 5 and Table E1 are not clear (e.g., the maximum emission rate in Table 5 for shallow shank application with a tarp is not consistent with the value reported in Table E1 even though both are based on the same application rate). Finally, the AITC study considered both totally impermeable film (TIF) and polyethylene film (PE), but Table 1 does not make clear which of these films (or an average) were used in determination of the reported emission rate.

The Emission Memorandum outlines the justification for choosing surrogates to model AITC soil emissions and makes the point that such a process would be expected to result in conservative estimates (greater than actual AITC emission rates). While this would be expected based on the physical properties of the surrogates, a comparison between studies also supported this conclusion.

The memorandum titled "Determination of Allyl Isothiocyanate Air Concentrations Around Fields Fumigated using Shank or Drip Applications" dated February 19, 2020 (AERMOD Memorandum) outlines the methods used to estimate airborne concentrations of AITC for occupational and residential bystanders using AERMOD. Representative counties were selected to model air concentrations because of varying meteorological conditions expected in those areas of AITC use. The report summarizes the procedure used to compile 5-year meteorological information for input to AERMOD, and the approach taken in the report is found to agree with AERMOD concentration predictions using air pollution control district meteorological files where available. Emission estimates were taken from the Emission Memorandum. Receptor locations were identified to make AERMOD predictions of AITC concentrations at appropriate locations. The importance of timing of emissions was discussed. Ultimately, the counties with the highest predicted concentration at a given receptor location were used to represent the highest possible bystander exposure to AITC for all of California. The process was repeated for all application methods under consideration. Because of the timing of the original study, meteorological data from 2013-2017, and the study considered whether use of 2018 data could reach a different conclusion by considering the results for Ventura County. The study found that using 2013-2017 data would not be expected to underestimate AITC concentrations.

My understanding is that I am asked to determine whether the scientific work product in support of Assumption 6 is based on sound knowledge, methods, and practices, and in response, I have determined that this assumption is based on sound knowledge, methods, and practices provided that the supporting conclusions are confirmed in the review process. The reports considered here provide justification for the use of AERMOD by DPR to estimate bystander exposures to AITC. There are aspects of the Emissions Memorandum that could be clearer, but the validity of the conclusions will likely be unchanged.

Conclusion 9. Risk to occupational and residential bystanders were [accurately] estimated for acute exposures.

The discussion above related to Assumption 6 forms the basis for my evaluation of Conclusion 9, particularly from the report by Weiying Jiang titled "Human Exposure Assessment for Allyl Isothiocyanate as Soil Fumigant" which is included in the main report as Appendix 1. Appendix 1 includes two memoranda from Weiying Jiang to Shelley DuTeaux (via Eric Kwok) outlining the method used to estimate the soil emissions of allyl isothiocyanate (AITC) and the method used to estimate air concentrations of AITC. Both memoranda are included in Appendix 1 of "Human Exposure Assessment for Allyl Isothiocyanate as Soil Fumigant." The discussion that follows mirrors the statements made concerning Assumption 6.

The memorandum titled "Using Allyl Isothiocyanate-Specific and Surrogate Data to Determine AITC Soil Emissions for Residential and Occupational Bystander Exposure Assessments" dated February 18, 2020 (Emission Memorandum) outlines the methods used to estimate soil emissions of AITC which is a necessary pre-requisite for estimating airborne concentrations of AITC for occupational and residential bystanders. This memorandum addresses the soil emission estimates depending on the method of AITC application including shallow shank injection (with and without post-treatment tarp coverage), deep shank injection (without post-treatment tarp coverage), drip chemigation (with post-treatment tarp coverage), and deep drip chemigation (without post-treatment tarp coverage). Data for all of these emission scenarios are unavailable for AITC, so surrogate data was used in these cases based on emission estimates for 1,3-dichloropropene (1,3-D) and chloropicrin (Pic). The calculated maximum soil emissions for three different averaging periods (4, 8, and 24 hr) were subsequently used to estimate airborne AITC concentrations.

In the Emission Memorandum, A review of AITC emission study data was summarized, and previously identified issues were resolved satisfactorily so that this data was used (after normalization to the maximum AITC application rate) in the summarized emission rates. The normalization process uses different rates which makes direct comparison of the reported values difficult (e.g., Table 5 is normalized to 340 lb/ac for drip and shallow shank application methods, but Table E1. normalizes drip to 245 lb/ac and 340 lb/ac for shallow shank). Furthermore, the differences between Table 5 and Table E1 are not clear (e.g., the maximum emission rate in Table 5 for shallow shank application with a tarp is not consistent with the value reported in Table E1 even though both are based on the same application rate). Finally, the AITC study considered both totally impermeable film (TIF) and polyethylene film (PE), but Table 1 does not make clear which of these films (or an average) were used in determination of the reported emission rate.

The Emission Memorandum outlines the justification for choosing surrogates to model AITC soil emissions and makes the point that such a process would be expected to result in conservative estimates (greater than actual AITC emission rates). While this would be expected based on the physical properties of the surrogates, a comparison between studies also supported this conclusion.

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My understanding is that I am asked to determine whether the scientific work product in support of Conclusion 9 is based on sound knowledge, methods, and practices, and in response, I have determined that this conclusion is based on sound knowledge, methods, and practices provided that the supporting conclusions are confirmed in the review process. As discussed above, the reports considered here provide justification for the use of AERMOD by DPR to estimate bystander exposures to AITC. Consequently, the risk to occupational and residential bystanders were properly estimated for acute exposures of allyl isothiocyanate for the application methods considered. There are aspects of the Emissions Memorandum that could be clearer, but the validity of the conclusions will likely be unchanged. Furthermore, the risk to occupational and residential bystanders were properly estimated for acute exposures.