OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

Subject: Transmittal of Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Public Virtual Meeting "**Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde"** held May 20-23, 2024

TO: Elissa Reaves, PhD
Director
Office of Pollution Prevention and Toxics

FROM: Tamue Gibson, MS
Designated Federal Official and Executive Secretary
Science Advisory Committee on Chemicals
Peer Review and Ethics Branch
Mission Support Division
Office of Program Support

TAMUE GIBSON
Digitally signed by TAMUE GIBSON
Date: 2024.08.01 16:45:03 -04'00'

THRU: Hayley Hughes, DrPH, MPH, CSP
Director
Office of Program Support

HAYLEY HUGHES
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Date: 2024.08.01 16:50:20 -04'00'

Attached, please find the meeting minutes and final report for the Science Advisory Committee on Chemicals public virtual meeting held via Zoom on May 20-23, 2024. This report addresses scientific issues being considered by the Environmental Protection Agency regarding EPA's "**Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde."**

Attachment

cc:
Michal Freedhoff, PhD
Mark Hartman, MA
Jeffrey Morris, PhD
Karen Eisenreich, PhD
Rochelle Bohaty, PhD
Jacqueline Mosby, EdD
Steven Knott, MS
OPPT Docket

Science Advisory Committee on Chemicals (SACC) Members

George Cobb, PhD, SACC Chair
Udayan Apte, PhD
Marissa Baker, PhD
Christine Chaisson, PhD
Stephanie Eick, PhD
Mary A. Fox, PhD
Cynthia Graham, PhD
Wendy Heiger-Bernays, PhD
Francheska Merced-Nieves, PhD
Mary Ottinger, PhD
Jennifer Przybyla, PhD
David Reif, PhD
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Marc Rumpler, PhD
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Michael Wright, MS

SACC *ad hoc* Peer Reviewers

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Anita M. Kelly, PhD
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Wayne G. Landis, PhD
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Lisa M. Sweeney, PhD
Douglas C. Wolf, PhD, DVM
Luoping Zhang, PhD

Science Advisory Committee on Chemicals
Meeting Minutes and Final Report
No. 2024-01

Docket ID: EPA-HQ-OPPT-2023-0613

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde

May 20-23, 2024
Virtual Meeting via Webcast

NOTICE

The Science Advisory Committee on Chemicals (SACC) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) and established under the provisions of the Toxic Substances Control Act (TSCA) as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The SACC provides advice, information, and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) Administrator on chemicals and chemical-related issues regarding the impact of regulatory actions on health and the environment. The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and employed on an ad hoc basis to assist the reviews conducted by the SACC. The meeting minutes and final report are provided as part of the activities of the SACC.

Minutes represent the views and recommendations of the SACC and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes and final report do not create nor confer legal rights nor impose legally binding requirements on the EPA or any other party.

The meeting minutes and final report of the May 20-23, 2024, SACC meeting represent the SACC's consideration and review of scientific issues associated with the "2024 Draft Risk Evaluation for Formaldehyde." The SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public.

EPA's Office of Program Support reviewed the quality of the minutes and final report. The SACC Chair, Dr. George Cobb and SACC Executive Secretary and Designated Federal Official (DFO), Tamue L. Gibson, MS, reviewed and certified the minutes and final report, which is publicly available on the SACC website https://www.epa.gov/tsca-peer-review under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPPT-2023-0613, accessible through the docket portal: http://www.regulations.gov. Further information about SACC reports and activities can be obtained from its website at https://www.epa.gov/tsca-peer-review. Interested persons are invited to contact Tamue L. Gibson, MS, SACC Designated Federal Official, via e-mail at gibson.tamue@epa.gov.

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Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde

May 20-23, 2024

Virtual Meeting via Webcast

George Cobb, PhD
SACC Chair
Science Advisory Committee on Chemicals

George P. Cobb Digitally signed by George P. Cobb Date: 2024.08.01 15:05:58 -05'00'

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Tamue L. Gibson, MS
Designated Federal Official
Office of Program Support

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Date:

Science Advisory Committee on Chemicals Meeting
May 20-23, 2024
Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde

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Designated Federal Official

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Luoping Zhang, PhD
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LIST OF ACRONYMS AND ABBREVIATIONS

AEGL	Acute Exposure Guideline Levels
ADH5	Alcohol dehydrogenase 5
AHHS II	American Health Homes Survey II
AMTIC	Air Monitoring Technology Information Center
ANOVA	Analysis of Variance
BMCL	Benchmark Concentration Lower Bound
BMD	Benchmark Dose
BMR	Benchmark Response
BW	Body Weight
CEM	Consumer Exposure Model
COU	Conditions of Use
ECHA	European Chemicals Agency
ECx	Effective Concentration
EC3	The concentration required to induce a simulation index of 3 relative to the concurrent vehicle control
EC50	Half Maximal Effective Concentration
EFAST	Exposure and Fate Assessment Screening Tool
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GLP	Good Laboratory Practice
HC5	Hazardous Concentration for 5% of the Species
HCHO	Formaldehyde
HSRB	Human Studies Review Board
IBT	Industrial Bio-Test Laboratory
ICL	Interstrand cross-link
IET	Indoor Experienced Temperature
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
LC	Lethal Concentration
LLNA	Local Lymph Node Assay
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
Mg/M^3	Milligram per Cubic Meter
MIRA	Multicriteria Integrated Resource Assessment
NAS	National Academy of Sciences
NASEM	National Academies of Sciences, Engineering, and Medicine
NASM	National Association of State Motorcycle Safety Administrators
NER	Nucleotide Excision Repair
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPC	Nasopharyngeal Cancer
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PECO	Population/Exposure/Comparator/Outcome
PESS	Potentially Exposed or Susceptible Subpopulations

POD	Point of Departure
PPE	Personal Protective Equipment
SACC	Science Advisory Committee on Chemicals
SARA-ICE	Skin Allergy Risk Assessment-Integrated Chemical Enforcement Model
SCC	Squamous Cell Carcinomas
SE	Standard Error
SI	Stimulation Index
SPES	Swedish Performance Evaluation System
SSD	Species Sensitivity Distribution
STEL	Short-term Exposure Limit
TRI	Toxic Release Inventory
TRPA	Transient Receptor Potential Ankrylin
TSCA	Toxic Substances Control Act
TWA	Time Weighted Average
UF	Uncertainty Factor
UF_H	Intraspecies Differences
VOC	Volatile Organic Compound
WES	Workplace Exposure Standard
WHO	World Health Organization

INTRODUCTION

The Science Advisory Committee on Chemicals (SACC) completed its review of the set of scientific issues being considered by the Environmental Protection Agency regarding the Peer Review of the 2024 Draft Risk Evaluation for Formaldehyde. Advanced notice of the meeting was published in the Federal Register on December 26, 2023. The peer review public virtual meeting was held May 20-23, 2024. The Agency position paper, charge questions, and related documents in support of the SACC meeting are posted in the public e-docket at http://www.regulations.gov (ID: EPA-HQ-OPPT-2023-0613). George P. Cobb, PhD, chaired the meeting. Tamue L. Gibson, MS, served as the Designated Federal Official.

In preparing these meeting minutes and final report, the Committee carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. The meeting minutes and final report address the information provided and presented at the meeting, especially the Committee response to the Agency charge.

The U.S. EPA presentations were provided during the SACC meeting by the following (listed in order of presentation):

May 20-23, 2024: Summary of Meeting Agenda

Day 1 – May 20, 2024

Opening of Meeting – Tamue L. Gibson, MS, Designated Federal Official, Mission Support Division (MSD), Office of Program Support (OPS), Office of Chemical Safety and Pollution Prevention (OCSPP), EPA

Introduction and Identification of Committee Members – George Cobb, Ph.D., Science Advisory Committee on Chemicals (SACC) Chair

Introduction and Welcome – Elissa Reaves, Ph.D., Director, Office of Pollution, Prevention, and Toxics (OPPT), OCSPP, EPA

Remarks – Elissa Reaves, Ph.D., Director, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Toxics Substances Control Act (TSCA) Existing Chemical Overview** – Rochelle Bohaty, Ph.D., Branch Chief, Existing Chemicals Risk Assessment Division, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Formaldehyde History and Risk Assessment Overview** – Rochelle Bohaty, Ph.D., Branch Chief, ECRAD, OPPT, OCSPP, EPA; Anna Lowit, Ph.D., Science Advisor, OCSPP, OPPT

OPPT Technical Presentation – **Formaldehyde Human Health Hazard Overview** – Susanna Wegner, Ph.D., Toxicologist, ECRAD, OPPT, OCSPP, EPA; John Allran, M.S., Toxicologist, ECRAD, OPPT, OCSPP, EPA; Colleen Rossmeisl, D.V.M., Senior Science Advisor, Antimicrobial Division, OPP, OCSPP, EPA

OPPT Technical Presentation – **Assessment of Formaldehyde Exposures via Water and Land Pathways –** Shawn Shifflett, Ph.D., Physical Scientist, ECRAD, OPPT, OCSPP, EPA; Melody Bernot, Ph.D., Toxicologist, ECRAD, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Formaldehyde Occupational Exposure and Risk Assessment** – Whitney Hollinshead, Ph.D., Chemical Engineer, ECRAD, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Formaldehyde Consumer Exposure Assessment** – Giorvanni Merilis, Ph.D., CPH., Physical Scientist, ECRAD, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Formaldehyde Residential Indoor Air Exposure Assessment** – Giorvanni Merilis, Ph.D., CPH., Physical Scientist, ECRAD, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Approaches to Analyzing and Interpreting Ambient Air Monitoring and Modeling Data** – Bryan Groza, M.S.., Physical Scientist, ECRAD, OPPT, OCSPP, EPA; Kevin Vuilleumier, M.S., Environmental Engineer, ECRAD, OPPT, OCSPP, EPA; Grant Goedjen, Ph.D., Environmental Engineer, OPPT, OCSPP, EPA

OPPT Technical Presentation – **Formaldehyde Aggregate Exposure and Risk Assessment** – Kevin Vuilleumier, M.S., Environmental Engineer, ECRAD, OPPT, OCSPP, EPA; Susanna Wegner, Ph.D., Toxicologist, ECRAD, OPPT, OCSPP, EPA; Bryan Groza, M.S., Physical Scientist, ECRAD, OPPT, OCSPP, EPA

EPA Summary and Wrap-up – Shawn Shifflet, Ph.D., Physical Scientist, ECRAD, OPPT, OCSPP, EPA; Rochelle Bohaty, Ph.D., Branch Chief, ECRAD, OPPT, OCSPP, EPA; Anna Lowit, Ph.D., Science Advisor, OCSPP, OPPT

PUBLIC COMMENTERS

Oral statements were presented as follows in the order received:

1) Ashley Amidon, International Wood Products Association: Ashley Amidon
2) Scott Arnolds, Dow
3) Lyle Burgoon, Raptor Pharm & Tox, Ltd
4) Benjamin Idzik, Independent Lubricant Manufacturers Association
5) Andrea Chiger, Environmental Defense Fund
6) Harvey Clewell, Ramboll
7) Sean Hays, SciPinion
8) Joel Cohen, Gradient
9) Rory Conolly, Self
10) Paul Deleo, American Chemistry Council
11) Linda Dell, Ramboll
12) Dan Dix, ALL4, LLC
13) Elaine Freeman, Exponent
14) Robinan Gentry, Ramboll
15) Reagan Giesenschlag, The Fertilizer Institute
16) William Goodfellow, Exponent
17) Stewart Holm, American Forest & Paper Association
18) Gary Huddleston, American Feed Industry Association
19) Curtis Shelast, Bakelite Synthetics
20) Jonathan Kalmuss-Katz, Earthjustice
21) Renee Kalmes, Exponent
22) Rashmi Joglekar, University of California, San Francisco
23) Pamela Dalton, Monell Chemical Senses Center
24) Heather Lynch, Integral Consulting
25) Jacob Miller, Hexion, Inc.
26) Peggy Murray, The Center for Truth in Science
27) Lawrence Navin, Methanol Institute
28) Sahar Osman-Sypher, American Chemistry Council
29) Dennis Paustenbach, Paustenbach & Associates
30) Tunga Salthammer, Fraunhofer WKI
31) Elliot Sigal, Intrinsik Corporation, On behalf of American Home Furnishings Alliance
32) Jim Sherman, Independent Contractor
33) Chad Thompson, ToxStrategies, LLC
34) Melissa Vincent, ToxStrategies, LLC
35) Clint Woods, Hexion

Written statements were provided to the docket as follows:

1) Steven Gibb, individual commenter
2) James McFadden, PhD, Sr. Director, Regulatory Affairs, Central Garden & Pet
3) Sahar Osman-Sypher, American Chemistry Council Formaldehyde Panel
4) Andrew O'Hare, President, Composite Panel Association
5) Robert Skoglund, Director, Product Safety & Regulatory, Affairs, Covestro, LLC
6) Katherine Homra, American Forest & Paper Association and American Wood Council

7) Environmental Protection Network
8) Janet Dolin, Executive Vice President and CEO, American Veterinary Medical
9) Sebastian Belle, President, National Aquaculture Association
10) The Engineered Wood Association
11) Ruth Jewkes, Chief Marketing Officer, Anitox Corporation
12) Reagan Giesenschlag, Manager of Government Affairs, The Fertilizer Institute
13) Angus Crane, Executive VP, General Counsel, North American Insulation Manufacturers Association
14) On behalf of Lubricant Manufacturers Association: Robin Dilts, Sr. Global & Regulatory Affairs Manager, Quaker Houghton Independent
15) Center for Truth in Science
16) Center for Environmental Health et al.
17) University of California, San Francisco Program on Reproductive Health and the Environment
18) Kimberly Hazard, individual commenter
19) U.S. Senator Mike Braun et al.
20) Decorative Hardwoods Association
21) International Wood Products Association
22) Mark Schumacher, CEO, American Home Furnishings Alliance
23) Paul Selberg, individual commenter
24) Larry Jackson, individual commenter
25) Greg Esposito, individual commenter
26) Tom Morley, individual commenter
27) United States Small Business Administration
28) Dustin Theis, individual commenter
29) Max Carter, individual commenter
30) Darryl Moss, Board Member, Golden Leaf Foundation, North Carolina
31) Lela Graham, individual commenter
32) Greg Dolan, CEO, Methanol Institute
33) Erik Somerfeld, individual commenter
34) Gary Kanan, UAW member
35) Fay Beydoun, individual commenter
36) Theresa Stechschulte, individual commenter
37) Sandra Jauregui, individual commenter
38) Anna Toma, VP Public Affairs and Chief Sustainability Officer, Potlatch Deltic Corporation
39) Jacob Welch, individual commenter
40) U.S. Senator Emanuel Jones
41) Braden Gourley, Agriculturalist, Beaver County, Pennsylvania
42) Jared Nace, Farm Owner, Pennsylvania
43) Caleb Wright, Livestock producer and Farmer, Halifax, Pennsylvania
44) Steven Rzeppa, individual commenter
45) Kattya Valdez Douglas, Care Coordinator, Chiricahua Community Health Centers, Arizona
46) Dave Lewis, Former State Senator and Budget Director, State of Montana
47) Nicholas Tellez, individual commenter
48) Alec LaPlante, individual commenter
49) Jeff Winston. IBEW Local 1106 Member, Michigan
50) Michael Andazola, individual commenter
51) Reuben D'Silva, individual commenter
52) State of Georgia House of Representative, Billy Mitchell

53) Sam Deley, individual commenter
54) Valerie Adams, individual commenter
55) Michael Wray, individual commenter
56) Joe Rozell, Huntington Woods, Michigan City Commissioner
57) Marco Rauda, CEO, El Faro Consulting
58) Matthew Hieshetter, Louisiana-Pacific Corporation
59) Chad Thompson, Sr. Managing Scientist, ToxStrategies, LLC
60) Melissa Vincent, Supervising Scientist, ToxStrategies, LLC
61) Assembly woman, State of Nevada, Michelle Gorelow
62) Harvey Checkoway, Professor, University of California, San Diego
63) Jesse Neese, Bakelite Synthetics
64) Robert Mann, Sr. Director of Technical and Regulatory Affairs, National Association of Landscape Professionals
65) Raptor Pharm & Tox Ltd
66) Shelly Russel, individual commenter
67) Jonathan Pattillo, individual commenter
68) U.S. Representative Donald G. Davis et al.
69) Dennis Paustenbach, President, Paustenbach and Associates
70) Doug Neil, individual commenter
71) Lester Jackson, individual commenter
72) American Feed Industry Association
73) California Air Resources Board
74) American Association of Veterinary Laboratory Diagnosticians
75) Jimmy Avery, Thad Cochran National Warmwater Aquaculture Center, Mississippi State University
76) Clint Woods, Global Director, Product, Stewardship & Regulatory Affairs, Hexion Inc.
77) ToxStrategies LLC
78) Celanese Corporation
79) Craig Gilchrist, Union Leader, Brotherhood of Locomotive Engineers and Trainmen
80) U.S. Georgia State Senator Donzella James
81) Squire Patton Boggs LLP
82) Jonathon Stephens, Plant Manager Finance/Administration EGGER Wood Products LLC
83) Tunga Salthammer, individual commenter
84) Christoph van Thriel, individual commenter
85) Exponent
86) Patty Stinson, individual commenter
87) Dan Dix, Technical Director, ALL4 LLC
88) Jasen Stock, Executive/New Hampshire Timberland Owners Association
89) Patrick Strauch, Executive Director, Maine Forest Products Council
90) Kennis Wilkins, North Carolina Human Relations Commission
91) Southeastern Lumber Manufacturers Association
92) American Wood Council
93) Mark Cardenas, former member, Arizona State House
94) Kevin Korpi, Executive Director, Michigan Forest Products Council
95) John Bird, Environmental Director, Roseburg Forest Products Co.
96) Rory Conolly, independent toxicologist
97) Arizona State Representative Myron Tsosie
98) Jason Spadaro, Executive Director, Washington Forest Protection Association

99) Georgia-Pacific Gypsum LLC
100) Grace Thomas, individual commenter
101) Mark Richardson, Executive VP & General Manager, Wood Products, The Westervelt Company
102) LeeAnn McLaughlin, Dairy Farmer at Eleven Farms, Pennsylvania
103) Robert Boyles, Executive Director, West Virginia Forestry Association
104) David Hyde, Sr. Director, Sustainability, Aerospace Industries Association
105) Melissa Vincent, individual commenter
106) Lydia Hernandez, Arizona State Representative
107) Jason Rano, VP, Government Affairs, RV Industry Association
108) Harvey Clewell, Principal Consultant, Ramboll
109) Grant Gulibon, Regulatory Affairs Specialist, Pennsylvania Farm Bureau
110) Edie Marshall, Branch Chief, Antimicrobial Use and Stewardship, California Department of Food and Agriculture
111) State of Iowa Department of Justice Office of the Attorney General
112) William Thompson, Independent Consultants in Epidemiology
113) On behalf of: ACC Formaldehyde Panel: Robinan Gentry, Principal, Ramboll and Chad Thompson, Sr. Managing Scientist, ToxStrategies, LLC
114) Jennifer Gibson, Sr. VP, Regulatory Affairs, Alliance for Chemical Distribution
115) Harold Wolle, Jr. President, National Corn Growers Association
116) Jos Huxley, Sr. VP of Technical Affairs, CentThe Toy Association
117) Center for Environmental Accountability
118) Lesley Witter, Sr. VP, Advocacy, National Funeral Directors Association
119) Catherine Palin, Sr. Attorney & Director of Environmental Policy, Alliance for Automotive Innovation
120) National Council for Air and Stream Improvement Inc.
121) James Sherman, Independent Toxicologist Consultant
122) On behalf of: The Hardwood Federation, the National Wood Flooring Association: Keith Christman, President, Decorative Hardwoods Association
123) Pamela Dalton, Monell Chemical Senses Center
124) Jenn Klein, President, Ohio Chemistry Technology Council
125) Jeff Hannapel, American Foundry Society
126) Linda D. Dell, Principal, Ramboll Americas Engineering Solutions, Inc.
127) Russ Batson PFA Executive Director, Polyurethane Foam Association
128) Catherine Trinkle, VP & Deputy General Counsel-Regulatory, Environmental & Government Affairs, BASF Corporation
129) Kelly Scanion, Lead Sustainability Strategist, IPC International Inc
130) Asphalt Roofing Manufacturers Association
131) North American Home Furnishings Association
132) Environmental Defense Fund
133) Steven, Bennett, Executive, VP, Scientific & Regulatory Affairs, Household & Commercial Products Association
134) Megan Provost, President, Responsible Industry for a Sound Environment
135) Andy Maier, Principal and Heather Lynch, Principal, Integral Consulting Inc.
136) William Almond, IV, President, The Adhesive and Sealant Council
137) Janelle Restum, VP, Regulatory Affairs and Environmental, Health and Safety, The Scotts Company LLC
138) American Feed Industry Association et al.
139) Joel Cohen, Gradient

140) Josh Gackle, President, American Soybean Association
141) Brandon Farris, VP of Domestic Policy, The National Association of Manufacturers
142) SciPinion
143) Riaz Zaman, American Coatings, Association
144) Matt Espenshade, President, Pennsylvania Grange
145) Stephanie Schlea, VP EHS&S, U.S. Tire Manufacturers Association
146) American Chemistry Council Diisocyanates Panel
147) Justin Parker, Executive Director, Northwest Indian Fisheries Commissioner
148) Dow Chemical
149) On behalf of: the American Home Furnishings Alliance; International Wood Products Association: David French, Executive Vice President of Government Relations, National Retail Federation
150) Ashley Amidon, Executive Director, International Wood Products, Association

EXECUTIVE SUMMARY

The Science Advisory Committee on Chemicals (the Committee) considered a series of questions posed by the Environmental Protection Agency (EPA) on the Draft Risk Evaluation for Formaldehyde (the Evaluation) and the public comments that were offered related to the Evaluation. As with any endeavor with the complexity of the Formaldehyde Evaluation, there was robust discussion wherein varying perspectives were shared from different Committee members.

The Committee commended the EPA for undertaking a complex and essential evaluation that has potential to improve human and environmental health. The Committee acknowledged that timelines, information complexities, concerns from numerous stakeholders, and budgetary constraints further complicate the implementation of this, and other Risk Evaluations being conducted by the EPA.

Overall, the draft documents are comprehensive and rely on the best available science. Several areas that could be improved include the need to 1) use high centile exposure estimates when robust exposure data are unavailable, 2) harmonize formaldehyde concentrations in the environmental exposure and effects assessments, 3) aggregate exposure data to more accurately capture aggregate risks, incorporating National Academy of Sciences (NAS) comments related to formaldehyde effects, 4) consider the usefulness of threshold responses for assessing cancer, and 5) improve the robustness of air quality data evaluations. Better explanations are requested for several aspects of the documents the Committee evaluated. The Committee also noted a need for more robust data sets, improved modeling approaches, and inclusion of probabilistic approaches in the Toxic Substances Control Act (TSCA) Risk Evaluations. The Committee found many Charge questions to be interrelated and this document attempts to note such relationships while not duplicating text in multiple places. Specific comments in response to the charge questions follow:

Question 1 – Human Health Hazard

The human health hazard section evaluated the potential adverse health effects of formaldehyde exposure, including acute and chronic noncancer impacts. The Committee's review aimed to ensure that the assessment is thorough, scientifically robust, and appropriately addressed uncertainties.

The Committee members agreed that the human health hazard assessment within the Formaldehyde draft risk evaluation is comprehensive for the acute inhalation point of departure, however adequate documentation of key studies and rationale was lacking. Committee members identified several areas for improvement: In addition, the reliance on sensory irritation as a POD for the acute inhalation POD requires clearer justification. Sensory irritation is not universally considered an adverse effect, and its selection should be supported with a rationale explaining why it is an appropriate endpoint and what, if any, uncertainty factors should be applied. The Committee recommended that EPA review approaches taken by other regulatory authorities to ensure exposure limits are consistent with the best available science.

Clarity and Justification of PODs: When multiple PODs are developed, EPA should provide clear documentation of the POD to be used for risk assessment, along with the rationale for its selection.

Regulatory Comparison: The assessment should incorporate international standards and guidelines to achieve greater credibility, consistency in regulation, and acceptance.

Application of Uncertainty Factors: Uncertainty factors should be carefully considered, especially when sensitive human populations have been included in the studies. A clear rationale should be provided for the application of these factors to enhance transparency and identify areas where further data might reduce uncertainty.

Impact on Normal Functioning: Sensory irritation effects should be evaluated within the context of their impact on normal functioning, particularly in occupational settings. This is essential for assessing the real-world implications of formaldehyde exposure on workers' health and productivity.

Confidence in Hazard Assessment: The overall confidence in the hazard assessment should be strengthened by using high quality human data where available and addressing interindividual variability transparently. Emphasizing human data enhances the relevance and applicability of the findings to real-world scenarios.

Question 2 – Water and Land Pathway

Introduction: This section addressed the environmental fate and transport of formaldehyde, emphasizing its behavior in water and soil. The Committee evaluated the assessment's coverage of formaldehyde's degradation, its byproducts, and the implications for environmental and human health.

The Committee reviewed the environmental fate and transport assessment for formaldehyde and concluded that:

Consideration of Degradation Products: Formaldehyde's rapid degradation in water and soil is well-documented, but the degradation products (e.g., methylene glycol) should be considered in the risk evaluation due to their potential toxicity. Including these products ensures a more comprehensive understanding of environmental risks.

Need for Robust Monitoring Data: More robust environmental monitoring data are needed to validate assumptions about negligible exposure levels in water and soil. Enhanced monitoring efforts would provide a stronger empirical basis for risk assessments and regulatory decisions.

Model Validation with Monitoring Data: The use of the E-FAST model should be complemented with actual monitoring data to provide a more accurate assessment of formaldehyde's environmental impact. This dual approach would enhance the reliability of exposure estimates.

Harmonizing Exposure Concentrations: The inclusion of formaldehyde and all transformation products in calculation of treatment concentrations used in the toxicity tests for the Effects Assessment must be reconciled with express omission of these products in the Exposure Assessment. To do otherwise potentially leaves all aquatic resources at risk.

Aggregate Environmental Exposure: The potential for formaldehyde emissions from various sources to contribute to TSCA related environmental exposure should be more thoroughly evaluated.

Probabilistic Risk Assessment: It is important to conduct a probabilistic risk assessment using current approaches and dose-response modeling. This approach will facilitate the inclusion of the degradation products, monitoring data, the inclusion of transformation products cumulative exposure, and toxicological responses into risk evaluations.

Question 3 – Occupational Assessment

The Occupational Assessment section examines formaldehyde exposure in workplace settings, including both direct users and occupational non-users (ONUs). The Committee primarily evaluated the accuracy and comprehensiveness of exposure estimates and the assumptions regarding protective measures. The Committee also discussed the development and application of the cancer Inhalation Unit Dose (IUR) in the occupational context and recommended a review of the literature supporting both threshold and non-threshold models of formaldehyde carcinogenicity to carefully justify the conclusion.

The Committee noted several key points in the occupational exposure assessment:

Detailed Task and Movement Data: There is a need for more detailed data that describe tasks and movements of workers to better distinguish between workers and occupational ONUs. This granularity is necessary for accurately assessing exposure concentrations and health risks.

Integration and Consideration of Additional Data: Additional data from Occupational Safety and Health Administration (OSHA) and international counterparts should be integrated to enhance the occupational exposure assessment. Utilizing diverse data sources strengthens the robustness and credibility of the assessment. Many examples were offered such as considering the best available science to better explain mode of action and to determine if the point of departure (POD) can be refined.

Aggregate Exposure Consideration: The evaluation should consider cumulative exposures from multiple chemicals and aggregate exposure across different routes (inhalation, dermal). This comprehensive approach is crucial for understanding the full scope of health risks in occupational settings and the relative contribution formaldehyde may be making to the health outcomes of concern.

The Committee acknowledged that given that cancer from formaldehyde is likely a nonlinear effect there is an opportunity to take a unified approach to both cancer and noncancer effects. The National Research Council's Science and Decisions report (NRC 2009) recommendation for a unified approach to dose-response assessment is a useful framework to evaluate and organize the evidence to develop and document that approach.

Question 4 – Consumer Assessment

This section evaluates the risks posed by formaldehyde in various products and the environments in which those products are manufactured, distributed, stored and used by individual customers and by service workers, emphasizing long-term exposure, and aggregate risks. The Committee's review aimed to ensure that consumer exposures are realistically assessed and conservative due to the lack of data to adequately inform exposure profiles.

In evaluating exposure, the Committee recommended:

Expansion of the exposure opportunities by considering manufacturing, transport, and distribution within the marketplace, use by individuals and retail or service workers, and off-gassing into contained spaces (especially vehicles). Workers who are exposed through their jobs may also

experience exposures as consumers.

Inclusion of additional scenarios of exposure, especially ambient air exposure reaching residences in mixed use urban scenarios where all categories of vulnerable subpopulations are unknowingly repeatedly exposed.

Conservative Exposure Estimates: Conservative exposure estimates should be used in deterministic assessments, especially given uncertainties in consumer behavior and product formulations. This ensures that the risk assessment errs on the side of caution, protecting public health. Identifying conservative values for use in exposure assessment requires proper statistical evaluation of the data. Exposure assessments then require application of the data to probabilistic models capable of handling aggregated exposure scenarios and data. Those tools should be made available to the EPA scientists. This holistic view is essential for understanding the total exposure consumers might face.

Inclusion of Chronic Exposure Assessments: The categories of long-term use patterns and exposure opportunities should be significantly expanded. Scenarios that include Potentially Exposed and Susceptible Subpopulations should be considered, some of which were identified by the Committee. Aggregated chronic exposure scenarios should be assessed in probabilistic models functioning as described by EPA's own guidelines. This is important for identifying and mitigating long-term health risks associated with continuous exposure to formaldehyde.

Hazard Assessments: The Committee suggested providing a more thorough discussion of uncertainties related to data on formaldehyde sources and consumer uses in the study(ies) underlying the POD. The Committee also asks the EPA to justify and explain the application of the POD, based on health effects in children, to adult consumers. It would also be helpful to have clarification of whether benchmark dose modeling (BMD) was applied to the oral exposure studies.

Question 5 – Indoor Air Assessment

The indoor air assessment section addressed the presence and impact of formaldehyde in indoor environments, highlighting the importance of monitoring and regulating indoor sources to protect public health.

The Committee's review of indoor air quality assessments highlighted that:

Use of Existing Data for Values in Exposure Factors: The Committee recommended comprehensive statistical evaluation of the existing information, studies, data for parameters of the Consumer Exposure Model (CEM) and for scenarios not yet covered in the CEM. Principles of person-oriented-modeling should be adopted to coherently aggregate risks associated with durable periods of exposure and changes in relative contributions of exposure sources over long periods of time. The Committee supported making those models available to EPA scientists.

The Committee recommended EPA calculate risk, even when there are uncertainties and necessary assumptions. That is preferable to discussions of risk scenarios with no accompanying quantitative estimate. Issues contributing to uncertainty can be presented, but some of the uncertainties can be minimized with better supporting information, current techniques of statistical examinations and mathematical analysis.

The Committee agreed that the American Healthy Homes Survey II (AHHS) II study was valuable and relevant for the formaldehyde assessments. However, the study provided more information and statistical perspectives than used by EPA. That, along with other studies for other exposure sites were recommended to EPA to improve the application of data and approach to the exposure assessments.

Impact of Emission Standards: Recent emission standards for new wood products are expected to reduce indoor formaldehyde concentrations, but ongoing monitoring is necessary to ensure these benefits are realized. Continuous assessment ensures that regulatory measures achieve their intended health benefits.

Comprehensive Evaluation of Indoor Sources: Indoor sources of formaldehyde should be comprehensively evaluated to provide a clear picture of potential health risks. This thorough approach is necessary for effective risk management and mitigation strategies.

The Committee delved deeply into the question of cancer assessment. Much of this discussion involved the consideration of the IUR to evaluate carcinogenesis. The majority of the information presented in session did not favor a IUR approach, and rather supported a threshold approach. The Committee recommended that the EPA consider the best available science to determine if a threshold or non-threshold approach is best for evaluating cancer, and if needed revise the Draft Human Health Hazard Assessment.

Question 6 – Ambient Outdoor Air Assessment

The ambient outdoor air assessment section examines the concentrations and effects of formaldehyde in the outdoor environment, considering both industrial and non-industrial sources. The Committee evaluated the assessment's adequacy in addressing environmental and public health risks associated with outdoor formaldehyde exposure.

The assessment of formaldehyde in ambient outdoor air provides many recommendations that include:

Relative Risk from Indoor Sources: While industrial emissions contribute to formaldehyde levels, indoor sources may pose a greater relative risk. Indoor exposures (including vehicles) require more robust assessment.

Environmental Monitoring and Regulation: Comprehensive environmental monitoring and regulation of formaldehyde precursors are essential to protect ambient air quality. The Committee recommended increased efforts to monitor and control formaldehyde concentration to ensure broader environmental health and safety. The Committee also recommended more robust assessment of formaldehyde exposure in ambient air, such as better use of Air Monitoring Technology Information Center (AMTIC) and other data sources to improve temporal and spatial consideration of exposure; expansion of scenarios; and better explanation of data handling, including non-detect data.

Interagency Cooperation: This area was one in which the Committee felt strongly that the evaluation could benefit from cooperation with other EPA Offices, such as the office of Air and Radiation.

Question 7 – Aggregate Assessment

The aggregate assessment section describes multiple pathways of formaldehyde exposure, that could be integrated to provide a comprehensive evaluation of risks from total aggregate formaldehyde exposure. Unfortunately, these exposures were not quantitatively aggregated, despite Committee members noting that there is a substantial amount and diversity of available data to support a probabilistic approach to evaluate aggregate exposure across different scenarios. The Committee reviewed the assessment's approach to qualitatively combine various exposure sources to understand the total impact on public health.

The Committee emphasized the importance of a holistic approach to formaldehyde exposure, integrating multiple pathways:

Perform a Quantitative Aggregate assessment. Ample computational tools exist to produce an aggregate risk evaluation for formaldehyde. This is needed to better define relative contributions from various exposures and to avoid the possibility that multiple single exposure scenarios fall below a risk threshold while the sum of exposures would, perhaps easily, exceed risk thresholds. These benefits would improve identification of situations where mitigation strategies may be needed.

Focus on Vulnerable Populations: Vulnerable populations, such as children, those in urban areas, and those at high risk for exposure through multiple pathways, should be given special consideration. This focus ensures that the most at-risk groups receive adequate protection against formaldehyde exposure.

Unified Risk Management Strategy: A unified risk assessment and risk management strategy should address both cancer and non-cancer risks. The Committee recommended using frameworks like RISK21 to enhance communication and transparency in risk evaluations. This comprehensive strategy is essential for effective public health protection and regulatory compliance.

DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS

1. HUMAN HEALTH HAZARD

Charge Question 1.1

As described in Section 4.1.2.1 of the Draft Human Health Hazard Assessment for Formaldehyde (U.S. EPA, 2024f), the HSRB reviewed the ethical and scientific conduct of four key studies used as the basis for draft point of departure (POD) derivation, and associated draft weight of evidence analysis (HSRB, 2023a, 2022). EPA considered comments received by the HSRB in revising the draft weight of evidence as appropriate. Please comment on the updated weight of evidence used to establish the POD for acute inhalation of formaldehyde and the application of an extrapolation/uncertainty factor for intraindividual variability as well as the characterization of the overall confidence in the value presented in the draft human health hazard assessment.

Response to Charge Question 1.1: Acute Inhalation Hazard Value

The Committee recognized the Environmental Protection Agency (EPA) used the *Draft Integrated Risk Information System* (IRIS) values, which were extensively commented on by the National Academy of Science, Engineering and Medicine (NASEM) (NRC, 2011) and the Human Studies Review Board (HSRB) (HSRB 2023a), but the current draft does not yet reflect these comments. Based on the EPA's response to questions raised by this Science Advisory Committee on Chemicals (SACC) during the May 2024 meeting, it is unclear whether the IRIS values will be finalized before the Agency's completion of the formaldehyde risk evaluation. Most Committee members suggested that the EPA finalize its IRIS assessment, incorporating the recommendations of NASEM. Some Committee members pointed out that the values should be re-evaluated before being used in this risk evaluation.

Some Committee members recognized sensory irritation as the most relevant and scientifically justifiable endpoint, although there was a lack of agreement that sensory irritation is an adverse health effect and therefore questionable as the basis for the point of departure (POD) in this risk analysis if identification of a frank adverse effect is needed rather than a protective exposure response.

Recommendations:

- **Review the approaches taken by other governmental authorities, which set exposure limits consistent with the best available science based on the weight of the scientific evidence (e.g., Acute Exposure Guideline Levels (AEGL), Canada (2021), EU).**
- **Clearly justify the selection of sensory irritation as an adverse effect and as the basis of the POD for use in this assessment.**
- **Clearly justify the selection of an uncertainty factor (applied to the POD of sensory irritation).**

Some Committee members recognized that sensory irritation is not conventionally defined as an adverse effect. Other Committee members recognized that sensory irritation could interfere with normal functioning of people engaged in certain tasks and POD values based on sensory effects could be useful to avoid worker decrements in function. Committee members who do not support the identification of sensory irritation as the basis for the POD also saw no need for the application of Uncertainty Factors (UFs). For those Committee members who support application of an UF to the

POD, the lack of pharmacokinetic differences for a direct-acting portal of contact toxicant supports a lower UF.

Recommendations:

- **Further clarify developing "peak threshold concentration levels" regarding the design of some of the key studies that expose subjects to short-term higher concentrations during a continuous exposure to a lower concentration.**
- **Use the lowest continuous concentration at which an effect was reported versus the peak concentration.**
- **Improve documentation of the Benchmark Dose (BMD) modeling for this study in the risk evaluation, including reporting the Benchmark Dose Response (BMR) and actual dose-response data that were used as the input for the BMD modeling.**
- **Utilize probabilistic methodologies within the Formaldehyde Risk Evaluation. Committee members emphasized that there were quantitative approaches to address uncertainties and probabilistic datasets (WHO, 2017). A similar approach was supported by recommendations from the National Research Council (2009).**

Updated weight of evidence used to establish the POD for acute inhalation of formaldehyde
Committee members discussed whether sensory irritation was an adverse effect before identifying the POD. Provided for context is the IRIS glossary definition of an "**Adverse Effect:** A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge."

As an example, AEGLs are used by emergency planners and responders worldwide as guidance in dealing with rare, usually accidental, releases of chemicals into the air. AEGLs are expressed as specific concentrations of airborne chemicals at which health effects may occur. They are designed to protect the elderly and children, and other individuals who may be susceptible." (https://www.epa.gov/aegl/about-acute-exposure-guideline-levels-aegls). In general, "mild sensory irritation" is not seen as being adverse for AEGLs and is considered on a case-by-case basis.

Sensory Irritation as the basis of the POD
Although sensory irritation is the most sensitive health endpoint, some Committee members pointed out that mild sensory irritation may not be an adverse effect and in addition, it is a reversible effect. Sensory irritation is also a subjective endpoint that can be influenced by odor (which is why the Lang et al 2008 study included a masking agent). The sensory irritation effects used to establish the POD could therefore reasonably be defined as not adverse.

Some Committee members pointed out that eye or other mucous membrane irritation can have adverse impacts if the worker or individual in the general population is hampered in the safe performance of their occupation or transportation, as examples.

Elaboration of Evidence/lack of Evidence for Sensory Irritation as basis of the POD
The Draft Human Health Hazard Assessment (HHHA) for Formaldehyde (U.S. EPA, 2024f), stated that "symptoms have been shown to occur within seconds at high enough doses (Andersen and Molhave, 1983)" without specifying how high is "high enough," further implying that time to symptoms is longer at lower concentrations. The U.S. EPA (2008) Draft AEGL document for formaldehyde states that 6-minute exposures at 1 part per million (ppm) caused slight to moderate eye irritation in a 6-minute study with sensitive human subjects (Bender et al., 1983). Descriptions of

onset of symptoms in the key studies in the Draft HHHA may not have been present. The findings of Bender et al. (1983) support the plausibility of noticeable eye irritation within 15 minutes (the risk characterization's exposure sample duration) in the range of the POD. However, at lower concentrations (e.g., after application of uncertainty factors), time to symptoms, if any, could take long enough that no effect would be observed during a "peak″ exposure.

At least one Committee member considered the rationale in the last sentence of the preceding paragraph as an improper application of uncertainty for predicting no effect during peak exposures. The use of an uncertainty factor implies the effects will be similar for some, perhaps sensitive individuals, at the lower bound concentrations. So, response times would be similar after application of uncertainty factors.

In the supporting study (Mueller et al., 2013), hypersensitive subjects perceive even clean air in a way that increases the Swedish Performance Evaluation System (SPES) score. Considered in the absence of any judgement on impacts of formaldehyde exposure, this reflects human variability in perception that has nothing to do with exposure—perhaps a nocebo-type effect, wherein test subjects anticipate a negative outcome from test conditions. For some people, it is impossible to eliminate this effect/perception at any level of formaldehyde (or other irritant airborne substance). Similarly, one of 20 subjects in Kulle et al. (1987) found exposure to control levels of formaldehyde (nominally 0 ppm) mildly irritating.

TABLE 1: Eye irritation reported by subjects for each Formaldehyde Concentration (Table 3 from page 328 of Kulle (1993))

HCHO (ppm)	Subjects (*n*)	Percent of Subjects Reporting Symptom[a]		
		None	Mild	Moderate
0.0	19	95 (9/9)	5 (1/0)	0 (0/0)
0.5	10	100 (4/6)	0 (0/0)	0 (0/0)
1.0	19	74 (8/6)	21 (2/2)	5 (0/1)
2.0	19	47 (5/4)	32 (2/4)	21 (3/1)
3.0	9	0 (0/0)	56 (3/2)	44 (3/1)

[a]Numbers in parentheses represent numbers (M/F) of males and females reporting symptom.

Kulle et al. (1987) and Kulle (1993) benchmark concentration lower bound (BMCL) (from the data set above) was based on mild eye irritation. Committee members proposed that the appropriate data set for BMD modeling is "moderate" eye irritation, where, moderate irritation is more arguably an adverse effect, while "mild" effects are not. Some committee members argue that moderate effects are not debilitating, so there is still no effect here. At least two Committee members suggested that the question is not debilitating effects, but rather adverse effects.

In the same study, other forms of irritation are also reported independent of formaldehyde concentration:

TABLE 2: Nose/Throat Irritation Reported by Subjects for Each Formaldehyde Concentration (Table 4 from page 329 of Kulle (1993)

HCHO (ppm)	Subjects (*n*)	Percent Reporting Symptom[a]	
		None	Mild
0.0	19	84 (9/7)	16 (1/2)
0.5	10	90 (4/5)	10 (0/1)
1.0	19	95 (9/9)	5 (1/0)
2.0	19	63 (8/4)	37 (2/5)
3.0	9	78 (6/1)	22 (0/2)

[a]Numbers in parentheses represent numbers (M/F) of males and females reporting symptom.

Evidence such as these examples call into question "mild" irritation effects as adverse in general. As acknowledged by the Agency in the Draft IRIS assessment, formaldehyde irritation effects may be mediated by neuronal receptors such as TRPA (a family of transient receptor potential ion channels, also known as Transient Receptor Potential Ankrylin). Formaldehyde activates the TRPA1 ion channel by covalent interactions resulting in pain (reviewed by NRC, 2011). This receptor also responds to other irritants including mustard oil, cinnamaldehyde, and metabolites of pollutants such as styrene, ozone, naphthalene, and acrolein. However, such chemical/receptor interactions are part of a sensory process and should not be considered the same as histopathologically detectable irritation (i.e., an inflammatory response) or an adverse health effect (also reviewed in NRC, 2011). The World Health Organization (2010) noted that the TRPA1-mediated response occurred quickly, so longer exposures (i.e., beyond the 4 hours in the chamber studies of Lang et al., 2008 and Mueller et al., 2013) are not anticipated to increase the response.

Importantly, the Draft HHHA for Formaldehyde (document 11; Regulations.gov) uses the peak concentration rather than factoring in duration of exposure. This is appropriate as Haber's Law does not apply in the case of formaldehyde. For sensory irritation, in particular, very brief exposures elicit the same intensity of response as longer exposures (as can be seen in the various controlled human exposure studies). As mentioned previously, this sensory irritation is reversible and goes away when exposure stops.

The supporting studies cited in the Draft HHHA (Liu et al., 1991 and Hanrahan et al., 1984) are of limited quality as they were observational epidemiology studies. However, the final four studies used by the EPA (Kulle, 1993; Kulle et al., 1987; Lang et al., 2008; Mueller et al., 2013), which involved intentional exposures and effect measures, were of high quality.

A definite adverse health endpoint should serve as the basis of the risk assessment for occupational exposures. Several committee members agreed that sensory irritation does not reflect an adverse health effect unless the sensory organs are overwhelmed to the point of being functionally impaired or objectively incapacitating. An alternative health endpoint might be histopathologically detectable irritation (i.e., an inflammatory response), where the vast body of animal study literature showing

tissue cytotoxicity would be relevant. Such studies include those emphasizing objective measurements of cell proliferation and cytotoxicity following short-term repeated dose exposures (Monteiro-Riviere and Popp, 1986; Monticello et al., 1991; Swenberg et al., 1983).

Note that at formaldehyde inhalation concentrations of 1-2 ppm (~1.2-2.4 milligrams per cubic meter [mg/m^3]), the rate of removal or detoxification of formaldehyde from tissues in the nose and upper airways remains sufficient to limit its accumulation in these tissues, preventing the occurrence of tissue irritation (Brüning et al., 2014; Golden, 2011; van Thriel et al., 2006). As exposure concentrations increase to or beyond 2 ppm, compensation, detoxification, and repair mechanisms will progressively be overwhelmed, and tissue damage and associated irritation or inflammation begins to occur, leading to cell damage to multiple cell types in the eye and nasal epithelia. This observable tissue irritation or inflammation is the most sensitive histopathologically defined adverse human health endpoint in the dose-response continuum.

Selection of POD

Committee members provided additional insight into the studies identified by the HSRB review for the selection of the POD. While there was no consensus by the Committe on whether sensory irritation was an adverse effect, there was consensus that effects are occurring at the point of entry, and data from these studies could be useful in supporting the selection of the POD.

The HSRB review of the formaldehyde (HCHO) study by Mueller, Bruckner, and Triebig (2013) stated:

- "For any response measured or symptom reported, this study did not observe conjunctival and nasal irritations at tested concentrations."
- Olfactory symptom score "…was also observed for control (background HCHO concentration) exposures. This indicates HCHO may not be the factor causing the changes of olfactory responses."

"Formaldehyde exposures to 0.7 ppm for 4 hr. and to 0.4 ppm for 4 hr. with peaks of 0.8 ppm for 15 min, respectively are not associated with chemosensory effects on hypo- and hypersensitive males. Therefore, a No Observed Adverse Effect Level (NOAEL) of 0.7 ppm as constant exposure and of 0.4 ppm with peaks of 0.8 ppm can be derived from this study" (Mueller, Bruckner, and Triebig, 2013).

A statistical re-analysis of the data presented in the Lang, Bruckner, and Triebig(2008) publication by the EPA found significant differences in conjunctival redness across all concentrations at 195 minutes. Some study endpoints (e.g., the blinking frequency, reaction times) could not be reproduced due to insufficient data presented in the paper. Specifically, the EPA's reanalysis did not support the finding of exposure-dependent increase in blinking rate although the correlation between eye irritation and blinking rate was confirmed in the presence of ethyl acetate. The re-analysis confirmed respiratory irritation at 0.5 ppm with 1 ppm peaks in the presence of ethyl acetate.

Recommendation:

- **Carefully reevaluate the available data to determine if 0.5 ppm or a concentration that is lower or higher should be used as a lowest observed adverse effect level (LOAEL) POD.**

Some Committee members concurred with the Agency's selection of a POD of 0.5 ppm based on studies by Kulle (1993) and Kulle et al. (1987), since elements of the scientific evidence show that a

lower POD should be applied for purposes of the Toxic Substances Control Act (TSCA) risk characterization.

The EPA characterizes 0.5 ppm as a no-observed-adverse-effect-concentration (NOAEC) and *also* as the lower confidence limit on a BMCL. Some Committee members recommended that, consistent with EPA guidance, benchmark dose modeling should be used whenever possible to determine a POD. The BMCL modeling in the Draft IRIS assessment documents that the appropriate estimate of the BMCL from Kulle (1993) and Kulle et al. (1987) is lower than the TSCA risk evaluation NOAEC of 0.5 ppm.

Some Committee members encouraged the EPA to more heavily weigh the Kulle (1993)/Kulle et al. (1987) studies as the basis for the candidate POD. The Draft formaldehyde IRIS assessment stated: "The BMD models did not account for the correlated measures between concentration levels (each participant was exposed to each concentration). Therefore, the 95% confidence limit for the BMC estimated by the model is too narrow to use as the POD. A factor of 2 was used to adjust the BMC to identify a lower estimate that approximates the BMDL" (EPA, 2022). The IRIS assessment divided the BMC of 0.69 ppm by "2" to derive the POD for Kulle (1993)/ Kulle at al. (1987), which equals 0.34 ppm.

The text presenting the POD selection uses the term "threshold" to describe the POD (EPA, 2024a). Even if the EPA-selected POD was characterized by study authors as a NOAEC or NOAEL, the BMD modeling demonstrates that a 10% elevation in symptoms may occur at lower doses, and other studies described by EPA also demonstrate effects at lower doses. As discussed in the EPA's benchmark dose guidance, a NOAEL cannot be interpreted as a level of exposure at which there is no effect. The NOAEL is a function of study design and is of little practical utility in describing toxicological dose-response relationships; it does not represent a biological threshold and cannot establish that lower exposure concentrations are necessarily without risk (EPA, 2024b).

<u>Application of an extrapolation/uncertainty factor for intraindividual variability</u>
Committee members did not reach consensus with regard to 1) the need or suitability for application of an uncertainty factor and 2) if an uncertainty factor is needed. Of the members supporting an UF some supported the use of "10" and others support the use of "3."

Committee members noted that the Agency used an UF of 10 for all controlled human exposure studies when one of these studies (Mueller et al., 2013) included a sensitive subgroup. With regard to an overall UF of 10, further justification is needed, in light of the fact that the AEGL-1 values do not use an UF.

<u>Comments on the Draft HHHA</u>
Application of an UF for interindividual variability is consistent with irritation reported by (Mueller et al., 2013) in hypersensitive individuals following exposure to 0.3 ppm with peak exposures of 0.6 ppm. It is also consistent with high variability across individuals reported in all controlled exposure studies. Although Kleinbeck and Wolkoff (2024) asserted that uncertainty factors >2 for human variability are not generally warranted for sensory irritation.

Some Committee members suggested that sensory irritation is not an adverse effect and there is no scientific justification to apply an UF to the POD. Other Committee members do recognize sensory irritation as an adverse effect and support the application of an UF for sensitive members of the

general population. While the Mueller et al. (2013) study included a sensitive young adult population, the population evaluated in the risk analysis is intended to protect the exposed population (consumer, indoor air, ambient air scenarios) including children and adults who may be more susceptible, justifying the need for an UF.

Some Committee members suggested that the intraspecies differences (UF_H) of 10 for the Mueller et al. (2013) study be reconsidered because Mueller et al. included members of a sensitive subpopulation. Although they do not represent the entire population of (hyper)sensitive individuals, the UF_H could be reduced to 3 or 1.

Recommendation:

- **Consider the application of an UF of 1 or 3 since the study populations consisted of individuals sensitive to formaldehyde.**
- **Carefully consider the use of UFs for the cases where sensitive populations were tested. Also ensure that UFs capture uncertainty in data sets.**

TABLE 3. Mean Symptom Differences (t_{180}-t_0) ± SE with Formaldehyde Exposure in Group II (n=9).[a] Table II from page 921 of Kulle et al. (1987))

	HCHO concentration, ppm				Linear[b] dose significance
	0.0	1.0	2.0	3.0	
Odor sensation	0.00 ± 0.00	0.22 ± 0.15	0.44 ± 0.18	1.00 ± 0.29	$p < 0.0001$
Nose/throat irritation	0.00 ± 0.00	0.11 ± 0.11	0.33 ± 0.17	0.22 ± 0.15	$p = 0.054$
Eye irritation	0.00 ± 0.00	0.44 ± 0.24	0.89 ± 0.26	1.44 ± 0.18	$p < 0.0001$
Chest discomfort	0.00 ± 0.00	0.00 ± 0.00	0.11 ± 0.11	0.00 ± 0.00	$p = 0.62$
Cough	0.00 ± 0.00	0.11 ± 0.11	0.00 ± 0.00	0.00 ± 0.00	$p = 0.11$
Headache	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.11 ± 0.11	$p = 0.33$

[a] Presence and severity of symptoms were scored as: 0 = none; 1 = mild (present, but not annoying); 2 = moderate (annoying); 3 = severe (debilitating).
[b] No significant nonlinear trends were detected.

Kulle et al. (1987) contains the same underlying study as Kulle (1993). Table 3, above, replicates Table II from Kulle et al. (1987) entitled "Eye irritation reported by subjects for each Formaldehyde Concentration." These standard error (SE) ranges are not unduly large and lack extensive variability. And these outcomes are subjective, self-reported data. At control and high, all subjects are in one or two bins for eye irritation. The dose-related effect of eye irritation is evident and progressive despite close dose spacing. Studies with inbred animals do not always show this level of consistency with objective data. For the Kulle (1993) eye irritation data, the BMDL is 0.502 ppm and BMD is 0.694 ppm (from the IRIS Supplemental Information):

Overall Confidence in the Value Presented in the Draft Human Health Hazard Assessment.

Committee members noted that one source of confidence that could be added to this section is that the POD was developed using human rather than animal (or other) data.

The statement that the POD based on Kulle (1993) and Kulle et al. (1987) emphasizes peak concentration (lines 625-626, page 19 of the Draft HHHA) mischaracterizes the POD because the selected POD was not based on a study that incorporated peaks of exposure. If the EPA intended to

remark on the fact that exposure concentrations were not extrapolated from one duration to another, Committee members suggested that the Risk Evaluation state that exposure concentrations were not "time weighted" or "normalized" or "extrapolated" to 8- or 24-hour periods.

Reliance on a POD with no extrapolation to lower doses, limits the use of the available science for the hazard assessment conclusions and refer the EPA to Chiu et al., 2020 and Nielsen et al., 2023.

"Intraindividual variability" means variability for an individual over time e.g., over multiple trials, whereas "interindividual variability" means differences among individuals in a population. This should be defined in the report.

Recommendation:

- **Define "intraindividual" variability", which appears in the Draft HHHA, line 623, page 19 and line 977, page 27.**

The key studies as delineated in the Draft HHRA (Table 4-2, page 18, Exposure Scenario: Inhalation; acute (15-minute duration)) were controlled and well documented. Additionally, there are only three acute studies listed in this key table (Kulle et al., 1987; Mueller et al., 2013; Lang et al., 2008), but Charge Question (CQ) 1.1 indicates that four studies were used to establish the POD.

Comments on specific sections/statement in Section 4.1.2.1, Draft Human Health Risk Assessment
Line 424-426, page 13, mentions effect concentrations reported in Andersen and Molhave (1983) that are not included in Table 4-1. It is advisable to check the accuracy of this figure.

Lines 512 and 523, page 15. The references to Andersen et al. for 1983 should be revised to Andersen and Molhave (1983). The appropriate citations for both listings are Andersen (1979) and Andersen and Molhave (1983).

Table 4-1, page 17, second cell in the far-left column is missing "Andersen and Molhave" directly in front of "1983."

Lines 589-590, page 17, should provide the appropriate reference citations for the two groups of studies mentioned.

Charge Question 1.2

The Draft Human Health Hazard Assessment used the chronic, non-cancer inhalation hazard endpoints and PODs derived in the draft IRIS assessment (U.S. EPA, 2022). As described in Section 4.1.2.2 of that assessment, IRIS chose a suite of impacts to the respiratory system from formaldehyde exposure and selected the overall reference concentration (RfC) of 0.007 mg/m3 (see Section 2.1.4 of the external review draft IRIS assessment). Uncertainty factors are embedded in the calculation of each candidate toxicity value supporting the RfC. OCSPP does not use an RfC per se. Instead, OCSPP estimates inhalation risk by calculating margins of exposure (MOE) with a POD that is compared to levels of concern derived from uncertainty/extrapolation factors. As a result, EPA used one of the PODs cited in the IRIS Table 2-3; i.e., 0.017 ppm or 0.021 mg/m^3 from Krzyzanowski et al. (1990) and its attendant total UF of 3, which is equivalent to the RfC of 0.007 mg/m^3. Please comment

on OCSPP's use of the chronic RfC from the draft IRIS assessment as described above and in Section 4.1.2.2 the Draft Human Health Hazard Assessment. In your comments, please consider the strengths and uncertainties of the underlying studies identified by the Office of Research Development (ORD) IRIS for the weight of evidence for chronic human health non-cancer hazard.

Response to Charge Question 1.2: Chronic, Non-Cancer Inhalation Hazard Value

Several Committee members disagreed with using the toxicity values in the current Draft Risk Evaluation (DRE) for formaldehyde, and the majority of committee members recommended incorporating NASEM and HSRB recommendations to revise the formaldehyde toxicity values reached by IRIS. Specifically, the approach of using the information from the Draft IRIS document, which has undergone NASEM review but has not yet changed, was considered an effective use of resources by some members of the committee, but others disagree. Many members expressed reservations about the specifics surrounding the value of using the unedited 2022 Draft IRIS document since it is not final and the comments from NASEM review have not yet been incorporated. The Committee also suggested that the current authors revising the IRIS document take the SACC's comments into consideration.

Questions were raised by the Committee regarding the sole use of the Krzyzanowski et al. (1990) study for determination of the POD including questions discrepancies between controlled human exposure studies such as Lang et al. (2008) and epidemiological studies such as Krzyzanowski et al. (1990). The Committee recommended that the EPA should consider all available data including the Krzyzanowski et al. (1990), Lang et al. (2008) and other studies for determination of POD. It was deemed appropriate to focus on respiratory effects for chronic POD given the high reactivity of formaldehyde.

There were some disagreements within the Committee about the uncertainty factors to be applied to the POD given that human data were used. Some members thought it was appropriate to use UF of 3 while others believe no UF is needed. As the application of UFs is essentially a policy decision, it will ultimately be up to the Agency to sort it out. However, the Agency should be clear on the uncertainties that support the use of each UF that is greater than 1, as well as the certainties that support UFs of 1. These explanations, if done routinely would help any future studies, if determined feasible, to address the uncertainties as they are described.

An important strength of the studies evaluated by IRIS is that they include potentially exposed or susceptible subpopulations (PESS) (e.g., children and pregnant people). The text describing how TSCA will use/apply the POD and UF of 3 is logically presented. The studies evaluated by IRIS include settings where formaldehyde was measured in schools and residences and two studies with controlled exposures. Other than the school-based studies, there were no studies from occupational settings.

Recommendations:

- **Summarize the acknowledged comments from HSRB and NASEM (lines 653-656, page 19 of the Draft HHHA) in the Weight of Scientific Evidence (WOSE) section. Provide a rationale for selecting the middle toxicity value of the three candidate values considered to develop a POD.**

- **Expand the discussion of the WOSE in Section 4.1.2.2 to cover key studies in detail and include a table of these key studies.**
- **Discuss the strengths and uncertainties of key studies in Section 4.1.2.2. Note the use of human data and the similarity of PODs as strengths.**

Editorial comments

- Line 4 of the charge (as it is placed at the beginning of this section on Charge Question 1.2) refers to Section 4.1.2.2 of the IRIS assessment, but the IRIS assessment has only two major sections. It is suggested that the text should be edited so that it refers to the human health hazard assessment. Line 12 of the charge refers to OPPT's "application" of the Reference Concentration (RfC) in the human health hazard assessment. It is suggested that it should refer to OPPT's "adoption" or "adaptation" (because OPPT uses the POD rather than the RfC) of the RfC.
- This document is heavily based on the Draft IRIS document, which has not yet been finalized, making it difficult to understand the review and selection process for RfC.

As pointed out during the HSRB review, the Hanrahan et al. (1984) study is of low quality and should not be the basis of a POD. Although it was proposed in the IRIS assessment as one basis of a candidate RfC, it is reassuring that the TSCA risk document did not include this poor-quality study.
There are major concerns raised about the Krzyzanowski et al. (1990) study, some of which were also part of the NASEM Committee peer-review. These concerns are as follows:

- Most participants (86.9%) fell in the lowest exposure group of <40 parts per billion (ppb). Thus, changes are based on a very small part of the study population.
- In this study, the outdoor formaldehyde concentrations were not measured. Further, it is impossible to tell how many of the participants were exposed to higher formaldehyde in the absence of Environmental Tobacco Smoke (ETS). The high proportion of smokers and ETS in the study complicates understanding the impact of formaldehyde on health endpoints.
- Asthma finding was only significant in homes with ETS (Table 4 of the study). Authors discount the impact of NO_2, without presenting NO_2 data. Although the main health endpoint of significance was Peak Expiratory Flow Rate (PEFR), only 4 asthmatic children lived in houses with formaldehyde values over 50 ppb. In nonsmoking adults living with smokers, PEFR was lower than in other nonsmokers. If analyses were performed separating ETS from non-ETS homes, only those with individuals living in homes with ETS show an effect. Original data from modelling was not available with the paper. These issues, along with a lack of transparency in modelling should have led to "low" confidence ranking from the EPA.
- The EPA concluded, justifiably, that Haber's law does not apply to formaldehyde. However, it is difficult to reconcile the impacts of formaldehyde in briefer controlled human exposure studies (Lang et al., 2008, using the sensory irritation endpoint) as compared to the Krzyzanowski et al., 1990.
- Airway resistance (Rtot), Peak Expiratory Flow (PEF), Forced Expiratory Volume in 1 sec. (FEV1), and Maximum Mid-expiratory Flow (MMEF) were examined in the Lang et al. (2008) study. No statistically significant differences in pulmonary function were observed (comparing baseline and post-exposure). The highest formaldehyde exposure in that study was 0.5 ppm (500 ppb) superimposed with four peaks of 1.0 ppm (1,000 ppb). In contrast, the EPA used Krzyzanowski et al. (1990) as the basis of the chronic noncancer inhalation POD of 0.021 mg/m^3 (17 ppb), using BMCL10 and adding an

uncertainty factor of 3 to derive a component specific RfC of 0.007 mg/m^3 (5.7 ppb). Even applying a 3-fold uncertainty factor to the 500 ppb exposures in the Lang et al. study would lead to a RfC of 167 ppb. This concentration is approximately 29-fold higher than that derived from the poorer quality Krzyzanowski et al. (1990) study. Similarly, the Kulle et al. (1987) study found no significant decrements in pulmonary function (FVC, FEV1, FEF25-75%, SGaw) following 3-hour formaldehyde exposures up to 3 ppm (3,000 ppb) with exercise, or 2 ppm (2,000 ppb) at rest. Applying a 3-fold uncertainty factor to the exercising subject exposed to 3,000 ppb would result in a RfC of 1,000 ppb. This concentration is approximately 175-fold higher than that derived from the Krzyzanowski et al. (1990) study. Without some justification for why individuals in the Krzyzanowski et al. (1990) study would be so much more sensitive to the effects of formaldehyde than individuals in the set of controlled human exposure studies (where no pulmonary impacts were found), it is difficult to accept the POD of 0.021 mg/m^3 (17 ppb) as being scientifically sound.

- In regard to pulmonary function: Krzyzanowski et al. (1990) study is inconsistent with the Population/Exposure/Comparator/Outcome (PECO) considerations relevant to adults-only conditions of use. The report is lacking in detail: average concentration 26 ppb; 83% of subjects in houses with average levels below 40 ppb, "few" above 90 ppb, "max" 140 ppb. No plot of PEFR decrement with formaldehyde is shown. Dose-response analyses limited to the low concentration data could potentially tell a different story. Area monitoring rather than personal monitoring was used, but since children generally spent more time in the home than anywhere else, home is likely the best surrogate for total exposure. As such, the exposure characterization for this study is not optimal.
- Cross-sectional epidemiological analyses are problematic and cannot be used to determine the cause of asthma (or any other disease for that matter). This is a limitation of the Krzyzanowski et al. (1990).

Concerns were raised by some Committee members regarding studies selected by ORD IRIS for chronic non-cancer hazards. These studies are mainly observational and unreliable for identifying a point of departure. The studies identified by ORD IRIS for the weight of evidence for chronic human health non-cancer hazard do not adequately address the chosen endpoint due to several limitations, including but not limited to the ability to determine causality specific to formaldehyde, confounders that were not addressed and including use of self-completed questionnaires instead of measured health effects which decreases the reliability of results. In addition, the use of an uncertainty factor is not necessary when study population for all studies were mainly sensitive, asthmatic children; therefore, sensitive populations have been addressed. Specific concerns are as follows:

- Krzyzanowski et al. (1990) reported "Significantly greater prevalence rates of asthma and chronic bronchitis were found in children from houses with HCHO levels 60-120 ppb than in those less exposed, especially in children also exposed to environmental tobacco smoke. Adult effects were seen mainly in smokers and seen only in the morning. Therefore, there was a confounding effect of tobacco smoke and other irritants connected to the smoke (e.g., particulate matter and nitrous oxide).
- The study by Venn (2003) found no evidence of an association between persistent wheezing illness and total VOCs, individual VOCs, or formaldehyde. They saw no effect of formaldehyde on asthma risk, unlike Krzyzanowski et al. (1990) where an increased risk was evident above 74 µg/m^3.
- There was no statistically significant exposure-response trend in the Annesi-Maesano (2012) study, and there was an unexplained inconsistency between results for

rhinoconjunctivitis and allergic asthma. There was also no statistically significant exposure-response trend for current asthma.

Additional specific comments on key studies used in IRIS are below. This refers to IRIS TR Table 2-11.

- Regarding allergy as an endpoint, PECO should exclude Annesi-Maesano et al. (2012) from consideration as a key study for an adult POD. The odds ratio for the EPA-designated LOAEL has a p-value of 0.1013 for differences between "low" and "high" tertile groups, which is not strong evidence of a dose-response relationship. The formaldehyde levels were for two weeks and the rhinoconjunctivitis occurrences in the past year, so the correlation is not optimal, but the study is given "high confidence." Furthermore, exposure monitoring is at the school, and children spend more time outside of school than at school, so the concentrations may not be representative of average daily exposures. As a result, the dose used for the dose-response relationship may not be appropriate and is of questionable validity.
- Venn et al. (2003): The subjects were school age children so relevance to adult risk is unclear, and this study should not be a key study for an adult POD. Area samples (at home) were used, rather than personal samples that would reflect a full day average (preferred for a chronic effect), but since home is the place where children spend the largest portion of their time, it is likely the most appropriate area monitoring data.
- Matsunaga et al. (2008): In the allergy study of Matsunaga et al. (2008), EPA interpreted the findings as an adverse effect of formaldehyde on eczema. The authors, however, found that the odds ratio difference between the lowest and highest tertiles was not statistically significant. Only when the data were collapsed to two groups of highly disparate size (90th percentile cutoff) did the 95th percent lower confidence interval of the OR exceed 1 (value of 1.01).
- None of the human health hazard evaluations had any information on lifetime, long-term personal histories of exposure versus current exposure so the time from elevated formaldehyde exposure to identifiable effect and how time and intensity relates to prevalence or severity is unknown.
- Sensory irritation as a possible acute endpoint is addressed in CQ 1.1. A chronic POD could also be based on acute effects, if appropriate. Given the preference for high-quality human data, EPA should consider using sensory irritation as the key effect for concerns pertinent to chronic exposure of adults and children to formaldehyde.

- Some Committee members noted positive aspects of the Krzyzanowski et al. (1990) study. Mainly, this study does include the susceptible human population - with documented rates of asthma and respiratory disease. According to the CDC, 7.7% of Americans have asthma, with 8.0% of the population reporting having current asthma between 2016 and 2018. This is higher in adults (8.0%) than in children (6.5%), and higher in females (9.7%) than males (6.2%). Also, the study did find adverse effects in adults and children. Finally, controlled human exposure studies do not adequately reflect the breadth of human response - particularly for susceptible populations who already have elevated rates of biologically relevant disease.

Recommendations:

- **Follow the HSRB recommendation to rely on Mueller et al. (2013) and Lang et al. (2008) to derive a POD consistent with the best available science using a weight of the evidence**

approach.

- **Strengthen its discussion of the limitations and of the uncertainties of the study.**
- **Consider using RISK21 to better communicate the data and differences in assessments. This suggestion is more completely addressed in the comments to CQ 1.4., internet address:** https://risk21.org/webtool/

Charge Question 1.3:

As described in Section 4.2 of the Draft Human Health Hazard Assessment, the available human, animal, and in vitro evidence on skin sensitization from formaldehyde exposure were reviewed. The ethical and scientific conduct of the two human studies used to support dose-response analysis was previously reviewed by the HSRB (HSRB, 2023b). In the development of the dermal hazard identification, dose-response analysis, POD selection, and weight of scientific evidence (WOSE) narrative HSRB comments were considered. The HSRB did not review the overall WOSE or the draft dermal POD. Please comment on selection of the dermal sensitization POD, draft WOSE narrative, application of uncertainty/extrapolation factors, and characterization of overall confidence.

Response to Charge Question 1.3: Dermal Hazard Value

Dermal sensitization PODs.

The Draft HHHA used human data, animal data, and computational data based on in-vitro results to develop a number of PODs. The "Sources of Confidence and Uncertainties" section uses "POD" in the singular, but it is unclear which POD EPA will actually adopt. Human data should be preferred when both high-quality human and animal data are available. Although techniques to integrate multiple data streams, such as the Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model should also be considered (Maxwell et al., 2024).

The assessment justifies using a POD based on two human studies of elicitation rather than induction of skin sensitization to protect sensitive subpopulations that are already sensitized to formaldehyde. In Flyvholm et al. (1997), the non-occluded tests demonstrated no definite positives up to 10,000 ppm. By contrast, in occluded tests, 19/20 positives were demonstrated at 10,000 ppm and the 20th person was positive at 5,000 ppm. Tests were read at 2 days, 3 days, and 6-9 days. This difference, which is not surprising, should inform the understanding of assumptions related to the use cases. The EPA's assessment did not justify using the Flyvholm data over the Fischer et al. (1995) data when the Fischer study had the lowest Benchmark Dose Lower Confidence Limit value at 10% (BMDL10); however, the Human Studies Review Board (HSRB) recommended that the Fischer study only be used in a supporting fashion. In addition, HSRB suggested the Flyvholm study 'could' be used as part of endpoint selection and derivation of a POD for elicitation of dermal sensitization from dermal exposure, given the limitations and recommendations provided by the HSRB are considered. It is not apparent that the EPA applied the recommendations by the HSRB to this assessment.

The assessment provides a good rationale for deriving a POD based on elicitation, but then goes on to develop a POD based on induction anyway. Elicitation is a more sensitive endpoint than induction and will protect sensitive subpopulations. Deriving an induction POD may verify that the elicitation POD is more sensitive, however the EPA's assessment provides no rationale for this derivation. The

assessment also provides no rationale for selecting an animal study to derive an induction POD when there are multiple human studies available. There are six human induction studies in the human predictive patch test database compiled by NICEATM and the German Federal Institute for Risk Assessment, which is available in an Excel file that includes references for each study (NICEATM, 2023).

As for the animal-derived induction POD, the health hazard assessment should provide the rationale for focusing on this one local lymph node assay (LLNA) study from Basketter et al. (2003) to derive an induction POD. There are more than two dozen LLNA studies in the peer-reviewed literature, including those mentioned in Hoffmann et al. (2018). The Organization for Economic Cooperation and Development (OECD) also heavily curated LLNA data to evaluate the defined approaches in Test Guideline 497 and found multiple acceptable studies (Annex 3 of OECD, 2023a).

The Committee disagreed with the HSRB's statement that any of the results of the human studies reviewed here were based on one individual. These results are based on the entire test population. However, there is agreement with the BMD analyses because they use data from the entire dose-response curve rather than a single endpoint such as the NOAEL or LOAEL, which are based entirely on the doses selected for testing. The EPA is commended on the use of BMDL to obviate the possibility of 1/20 response being considered a LOAEL.

Recommendations:

- **Provide the rationale for using Flyvholm et al. (1997) as the primary study for development of the elicitation POD.**
- **Provide the rationale for derivation of an induction POD as well as the rationale for using a single animal study when multiple animal studies and human studies are available.**
- **Provide the input data as well as the output data for the BMD models in Appendix B2.**

Weight of Scientific Evidence Narrative

There are several areas where the scientific WOE assessment should provide more information and documentation. The EPA relied on two studies; however, OPP and OPPT identified additional intentional dosing human studies through systematic review but did not rely on them to establish a POD. It is stated that some of the studies represented less sensitive elicitation threshold values than the studies chosen and therefore would not impact the selection of the POD. Other human intentional dosing studies tested at lower concentrations but were not informative in the determination of the POD for skin sensitization for various reasons including limited or no data on the quantitative analytical methods, no dose provided for skin loading (in the units used in the risk assessment for exposure) or limited study participant information (lines 863-868, page 24). These studies could, however, provide information in the WOSE and should be referenced and discussed in more detail in order to make transparent the rationale to use only two studies.

Section 4.2.1, page 20, of the Draft HHHA, indicates methanol is not a sensitizer and cites the European Chemicals Agency (ECHA) 2024. The ECHA's determination was based on animal studies, thus the statement should be qualified as such; has EPA searched for human skin sensitization data for methanol? It was agreed and understood that methanol could increase absorption of formaldehyde, but that was also the purpose of any vehicle used in these tests. Neat formaldehyde would not be applied in any of the tests evaluated.

Skin irritation

Within the Draft HHHA, lines 708-714, pages 20-21, the doses applied should be converted to micrograms per square centimeter ($\mu g/cm^2$) so that they can be readily compared to one another and with the doses applied for skin sensitization assessments. It is not readily apparent that the irritant effects are not consistent across studies, and it is also not apparent that the doses shown for irritation are larger than those for the skin sensitization studies. Line 710, page 20 should note that 37% formaldehyde was applied. Also, the Industrial Bio-Test Laboratory (IBT) study results should be qualified with some uncertainty due to the scientific integrity controversy at the IBT labs during the 1970s where fraudulent data were produced (Rosner and Markowitz, 2023; Schneider, 1983). This controversy was the motivation for the development and publication of Good Laboratory Practice (GLP) guidelines.

Skin sensitization and other immune effects

Within the Draft HHHA, lines 753-756, page 21, mentioned one LLNA study by Basketter et al. (2003). The health hazard assessment should provide the rationale for emphasizing one study when there were more than two dozen LLNA studies in the peer-reviewed literature, including those mentioned in Hoffmann et al. (2018). The OECD also heavily curated LLNA data to evaluate the defined approaches in Test Guideline 497 and found multiple acceptable LLNA studies (Annex 3 of OECD, 2023a). Results from the multiple studies in Hoffmann et al. (2018) were integrated to determine a reference EC3 value (the concentration required to induce a SI of 3 relative to the concurrent vehicle control) of 0.85% (212.5 $\mu g/cm^2$) for formaldehyde. The reference value used by OECD was an EC3 of 3.8% (950 $\mu g/cm^2$) on the more heavily curated data (Annex 2 of OECD, 2023a).

4.2.2 Identification of endpoints for dose-response and POD derivation

Section 4.2.2 of the Draft HHHA, page 22, indicates that skin sensitization is the most sensitive non-cancer endpoint with which to derive a dermal POD. This statement would be more convincing if all the doses for studies reviewed in the WOSE were converted to the same units so that the reader could compare the effect doses. Data presented for the Flyvholm et al. (1997) study were not adequate, and the number of subjects reacting at each dose should be provided.

Although LLNA doses are typically reported as % concentration, the Committee recommended converting doses in lines 889-890, page 24, to $\mu g/cm^2$ for comparability to the human studies.

Recommendations:

- **Within the Draft HHHA, provide a discussion of the available additional human studies.**
- **Provide a rationale for using a single animal study when additional animal studies and human studies are available for the induction POD.**
- **Convert all doses to $\mu g/cm^2$ for ease of comparison.**

Application of uncertainty/extrapolation factors

The Committee in general disagreed with the selection of an uncertainty factor of 10. The POD for elicitation does not require an intraspecies uncertainty factor (UF_H) of 10 because it was based on reactions of human adult subjects that were sensitive to formaldehyde, although impacts on children are not known.

When using LLNA data, it is well accepted that uncertainty factors for interspecies extrapolation are unnecessary. For example, Basketter and Safford (2016), state "the LLNA EC3 value, has been correlated directly with human experimental induction threshold data, which therefore has any interspecies variation implicitly built into it."

Recommendation:

- **Reconsider and justify the use of an UF_H of 10 that has been applied to the POD to derive the appropriate Margin of Exposure (MOE).**

Characterization of Overall Confidence

Under "Sources of Confidence and Uncertainties" beginning on page 26 of the Draft HHHA, the dermal PODs are characterized as being derived from an extensive dataset. However, the WOSE narrative does not show that because the extensive data set is not provided. Another source of uncertainty that should be discussed for the induction POD is that the LLNA does not measure the apical endpoint of skin sensitization. It measures a lymphocyte proliferation response in the lymph nodes that drain the site of application.

The text regarding the difference between induction and elicitation doses is missing a reference to the study by Griem et al. (2003) which compares induction and elicitation doses in humans for a number of chemicals, including formaldehyde (see Griem et al. (2003),Table 3, page 279).

Recommendations:

- **Incorporate discussion of an additional source of uncertainty for use of an LLNA to derive a POD.**
- **Consider the induction and elicitation doses in humans provided by Griem et al. (2023).**

Editorial Comments

- Within the Draft HHHA, line 693, page 20: the word "formaldehyde" at the end of this line is not needed if this sentence relates to a comparison of dermal exposure to air exposure of formaldehyde. The suggested edit is "Two observational epidemiologic studies investigated the association between formaldehyde dermal exposure and air exposure with adverse dermal effects." The text should also note which study involved air exposure and which study involved skin exposure.
- Within the Draft HHHA lines 753-755, page 21 should be revised because this text has conflated the LLNA stimulation index with the LLNA EC3, which is the concentration producing a stimulation index of 3. Thus, the sentence should be edited to read "Lastly, in an LLNA in 6- to 12-week-old CBA/Ca mice, formaldehyde application to the ear increased their stimulation index (SI) to three times the concurrent vehicle control, which is the threshold for a positive response~~)~~ (Basketter et al., 2003)."
- Within the Draft HHHA, line 782, page 22 indicates that formaldehyde was discussed in the chemical list in OECD No. 336 (OECD, 2023a). It was not discussed, but simply included in the chemical dataset (Annex 2) analyzed in the OECD document.
- Within the Draft HHHA, lines 784-786, page 24 indicate that the additional intentional exposure skin sensitization studies are in the systematic review protocol, however, the studies could not be located. The Committee recommended that the appropriate section of the systematic review protocol be noted.
- Within the Draft HHHA, line 935, page 26, Flyvholm is misspelled.

Charge Question 1.4

As described in Section 4.3 of the Draft Human Health Hazard Assessment available laboratory animal evidence from oral studies on formaldehyde were reviewed. Although OPPT reviewers initially identified uncertainties in several of the key studies when considered in isolation, EPA concluded that information across several of these studies when considered together can be used to support dose-response analysis and WOSE conclusions (U.S. EPA, 2024f). The draft human health hazard assessment includes identification of draft oral hazard effects and draft oral PODs. Please comment on selection of the oral POD, draft WOSE narrative, and characterization of overall confidence.

Response to Charge Question 1.4 Oral Hazard Values

General Comments

The EPA is commended for deriving a POD for chronic, non-cancer effects via oral exposures. ***The POD, draft WOSE, uncertainty factor calculations, and overall confidence are reasonable, given the available literature and IRIS analyses.*** Specific recommendations and comments are provided to strengthen EPA's oral hazard values.

The current formaldehyde risk analysis relies on the Draft Formaldehyde IRIS Assessment of 2022 that was reviewed by the National Academy of Sciences, Engineering and Medicine (NASEM) which issued a report in 2023. The IRIS assessment has not been updated since the NASEM report. Therefore, some Committee members comments may appear redundant to those in the NASEM report.

Committee members concurred that the point of entry action of formaldehyde is well documented. Less well documented is systemic distribution beyond the point of entry. Several of the comments reflect the need to justify the inclusion of target organs beyond point of entry. Some Committee members recognized that the focus on point of entry effects may minimize additional physiological effects, including allergies, immune system impairment, reproductive and neural effects. Discerning clear physiological outcomes is complex due to variations in animal model, design, carrier/stabilizing solutions, lifestage, and other factors, such as methods available for papers from the 1980's versus more recent studies.

The text presenting the POD selection uses the term "threshold" to describe the POD. Even if the EPA-selected POD was characterized by study authors as a NOAEL, symptoms/effects may occur at lower doses, and other studies described by EPA also demonstrate effects at lower doses. As discussed in EPA's benchmark dose guidance, a NOAEL cannot be interpreted as a level of exposure at which there is no risk: the NOAEL is a function of study design and is of little practical utility in describing toxicological dose-response relationships; it does not represent a biological threshold and cannot establish that lower exposure concentrations are necessarily without risk.

Selection of the oral POD

Animal studies span short-and long-term exposures, with potentially different routes of exposure, most commonly through oral exposure via water, diet or gavage and can produce a range of dose-related effects including behavioral and adverse health indicators. In regard to formaldehyde exposure, the specific adverse outcomes observed included adverse effects from the direct irritating and cytotoxic effect from formaldehyde in the skin respiratory system and stomach.

The three studies selected were the most appropriate for developing candidate PODs and the final POD selected was adequately supported by the discussion. Section 4.3.2, lines 1075-1076, page 29 of the Draft HHHA reminded the reader that portal of entry effects (i.e., gastrointestinal (GI) effects) would be expected for formaldehyde due to its high reactivity. Thus, GI effects are plausibly the most sensitive effects.

The Agency's POD determinations after dermal and oral formaldehyde exposure based on human and animal data generally seem reasonable. However, rating the two animal oral studies as uninformative (due to the lack of a water-restricted control group) may be too severe given that there is no evidence that reduced water intake can induce stomach pathology.

The detailed analysis supports the effects of formaldehyde exposure in studies in which animals were exposed by concentrations in drinking water. There is concern about a potential confounding factor of reduced water intake. A recent publication demonstrated GI tract effects of toxicants in addition to any effects of dehydration (Schreurs et al., 2023). Data summarized in Table 4-5, pages 33 and 34 of the Draft HHHA, demonstrated consistent effects of oral treatments. Table 4-6, page 35 is helpful in showing these consistent responses in GI effects with some variation in the POD, but all demonstrate effects despite differing treatment designs and treatment durations.

Recommendations:

- **Strengthen the justification for effects beyond local, point of entry effects.**
- **Consider life stage susceptibility, unless data support evidence of no differences in early life. Animal studies should be considered since outcomes from oral exposure in humans is not documented.**

Draft WOSE Narrative

While EPA mentioned several non-cancer outcomes, such as neurotoxicity, developmental toxicity, and reproductive toxicity, it stated that the data are insufficient. It would be helpful if the Agency provided more detail about this insufficiency.

Recommendations:

- **Strengthen the WOSE by providing the doses tested for all major effects considered in Section 4.3.1 beginning on page 27 of the Draft HHHA so they can be easily compared by the reader.**
- **Fully summarize why several non-cancerous outcomes (neurotoxicity, developmental toxicity, reproductive toxicity) data are insufficient.**

The Draft HHHA indicates that target doses were achieved as indicated in lines 1209 and 1219 on page 32. The target doses were adjusted based on stability and water consumption, which made the adjusted doses lower than the target doses for the 2-year study. Thus, EPA should review and revise their statement that the target doses were achieved (on lines 1209 and 1219 of page 32).

The administered doses were emphasized in bold type. However, the narrative in line 2010 in the Draft HHHA, page 32 should be more specific and replace "this is the NOAEL" with the adjusted NOAEL (e.g., "the NOAEL is 15 mg/kg/day"). The same adjustments should be performed for the LOAEL (line 1216, page 32). These revisions would match the NOAEL and LOAEL in Table 4-5, page 33.

Recommendations:

- **Clarify the NOAEL and LOAEL in the Draft HHHA.**
- **Revise the narrative for "Reproductive and Developmental Effects," page 28, to state that developmental effects were the most sensitive adverse effects for methanol exposure per the current IRIS file (https://iris.epa.gov/static/pdfs/0305_summary.pdf). As an alternative to this revision, provide a reference citation for the statement that methanol may contribute to developmental effects (lines 1045-1046, page 28). There are data supporting the potential for exposure and adverse effects during development (Duong et al., 2011; Pidoux et al., 2015).**

Several Committee members suggested a reevaluation of systemic distribution and resultant toxicity is unlikely since formaldehyde exerts its effects locally because of its high reactivity. Systemic toxicities such as neurotoxicity, developmental toxicity, and reproductive toxicity are unlikely.

Some Committee members suggested that EPA reconsider the use of oral hazard data in the human health risk assessment. These Committee members posited that the potential exposure to young children from plastic products and via pesticide residues in food, and formaldehyde in drinking water; and, noted that some of these potential exposure routes are currently considered outside the current scope of the draft report. These Committee members recognized that other federal agencies (Food and Drug Administration, Consumer Product Safety Commission) can regulate plastic products in food storage and distribution, pesticides, and pacifiers/baby bottles/toys.

Characterization of Overall Confidence

Committee members noted that the "sources of confidence and uncertainties" section on page 36 of the Draft HHHA was generally well presented.

One important limitation missing from page 36 of the Draft HHHA is that no human studies were available from which to derive a POD. This limitation should also be mentioned at the beginning of Section 4.3.1 of the Draft HHHA, page 27. The section on "Sources of Confidence and Uncertainties", (page 36), should also provide a citation for the statement that "methanol may contribute to developmental effects." A rating of "moderate" may be more appropriate especially since one of the oral studies did have a water-restricted control group and found no stomach pathology.

The EPA's assignment and justification of an Uncertainty Factor of "30" is presented Table 4.7 (page 39) of the Draft HHHA, based on two studies in rats. The WOSE is based on drinking water treatments in rodents. Despite some technical issues, GI tract effects were clear in a controlled 28-day study. Some Committee members suggested that the text needed to reflect data that require characterization of the POD at appropriate sensitivity with life stage. Also, characterization of developmental stages potentially more susceptible, with an explanation as to whether rodent models are predictive of effects in infants/children, is warranted (Thrasher and Kiburn, 2001; Duang et al., 2011).

Specific Comments and Recommendations for the Draft HHHA

The study by Abd-Elhakim (2016) should not be characterized as a single dose study (line 1031 of the Draft HHHA, page 28). Because formaldehyde was administered for 60 days, it was a repeated dose study that used only one exposure concentration. A single dose study would be an acute study.

Within the Draft HHHA section 4.3, 4.3.1, lines 997-999 and 1005, page 27, although the interpretations of these studies may appear complicated, they are interpretable and can be informative as well as providing additional confidence of negative results since most of these studies are high dose studies. Using data to predict negative risk is an approach used in drug evaluation. (Van der Laan et al., 2016, doi:10.3389/fmed.2016.00045).

Immune Effects

Line 1022, page 28, Immune effects. Hematology, especially red blood cell (RBC) parameters, are not directly associated with evaluating immune response.

Reproductive and Developmental Effects

Line 1042, page 28. A justification is needed to associate reproductive and developmental responses with the proposed treatment related effects to differentiate from nonspecific high dose treatment related effects from the gastric irritating effects of formaldehyde causing general malaise versus chemical specific responses in these tissues. The chronic studies show no histologic changes in the reproductive tract tissues. Based on the direct macromolecular interaction of formaldehyde with the initial site of exposure, justification for how formaldehyde would get to the target site and produce the associated responses is warranted.

Some Committee members requested that the EPA consider lifestage susceptibility as an important topic unless data provide evidence that support a conclusion of no differences for early life stages. An example of potential adverse effects on embryonic cardiac development can be found in Zhang et al., 2021.

Neurologic effects

Line 1065, page 29, as stated above, based on the direct macromolecular interaction of formaldehyde with the initial site of exposure, the Committee found that justification is needed to describe how formaldehyde might reach the target site and whether the associated responses are specific to formaldehyde.

Section 4.3.2

Line 1090-1091, page 29. Committee members agreed that the Til et al. (1989) and Civo Institute TNO, (1987) studies are useful. Perhaps the predetermined criteria in the Systematic Review Protocol are too restrictive and should be re-evaluated to make them more relevant.

Line 1135-1141, page 3. The predetermined search criteria in the Systematic Review Protocol should be adjusted. The decreased water intake in Til et al. (1989) and Civo Institute TNO (1987) is a consequence of other factors and has no impact on the interpretation. Refer to Hard et al. (2000) (DOI:10.1093/toxsci/53.2.237) for a similar consideration. Chemical palatability or sore stomachs can impact food and water intake, but one can determine a treatment related effect or lack of an effect.

Line 1161-1171, page 31. The discussion should have been why there was decreased water intake. Decreased food intake and the oral irritating effects of formaldehyde could have decreased water intake, but the effects of treatment still occur and should not have been discounted.

Line 1167, page 31 “While the results of the 28-day study cannot be directly extrapolated to the longer duration and increased severity of water restriction in the chronic studies, it does provide evidence that the gastrointestinal effects seen in the histopathology are treatment-related”. These shorter term responses can be extrapolated to the longer term effects from a direct acting gastric irritant and continued exposure for an additional 23 months would only exacerbate the effects.

Line 1207-1214, page 32. EPA should consider that 25 mg/kg/d be a NOEL and 50 mg/kg/d be considered a NOAEL as the mild effects in the forestomach of a single animal could be considered adaptive and not adverse.

Line 1238-1239, page 32. OPPT should reexamine its procedures regarding usefulness of data and not arbitrarily exclude studies.

Page 35

Subchronic and Chronic POD Derivation – EPA should consider whether data are adequate for BMD modeling and if so, is there an advantage to conducting the analysis.

Lines 1154-1159, page 31, mention stability and water intake issues that are further discussed in the next two paragraphs. A committee member suggested that the subsequent two paragraphs are sufficient and that the text in lines 1154-1159 is not needed.

Line 1157, page 31, should provide citations for the “other studies” to which it refers.

A Committee member provided an example of using the RISK21 (www.risk21.org) framework approach to enhance communication of conclusions in a sample plot embedded file. This publicly available tool, developed through a Health and Environmental Sciences Institute (HESI) collaboration of which multiple government scientists were instrumental contributors, including staff from the EPA, should be considered as a very useful tool to improve communication to senior leaders within the agency as well as the general public. The OECD, Health Canada, and the Chinese Food Safety Authority endorse this framework tool. The Chinese Food Safety Authority routinely uses RISK21 as their primary decision support tool.

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2. WATER AND LAND PATHWAY

Charge Question 2.1

As described in Section 2 of the Draft Chemistry, Fate, and Transport Assessment for Formaldehyde (U.S. EPA, 2024b), available data show that formaldehyde rapidly undergoes chemical reactions including nucleophilic addition and hydration to form methylene glycol in water. Further polymerization of methylene glycol to form oligomers of various chain lengths—mainly low molecular weight poly(oxy)methylene glycol. Formaldehyde is also expected to undergo reactions with soil particle surfaces. Similar reactions in biosolids are expected. In dry soils, formaldehyde is expected to volatilize. All these considerations support negligible amounts of formaldehyde in soil or water from TSCA conditions of use. Therefore, both the Draft Environmental Risk Assessment and the Draft Human Health Risk Assessment conclude no risk from formaldehyde exposure in water and soil to aquatic organisms and humans (U.S. EPA, 2024b, e, g). Please comment on the draft WOSE narrative that concludes negligible exposure to aquatic organisms, terrestrial organisms, or humans

via the water and land pathways. In your comments, please consider the strengths and uncertainties of the underlying data.

Response to Charge Question 2.1

To evaluate the charge, the Committee reviewed the *Draft Environmental Hazard Assessment* and the *Draft Environmental Exposure Assessment for Formaldehyde*. The Committee disagreed with each of the following conclusions from the *Draft Environmental Risk Assessment for Formaldehyde*:

- No risk to aquatic organisms as formaldehyde does not persist in water and exposure is not expected;
- No risk to terrestrial organisms through soil exposure as formaldehyde does not persist in or on land and exposure is not expected;
- No risk to terrestrial mammals through inhalation as air concentrations are at least an order of magnitude lower than the most sensitive toxicity value;
- No risk to other terrestrial taxa, even though no inhalation toxicity data are available for other terrestrial species, as there is at least an order of magnitude difference in the toxicity and exposure for mammals; and
- No risk to plants from formaldehyde exposures in ambient air because air concentrations are seven times lower than the most sensitive toxicity value.

The Committee disagreed with the *Draft Environmental Hazard Assessment* assumption that formaldehyde is not expected to be detected or to persist. EPA Region 10 (EPA-910-R-17-005) does report discharges containing formaldehyde from hatcheries. Exposure to aquatic systems critical to endangered salmon has been measured at a screening level. It is known that formaldehyde degrades to methylene glycol and paraformaldehyde. These chemicals are also toxic, or a QSAR predicts toxicity, as demonstrated in the Hazard Assessment document. Therefore, the degradation of formaldehyde will add to the toxic loading of the receiving system until further physical or biological transformations occur. The Committee did not find a study measuring those compounds as a result of the input of formaldehyde in receiving waters. Furthermore, the effects assessment for fish (see response to CQ 2.2) reports only concentrations of all formaldehyde related compounds and not formaldehyde alone. Using this transformation consideration for the toxicity tests included in this risk evaluation would reach an exceedingly low toxicity concentration threshold for formaldehyde in water.

Recommendation:

- **Assess the release of formaldehyde to water and include a high centile exposure estimate in the risk evaluation.**

The exposure document also states that 150,000 kg/year of formaldehyde is released to surface water and 2,000,000 kilograms (kgs) to wastewater treatment facilities. While formaldehyde may degrade, the degradation products themselves are toxic. The Committee assumed these loadings would give similar values to the degradation products.

The *Draft Environmental Exposure Assessment for Formaldehyde* should, at a minimum, include the range of formaldehyde concentrations in water that were excluded from the current draft of the document. If all monitoring data that show formaldehyde in water are not used due to low confidence in analytical results, more monitoring data are needed; specifically at the facilities where detects were

found and discharges are known to occur.

Recommendation:

- **Report the measured data for formaldehyde in water and the number of data points that are below detection limits along with the detection limits.**

L326 in the *Draft Environmental Exposure Assessment for Formaldehyde*: There is insufficient information presented here to draw any conclusion, much less one that states that negligible formaldehyde concentrations are present in water. If inefficient Wastewater Treatment Plants are known to remove 58% of formaldehyde, then why would we expect a natural system to be any better?

L319-327 in the *Draft Environmental Exposure Assessment for Formaldehyde*: This approach is contrary to the standard approach for TSCA review. If there are no monitoring data, then the *Exposure and Fate Assessment Screening Tool* (EFAST) modeling of release data would provide a conservative estimate of exposure. If those concentrations are considered overestimated by the regulated industries, then they have the opportunity to provide monitoring data to demonstrate in-stream (or lake or estuary) concentrations.

Recommendation:

- **If measured values are not used for the exposure assessment, then use EFAST with output estimates as the EPA has similarly completed with other Risk Determinations/Evaluations and incorporate previous SACC comments regarding the need to ensure conservatism when data are not available or of adequate quality to be used. In the absence of monitoring data, this conservatism would include, for example, 58% or some low centile of formaldehyde removal by Wastewater Treatment Systems.**

In the human health atmospheric modeling, formaldehyde was found to spread from facilities and generate exposure to human populations. Such transport does not seem to be considered in the environmental exposure analysis. Many important environmental endpoints exist in these environments, including protected species of birds, mammals, plants, and insects that are critical to pollination.

Specifically, potential adverse outcomes for aquatic species can be due to high concentrations that can have toxic effects. Non-lethal effects such as on growth and more long-term on reproduction, lifespan, and metabolic function with implications for disease resistance can be highly damaging to these aquatic populations. The assumption is that formaldehyde, paraformaldehyde, and other products are primarily irritants. Although this is the case, there can be other effects due to the cross-linking properties of formaldehyde actions. Unfortunately, there are no publications that addressed other toxicants in the environment and few that document the direct effects of these chemicals on wildlife, aquatic and terrestrial. Given the gap in information, the temptation to conclude no measurable effects is understandable, but actual data (traditional or new approach methodology (NAM) are needed before such a conclusion can be reached. In the future, there may be additional data that allow for an assessment of potential adverse effects on aquatic and terrestrial organisms. Finally, the response of organisms to formaldehyde and associated products is likely to be based on conserved physiological mechanisms, meaning that similar adverse outcomes occur in humans and other vertebrate species. The conserved nature of these responses would allow NAMs to be used for determining adverse effects of formaldehyde.

In addition, the atmospheric transport pathway may lead to exposure to agricultural resources such as cattle, birds, and crops. It does not appear that such exposures or effects were considered.

At the end of section 2.4.1, the overall conclusion was that uncertainties are not expected to impact the draft risk assessment conclusions meaningfully. No quantitative probabilistic analyses are presented to support this conclusion. Given this review and the review for the Hazard and Risk assessments, the EPA should revise the assumption of: no risk and, therefore, uncertainty is not an issue.

Several Committee members suggested that probabilistic approaches be required throughout the Risk Evaluation. One Committee member stated that Weight of Evidence approaches (WOE) must be viewed with caution when considered as part of a probabilistic risk assessment. The WOE compares relative evaluations of information, and while they may indicate a cause-effect pathway they are not quantitative, and the uncertainties are difficult to evaluate. Further, the uncertainties exist because of the lack of definitive information. Other Committee members strongly supported the WOE (WOSE) approach.

Editorial Comment
L309-313, page 13, in the *Draft Environmental Exposure Assessment* for Formaldehyde: The link for EPA 2024c connects the reader to the document that contains the reference (*Draft Environmental Exposure Assessment for Formaldehyde*). The reference needs to be repaired.

Charge Question 2.2

As described in Section 3 of the Draft Chemistry, Fate, And Transport Assessment (U.S. EPA, 2024b) and Section 2 of the Draft Environmental Exposure Assessment (U.S. EPA, 2024d), exposure to formaldehyde transformation products is not expected as these products are highly reactive and there are limited data to corroborate presence of these residuals in water and soil. As such, transformation products of formaldehyde were not quantitively assessed for aquatic organisms or terrestrial organisms. Similarly, humans are also not expected to be exposed via the water and land pathways as described in the Draft Human Health Risk Assessment for Formaldehyde (U.S. EPA, 2024b, d, e, g). This approach was taken because of the highly reactive nature of the transformation products and a lack of data to corroborate presence of these formaldehyde residuals in water and soil (U.S. EPA, 2024e). Please comment on the strengths and limitations of this approach.

Response to Charge Question 2.2

The *Draft Environmental Hazard Assessment for Formaldehyde* is a strong review of the literature and included an evaluation of the toxicity of formaldehyde degradation products. The Committee appreciated the review of the information, but an accurate estimation of the toxicity of formaldehyde is hampered by the historical design of toxicity tests and data evaluation. The Committee noted that the approach that EPA used to assess formaldehyde risks is not probabilistic, and probabilistic assessment is the current state of the science for risk evaluation.

Table ES-1, page 6 reported results either as ECX, LC50s, or NOAECs/LOAECs. EC50 values are derived from a regression model and consider the entire exposure-response curve. LOAECs and

NOAECs are calculated using Analysis of Variance (ANOVA) with a multiple comparison test. The values are those chosen to be tested by the experimenter and do not describe the continuous nature of the exposure-response function.

Reporting styles in the literature, presented challenges for evaluation of reported data for a state-of-the-art probabilistic risk assessment. In the regression case, it is unclear how many concentrations were tested and the breadth of the tested range. Also, an LC50 value is one that would devastate populations of fish, wildlife, and other species of value. The Committee preferred an LC20 be reported along with data describing the concentrations tested and the equation for the regression. Selection of a more conservative LC value (LC05 to LC20) has been recommended by the SACC in previous reviews. Confidence intervals for the regressions should also be reported.

In the case of ANOVA multiple comparisons, toxicity is more difficult to evaluate without the accompanying datasets. Rarely are data supplied in publications and the statistical power of the study design coupled with the analysis type reported.

The number of studies examined represents a broad range of species and is to be commended. Many of the datasets are from the 1970s to late 1990s when detailed reporting of data and the easy computation of regressions and even ANOVAs could be challenging. Limitations of the dataset adds to the uncertainty, but these limitations are common in many toxicity tests. However, the limitations add to the overall analysis's epistemic uncertainty.

The inclusion of the species sensitivity distribution (SSD) for the fish species was informative. The HC5 value for acute exposure appears to be in the range of 11.2 mg/L and is based on a few species. As above, a source of uncertainty is using values generated from the ANOVA-multiple comparison data analysis.

Toxicity values for a range of terrestrial species are not included. Toxicity studies with mammals and birds related to wild species can be challenging and costly. As is typical, no studies have been reported examining potential changes in aquatic or terrestrial community structure. The Committee did not discover any relevant studies. However, mammalian studies are reported in the human health assessment and could improve the assessment for terrestrial wildlife.

Table A.4, page 32 is a good summary of the various uncertainties in the hazard evaluation. The acute aquatic vertebrate assessment (fish) is the most robust (least uncertainty). For the risk assessment of valued species (commercially important or threatened and endangered), chronic assessments are usually the key to estimating risk to populations. That information is not presented.

Draft Human Health Risk Evaluation

Committee members were not in agreement that the information presented in the Exposure and Hazard supported the conclusion of the risk evaluation that no risk occurred. The draft risk evaluation relates to the discontinuity of formaldehyde concentration specification in toxicity studies compared to formaldehyde considerations in water. For the draft exposure assessment of formaldehyde in water, the EPA assumed that virtually all formaldehyde hydrolyzes or polymerizes (*Draft Environmental Hazard Assessment* L238-240, page 10). Thus, measured formaldehyde concentrations would be negligible. However, in most toxicity test evaluations, formaldehyde exposure was calculated from the preparatory formalin solutions' total formaldehyde, methylene glycol, and polymeric forms (Tables 2-3 to 2-9, pages 13-18). These exposure and effect data cannot be compared in this way. If

the total formalin values are used in toxicity determinations, the assertion that formaldehyde hydrates in water is moot in the aquatic exposure assessment. The inclusion of all formaldehyde and associated glycols and polymers in the evaluation of toxicity tests requires that similar assemblages of formaldehyde related compounds be considered toxic when present in the environment. If an aqueous solution of 5 mg/L formalin causes toxicity, then that must be compared to measured (or modeled concentrations) aqueous formaldehyde + methylene glycol concentrations in the environment. Thus, the entire premise of no exposure within the risk assessment is fundamentally flawed and is not scientifically supported.

The Committee noted that there are ways to use measured hydration and dimerization rate constants to estimate the amount of formaldehyde in an aqueous solution. When considering Figure 3.1 in the Formaldehyde DRE, formaldehyde kinetics favor the production of methylene glycol. However, the reverse reaction is not considered in this risk determination. When considering both reactions rates, the equilibrium constant for formaldehyde producing methylene glycol has a K_{hyd} of 2100 at a pH of 6.5 (Rivlin et al., 2015). Furthermore, the dimerization rate is a bimolecular process, as it is concentration-dependent and is not expected to be rapid at environmentally relevant concentrations. In other words, two formaldehyde molecules are required for dimerization to proceed, and lower concentrations lower rates in a geometric, not linear fashion. Dimerization has a K_{dimer} of 5.4-6.5. Therefore, all of the formaldehyde will not be depleted. Overlooking these facts illuminates one of the challenges with using formulation chemistry (which includes percent concentrations) when attempting to predict environmental behaviors, where concentrations are considerably lower. Data by Rivlin was obtained at 2.4 M (72 mg/L) formaldehyde, which will increase formaldehyde depletion relative to environmental systems containing lower formaldehyde concentrations. It should be noted that these kinetics need not be considered if the EPA directly compared exposure and effect data using the sum all formalin related compound.

Formaldehyde consists of a Henry law constant (Ca/Cw). At 22°C and 50 g/L, the dimensionless value is $1.06x10^{-5}$, increasing to $2.22x10^{-5}$ at 40°C. There is also a value of $1.55x10^{-5}$, measured at formaldehyde concentrations of 10 g/L and 22°C. This can neither be ignored nor assumed to be a one-way transport process. It is at an equilibrium. Thus, atmospheric formaldehyde may partition into water, which the DRE does not consider.

DasGupta et al. (2005) measured 60 ug/m^3 of formaldehyde in ambient air within greater Houston, Texas. In the absence of direct formaldehyde inputs to water, equilibrium of this concentration with water would allow aqueous formaldehyde to exist at concentrations exceeding 5 mg/L. The Agency's estimation of formaldehyde in outdoor air is similar to that of Dasgupta et al. (2005). Both of these measures of airborne formaldehyde allow prediction of formaldehyde concentrations in water that exceed the toxicity values described in this report (Figure 1, page 27 below). In the absence of monitoring data, these exposures are part of total risk and must be considered as such. The SACC has repeatedly identified the need to correct these types of inconsistencies that improperly reduce exposure estimates.

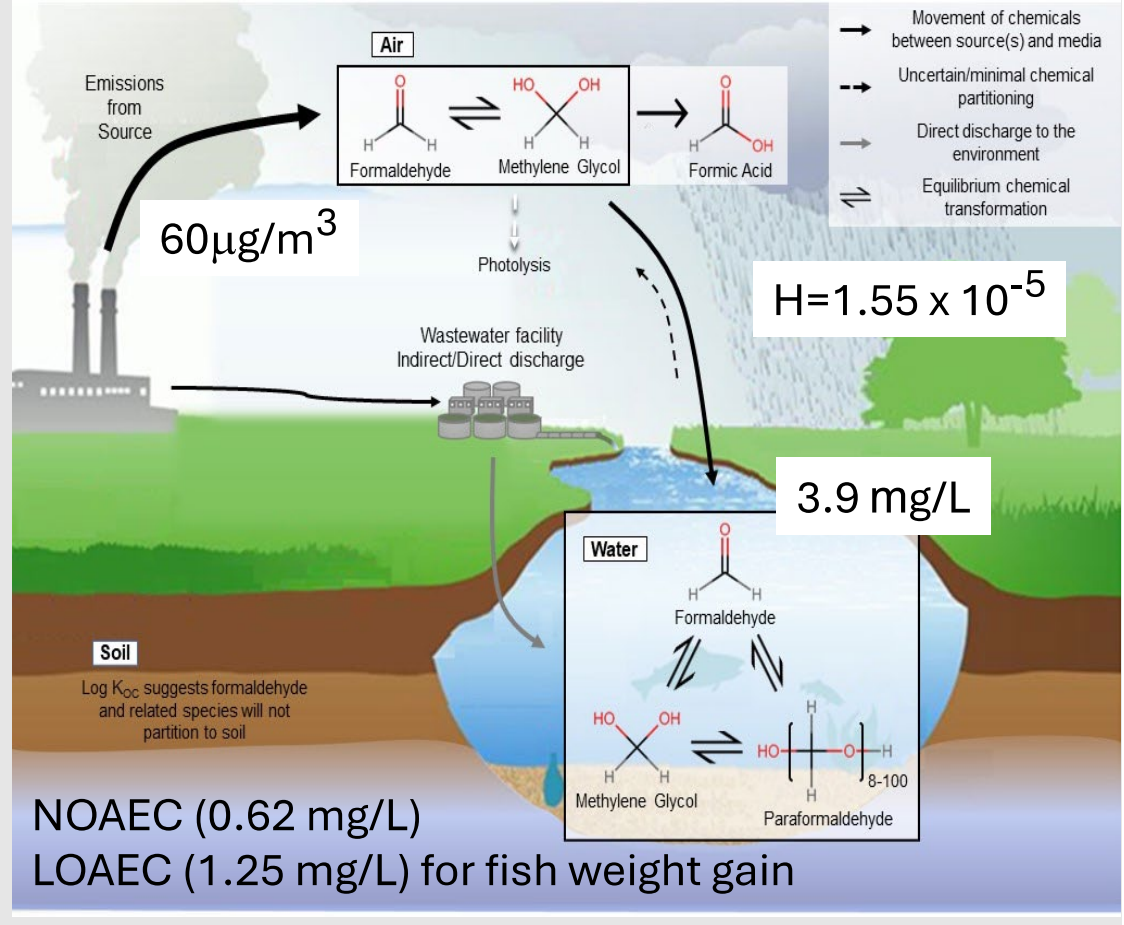

FIGURE 1: Estimation of equilibrium formaldehyde concentration in water given an observed concentration in the atmosphere. As modified from EPA's Environmental Exposures presentation made during the SACC Public Meeting

Comment on specific section/statement in the DRE

L621: The lack of comparison of formaldehyde concentrations in the environment to the large amount of toxicity threshold data described in the Hazard assessment cannot be justified without empirical monitoring data. There is no basis for the statement that there is high confidence in no risk to aquatic receptors. This claim also holds for terrestrial organisms. Given that there are often wildlife refuges and other protected areas around industrial areas, there is likely exposure due to atmospheric transport.

Uncertainties with the exposure to formaldehyde

Demonstrating no risk is a challenging task; as is proving a negative. To arrive at this conclusion, the assumption is that there is no probability of an effect on an endpoint as defined by an entity and the attribute. In this case there are several uncertainties with the exposure to formaldehyde, exposure to the degradation products, and sensitivity to the receptors, and there was not an explicit statement of the endpoint. What is the definition of the endpoint in this evaluation? Is it not a net effect on any species (unlikely), and is it no change to populations of valued or threatened and endangered species? Is it a change to aquatic or terrestrial ecosystems? These definitions may also differ depending on whether it is a TSCA, Federal, Insecticide, Fungicide, and Rodenticide Act (FIFRA), or state/tribal agencies. There is no consideration of atmospheric transport as there is in the human health

assessment process. If humans can be exposed via this pathway, so can terrestrial and aquatic wildlife.

The Committee noted that the methodology relies on a deterministic approach. The current state of the art is using probabilistic tools to describe the range of outcomes better and evaluate the impacts of various uncertainties. Probabilistic approaches are not limited to research questions but are now expected for risk assessments of many different types.

Recommendations:

- **The original assessments in this report are limited because they are not probabilistic, they should include atmospheric exposures to wildlife, and atmospheric as a mode of transport to aquatic systems.**
- **Determine a means to translate environmental exposure estimates to laboratory exposure data. The current assumption that there is insufficient "free" formaldehyde in water is unacceptable given the lack of measuring this in reported toxicity tests.**

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3. OCCUPATIONAL ASSESSMENT

Charge Question 3.1

To assess occupational inhalation exposures for formaldehyde, workplace inhalation monitoring data from governmental agencies such as the Occupational Safety and Health Administration (OSHA), monitoring data found in published literature, and other monitoring data submitted to the Agency were considered. As described in Section 2.5.1 and Appendix E of the Draft Occupational Exposure Assessment (U.S. EPA, 2024i), monitoring data from OSHA with sampling duration greater than 5.5 hours were used to estimate the 8-hour time-weighted average exposures. It was assumed that for any unsampled time, the exposure was zero. Please comment on the strengths and limitations of this approach and underlying assumptions for estimating full-shift exposure concentrations from the OSHA data. In your response, please consider the available monitoring data and if there are other potential sample durations (e.g., 4 hours) that should be considered to understand threshold effects data and associated risks. Furthermore, discuss what information should be considered when assuming the concentration for any unsampled period.

Response to Charge Question 3.1

The Committee acknowledged that it is challenging to make assumptions about unsampled time and to decide a minimum length of sample time that could be used to infer a full 8-hr shift exposure. Overall, the committee felt that the strengths and limitations of using partial-period samples (samples collected for less than a full 8-hr shift) were clearly described in the *Draft Occupational Exposure Assessment*. For long-term exposures, EPA only included a sample if it was collected for longer than 5.5 hours, and EPA assumed 0 exposure for any unsampled time, up to 8 hours. The Committee recognized that the chosen approach is in line with OSHA guidelines for including and interpreting partial-shift air samples. However, OSHA follows this approach for legal reasons and cannot issue a citation otherwise. When using occupational exposure data in a human health risk assessment, the committee recommended that more health-protective approaches should be explored.

Without additional information, the committee noted that assuming no exposure during the unsampled period could underestimate the true full-shift exposure. The committee appreciated that EPA

undertook a sensitivity analysis to this effect, included in Appendix E (Table E2, page 235) of the *Draft Occupational Exposure Assessment* document. The EPA reported that including samples collected for a minimum of 5.5 hours, and assuming zero exposure for any time less than 8 hours resulted in, on average, a 10% lower exposure than calculating a concentration using just the time sampled. Several committee members acknowledged 10% is an acceptable underestimation to justify the chosen approach, but also noted that shifts longer than 8 hours are common among industrial workers, which could lead to even greater underestimation. Unfortunately, the OSHA data supplied to the EPA contained no information on shift length, so there is no practical way to estimate the magnitude of this effect.

In considering other potential sample durations, the Committee recommended EPA repeat the analysis in Appendix E (Table E2, page 235) using samples of other times (such as at least 4 hours). This analysis would inform a possible decision to include additional sampling results collected for shorter durations. This could in particular benefit Occupational Exposure Scenario (OES) for which there are few or no samples of at least 5.5 hours.

The Committee recommended that if available, EPA could rely on OSHA inspector notes to consider how to interpret a sample that is not 8 hours in duration. For example, if an inspector indicated that they only took a partial sample due to (for example) pump failure, or the worker prematurely removing the pump, but the worker was continuing to work in a similar task for the full shift, the partial-period concentration could be counted as a full-shift concentration, with no zero-exposure assumption needed. If the inspector indicated they only took a partial sample because the worker stopped doing the task for the rest of the shift, that would be justifiable reason to count the rest of the 8-hr shift as zero exposure. However, the Committee recognized that the data the OSHA supplied to EPA does not include the logs kept by the Compliance Safety and Health Officers (CSHOs). Thus, the Agency had no practical process to implement an analysis.

Recommendations:

- **Do not assume that occupational exposure is zero for times beyond the 5.5-hour sampling interval.**
- **Repeat the analysis in Appendix E (Table E2) using samples of other times. (such as at least 4 hours) to inform a possible decision to include additional sampling results collected for shorter durations.**

Charge Question 3.2

As described in Section 4.2.1 of the Draft Human Health Risk Assessment (USEPA 2024g), occupational monitoring data were used as the best available data to estimate occupational exposures. Specifically, 15-minute samples were compared to the acute (threshold) inhalation hazard information. Please comment on the strengths and limitations of this approach and underlying assumptions for estimating acute risk to workers from inhaling formaldehyde. Please comment on the alignment of the health effect (i.e., sensory irritation) with the 15-minute samples intended to represent peak exposures. In your response, please consider the available monitoring data and if there are other potential sampling and averaging times that should be considered to understand Threshold effects data and associated risks.

Response to Charge Question 3.2

1. The Use of Sensory Irritation to Address Acute Risk
Several Committee members agreed that the use of sensory irritation is an appropriate way to assess the acute, non-cancer occupational risks for formaldehyde.

Pre-existing respiratory conditions and/or co-exposure to other respiratory irritants in the workplace could act synergistically in increasing likelihood of sensory irritation from formaldehyde. These aspects are not routinely considered during typical industrial hygiene (IH) monitoring, given that it is usually a single chemical assessment, and would not be something that EPA could consider based on the occupational monitoring data they possess. (EPA commented on this in lines 2038-2041, page 82 of the Draft HHRA).

Target and non-target responses appear to be considered in the modeling (also pertinent to other CQs). Specifically, monitoring data are linked to potential risk to individuals with occupational exposure at likely highest concentrations. Risk should also reflect non-target individuals also considered for potential risk, for example office workers and others with possible exposure. (Figures 2.1 and 2.2, pages 49-50 of the Draft HHRA).

2. The Role of Uncertainty Factors
Many Committee members agreed that since the data were derived from human volunteers, including hypersensitive adults, no uncertainty factor is needed for the POD value of 0.5 ppm (0.62 mg/m^3). An alternative view was that the POD should include an uncertainty factor. Uncertainty factors are useful in evaluating risk, since no study can ensure that the most sensitive individuals are enrolled as volunteers or included in the cohort. Uncertainty factors also provide a buffer against workplace variability, although this is a matter more of risk management than risk assessment.

3. Monitoring Data
It is unclear whether EPA used monitoring data other than those data supplied by OSHA. If so, EPA should explain how such data were used. If not, EPA should consider utilizing those data, or explain its decision not to do so.

The Committee agreed with the hierarchy delineated by EPA in the *Draft Occupational Exposure Assessment for Formaldehyde*, lines 811-12, page 26, where monitoring data are prioritized relative to modeling approaches and OELs. As explained above with respect to OSHA, "typical" collected monitoring data does not necessarily align with "typical" expected exposure. As such, the 95th percentile data (or 90-99.9th percentile data, where the 95th percentile data is not available) is suitable for use as a high-end value. However, an OES with a small number of samples (e.g. leather tanning) might benefit from modeling as a comparison. There was general agreement that the 50th percentile is a reasonable measure of central tendency. Presumably the data do not follow a Gaussian distribution; a lognormal distribution is more likely. The geometric mean is often used, but in a lognormal distribution the median approximates the geometric mean. However, the central tendency is not an appropriate value to use as the exposure in a risk assessment. High centile values are appropriate when limited data are available or probabilistic approaches are possible when robust data sets are available.

Data that were excluded due to an inability to assign an OES (DOEAF lines 1023-6, page 31) could have been assigned to an "unknown" OES for comparison to "assigned" OES data. However, if the

numbers of these samples are small relative to the typical numbers of samples, or skew to low concentrations, the Committee is concerned that excluding high-exposure, unassigned data might lead to underestimates of risk.

The OSHA data are likely to represent higher end exposures and may not represent the full range of exposures in different occupational settings. Some Committee members suggested that using the median from OSHA data as a measure of central tendency might still be a health-protective approach for all workers. But there is disagreement on this point, since workers who do not use formaldehyde or formaldehyde releasing products are considered separately, as Occupational Non-Users. The EPA also identified the high-end of air concentrations which would represent a more health-protective approach. (For example, Figure 4-1, page 42 of the DOEAF is likely skewed high relative to all workers in a given occupation). Utilization of these higher quality datasets will reduce the uncertainty of risk calculations and improve models developed from the data.

Data were intended to be included since the year 1992. As Lavoue et al. (2008) found in an analysis of OSHA formaldehyde sampling data (https://pubmed.ncbi.nlm.nih.gov/18618336/), exposures to formaldehyde decreased over time (his database timeline spanned from 1979 to 2001). Therefore, the EPA should consider restricting data in the last 10 years, or investigating if there are changes over time to decide what the most appropriate time period to use would be.

4. The Use of OSHA 15-Minute Samples

The Committee concluded that EPA relied upon the best available monitoring data to estimate peak occupational exposures. The committee noted that additional data from industrial trade organizations may be available. It is common industrial hygiene practice to measure this using 15-minute samples. Concentrations may be highly variable during a shift or between shifts, especially for maintenance workers, or in job shops. Therefore, one limitation of this approach is that it depends on the ability of the person collecting the sample to identify the conditions and practices likely to produce the highest short-term exposures. For example, much of the data were collected by OSHA Compliance Safety and Health Officers (COSHOs), who may or may not be familiar with the particular operations they are assessing. Since exposures exceeding the OSHA limits are penalized, managers have an incentive to steer the COSHO away from worse case exposures or even to shut down high exposure operations while the COSHO is present. Nevertheless, workplaces OSHA visits may have higher exposures in general since the inspection may have been triggered by a complaint or a belief by OSHA that overexposures were probable.

It appeared the EPA only used samples that were equal in time to 15 minutes. The EPA could consider including samples less than 15 minutes and see how those exposures differ (it could be that a 5-minute exposure could be higher than a 15-minute exposure, or comparable, depending on the nature of the task). This could help to increase data for some of the tasks. However, OSHA, and industrial hygienists generally, rarely take personal samples of less than 15 minutes, so shorter exposure data may not exist.

While Committee members concluded that EPA's 15-minute approach is appropriate, the key studies for the health effect (irritation) involved daily exposures of 3-5 hours; some study designs included peaks interspersed among otherwise continuous lower-level exposures. It is valid to characterize acute risk in the OES by comparing 15-minute data (representative of a worker's peak exposure) with PODs derived from these 3-5 hour sensory irritation studies. The MOA for sensory irritation has been characterized, and both the measured effects and self-reported effects are understood to be sustained

with, at most, minimal diminution over the observation period (Brüning et al, 2014). Thus, a POD based on these studies will likely not misrepresent the nature or severity of effects from a 15-minute workplace exposure, at least over the course of a workday. However, it should be noted that for some irritants, sensory fatigue or habituation may set in over longer periods of multiple workdays. Two examples are bakeries (baker's lung) and metal pickling, where the typical new worker experiences significant sensory irritation, which the long-term workforce barely notices. It is not known whether this is true for formaldehyde.

Monitoring data from full-shift samples could be compared to the acute POD in some circumstances. For example, when workplace conditions of use (COUs) reflect tasks not performed every day, the acute POD may be more relevant to worker health than the chronic concerns addressed by the chronic occupational exposure guidance value and should be considered as an alternative.

Despite these concerns, the Committee concluded that monitoring data based on 15-minute samples that have been extracted from larger data sets for full workdays should provide a realistic estimate of occupational exposure via inhalation.

5. Other Concerns

The EPA does not appear to have reviewed the work of other regulatory bodies to refine their methodology. For example, a board of experts from German committees in charge of the regulatory toxicology published their findings (Brüning et. al., 2014). In July 2023, the EU finalized its formaldehyde risk evaluation and, in careful consideration of the data, implemented a permissible worker exposure level of 300 parts per billion (ppb). (EU Council Directive 98/24/EU, Annex 1.)

Recommendations:

- **Determine if the 15-minute sample is reflective of high and low levels due to variation of materials used in manufacturing processes during the workday.**
- **Is there a background level against which the sample could be compared? If so, does this background constitute a control?**
- **Determine any residual exposure, dermal or other exposure routes that can be affecting individual exposure/sensitivity.**
- **Explain the criteria for using 'task-based monitoring data' in lieu of 15-minute peak exposure peak data' (L 1049, page 45 Draft HHRA).**
- **Document if Monte Carlo or Latin Hypercube sampling methods were used to estimate inhalation exposures.**
- **Age and duration of exposure along with exposure frequency are critical variables (Section 2.1.2). Please explain if significant changes in the exposure model are associated with these variables?**
- **Determine or estimate whether exposure estimates are decreased by using zero exposure for the time interval not sampled in an 8-hour shift.**
- **State whether there is information about variable times during the workday that are likely to have multiple sources of exposure to workers due to manufacturing processes.**
- **Provide information that describes factors that influence exposure at different job sites, such as the building, work conditions, air flow, and type of manufacturing. State whether these factors were included in the analysis.**
- **Use higher centile values such as 90^{th} or 95^{th} centile to represent exposures for a deterministic evaluation.**

- **Review the work of other regulatory agencies, such as OSHA and the European Council, for methodological insights.**

Charge Question 3.3

The Draft Human Health Risk Assessment (U.S. EPA, 2024g) relies on the chronic inhalation hazard endpoints and PODs derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022). The IRIS assessment considered a range of respiratory and non-respiratory health effects in humans including reduced pulmonary function, increased asthma prevalence, decreased asthma control, allergy-related conditions, sensory irritation, male and female reproductive toxicity, and developmental effects. Section 4.2.1 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the chronic inhalation POD to assess risks to workers with occupational exposure to formaldehyde. Please comment on the strengths and uncertainties associated with use of the chronic non-cancer POD from the draft IRIS assessment for evaluation of formaldehyde risks to workers.

Response to Charge Question 3.3:

A number of general strengths of the Agency's approach and application of the chronic non-cancer POD were identified. However, the majority of the Committee's discussion was directed at uncertainties related to the POD and concerns with its development as described in the *Draft Toxicological Review of Formaldehyde – Inhalation* (IRIS assessment). Also identified were concerns about defining occupational non-users and types of workers considered in the assessment. The Committee elaborated on several areas of concern for the study of Krzyzanowksi et al. (1990), and its use to derive a POD which is detailed in charge question 1.2.

The Committee also discussed applying a unified dose-response assessment approach for cancer and noncancer chronic effects (See charge question 1.2, 4.4, and 5.6).

Strengths of the studies considered in developing the chronic non-cancer point of departure (POD)
Strengths of the studies evaluated by IRIS for the chronic inhalation (POD) are: 1) the majority of the studies are in humans; and 2) the human populations studied include PESS (e.g., children and pregnant people).

Strength of the POD As Applied to Protect Workers
The POD is based on pulmonary function response in children. The POD representing this PESS will be protective of adults and workers. However, several Committee members hold the view that applying the POD (based on responses in children) to adult workers is not appropriate.

Strengths of EPA's Approach to Exposure Assessment
The EPA calculated exposure without regard to the use of respirators or other personal protective equipment (PPE), which is appropriate. PPE belongs under risk management, not risk assessment. Further, PPE is the least effective form of risk management – sometimes necessary as a last line of defense, but inferior to strategies higher on the hierarchy of controls, such as engineering changes and better work practices, due to the need for worker training, proper use, and compliance.

Strengths of collaborative approach within EPA

Collaboration across offices/programs at EPA is seen as a strength and efficient use of resources and ideally promotes consistency. The EPA should strengthen these interactions and develop synergies across offices and programs. As illustrated in this assessment, the TSCA program can draw on existing datasets, models, and scientific evaluations rather than 'reinventing the wheel'. The Committee noted that the IRIS assessment is not finalized, however, text in section 4.1.2.2 (lines 644-665, page 19) of the *Draft Human Health Hazard Assessment* described ongoing collaboration between TSCA and IRIS as IRIS responds to the NASEM review. The Committee also noted that collaboration with other offices would benefit the assessment, particularly the Office of Air and Radiation.

It will be important that the Offices work collaboratively and resolve issues and differing opinions before finalizing the IRIS assessment and the OPPT/OPP assessments. It will not benefit the public or the programs if the IRIS document presents a view that is contrary or calls into question the decisions of the program offices.

Uncertainties relative to occupational exposures/workers

The Committee noted that EPA introduced an inhalation rate adjustment for workers versus the general population. Explanation of this deviation from their previous practice in other TSCA assessments is needed.

Studies reviewed by IRIS for the non-cancer POD did not include occupational settings, and adverse findings in children were not found in adults (the relevant age group for occupational populations). The Krzyzanowski et al. (1990) findings for adults differed from those reported for children, "The effects of HCHO in adults were much smaller than in children: the decrements in PEFR were transient, limited to morning measurements and seen mainly in smokers exposed to higher concentrations of HCHO" (Krzyzanowski et al., page 124).

Further explanation of the relevance or interpretability of the POD in the context of occupational exposure is needed.

Regarding allergy, Annesi-Maesano et al. (2012) and Venn et al. (2003) are studies of school children and area samples (school and home) that were used rather than personal samples to characterize exposure. Thus, these studies do not align to a PECO statement appropriate to an OES and risk characterizations conducted with a toxicity reference value for adult workers based on these studies will be unnecessarily conservative. Perhaps a stand-alone occupational exposure limit (OEL), i.e., not derived from a general population RfC, would not be derived from responses of children and smokers (Krzyzanowski et al., 1990).

One Committee member noted that an OEL derived study finding in children PESS would be protective of adult workers. One Committee member stated that an OEL that is lower than background concentrations in a normal home is not a suitable OEL and suggested that the POD needs to be revisited. This member suggested that the EPA should review the derivations of other country's OELs and recalculate an appropriate OEL. A board of experts from German committees in charge of the derivation of OELs discussed the major challenges of this particular end point for regulatory toxicology and the agency would be advised to consider those comments offered during the public comment portion of the public meeting. Some Committee members offered that OELs are based on feasibility and risk, and the EPA should consider in the TSCA process evaluated risk, not feasibility.

The human lowest observed [adverse] effect concentration LOAEC of 0.5 ppm and no observed [adverse] effect concentration (NOAEC) of 0.3ppm was derived by (Brüning et al., 2014). Note, the Brüning et al. (2014) study stated that sensory irritation is reversible and not an adverse effect. Note that in addition to sensory irritation endpoints, the study by Mueller et al. (2014) includes objective irritation effects as an endpoint. Formaldehyde concentrations of 0.7 ppm for 4 hours and of 0.4 ppm for 4 hours with 15-minute peaks of 0.8 ppm did not cause adverse effects related to irritation, either in hyposensitive or hypersensitive subjects. Thus, a 0.8 ppm might be considered as a NOAEL (POD) from human studies. Although the Mueller et al. (2014) study is an acute duration study, formaldehyde does not accumulate in the body and Habers' Law does not apply for formaldehyde. Thus, use of this study may be appropriate for setting a POD for chronic exposures.

The occupational exposure levels used in Ontario, Canada, are Short-term Exposure Limit (STEL) of 1 ppm and a ceiling limit of 1.5 ppm (2022) and Australia are: Maximum 8-hour Time-Weighted Average (TWA): 1 ppm or 1.2 mg/m³ and the Maximum Short-Term Exposure Limit (STEL): 2 ppm or 2.5 mg/m³. The more conservative EU OEL for formaldehyde was determined as 8-hour TWA: 0.3 ppm or 0.369 mg/m³ and 15-min STEL: 0.6 ppm or 0.738 mg/m³. (European Commission, 2016). (EU OEL formaldehyde).

Defining workers versus occupational non-users (ONUs)

The Committee determined that there is inadequate consideration of ONUs. The EPA provided an inaccurate distinction between "workers" and "occupational non-users" (ONUs), and then calculates only risks to workers. ONUs are expected to have exposures that are equal to or less than "workers." Workplaces where toxic chemicals are present are characterized by a wide range of exposures, and individual exposures may fluctuate greatly over time. A janitor, for example, may have zero exposure while cleaning offices, followed by very high exposure while cleaning equipment or dealing with spills. Another example is maintenance, where an employee could have low or no exposure for days followed by high exposures while repairing equipment used in a process making or using formaldehyde. Many manufacturing sites have quality control labs. Employers tend to classify lab employees as "office and technical" employees. As such, they may be lumped into the ONU category, even though they open process equipment, take samples, and analyze them, sometimes under hooding, sometimes not. TWA exposures may be lower for ONUs, on average. This is less likely to be true of 15-minute peak exposures. The EPA's process descriptions and lists of worker activities in Section 4 of the *Draft Occupational Exposure Assessment for Formaldehyde* are excellent, but ONUs are described in general terms. For example, it is not clear whether janitors, maintenance employees, and lab workers should be classified as "workers" or ONUs.

Uncertainties about how chronic exposure is defined

Workers whose formaldehyde tasks are infrequent, or variable might be better served by risk characterizations where their 8 hour TWA exposures are compared to the acute POD.

Uncertainties/gaps in occupational settings evaluated

It is unfortunate that the EPA could not calculate peak exposures for many activities in the oil and gas industry. Exposure in oil and gas industry settings tends to occur in short bursts, during maintenance and repair, or when a chemical mixture, such as a fracking fluid is introduced into the system. This comment is also relevant to CQ 3.2.

Exposures in hair and nail salons are not included in the occupational exposure scenarios. These jobs are often done by women and women from racial or ethnically minority populations—populations that have systematically been left out of OSHA protections. The Committee recognized that its use in hair and nail care products has been deemed a non-TSCA use, however it appeared that it's use in a salon by a worker interacting with members of the public should be considered a TSCA use, even if its manufacture or distribution is not considered a TSCA use. In particular, the cosmetologist's use of keratin treatment and similar hair-straightening hair care products at elevated temperature has been reported to release high concentrations of formaldehyde (Maneli et al., 2014; Monakhova et al., 2013; Pierce et al., 2011).

Comments directed toward the IRIS assessment/approach

A detailed critique of the IRIS confidence rating of Krzyzanowksi et al. 1990 can be found in CQ 1.2**.** As noted in the response to CQ 1.2, some Committee members suggested that Krzyzanowksi et al. (1990) study should have been rated as low confidence. Issues of concern discussion can be located there. The Draft IRIS assessment lists a series of studies that might serve as the basis for candidate RfCs (cRfCs). Several of these studies (Hanrahan et al., 1998; Krzyzanowski et al., 1990) are of low quality based on peer review but were nevertheless used as the basis for cRfCs on sensory irritation, pulmonary function, and current asthma.

It is difficult to see, from the draft TSCA risk assessment document, the basis for the chronic, noncancer inhalation RfC. One needs to access the IRIS document to understand the basis of the 0.007 mg/m^3 RfC. Since the IRIS document has not yet been finalized, it is difficult to understand the review and selection process. For example, IRIS draft document Table 2-3 outlines the POD calculated from the Krzyzanowski et al. (1990) study (0.017 ppm or 0.021 mg/m^3). Use of an UF of 3 results in a RfC of 0.007 mg/m^3.

Some Committee members expressed concern that mild sensory irritation is not an adverse health impact and should not serve as the basis of the RfC for occupational scenarios, while other Committee members noted that constant sensory irritation would be difficult for workers to endure. Instead, tissue irritation might be a better endpoint, and there are many animal studies showing respiratory tract irritation following formaldehyde exposure (summarized in Thompson et al., 2021). One advantage to this approach is that these studies could also serve as the POD for cancer endpoints, as formaldehyde-associated cancer requires the same cytotoxicity and compensatory cell proliferation that is seen in respiratory tract irritation studies. This would provide the opportunity for a uniform health protective assessment that addresses any chronic toxicity including a carcinogenic response.

Some Committee members held the position that without some justification for why individuals in the Krzyzanowski et al. (1990) study would be so much more sensitive to the effects of formaldehyde than individuals in the set of controlled human exposure studies (where no pulmonary impacts were found), it is difficult to accept the POD of 0.021 mg/m^3 (17 ppb) as being scientifically sound. Others noted that adults did show adverse effects in the Krzyzanowski study, and that Public Comments by Dr. Dalton of the Monell Chemical Senses Center provided reasons for sensitivity of children.

Questions related to the IRIS evaluation of non-cancer effects

In section 4.1.1 of the *Draft Human Health Hazard Assessment for Formaldehyde* a summary of inhalation hazard endpoints is presented. Each endpoint-specific summary includes the phrase "given appropriate exposure circumstances" or similar. Including the details of the appropriate exposure circumstances will improve the document.

"Pulmonary Function. IRIS concluded that evidence indicates that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given the appropriate exposure circumstances (*Draft Human Health Hazard Assessment for Formaldehyde*, lines 433-435, page 13)." However, those "exposure circumstances" are not detailed. Since the evaluations provided by the OPPT are designed to inform risk management decisions it will be important for the public and risk managers in occupational settings to know how to mitigate risks.

Considering the acute irritating effects of formaldehyde, would it be likely for these long-term exposures over many hours, days, weeks, and months to actually occur?

"Respiratory Tract Pathology. IRIS concluded that the evidence demonstrates that inhalation of formaldehyde causes respiratory tract pathology (primarily squamous metaplasia) given the appropriate exposure circumstances (U.S. EPA, 2022)." , taken from the *Draft Human Health Hazard Assessment for Formaldehyde*, lines 442-445, page 14.

Squamous metaplasia is a response to persistent and repeated direct irritant effects as an adaptive and protective response to a chemical exposure that caused direct cytotoxicity to the respiratory epithelium. Under what exposure circumstances would this occur with formaldehyde in humans? It would seem the irritating effects of formaldehyde exposure would prevent the long-term repeated exposure of sufficient inhaled concentrations to result in squamous metaplasia in humans. It would be expected that in an occupational setting where this type of exposure was possible appropriate PPE would be used to prevent this effect. However, several members noted that PPE is a risk management technique that should be considered after risks are determined.

"Reproductive and Developmental Effect**s**. IRIS concluded that the evidence indicates that inhalation of formaldehyde likely causes increased risk of developmental, and female and male reproductive toxicity given the appropriate exposure circumstances (U.S. EPA, 2022)", taken from the *Draft Human Health Hazard Assessment for Formaldehyde*, lines 447-450, page 14.

Since it is unlikely for oral or inhaled formaldehyde to get past the site of exposure, what exposure scenario would result in formaldehyde arriving into the reproductive tract or fetus? The Til et al. (1988) and Tobe et al. (1989) studies resulted in no histologic alterations in the reproductive or endocrine tissues. The studies that do identify some testicular effects could have been caused by frank toxicity to the whole animal and not site-specific toxicity to the organ.

"Neurological Effects. IRIS concluded that the evidence suggests but is not sufficient to infer that formaldehyde inhalation might cause multiple manifestations of nervous system health effects in humans given relevant exposure circumstances (U.S. EPA, 2022)." (*Draft Human Health Hazard Assessment for Formaldehyde*, lines 452-455, page 14)" What would these exposure circumstances be and how would formaldehyde enter the CNS via inhalation, dermal, or oral exposure? Also, the co-exposure with methanol, which is a known neurotoxicant, is a consistent confounder.

<u>Comment on a unified dose-response assessment approach</u>
Could there be a unified approach for the chronic and cancer risk assessments based on using the NOEL or NOAEL POD for irritancy effect via the relevant route of exposure? For example: respiratory cytotoxicity, without which no downstream effects would occur including cancer; and forestomach damage, without which no downstream effect would occur.

In the 2009 Science and Decisions: Advancing Risk Assessment report, a National Academies' panel recommended a unified approach to dose-response assessment to address limitations in current practices such as non-cancer dose-response and risk characterization metrics that lack an estimate of health risk (e.g., RfC and MOE) and lack of explicit consideration of factors that can contribute to variability in the population-level cancer response (National Research Council [NRC], 2009, Chapter 5, pages 127-187). One important goal of the unified approach is to facilitate the development of a risk-specific RfC and RfD. This unified approach has at its center three complementary analyses that together inform the selection of the conceptual model of the dose-response (see Figure 5-8, NRC 2009 page 144). A simplified presentation of the "new unified process for selecting approach and methods for dose-response assessment" is outlined below with the complementary analyses shown in item 3, namely the MOA description and evidence evaluation informs and then is considered in conjunction with vulnerable populations and background exposure assessments. These complementary analyses then inform the conceptual model selection (item 4).

1: Assemble health effects data
2: End-point assessment
3: MOA description and evaluation of evidence by end point - Vulnerable population assessment - Background exposure assessment
4: Conceptual model selection (linear or nonlinear):
- From linear models unless data sufficient to reject low-dose linearity
- From nonlinear models otherwise

5: Dose-response method selection based on:
- Conceptual model (from Step 4)
- Data availability
- Risk management needs or form of risk characterization

In addition to the Committee's comment regarding a unified approach, the Committee's discussion also referenced the need for further clarity on: 1) the MOA; 2) vulnerable, sensitive or susceptible populations; and 3) the conceptual model selection. A presentation of the formaldehyde evidence using this outline would be a valuable addition to the *Draft Human Health Risk Assessment*.

Other tools to communicate risk assessment findings
Use of the RISK21 framework and tool to better communicate risk assessment findings (www.risk21.org). This is more fully presented in the response to Charge Question 1.4.

Recommendations:

- **Reconsider the POD using the most appropriate studies as the basis of the chronic non-cancer POD and RfC.**
- **Further consider occupational non-users (ONUs).**
- **Explain the application of an inhalation rate adjustment for workers.**
- **Review other countries' occupational exposure limits (OELs) to identify other studies, outcomes and assessment approaches used.**
- **Further develop and explain the mode of action (MOA) and, if applicable, apply the unified approach for dose-response assessment following the National Academies' Science and Decisions report recommendations (NRC, 2009).**
- **Request staff members within the IRIS program expedite review of formaldehyde and consider recommendations in this SACC report.**

- **Include the details of the appropriate exposure circumstances for each inhalation hazard endpoint summary in section 4.1.1 of the *Draft Human Health Hazard Assessment for Formaldehyde* (pages 13-14).**
- **Consider use of the RISK21 framework and tool to better communicate risk assessment findings (www.risk21.org).**
- **Derive an occupational exposure limit (OEL) that is not derived from a general population RfC. Describe long-term exposure considerations that would cause decreased pulmonary function.**

Charge Question 3.4

The draft human health hazard assessment (U.S. EPA, 2024f) relies on the cancer IUR derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022). Section 4.2.1 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the cancer IUR to assess risks to workers with occupational exposure to formaldehyde. Please comment on the strengths and uncertainties associated with use of the cancer IUR from the draft IRIS assessment for evaluation of formaldehyde risks to workers.

Response to Charge Question 3.4

The Committee's response to charge question 3.4 included information, sources, and critiques that can apply to charge questions 4.5, 5.7, and 6.6, as all of these questions pertain to the use of the cancer inhalation risk unit (IUR) in different populations. As such, the EPA should consider that the points from this response could also apply to other charge questions concerning the application of the cancer IUR. A Committee member noted that unreasonable risk determinations in occupational settings are largely based on non-cancer effects, which would be reflected largely in charge question 3.3.

Strengths:
Regarding strengths of the *Draft Human Health Risk Assessment*, two Committee members noted that EPA calculated exposure without regard to respirators or other PPE, which is appropriate given that PPE oversight is under risk management, not risk assessment. Additionally, it is also the least effective form of risk management, and while PPE is sometimes necessary as a last line of defense, it is inferior to strategies higher on the hierarchy of controls such as engineering controls, better work practices, or product substitution/elimination.

One Committee member commended EPA's work to develop and establish for the first time the IUR that is applied to quantify the cancer risk in workers occupationally exposed to formaldehyde. Adoption of this approach would allow risk assessors to explore and pioneer the possibility of applying human data from epidemiological studies directly to evaluate human health risk, which is the major strength of OPPT's cancer IUR application. The same Committee member appreciated the use of human data obtained from one or more high quality and large epidemiologic studies, and the direct relevance of the risk assessment to humans. This Committee member also stressed that a similar unit risk estimate was derived using rat bioassay and mechanistic data and using low-dose linear extrapolation by mutagenic mode of action (mechanistic evidence). Other Committee members questioned the mutagenic mode of action. The same one Committee member commented the work by EPA could encourage more scientists, particularly epidemiologists, to conduct better designed human studies that could be eventually used in a future health risk assessment. However, many Committee

members had concerns about the use of the IUR, which will be detailed later in this response.

Uncertainties/Weaknesses

The primary concern with the IUR raised by many Committee members involved the mode of action for formaldehyde-induced carcinogenesis. The committee pointed out that the IUR should be based on an evaluation of all the data and informed by an understanding of the underpinnings of the process. For carcinogenicity, the fundamental aspect of a malignant neoplasm is that all tumors have a collection of genetic mutations and have cellular proliferation occurring. This is supported in Wolf et al. (2019). The rate limiting step in the process must be determined and described, which is an important step for describing mode of action analysis; this is supported in Boobis et al. (2006) and Meek et al. (2014). Of important note, many Committee members commented there is no evidence of multiple modes of action leading to the same adverse outcome in the same individual and the same tissue. Further information can also be found in Figures 2 and 3 of the responses to Charge Question 4.5.

Many Committee members explained that a chemical may have more than one mode of action that leads to different adverse outcomes in different tissues. Unleaded gasoline is an example of this as it is a nuclear receptor agonist in most livers which results in a mitogenic response promoting and enhancing spontaneous tumors, resulting in liver neoplasms. However, in the rat kidney, it induces renal neoplasms through persistent cytotoxicity and regenerative proliferation from alpha 2 urinary globulin accumulation. Similarly, a chemical may have the same mode of action in different tissues, such as chloroform. Chloroform can cause a cytotoxicity and regenerative proliferation in the liver and the kidney, resulting in tumors in both sites.

Some Committee members disagreed with the position that there was no evidence of multiple modes of action leading to the same adverse outcome in the same individual and the same tissue. These Committee members supported the consideration of studies that provide evidence of multiple modes of action. These studies include DNA-protein crosslinks detected in the nasal mucosa of formaldehyde-exposed rats and monkeys (Lai et al., 2016); DNA-adducts detected in the nasal respiratory mucosa of exposed animals, including rats and cynomolgus macaques (Lu et al., 2011); micronucleus formation in the buccal mucosa of pathology laboratory workers (Akhlaghi et al., 2023); and cell proliferations in the nasal tissues of exposed animals (Kerns, 1982; Monticello, 1996) as cited by the NASEM review, page 82. Another Committee member pointed out that DNA-protein adducts from exogenous formaldehyde do not appear until very high formaldehyde exposure concentrations, which is supportive of the threshold MOA.

Most of the Committee members did not agree with the conclusion that formaldehyde respiratory tract tumors have both a mutagenic mode of action and a cytotoxicity/regenerative proliferation mode of action. Most Committee members considered the conclusion to be an incorrect application of mode of action analysis and an incorrect interpretation of all available data. Many Committee members noted for formaldehyde, there is ample evidence to show that it is not a direct-acting mutagen, and that direct cytotoxicity is the rate limiting biological step. While formaldehyde has been shown to be a mutagen in *in vitro* studies, the evidence in animals and humans are less convincing and the mutations observed in the few studies showing effects are likely the result of *in vitro* expansion of the cell populations. One Committee member provided a review article by Albertini and Kaden (2017) to support this point. The same Committee member noted that, as outlined in the Albertini and Kaden (2017) paper, observed mutations do not occur as a result of interactions with formaldehyde, but instead occur while the cell population is expanded in the laboratory, allowing additional

opportunities for spontaneous mutation events to occur. Similarly, none of the studies that report changes in human bone marrow or hematopoietic precursor cells provided convincing evidence that exposure to formaldehyde is responsible for mutations arising *in vivo.*

However, a Committee member did not agree there was ample evidence to show formaldehyde was not a direct acting mutagen and that direct cytotoxicity is the rate limiting biological step. A minority of members agreed with the EPA's conclusion that "there is sufficient evidence that a mutagenic mode of action contributes to risk of nasopharyngeal cancer (NPC)from inhaled formaldehyde."

Committee members noted that formaldehyde is used as a preservative for biological tissues precisely because it reacts with and cross links biological macromolecules. It is also a highly reactive compound that is rapidly detoxified when inhaled. Committee members noted that if formaldehyde acted as a direct mutagen, then there would be a different tumor response in a number of the animal chronic studies. One committee member highlighted studies for EPA to consider—Til et al. (1989), Tobe et al. (1985)—which support this point. These studies looked at forestomach lesions and gastric lesions at up to 300 mg/kg/day for long-term exposure to formaldehyde, with significant toxicity at the site of exposure but no neoplasms. In summarizing the articles, the Committee member noted that if formaldehyde had a direct mutagenic potential, then one would expect a carcinogenic response at that site. An additional Committee member highlighted two additional studies for EPA, Swenberg et al. (2011) and Swenberg et al. (2013), which demonstrated that inhaled formaldehyde only reacts with cellular macromolecules such as DNA at very high concentrations (2 ppm) but at these high concentrations can cause considerable cytotoxicity.

A Committee member raised that the Monticello et al. (1996) Cancer Research paper provides additional support for the importance of not only sufficient cell proliferation but also for there to be a sufficient population at risk to result in an increased tumor response. A bigger population at risk will result in more cells proliferating, increasing the risk of spontaneous mutations —as reviewed in Wolf et al. (2019). A Committee member shared an example of this; there is a dose-dependent increase of proliferation across all of the sites in the rat nasal cavity, but tumors arise in the sites with the largest base population. The absolute numbers of cells proliferating are far greater in those sites with the highest base population. The Committee member concluded that if formaldehyde was acting as a mutagen, then tumors should be found across all the sites where there was sufficient dose to increase cell proliferation, which was not the case.

Many Committee members indicated that the evidence supports the well-established complicated mode of action that increased direct toxicity in a large enough population of cells will lead to increased proliferation and will increase the likelihood of spontaneous mutations. Because formaldehyde also cross-links macromolecules, then those cells that can survive but are damaged by the cross-linking could have an enhanced loss of DNA repair capabilities. An article by Hester et al. (2005) supports this point. Multiple Committee members stressed to EPA that mode of action is complex and not always linear, as would be the case with a MOA dependent on cytotoxicity. One Committee member further stated that multiple modes of action can be cross-linked, and that chemicals can have multiple modes of action and these modes of action may lead to a single outcome. Thus, observing relative contribution of the different modes of action should be a consideration of the Agency.

One Committee member questioned the comparison of hyperplasia and squamous metaplasia in the IRIS 2022 document. The same member commented that it is established that the respiratory tissue

will respond to persistent medium to long-term exposure to a direct irritant with squamous metaplasia which protects the surface being exposed by creating a skin like surface epithelium. This is, for example, a common response to cigarette smoke. The same member noted that the argument was presented that in some of these studies no hyperplasia was diagnosed in those tissues. They also indicated this would not be the case since squamous metaplasia is a hyperplastic response and can be an early stage leading to a neoplastic response in the affected tissue. A reference by Wolf et al. (1995) supports this point. The committee member also commented that the typical practice of a toxicologic pathologist is to diagnose the most advanced lesion in a tissue, so while respiratory cell hyperplasia may be present on the same slide with a squamous metaplasia, the study pathologist would diagnose squamous metaplasia as it is the most advanced lesion.

For non-respiratory tract tumors, a Committee member stated that it is inappropriate to lump tumor responses of unrelated cells of origin. While it might be useful to include a discussion regarding cells of the blood forming organs together, this is only useful in a clinical setting and not in toxicologic pathology. Further, regardless of the use of animal models to make a toxicologic pathology interpretation (rat, mouse, monkey, human), an accepted standard practice including how to lump tumors should be used even if the focus of the articles is on rodent tumors.

Committee members also discussed myeloid leukemia, which is defined as a disease that originates in the bone marrow although neoplastic cells are found in the peripheral circulation. Two references were noted supporting that any potential association between formaldehyde and myeloid leukemia does not necessarily support causation (Vincent et al. 2024; Cox et al. 2024). One Committee member noted that the overall confidence in the preferred IUR estimate selected by EPA is only medium and not high, and the IUR for nasopharyngeal cancer is more robust and stronger than the estimate for myeloid leukemia. The Committee member commented that the lack of confidence in both dose-response data and IUR estimate for myeloid leukemia remains a major source of uncertainty and there is insufficient data and large data gaps. These studies support delivery of formaldehyde from the site of exposure to distal tissues. Many Committee members recommended not using the IUR published in the 2022 Draft Formaldehyde IRIS assessment. The same members recommended using a mode of action approach where there is a threshold concentration below which no cancer is anticipated. One Committee member noted this should be put in a larger schema which includes the relationship between exposure and dose. The same Committee member explained that because formaldehyde is reactive, the dose is delivered to the tissues most proximate to the nasal cavity, so the mode of action is required to be examined for cancer in the nasal cavities as compared to the hematopoietic tissue where it does not reach given its removal from the nasal cavity. This mode of action approach would generate a value to take the place of an IUR, as cancers would not be anticipated at lower concentrations (as a unit risk value would). Several Committee members disagreed with this approach and supported the IUR approach as the most appropriate. EPA scientists have appropriately followed its guidelines for carcinogen risk assessment and appropriately applied the low-dose linear extrapolation (a non-threshold model) for formaldehyde's cancer IUR estimate, which is a health-protective approach.

One Committee member presented evidence of multiple modes of action in formaldehyde-associated myeloid leukemia. This Committee member provided evidence of formaldehyde-exposed workers experiencing hematotoxicity in both myeloid and lymphoid cell types (Zhang et al., 2010) and in hematopoietic stem/progenitor cells present in the bone marrow or circulating blood (Tang et al., 2009). Stem/progenitor cell toxicity of hematopoietic myeloid progenitors was also observed in mice exposed to formaldehyde *in vivo* via inhalation (Zhao et al., 2021) or orally (Wei et al., 2017). The

same Committee member indicated that chromosomal aneuploidy, a type of numerical chromosome aberration was detected in the circulating myeloid hematopoietic progenitor cells of individuals occupationally exposed to formaldehyde (Zhang et al., 2010; Lan et al., 2015). However, another Committee member identified deficiencies of this study, including the pooling of all cells (contrary to study protocol) before expanding for analysis (Gentry et al., 2013), as well as the pattern of mutations found which do not indicate clonal origin (Albertini and Kaden, 2017). One Committee member provided additional references that found structural chromosome aberrations in the circulating myeloid hematopoietic progenitor cells of formaldehyde-exposed workers (Lan et al., 2015), other types of genotoxicity in formaldehyde-exposed humans (Lin et al., 2013; Zendehdel et al., 2017; Bruschweiler et al., 2020), and DNA-protein crosslinks in formaldehyde-exposed humans (Shaham et al., 1996; Shaham et al., 2003) and mice (Ye et al., 2013). However, another Committee member noted that such circulating cells may have been exposed to formaldehyde while circulating through the blood, which passes through nasal passages, and that it is not possible to attribute exposure occurring in the bone marrow (Albertini and Kaden, 2020). Since these circulating cells do not repopulate the bone marrow, they would not necessarily reflect myeloid leukemia.

One Committee member acknowledged that cumulative exposure is the standard metric used for unit risk estimate, which assumes equal importance of the level of exposure and duration of exposure on cancer incidence. The same Committee member, however, recommended that for formaldehyde, the optimal exposure metric should be peak exposure, giving more weight to concentration than duration. Their reasoning was because most epidemiology studies, including Beane Freeman et al. (2013) and Beane Freeman et al. (2009) reported that the peak exposure to formaldehyde was related to a higher cancer risk in industrial workers than the cumulative formaldehyde exposure.

At least two Committee members discussed that EPA made an inappropriate distinction between "workers" and "occupational non-users", and only calculates risks to workers because ONUs are expected to have exposures that are equal to or less than "workers." As presented in the response to CQ3.3, many on the Committee noted that this description is unlikely to be uniform in workplaces that use toxic chemicals, where a wide range of exposures could fluctuate over time. Low exposure may occur while workers clean offices, followed by high exposure while cleaning equipment or dealing with spills. Maintenance work provides another example of potentially cyclical exposures. Employers tend to classify lab employees as "office and technical" employees and they may be lumped into the ONU category even though they open process equipment, take samples, and analyze them. Similarities in peak exposures for ONU and workers who "use/produce" formaldehyde was also noted.

<u>Additional Comments</u>

The goal of the evaluation was to establish an understanding of the margin of exposure to assure no appreciable risk of harm. More than one Committee member believed it was not necessary to list all the potential carcinogenicity responses that may or may not be associated with formaldehyde exposure. The same Committee members believed it was sufficient to highlight that there is evidence that formaldehyde exposure results in a carcinogenic response and to show that the human exposure levels are a sufficient margin from the level of exposure which can cause an adverse effect; it is a distraction from this goal to debate which tumors are associated with formaldehyde exposure and which are not.

One Committee member urged EPA to improve communication of results by using the publicly available RISK21 framework and webtool. This is more fully presented in response to charge question CQ 1.4.

Several Committee members agreed that given that cancer from formaldehyde is likely a threshold effect, only evident at the site of contact when formaldehyde concentrations are at or above 2 ppm, it might be worthwhile taking a unified approach to both cancer and noncancer effects. This is the type of approach taken by the WHO for formaldehyde in their Indoor Air Guidelines document (WHO, 2010). Many Committee members stated very strongly that a 2 ppm occupational threshold would be less protective than the thresholds that have already been established by OSHA and ACGIH. As such a 2ppm limit would not be sufficient to protect health during occupational exposures and should not be considered by EPA.

Charge Question 4.1

Please comment on the use frequency and duration along with the amount (i.e., mass) and weight fraction of formaldehyde used to parametrize the standard scenarios in the Consumer Exposure Model (CEM) (version 3.0) in the Draft Consumer Exposure Assessment (U.S. EPA, 2024c). In your response, please comment on the extent to which the standard scenarios represent current uses of formaldehyde-based consumer products.

Response to Charge Question 4.1

The lack of sufficient time prohibited a detailed examination of individual values throughout the parameters. However, the sources of information and assumptions *seemed reasonable*, though this is an intuitive review comment, missing the advantage of an opportunity to do independent evaluation of other information sources and consider the appropriate statistics to be applied to those sources. Also, the use of these values (choices of high end or central tendency, etc.) without knowing the distribution of possible values for some parameters is an issue which appears here and throughout the documents. That statistical issue will be addressed further in other sections of the Committee Report with related statistical concerns and modelling approaches. These statistical and modeling issues are significant and confound the Committee's opinion on whether or not the exposures are over-stated or under-stated by the Consumer Exposure Model (CEM).

More important than the values used in the CEM assessments, the Committee concluded that EPA's Standard 30 scenarios are incomplete. Examples of omissions are detailed here, although the Committee is not asserting that these additions are the only missing scenarios. The Committee recommended discussing the full range of "indoor enclosures" and "vehicle space" rather than "residence". Also, exposures of many populations are parsed by the scenarios when considered product-by-product or scenario-by-scenario, when actually exposures result from combinations of many scenarios. This might be acceptable if those were "reassembled" in a competent, probabilistic exposure assessment model that yielded representative exposure profiles when direct monitoring was absent or inadequate. The Committee was concerned about such presentations of exposure, especially when probabilistic statistical approaches for data usage and modeling are not employed. This issue is discussed in detail in CQ 7.1 and elsewhere.

Several Committee members have expressed the opinion that the standard scenarios in the EPA report represented only a fraction of the exposure opportunities expected to be considered by the TSCA rule. The Committee's logic for this conclusion and examples of missing exposure scenarios are summarized below.

TSCA requires risk assessment to health or the environment under the chemical's Condition of Use, which is defined as:

> *Conditions of use are the circumstances under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of.*

These "circumstances" are defined by the EPA by their standard scenarios but do not apply to the entirety of the elements of the Conditions of Use—manufacturing, processing, distribution in commerce, use and disposal.

The EPA presented a more limited view of Conditions of Use which overlooked a large array of potential exposures to much, perhaps all, of the U.S. population. The EPA limited the assessments to Articles and Products and Industrial Releases to Air, Land and Water. Starting with only those sources of formaldehyde, many parts of the TSCA rule are left unexplored.

Of particular concern is the absence of exposure and risk assessments for "processing", "distribution in commerce" and "use" scenarios. The environments in which such exposures could manifest are also too limited. The Committee strongly recommended the EPA consider example scenarios summarized below.

<u>Processing</u>

After formaldehyde-based materials are manufactured, they are distributed to other industries that construct complex products which go into commerce. Those industries have workers who will become exposed by working with the original products.

Examples:

- assembly line paint, grease, glues for vehicles
- leather and textiles, cutting and sewing, folding, and packaging processes which involve dust inhalation. The dust will be ladened with formaldehyde and dermal exposure will obviously exist as well. This is relevant to the process of making vehicles, furnishings, clothing, decorative products such as draperies, wallpaper, etc.
- Composite materials for construction of buildings, floors, furniture, ceilings, fabric coverings and other materials which require cutting and assembly. These exposures again result not only from the off-gassing of formaldehyde from the newly created bulk materials but also from the dust created during the processes of making them into useable products and buildings and furnishings.

<u>Distribution in Commerce</u>

Distribution in today's commerce, and certainly for the foreseeable future, involves movement, storage, and retrieval of the newly fashioned products through massive warehouses. The efficiency of today's commerce assures that newly minted products will pass through a series of warehouses within days, headed to the consumer or to showrooms and retail centers. Exposure opportunities exist throughout this distribution chain.

Examples and references:

- Accrual of formaldehyde in massive warehouses with thousands of products made with formaldehyde as part of the manufacturing process (wallboard and flooring composites), OR complex products with one or more components which are formaldehyde based (furniture for example). Exposure to the warehouse workers would result from gaseous inhalation and potentially from dust.

These products move through commerce in great part by trucks. Emissions from carbon burning vehicles are significant.[i] It appears TSCA does not apply directly to vehicle emissions. However this significant exposure due to high formaldehyde concentrations in air around roadways does play into TSCA considerations in the context of determination of PESS communities and perhaps fenceline communities. Even if not directly regulated by TSCA, constantly high formaldehyde concentrations are probable near highways and bring into question whether EPA's calculated ambient air concentrations could represent communities adjacent to busy highways. The formaldehyde emission rates for different types of vehicles have been defined and can be used along with estimates of road usage[ii] [iii] (especially in areas with clusters of distribution warehouse centers) to estimate the air concentrations along major highways and extending to the adjacent buildings, business centers, playgrounds, schools, etc., which border many of those highways in populated areas. These could be considered fenceline exposures or PESS subpopulations because of exceptional exposure to children and additional burdens associated with lower socioeconomic communities. Note: EPA introduced the concept of "bystander" in their document. The concept of fenceline exposure near roadways is a similar concept. Many highway routes cut directly through densely populated urban areas where buildings may be very close and where pedestrians and commercial and recreational land use is directly below the highways. These city areas are typically already challenged with high concentrations of PM2.5 and mixed-use land with industries co-existing with residences (discussed with ambient air review). The case can be made that these are PESS communities.

The Human Health Consumer Exposure document (LL124, 272-291) should be revisited to consider formaldehyde release from transportation to determine a fuller extent of formaldehyde exposure. If there is a policy decision not to include all transportation, then at a minimum transportation of goods and personnel for business purposes must be considered as these are commercial activities. This includes conveyance by air, water, rail, and road. This must be part of a comprehensive risk assessment that also includes industry specific releases." And "LL434-436: Road and non-road transportation must be included. The extensive monitoring data for cities can be used to estimate the industrial and transportation contributions to formaldehyde and formaldehyde precursor release estimates.

Recommendation:

- **Revisit the Human Health Consumer Exposure assessment to consider formaldehyde release from transportation to determine a fuller extent of formaldehyde exposure.**

Use

Use of these formaldehyde-based products and the complex products with formaldehyde-based components is not limited to residences or consumers using products in their homes. The monitoring studies cited by the EPA in the Ambient Air Monitoring and Residential Exposure documents catalogue formaldehyde concentrations in air of commercial buildings, offices, schools, etc. The logic presented by EPA that residences were expected to represent the most significant exposure to people fails on two important points. First, dismissal of obvious venues containing formaldehyde products could be the subject of quantitative exposure assessment and if those answers are indeed *de minimis,* they can be dismissed. However, the Committee found it scientifically unsound to characterize the

exposure and risk by intuitive reasoning. Second, the EPA strategy can be countered by other intuitive assumptions that schools, offices, libraries, public buildings of all sizes may have been constructed or remodeled recently and contain vast areas of ceiling, flooring, walls, fabrics, new furnishings, many desks in rooms (schools), etc., providing surface area and new products relevant to the exposure assessment.

The Committee was concerned that the *Draft Consumer Exposure Assessment* does not adequately address children's exposures. For example, EPA's assumption that air exchange rates in schools are adequate to avoid accrual of formaldehyde in air does not reflect what has been reported. Newly constructed or renovated schools often have suboptimal air exchange rates due to the building being built to be energy efficient and therefore "tight". Air exchange rates in schools are typically well below recommended levels. Batterman et. al. (2017) found that, in a sample of 37 recently constructed or renovated and mechanically ventilated U.S. schools, 78% of schools did not meet minimum ventilation rates[iv]. Concern about insufficient air exchange rates in schools was widely mentioned as a risk factor for COVID transmission during the recent pandemic. While newly built schools may have upgraded filtration in place, low outside air exchange would allow contaminants to linger in the air for longer periods of time and build up over time.

Also, the draft does not mention school buses as a possible source of exposure. Children can spend 1-2 hours per day riding to and from school. Nor does it consider potential exposure to children using playgrounds and sports fields covered in tire crumb rubber. The EPA recently found that formaldehyde emissions from tire crumb, based on chamber studies, can exceed background concentrations using temperatures consistent with hot ambient uses.

Recommendation:

- **More thoroughly address children's exposures in the *Draft Consumer Exposure Assessment*.**

Use of formaldehyde composites by other businesses is an important part of the assessment. The journey of a product from manufacture to homes involves multiple transportation steps and handling and short storage in multiple storage/distribution sites. These products may also be used by other businesses, and indeed some products may be used primarily by other businesses. Those include, but are not limited to, auto body repair and maintenance shops, small contractors working in construction, furniture making, and transportation, sales and showroom workers, and other, smaller warehouse workers. Even this list is unlikely to be complete.

Of special concern are small industries and businesses existing in densely populated, mixed use urban areas where the business must vent their interiors. This is not venting from combustion. This is venting of volatiles (including formaldehyde) from use of formaldehyde containing products. Within a few yards (certainly less than 100 meters) of those vents are residences, preschools, playgrounds, and other public areas. These businesses are operating in compliance with the environmental and business regulations, but the situation provides a daily dose of formaldehyde for those nearby people.
Note: Photographs were presented during the May 20-23, 2024, peer review meeting that showed residences in structures adjoining businesses that released formaldehyde.

The Committee concluded that the concept of exposure venue in the draft is incomplete and unnecessarily limiting. This is especially true for exposures in vehicles and a broader range of indoor environments. Use of term "residence" (Line 198-199 of [18] Consumer Exposure Assessment for

Formaldehyde as here and throughout the documents) connotes an incomplete, minimalist view of probable exposure venues. The Committee recommended that EPA consider "indoor environment" and "enclosures or vehicles" just "residence" together with the broader use scenarios discussed here.

"Indoor environment" is relevant for the extensive exposure opportunities plausible for formaldehyde.

- Apartments, houses, offices, libraries, community centers, schools, community centers, stores, warehouses, show rooms, hotels, etc. All of these indoor environments contain many products providing contributions to formaldehyde air concentrations.
- All have workers and/or volunteers and customers and public users, residents, cleaners and building maintenance or service people. The concept is relevant to both short term and long-term exposures to formaldehyde.

- Page 6, lines 147-148 of [18] Consumer Exposure Assessment for Formaldehyde

"consideration of retail" …. This skirts the issues of where component parts are assembled for purchase or use by consumers, including general public using venues with multiple products, each containing formaldehyde, each contributing to the air concentration in that space. The products aren't purchased in retail by the people exposed…customers in movie theatres, in public transportation vehicles, computer centers, offices, libraries, bookstores, etc. In many venues, exposed people include customers, workers, and others in areas where inventory of the retail-available items are in the "indoor environment" …perhaps in greater quantities than in "residences" and probably as newer retail items…providing potential for greater off gassing than similar retail products in a "residence."

Limiting the exposure scenarios appeared to exclude such venues that make daily contributions to any given person's daily exposure, and certainly across a population limits the range of exposure opportunities. Definitions of COU and the "standard scenarios" should not inhibit realistic exposure assessment, and do not need to be so limiting. If indeed these exposures are small, the quantitative assessment will reveal that and their contributions in a probabilistic aggregate model will be modest. However, limiting assessments by intuitive assumption cannot be scientifically supported.

- Note also that in the Occupational Exposure assessment, done for "workers and occupational non-users (ONU's) (Page 15, lines 634-641 of Occupational Exposure Assessment for Formaldehyde), [1]the exposure scenarios do not seem to reflect this large group of people who work in the interior space. Worker and ONU activities are described are clearly focused only on the manufacturing, processing type work…not those described above (Page 19, lines 762-766 and Table 1-1 of Occupational Exposure Assessment for Formaldehyde). However, it clearly states that "Workers and ONUs are exposed by the inhalation route as formaldehyde is a volatile chemical and is known to off-gas from formaldehyde-based products. The exposure assessments for 36 Occupational Exposure Scenarios (Page 15, lines 639-640 of Occupational Exposure Assessment for Formaldehyde) are based on monitoring data which could represent concentration contributions from multiple COUs (Page 18, Figure 1-1 of Occupational Exposure Assessment for Formaldehyde). This approach would be useful to assess the exposure from many COUs contributing to air concentrations in vehicles (see separate discussion here).
- Monitoring data for indoor spaces are not utilized in "Consumer exposure" assessment as compared to assessments of indoor Occupational Exposure. However, EPA recognized the advantage of monitoring information for indoor scenarios where multiple COUs contribute to the indoor air concentrations.[2]

[1] Page 15, lines 634-641 of Occupational Exposure Assessment for Formaldehyde

[2] Page 111, lines 2765-2768 of Draft Human Health Risk Assessment for Formaldehyde.

Vehicle interiors can be considered a unique enclosed environment which presents a significant opportunity for both short term exposures from peak air concentrations as well as long term, repeated exposures. A publication by Wang et al[v] reports concentrations of formaldehyde and other volatile organics off gassed from the components of relatively new cars. Formaldehyde concentrations were sensitive to interior temperatures and were the dominant volatile among the chemicals analyzed. The study carefully documents the formaldehyde air concentrations under conditions very relevant to likely exposures to many Americans in short term high concentrations scenarios when first entering warm vehicles (acute exposure values) and continued off gassing over potentially hours of car-time per day (chronic exposure). More than 15 million new cars were sold in the US during 2023, with expectations that more will be sold in 2024. Such exposures could be repeated multiple times per day, every day. Concentrations will, of course, diminish over time for each car, but that could take months or years before low levels are reached. The study predicts exposure via inhalation and dermal exposure (Refer to Figure 1 from the Wang et al. publication).

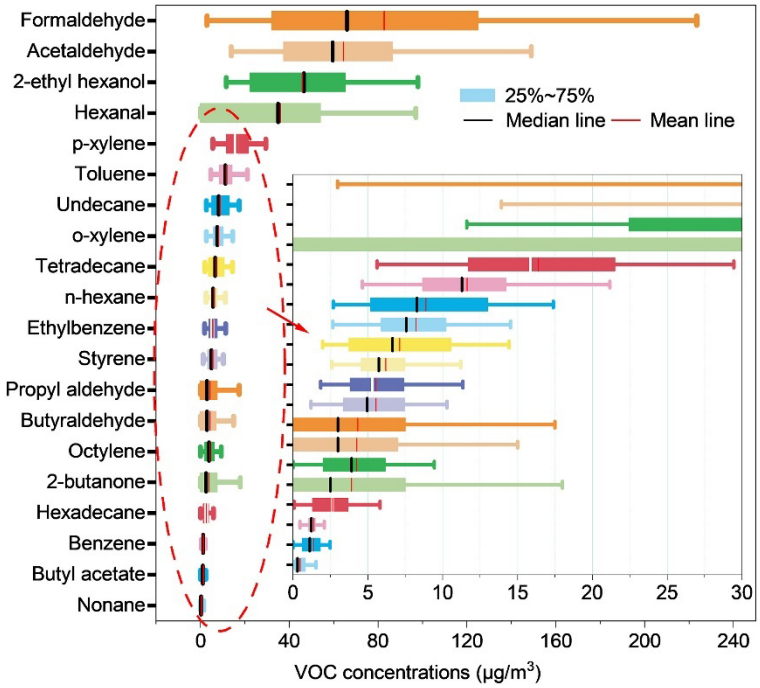

FIGURE 2: In CQ 4.1 Response

Another study[vi] monitored formaldehyde accumulation in air of vehicles, considered as a unique microenvironment due to its small, confined space where chemicals emitted from vehicle components may be concentrated. This publication includes a long list of reputable studies measuring volatile organics in vehicles and makes the case that vehicle interiors should be considered as its own venue, along with indoor spaces and outside air. Clearly, monitoring study results would provide the best estimates of formaldehyde concentrations in air from aggregated individual product contributions. Vehicles are also unique venues in that people of all ages and vulnerabilities will be in this space for some time, often entering after the air has accrued by off-gassing for several hours (or days). Both acute and long-term exposure values can be derived from these studies.

The Committee concluded that EPA's Standard 30 scenarios are considerably incomplete. Also, exposure to many populations are parsed by the scenarios when considered product-by-product or scenario-by-scenario, when actually exposures should be considered as combinations of many

scenarios. The current approach might be acceptable if those separate exposure scenarios were "reassembled" in a competent, probabilistic exposure assessment model that yielded a representative exposure profile when direct monitoring was absent or inadequate. The Committee is concerned about the current EPA presentations of exposure, especially when probabilistic statistical approaches for data usage and modeling are not employed. This issue is discussed in detail in CQ 7.1.

Charge Question 4.2

Please comment on additional information relevant to formaldehyde and not considered in the Draft Consumer Exposure Assessment (U.S. EPA, 2024c) that may support evaluation of current consumer activities and use patterns. In your comments, please describe the strengths and uncertainties associated with these identified sources.

Response to Charge Question 4.2

As described in the *Draft Consumer Exposure Assessment*, there are many potential sources of exposure to formaldehyde and its products, occurring as a gas, component of a solid or liquid product, and as a residue associated with manufacturing process. Because of the variation in exposure sources, patterns of usage, and nature of exposure, it is most expedient to categorize the types of potential exposure in order to assess the risk to the average consumer, while acknowledging that these are just best estimates. Charge question 4.1 considered relevant sources of exposure and articulates the array of both products and scenarios that can impact individuals and potentially subpopulations. Similarly, CQ 4.3 contains information about potential exposure scenarios pertinent to human health and specifically to cancer risk estimates.

Many of the comments are captured directly in the recommendations, below. Additionally, the Committee offered that lack of public information about the uses of formaldehyde may lead to misinformation and consumer overreactions. Conversely, the potential for exposure to consumers is also not generally clear and should be accompanied by appropriate labeling, that provides optimal use while protecting the user. Use of formaldehyde as an antimicrobial is generally not understood by the public, albeit beyond the scope of this charge. The use of formaldehyde as an antimicrobial in feeds (ex: poultry, pigs, etc.) should reduce the use of antibiotics, especially in young animals. There is a low probability of spread to the environment through the disposal of carcasses and other waste.

Recommendations for Consumer Activities and Use Pattern Evaluation—Considerations and Uncertainties

Recommendation: Consider using these to validate the ranges of concentrations produced by the Consumer Exposure Model.

- **Sources of potentially useful information includes a large amount of indoor air data collected in response to the Consumer Product Safety Commission investigation of the Lumber Liquidator use of flooring from China. Flooring from China was installed in over 600,000 homes over a 4-yr period. The limitations of these data are that they are not representative of "typical" use conditions. But these data might provide an additional source of flooring exposure information.**

Recommendation: **Attempt to normalize the data from the older literature, taking into consideration the sensitivity and measurement methods (and their limitations) used at that time to derive indoor air concentration of formaldehyde over past decades. This could provide some insights into possible mitigation of formaldehyde concentrations in the indoor air environment and information on current status of this source of exposure.**

- **It is important to distinguish types of structures (i.e., homes, mobile homes, age of structure, insulation, and outdoor air passage, etc) and as is discussed in the document and tables, and to emphasize greatest sources of risk. In addition, the change in permitted emission from composite wood products and other potential areas of mitigating exposure should be clearly articulated.**
- **Use of wood stoves and other sources of formaldehyde that are not in as frequent use should be part of any historical model, although some of these sources of exposure are outside of the scope of this draft document.**
- **Would there be merit in considering an integrated model that brings together the possible sources of indoor formaldehyde exposure to show changes in the consumer usage of products, wood stoves, and other sources of formaldehyde over time? This may not be possible within the scope of TSCA?**

Recommendation: **CEM inputs used for consumer product and scenario specific parameters should reflect the loss of loaded formaldehyde in consumer products during the transportation and/or the shelf life of consumer product(s), with the following rationale.**

- **The exposures to transportation workers, warehouse and bulk distribution centers would be represented by the initial, high off gassing phase of the products rather than mean values. Consumers of the product in businesses, public spaces, residences, and other venues as well as workers in those spaces (retail workers, teachers, cleaners, security personnel, etc.) could experience exposure as a function of any point of the distribution of values representing the off gassing over the lifetime of the product. The Committee recommended the EPA be provided probabilistic exposure models which could accommodate full value distributions for such parameters.**
- **Formaldehyde (gas) is highly reactive and volatile. Therefore, the amount of formaldehyde loaded into the finished consumer product(s) is not likely to remain the same during the shelf life, including the transportation/shipment, of product(s) as well as during its lifetime of use by the consumer.**

Recommendation: **Consider the types/forms of formaldehyde used in consumer products for assessing risk and potential outcomes in predictive models.**

- **For example, if a formaldehyde-donor, a chemical compound that slowly releases formaldehyde during the product shelf life, is used as a biocide or preservative in products, the consumer exposure level of formaldehyde from the use of a given product is likely to be dictated by the formaldehyde release rate of the formaldehyde-donor, rather than calculated amount or loaded amount of total formaldehyde. This life span chemical characteristic is an integral component of calculating accurate assessments of exposure and potential risk.**
    i. **The current CEM modeling may overestimate exposure levels of consumer products in the home, depending on the consistency and use patterns for individuals. However, there are scenarios as described in CQ 4.1 in which multiple types and venues of exposure have not been considered. In addition,**

the public presentations contained several consumer product manufacturers/associations have already generated or gathered the analytical data that describe the level of formaldehyde being released depending upon the age of consumer products manufactured. These types of data can be used to minimize/reduce the data gap or the uncertainty in consumer exposure assessment.

Recommendation: A "retention factor" should be applied in CEM inputs, defining "retention factor" as the mean average concentration of free formaldehyde (anhydrous) during the shelf life of a given consumer products. The retention factor could be measured by chemical analysis of the product at regular times during the shelf life of the designated consumer product.

- **In doing so the agency should review the quantitative analytic methods for measuring formaldehyde and associated chemicals concentrations and provide guidance on the recommended analytical method. This guidance is important because analytical methods (e.g., post column derivatization with High Pressure Liquid Chromatography (HPLC) and the analytical reagents (e.g., acetylacetone derivatization, enzymatic dehydrogenase assay) used for determination of free formaldehyde are destructive to formaldehyde molecules, which could affect the accuracy of the data.**

Recommendation: Consider the varying frequency of product use, acknowledging that while individual use may be intermittent for certain products, other sources of exposure may be more consistent. This should be taken into account when generating an Exposome-like estimate.

- **Textiles use formaldehyde as part of the finishing process. While the potential for exposure should diminish over time, some chemical additives to cloth (ex: flame retardants in children's clothing) are persistent and can pose a risk.**
    i. **Are there estimates of concentrations of formaldehyde remaining in the cloth and where is the chemical contained (i.e. on the surface finishes, cross linked chemically into the material, or as a transient residue that will be washed out)?**
- **There often is an assumption of negligible levels of exposure that is appropriate, given that it is not possible to delve into all the complexities of potential low-level exposures.**
    i. **The Committee discussed during the public comment period of possible low dose effects, which may become more important in future assessments as more sensitive indicators of short- and long-term effects on individual health.**

Recommendation: Consider using nested approaches such as Multicriteria Integrated Resource Assessment (MIRA) [Stahl and Cimorelli, 2013]. A demonstration of the necessity and feasibility of using a clumsy decision analytic approach on wicked environmental problems. Integr Environ Assess Manag. 2013 Jan;9(1):17-30. doi: 10.1002/ieam.1356. Epub 2012 Dec 4. PMID: 22893308. and Stahl C, Cimorelli A.eds., 2020 Environmental Public Policy Making Exposed: A Guide for Decision Makers and Interested Citizens, Springer Press] *to* integrate factors influencing levels of exposure associated with potential adverse outcomes. This type of analytical approach allows weighting of these potential influencing factors.

- **The Thin-Film Model used to estimate dermal exposures provides some insight into potential adverse effects.**
    - **Are there data on the allergies and other adverse non-lethal effects associated with longer term contact with skin from products containing formaldehyde?**

- **Similarly, are there data on exposure scenarios that yield chronic effects, such as early exposure of infants to plastics and toys?**
- **Reconsider and explain the estimates of exposure for users of arts, crafts, and hobby materials. The current EPA estimates for these exposures are vague. If these estimates are based on professional judgments, this should be clearly stated.**

Recommendation: Make every effort to inform the public with clear and current guidelines to help them make knowledge-based decisions on usage and protective clothing.

Recommendation: Consider physiological indicators as early warning signs for adverse effects and incorporate them into the assessment of potential risk.

- **These physiological indicators for exposure are already incorporated into Adverse Outcome Pathways (AOP) estimates and useful in assessing the potential risk for individuals. The emerging field of Exposomics considered these physiological indicators as potential associated metrics for exposure and later adverse effects. Both the Exposome for an individual and the measurements (Exposomics) will be useful tools for the agency to include in this and future risk assessments for humans.**
- **Although secondary formation of formaldehyde is not encompassed in this review, use of physiological measures could provide an indicator of exposures, with possible confounding findings due to additive unmeasured exposures.**

Recommendation: Consider several aspects of contributions from wood stoves and other combustion sources.

- **Exposomics can be applied to ecosystem inhabitants, specifically wildlife, to assess ambient levels of formaldehyde in the environment.**
- **Reevaluate emission rate assumptions, considering that many homes in the US do not have air conditioning and indoor temperatures can exceed the 70°F assumption used in EPA modeling, especially during heat waves. Kuras and colleagues (2015) found significant heterogeneity in indoor experienced temperatures (IET) within a Boston neighborhood, with IETs exceeding outdoor temperatures during heat waves.**

General Comments

Chemical Releases Document

LL137-139: Large networks of air monitoring data, like the Air Monitoring Technology Information Center (AMTIC), should be consulted to ground truth the TRI and National Emissions Inventory (NEI) reported values.

L186: The use of Figure 1.1 in several documents is helpful in placing the individual work products in context. This is especially true of an evaluation of this complexity.

L226: Using NAICS categories to assign Condition of Use is a good approach.

L346: Manufacturing is manufacturing so discounting the highest value is inappropriate. The maximum value is 14,272 kg/yr, not 10,161 kg/yr.

L357: Comparison of airborne formaldehyde maxima do not show similarity. The maxima differ by an order of magnitude.

LL443-450: This paragraph includes uses in commerce that should be regulated in total not haphazardly. Toxic responses to formaldehyde from a given exposure route are not dependent on the source of formaldehyde.

LL460-463: The only way for significant over or underestimation of releases from the methods described are if you have insufficient data to make a reasonable distribution. The solution is to gather the information not to fret over representing zeros.

LL466-470: Modeling both production timeframes is a good aspect of the approach.

L714: Can the newer NEI data be added to Table_Apx_D3?

Appendix G

LL966-967: The following statement does not make sense. "The highest emitter for stack emissions was Panda Sherman Power Station, which is unlikely to fit these COU…" If this emitter is part of the listing, how can it not fit COU?

LL982-983: The SACC has addressed the point of integrated exposures in previous meetings. The approach captured by the statement "…However, EPA OPPT believes the use of formaldehyde as a disinfectant would fall under FIFRA, and therefore would be a non-TSCA use." highlights a flawed approach to risk assessment. If there is a FIFRA emission and risk assessment (evaluation) for formaldehyde, it should be incorporated into this assessment (not reinvented, simply incorporated). In cases where there are uses or byproducts, but no data, then the EPA should gather needed data to evaluate that aspect of exposure. To repeat pesticide use is a part of commerce. This may introduce non-point sources to the evaluation.

LL1060-1061: Claiming CBI is immaterial for the number of pounds used or released. The agency can aggregate these numbers and protect the user's identity. This must be addressed. Even if the statement is that the businesses claiming CBI had emissions at least a factor of X below emissions reported for those who reported. This is a great case of EPA needing to require monitoring data to circumvent the veil of CBI that some users and/or producers are using to conceal emission data. This comment is not confined to the formaldehyde evaluation. It pertains to all current and future evaluations by the EPA.

Recommendation:

- **Require Users and producers to provide data needed for a thorough assessment of emissions.**

Chemical Fate Document

Figure 3.1, page 12 does not include hydrocarbon or other atmospheric organic compounds that are photochemically converted to formaldehyde or formaldehyde precursors.

Environmental Exposures Document

LL90-94: models need to consider ALL formaldehyde sources and then consider which if any should be reduced or eliminated to protect human and environmental health.

LL109, 123-128, L160-164: Releases of formaldehyde and precursors also need to be considered as do mobile sources. The abundance of formaldehyde from combustion is noted here and must be

addressed in any comprehensive risk determination. Industrial releases of formaldehyde precursors like ethane, ethylene, isoprene should be included as sources of formaldehyde. The industrial COUs can be overlain atop them.

Charge Question 4.3

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) describes uncertainties regarding chronic cancer consumer exposure estimates associated with assumptions on duration of use/exposures over a longer period (e.g., lifetime exposures from photo processing solutions), given that consumer habits and products may change over time. Uncertainty in such exposure estimates (e.g., to liquid photo processing solutions or arts and craft materials) contributes to uncertainty in cancer risk estimates for those consumer conditions of use. Please comment on information or approaches the Agency may want to consider that will increase confidence in long-term exposure estimates and corresponding cancer risk estimates (where appropriate) for consumer products.

Response to Charge Question 4.3

The EPA focused the SACC's attention onto values assigned to factors applied to deterministic algorithms utilized in exposure assessments for long-term exposure estimates associated with specific COUs and exposure scenarios. Many of these factors are catalogued in EPA's Exposure Factors Handbook (a valuable reference and resource) or easily found in national surveys while some represent assumptions…often based on common sense or past experience. Together, these factors mathematically define the exposures as per the EPA algorithms in the deterministic models.
In real life, these types of factors do indeed describe underlying mechanics of exposure scenarios for people in various environments at different stages of life and across different environmental circumstances. And of course, as time changes, those "typical" environments change, activities change, products change—concepts easily understood by the public. The fact of change with time presents a conundrum for every long-term exposure and risk assessment that has or will be considered by EPA. In the formaldehyde documents, EPA highlighted such circumstances as "uncertainties" which sometimes deterred EPA from making the exposure and risk calculations. The Committee recommended such calculations be made, with appropriate caveats presented as well.
Long-term exposure estimates for cancer risk for individuals and populations rely on multiple factors (see figure 3). As such, there is great uncertainty in the precise risk for an individual to develop diseases as shown in the figure below, including cancer, dementia, and other conditions associated with long-term exposures over the lifespan. The relative risk for an individual will also vary over the lifespan, generally with younger and older individuals being potentially more susceptible. Chronic environmental exposure concentrations experienced by populations, such as those residing in industrial areas, will create greater probability of later adverse outcomes.

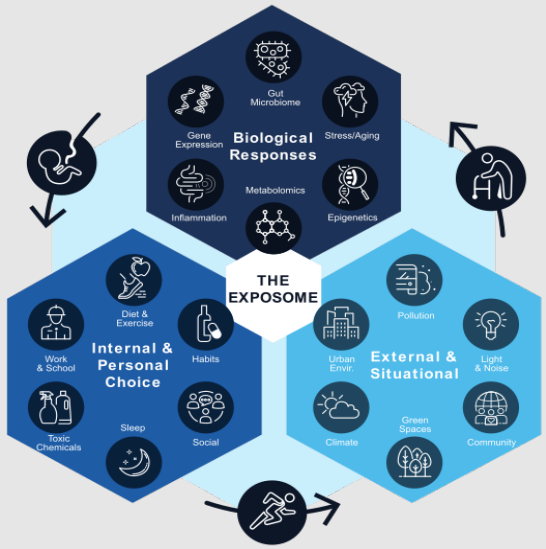

FIGURE 3: Chemical Exposure Scenario.
From: Ottinger and Geiselman, 2023. One Health Meets the Exposome. Elsevier Press.

However, for some chemicals, it is possible to provide guidance for proper use and to inform the consumer about practices to limit exposure, such as proper air flow and limited dermal contact and reduced inhalation. Conditions, such as asthma, conditions with reduced lung function, and skin conditions (dermatitis, psoriasis) involving immune function activation can alter the potential long-term adverse outcomes from chronic exposures.

- **While confidence in such assessments cannot be guaranteed, use of the best available science increases confidence in assessment results. Consideration of PESS and fenceline communities is required by TSCA and can be a real tool for EPA to build credibility and encourage participation by the public and collaborative information submission by communities, states, unions, and others across the nation. Including a broader range of exposure possibilities will present assessments relevant to what people actually experience and will provide perspective on the TSCA related exposures. Such transparent, and complete, aggregated assessments can satisfy the public's real question---"what am I exposed to?"-- and provides credible information to the TSCA risk managers and leadership for regulatory decision-making.**

<u>Recommendations:</u>

- **Implement the following information and approaches to improve confidence in assessments and ensure compliance with contemporary expectations of "best available science":**
  - **Include the broad scope of exposure opportunities, including all required by the TSCA mandate (see discussion in CQ 4.1). Also, exclusion of exposure scenarios, products, uses, or even non-TSCA exposure scenarios should be avoided if at all possible. Include these in the proper exposure/risk assessment tools that will reveal the contribution proportions from each exposure scenario. Assure PESS, and fenceline scenarios are identified and addressed. Two improvements on execution of this new requirement are possible:**

- **Provide a scope document before the assessment begins and circulate that document widely. Scenarios suggesting PESS and/or fenceline scenarios should be noted with requests for information and suggestions on such situations.**
- **Collaboration with wider community groups, states, and other stakeholders. It appears that EPA's efforts on this have improved significantly over the past few years. We encourage further efforts and commend EPA for the attention they have shown to this issue to date.**

Recommendations:

- **Compare conclusions reached in EPA assessments (hazard, exposure, risk) with decisions reached by other global regulatory authorities and scientific organizations.**
- **Include consideration of the underlying information, including how data were applied in assessment models. For significant differences, provide a thorough and coherent technical explanation of the differences.**
- **Collaborate with representatives (or other knowledgeable scientists) of the Authorities and/or Scientific Organizations holding the different assessment answers to develop this explanation. This should not be a competition over who is right. It should just be an explanation of WHY there are differences in the answers.**
- **Acknowledgement of these differences could be a big step toward credibility. These differences will certainly be highlighted after EPA's decision documents are published and without the comparison discussion, EPA's credibility will be questioned in forums not necessarily in concert with EPA's perspectives.**

Recommendations:

Statistical issues:

- **Present the full distribution of values for parameters used in any part of the algorithms and/or model assumptions, along with key statistical metrics. Explain how these values will be applied, specifying whether original distributions, parametric distributions, or single values for deterministic calculations will be used. Clearly justify the choice of single values (e.g., normative, sentinel, upper bound) and note that the selection may differ for various exposure questions (e.g., short-term vs. long-term). This issue and related statistical topics should be discussed more extensively in other charge questions or as overarching commentary.**

Recommendation:

Modeling issues:

- **Provide TSCA scientists with competent, probabilistic, and flexible modeling tools capable of aggregate exposure assessment, considering lifetime physiological factors and multiple exposure opportunities. This will enhance the current deterministic models and simplistic approaches used by the EPA.**
- **Provide and aggressively utilize statistical software for thorough data examination, including determination of variation versus multimodal distributions or unique data subsets. This is likely to reduce the issues of "uncertainty" noted many times by EPA in the formaldehyde assessments. These are expected standards for today's "best science" claims, and the EPA should use the available data to the fullest extent in formulating models. Together with good statistical understanding of the studies, probabilistic tools will enable EPA to use this wealth of information to full potential. The Committee sees this recommendation as a vital part of application of data in the spirit of best science for a regulatory purpose, not as a research endeavor as inferred in some conversation. This**

issue and related statistical topics are discussed more extensively in other sections of the overall Committee response.

- **Utilize the probability of occurrence of an exposure scenario for different populations, life stages, socioeconomics, etc. This is a key for aggregate exposure and risk assessments. A more detailed discussion will occur more extensively in other charge questions or as overarching commentary.**
- **Consider the potential health impacts of long-term dermal exposure, especially to vulnerable populations via clothing and other every-day exposures.[3] The lack of information for consumers regarding formaldehyde content in products is improving, but there needs to be more attention to sources of consistent exposure. For example, textile finishes, especially in children's clothing (including elastic) are a source of consistent skin contact which can be an irritant and predispose later sensitivity in the individual to formaldehyde containing products. Although non-cancerous effects, there is uncertainty in the relationship of immune activation and later disease. Department of Defense investigations can serve as prototypes (flame retardants, pesticides and now PFAS).**

<u>Recommendation:</u>

- **Although information for consumers regarding formaldehyde content in products is improving, increase attention to sources of consistent exposure.**
  For example, textile finishes, especially in children's clothing (including elastic) are a source of consistent skin contact which can be an irritant and predispose later sensitivity in the individual to formaldehyde containing products. Although non-cancerous effects, there is uncertainty in the relationship of immune activation and later disease.

<u>Recommendation:</u>

- **Clarify whether chronic exposure in Table 3-1 (page 74 of the *Draft Human Health Risk Assessment for Formaldehyde*) refers to periods of time per day or consistent exposure, such as living in an area with ubiquitous environmental pollutants in the air. This table captures the variation in POD derived from IRIS with consideration of sensitivities.**
  - **The confidence in POD is medium to high based on data from humans (pp 77-79). However, the lack of evidence for reproductive and developmental effects from inhalation should be given more attention.**

<u>Recommendation:</u> The Committee encourages the Agency to consider some approaches for providing public information:

- **Agency approaches for consideration:**
  - **Information bulletins online and through public venues**
  - **Working with industry on public information accompanying their product(s)**
  - **Figure 4-3 is particularly effective in showing relative levels of risk associated with exposure.**
  - **As explained on page 91, there are differences in the potential risk from various art and craft products. This information should be made accessible to the consumer and directly pertains to products with 0.1% formaldehyde content.**
  - **Lifetime Adjusted Cancer Inhalation Risk (Figure 4-8) is potentially useful for informing the public through website and other communications.**

[3] See CQ 4.1 response re: Formaldehyde from off gassing of components of new vehicles—inhalation and dermal exposure potential.

- **Emphasize the uses of formaldehyde, specifically the risk/benefit of uses, such as a biocide and other applications. As part of this approach, distinctions should be drawn between those industries that minimize the concentrations used in manufacturing and products so that the consumer can make informed selections.**

Charge Question 4.4

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the chronic inhalation hazard endpoints and PODs derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022) that have been peer reviewed by NASEM. Section 4.2.2 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the chronic inhalation POD to assess risks to people with exposure to formaldehyde through use of consumer products. Please comment on the strengths and uncertainties associated with OPPT's application of the chronic non-cancer POD for quantifying formaldehyde risks within the exposure scenarios outlined from use of consumer products.

Response to Charge Question 4.4

The Committee's comments presented in response to charge question 3.3 are applicable here particularly the general strengths/weaknesses of the chronic inhalation dataset and the Committee's detailed concerns with the Draft IRIS assessment and the development of the chronic non-cancer inhalation POD based on Krzyzanowski et al. (1990), as presented in response to charge question 1.2. Additional comments specific to applying the chronic non-cancer POD for estimating potential formaldehyde risks within the exposure scenarios outlined from use of consumer products are provided here.

Recommendations:

- **Strengthen the *Draft Human Health Risk Assessment* by providing a more thorough discussion of uncertainties related to data on formaldehyde sources and consumer uses in the study(ies) underlying the POD.**
- **Justify and explain the application of the POD, based on health effects in children, to adult consumers.**
- **Clarify whether benchmark dose modeling (BMD) was applied to the oral exposure studies.**

Strengths
See general strengths of the chronic inhalation dataset in CQ 3.3

Strength of the POD with respect to use of consumer products
The POD will be protective of PESS.

Uncertainties
Concerns with the Krzyzanowski et al. (1990) study are presented in CQs 1.2 and 3.3.

Uncertainties relative to use of POD to characterize risk of consumer products
There is limited information about formaldehyde sources in the Krzyzanowski et al. (1990) study and the related Quackenboss et al. (1989a,b) studies. We do know that there were smokers in some homes and there were older and newer homes sampled in these studies.

Concerns were raised about PECO relevance for adult risk characterization and POD determinations for many of the key studies as they seem to be potentially relevant to risk characterizations for children and youth. The same POD and benchmark MOE for adult consumers could potentially differ from the POD and benchmark MOE used for children and youth.

Additional uncertainty is introduced by the relative lack of clarity of how products are actually used by consumers and which COUs are better characterized via peak exposures tfor which chronic inhalation is relevant. In addition, some of the conditions of use (e.g., hobby materials) may be used more than once, but people's engagement with different consumer activities (e.g., having new furniture or other redecorating or remodeling [months]) may well be quite a bit more variable as compared to occupational tenure (similar job responsibilities for a decade).

Comments on the IRIS assessment/approach
In the *Draft Human Health Hazard Assessment* (page 22, lines 799-803) the Agency wrote: "OPP and OPPT also identified one dermal exposure developmental study in hamsters. The study did not identify any significant developmental effects of dermal formaldehyde exposure, but had substantial limitations related to uncertainty around the administered dose and concerns about the volatility of formaldehyde, and the limited timing of the exposure duration relative to sensitive windows of development (Overman, 1985)." The Committee suggested that this study may have informative value, acknowledging the limitations. The Overman (1985) study suggests that exposure by topical application during gestation reported no evidence of teratogenic effect (although the resorption rate was increased in the treated groups). This coupled with the fact that formaldehyde is a site of exposure based toxicant, it is highly unlikely that inhaled formaldehyde could arrive at the developing fetus based on this study.

Since sensitive windows of development are variable depending on the organ system, which organ systems would have fallen within the 8-11 days of gestation in hamsters whose gestation period is 20-22 days?

Charge Question 4.5

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the cancer IUR derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022) that has been peer reviewed by NASEM. Section 4.2.2 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the cancer IUR to assess risks to people with exposure to formaldehyde through use of consumer products. Please comment on the strengths and uncertainties associated with OPPT's application of the cancer IUR for evaluation of formaldehyde risks within the exposure scenarios outlined from use of consumer products.

Response to Charge Question 4.5

Many Committee members considered that the cancer Inhalation Unit Risk (IUR) used from the

unedited, *Draft 2022 Integrated Risk Information System Assessment for Formaldehyde* does not integrate all available data, despite the overwhelming weight of scientific evidence (WOSE) that the non-genotoxic mode of action (MOA) predominates and would be protective of any other MOA for formaldehyde carcinogenicity.

The use of conservative cancer IUR for evaluation of formaldehyde risks within the exposure scenarios outlined from use of consumer products may protect consumers who are very sensitive or susceptible to the effects of formaldehyde but requires expensive and unnecessary mitigations without any health benefits to the majority of consumers.

The inhaled formaldehyde is not distributed to an appreciable extent beyond portal-of-entry (POE) to distal tissues/organs based on the currently available experimental evidence. The sensory irritation is a local effect at POE that may progress to adverse effects under repeated and prolonged consumer exposure scenarios at POE. Therefore, the Agency could consider using sensory irritation as an end point for Points of Departure (POD) as a treatment effect that would protect against all downstream events including a carcinogenic response. The effects of formaldehyde by dermal contact or ingestion of consumer products are significantly less compared to those by inhalation. Several Committee members disagreed and found the IRIS assessment of formaldehyde to be a reasonable approach to be used for this assessment.

Recommendations:

- **Consider assessing the cancer potency using a threshold approach, rather than a linear, non-threshold IUR.**
- **Use a benchmark concentration (BMC)/benchmark concentration lower bound (BMCL) derived by Bayesian benchmark dose (BBMD) to obtain a POD, and subsequently the use of POD to further derive RfC.**

Uncertainties

MOA: Cancer IUR used from the unedited, *Draft 2022 IRIS Assessment on Formaldehyde* is not supported by a proper holistic interpretation of the collected data and should not be used by OPPT for risk assessment. The concept of mode of action enables the organization of data into a coherent explanation of the process that leads from exposure to a chemical to an identified chemically induced adverse outcome. While it is frequently illustrated as a linear process for ease of explanation, that is not typically how biology works. However, each key event that is dependent on other key events has a temporal relationship and dependency not only on the dose of the inciting agent but the magnitude of the response of the other Key Events. For more complete descriptions of the process, there are numerous publications that can be referenced, as well as the OECD AOP Wiki (https://aopwiki.org/; Boobis et al., 2006; Meek et al., 2014; Meek, 2017).

The interpretation should be based on a holistic evaluation of all the data as well as an understanding of the underpinnings of the process (Figure 4, page 85 below).

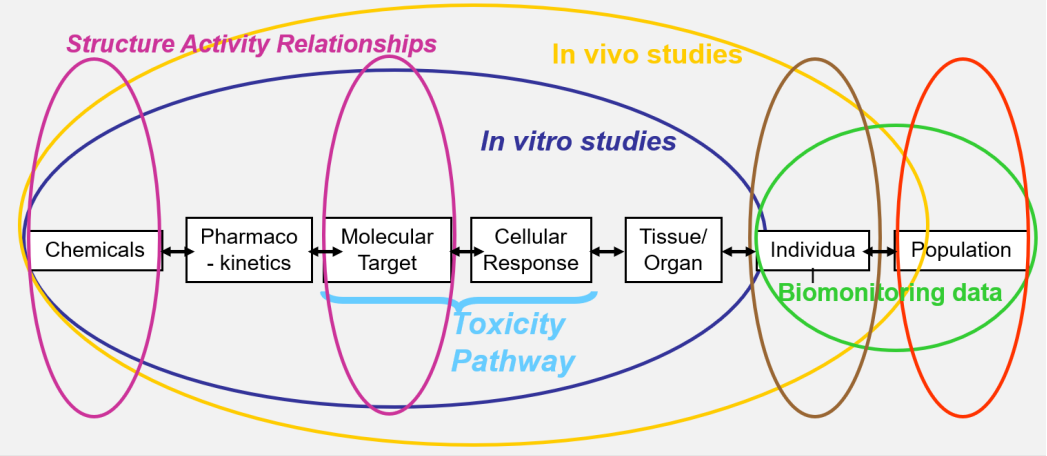

FIGURE 4: Adverse outcome pathway (AOP) and the data streams that inform the pathway. This enables the application of the most appropriate tools, including modeling and in vitro assays, to enhance understanding.

In the case of carcinogenicity, the fundamental aspect of a malignant neoplasm is that all tumors have a collection of genetic mutations and have cellular proliferation occurring (Wolf et al., 2019). The key is the rate limiting step in the process, as described in the numerous articles describing mode of action analysis (Boobis et al 2006; Meek et al., 2014). Most importantly there is no such thing as multiple modes of action leading to the same adverse outcome in the same tissue and individual (Figure 1, 2, 3, and 4). This likely arose from the idea that naming something makes it a separate mode of action. That chemicals that may cause several biological events such as oxidative stress, cell death, chromosomal, or DNA damage leading to or related to a specific adverse effect are working through 4 separate modes of action. That is not a factual statement that accurately depicts what occurs pathophysiologically in the tissue. These separate biological responses should be organized into a single mode of action which describes the relationship amongst the biological responses, their dose-response, and time course leading to the adverse outcome. This is consistent with the internationally accepted IPCS framework and OECD AOP collaborative (https://aopwiki.org/).

Instead, a single mode of action leads from exposure to the target cell that ultimately results in a specific adverse effect. A mode of action or adverse outcome pathway (synonymous for the human risk situation) has a set of related biological responses that are necessary (Key Events) that lead to a specific adverse outcome. Once a mode of action is described, one can then perform a quantitative risk assessment based on what the Key Events are, what the Molecular Initiating Event is considered to be, the dose-response for the key events, and which event(s) may be the rate limiting step. (https://aopwiki.org/; Simon et al., 2014).

Therefore, one describes the mode of action based on the collective data, determines the Molecular Initiating Event and Key Events, describes them and after one does that, determines if there is sufficient information, if other potential modes of action are ruled out, and if one can perform a quantitative assessment of the rate limiting steps leading to a RfC/RfD approach to risk characterization. One member suggested avoiding terms such as threshold in this context as it has a lot of baggage.

This is standard practice across the Agency as well as among most regulatory agencies and is based on the WHO IPCS and ILSI-Risk Science Institute work of the late 1990s that ultimately led to the 2005 US EPA Cancer Guidelines, which are still the most authoritative guidelines for mode of action evaluation.

Specifically, a chemical may have more than one mode of action that leads to different adverse outcomes in different tissues. For example, unleaded gasoline is a nuclear receptor agonist in the mouse liver that results in a mitogenic response, promotes, and enhances spontaneous tumors, and results in liver neoplasms. In the rat kidney, however, it induces renal neoplasms through persistent cytotoxicity and regenerative proliferation from alpha 2 urinary globulin accumulation.

A chemical may have the same mode of action in different tissues. For instance, chloroform causes a cytotoxic and a regenerative proliferation response in the liver and the kidney, resulting in tumors in those two sites.

Thus, to state that formaldehyde respiratory tract tumors have both a mutagenic mode of action and a cytotoxicity/regenerative proliferation mode of action is an incorrect application of mode of action analysis and an incorrect interpretation of data. Thus, the mode of action may be more complicated. However, regarding formaldehyde, there is ample evidence to show that it is not a direct acting mutagen, and that direct cytotoxicity is the rate limiting biological step.

FIGURE 5: Multiple modes of action – different chemicals may produce the same lesion through different MOAs.

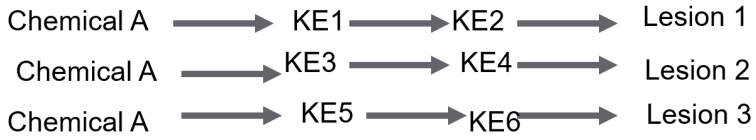

FIGURE 6: Multiple modes of action – a chemical may produce different lesions through different MOAs and thus the chemical can have multiple MOAs.

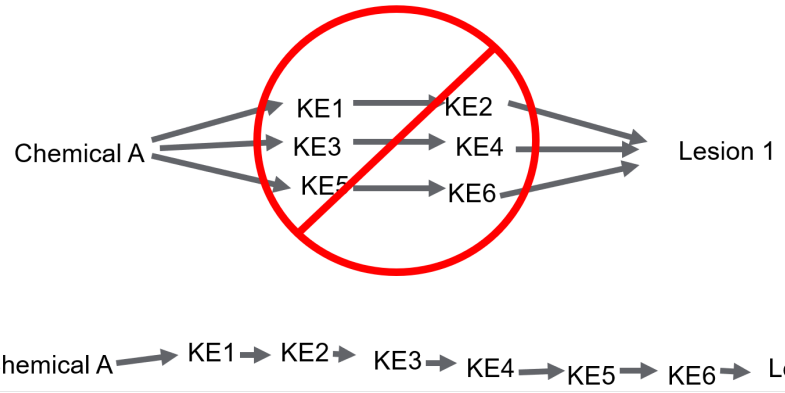

FIGURE 7: Multiple modes of action – a chemical does not produce a lesion through multiple separate MOAs. Instead, the key events should be organized into a single MOA. The mode of action is illustrated as linear, but this is rarely the case in pathobiology.

Formaldehyde, by its chemical nature, reacts with and cross links biological macromolecules, which is why it is used as a preservative for biological tissues. As described in the document, it is a highly reactive compound that does not get past the site of exposure.

If formaldehyde acted as a direct mutagen, then there would be a different tumor response in a number of the animal chronic studies.

Oral administration of formaldehyde at doses of 82 and 109 mg/kg/day to male and female rats for two years, respectively, caused severe damage to the gastric mucosa but did not result in gastric tumors or tumors at other sites (Til *et al*., 1989). If formaldehyde had a direct mutagenic potential, then one would expect a carcinogenic response to this chemical in the forestomach. The skin carcinogenesis study in SENCAR mice (a skin tumor susceptible model) was negative for formaldehyde at a 4% solution which neither acted as a complete carcinogen nor a promoter.

Monticello *et al*. (1996) provides additional support for the importance not only of sufficient cell proliferation but also that there needs to be a sufficient population at risk to result in an increased tumor response. The bigger the population at risk, the more cells are proliferating, which increases the risk of spontaneous mutations to occur (Wolf *et al*., 2019). There is a dose-dependent increase of proliferation across all the sites in the rat nasal cavity, but tumors only arise in the sites with the largest base population. Thus, the absolute numbers of cells proliferating are far greater in those sites with the highest base population. If formaldehyde acted as a mutagen, then tumors should be located across all sites where there was sufficient dose to increase cell proliferation, which was not the case.

The evidence supports the well-established complicated MOA that increased direct toxicity in a large enough population of cells leads to increased proliferation and will increase the likelihood of spontaneous mutations. By adding to the feature of formaldehyde cross-linking macromolecules, those cells that are able to survive could have an enhanced loss of DNA repair capabilities. This point is illustrated in Hester et al. (2005).

The importance of cell proliferation is discounted by a confusing comparison of hyperplasia and squamous metaplasia in the 2022 IRIS document. It is well established that the respiratory tissue will respond to persistent medium to long-term exposure to a direct irritant with squamous metaplasia,

which protects the exposed surface by creating a skin-like surface epithelium. For example, the respiratory tissue commonly responds in such a manner to cigarette smoke. The argument was presented that in some of these studies, no hyperplasia was diagnosed in those tissues. This is not the case since squamous metaplasia is a hyperplastic response and can be an early stage leading to a neoplastic response in the affected tissue (Wolf et al., 1995). Secondly, the typical practice of a toxicologic pathologist is to diagnose the most advanced lesion in a tissue, so while respiratory cell hyperplasia may be present on the same slide with squamous metaplasia, the study pathologist would diagnose squamous metaplasia, as it is the most advanced lesion.

Regarding non-respiratory tract tumors: First, as indicated in the National Academies (NAS) comments, it is inappropriate to lump tumor responses of unrelated cells of origin. While it might be useful to discuss cells of blood-forming organs conjointly as lymphohematopoietic origin tumors, this is only useful in a clinical setting, not in toxicologic pathology. Regardless of the source of the information being used to make a toxicologic pathology interpretation (e.g., rats, mice, monkeys, or humans), accepted standard practice should be used, even if the focus of the articles is on rodent tumors (Brix et al., 2020).

Regarding myeloid leukemias, by definition, they are bone marrow origin diseases which have neoplastic cells circulating in the peripheral circulation. There is no biologically plausible mode of action whereby formaldehyde can arrive at the bone marrow to result in direct toxicity, and the suggested circulating stem cell through the nose makes no biological sense. The speed of blood flow through capillaries can be 0.5-1.5 meters per second, which means a rare circulating myeloid stem cell would have to be exposed, get damaged, make it back to the bone marrow, avoid the intrinsic system that monitors for damaged cells, mutate, and proliferate. This indicates that formaldehyde is unlikely to pass through the respiratory surface due to its reactivity as described in the document. Furthermore, even if a circulating cell developed a mutation, it would not repopulate the bone marrow, Also, even if there is an association, which does not indicate there is causation (Cox et al., 2024; Vincent et al., 2024).

In a causal analysis to evaluate whether causal pathways lead from exogenous formaldehyde exposures to increased risk of acute myeloid leukemia (AML), and to quantify the causal contributions of such exposures in terms of how removing them from the causal model would change health risks, expressed as Interventional Probability of Causation (IPoC), no causal pathway leading from formaldehyde exposure to increased risk of AML was identified, consistent with much previous mechanistic, toxicological and epidemiological evidence; no reasonable causal directed acyclic graph (DAG) could be derived, primarily because the exposure → bone marrow concentration pathway cannot be completed, due in part to the inability of inhaled formaldehyde or its metabolites to reach beyond the portal of entry at biologically significant concentrations. No clear causal increase in AML risk in response to formaldehyde exposures has been established in either laboratory animals or in humans (Cox et al., 2024).

The Agency indicated the purpose of the current evaluation was to establish an understanding of the MOE to assure no appreciable risk of harm. It was therefore unnecessary to list all the potential carcinogenicity responses that might or might not be associated with formaldehyde exposure. It is sufficient to point out that there is evidence that formaldehyde could result in a carcinogenic response and to show that the human exposure concentrations have a sufficient margin from the potential for the early key event of an adverse effect that it will be protective.

As recommended by the Committee in the response to Charge Question 1.2, the Agency could better communicate their results using the publicly available Risk Assessment in the 21st Century (RISK21) (www.risk21.org) framework and webtool as more fully described in the response to CQ 1.4.

Endogenous formaldehyde: Cancer IUR used from the unedited, 2022 Draft IRIS assessment on formaldehyde does not consider how exogenous formaldehyde exposure impacts endogenous formaldehyde concentrations to produce portal of entry or systemic effects.

The Mode of Action for tumor formation by formaldehyde provides strong evidence that there is a threshold for the carcinogenic effects of formaldehyde. The following additional biological activities further support the importance of the early key events to select a point of departure that will be protective from chronic toxicity including a carcinogenic response: (1) the abundance of endogenous formaldehyde in biological systems, (2) the rapid metabolic detoxification to less hazardous chemicals, and (3) the efficient DNA interstrand cross-link repair system to maintain genomic stability.

Formaldehyde is involved in a fundamental metabolic process in cells that enables the synthesis of nucleotides and amino acids and is present in all forms of life (Burgos-Barragan et al., 2017). The level of endogenous formaldehyde in blood is relatively high in humans and is estimated to be 0.9–2.9 mg/g (Luo et al., 2001). According to the European Food Safety Authority (EFSA), endogenous turnover of formaldehyde in human is estimated to be approximately 0.61-0.91 mg/kg body weight (bw) per minute and 878-1310 mg/kg bw per day assuming a half-life of 1-1.5 min (EFSA, 2014). Due to the relatively high level of endogenous formaldehyde, organisms have evolved mechanisms to counteract formaldehyde (Burgos-Barragan et al., 2017; Schug, 2018). First, biological organisms have evolved a formaldehyde detoxification system centered on the enzyme alcohol dehydrogenase 5 (ADH5). This system converts formaldehyde to formate, a less reactive molecule that can be used for nucleotide biosynthesis. In this process, formaldehyde is also converted into carbon dioxide by taking part in the 1C cycle and is expelled from the lungs or oxidized to formic acid and discharged with urine. Second, the Fanconi anemia DNA repair pathway (Hashimoto *et al*., 2016) assures additional protection against formaldehyde by participating in interstrand cross-link (ICL) repair and the maintenance of genomic stability. In addition, nucleotide excision repair (NER) and mismatch repair (MMR) in humans play an important role for the ICL recognition and removal thereby reducing or eliminating the potential mutagenic effect caused by DNA ICLs in humans (Wu *et al*., 2005). This well-established biological detoxification and protection system, by multiple DNA repair enzymes, to formaldehyde provides additional evidence that there is a threshold for the carcinogenic effects of formaldehyde.

One Committee member stated that exogenous formaldehyde concentrations below approximately 2 ppm do not significantly impact the formaldehyde levels in the cells of the body as demonstrated by the extensive elegant adduct work by the Swenberg lab at UNC-Chapel Hill, NC (Edrissi et al.,2013; Rager et al., 2014; Yu et al., 2015; Lai et al.,2016 ; Edrissi et al., 2017; Liu et al., 2018; Leng et al., 2019). Furthermore, the formaldehyde dose to nasal tissues, as measured by formaldehyde adducts, is not impacted by exogenous sources of formaldehyde until exogenous formaldehyde concentrations of 1.9 ppm or more, and no exogenous adducts were detected in the bone marrow at exogenous exposure concentrations up to 6.1 ppm (Lu *et al*. 2010, 2011; Moeller *et al*., 2011). Thus, the body of scientific evidence does not support the elevated risks suggested by EPA in the Formaldehyde *Draft Human Health Risk Assessment*.

A protective point of departure and RfC can be used to protect from carcinogenic effects. Formaldehyde has been shown to induce nonlinear, concentration-related increases in nasal epithelial cell proliferation and squamous cell carcinomas (SCC) in rats (Monticello *et al*., 1996), which could also be selected as possible health protective points of departure and possibly modeling using the BMD modeling approach similar to how the US EPA OPP addressed Cacodylic Acid (dimethyl arsenic acid), previously reviewed by the US EPA SAB (https://archive.epa.gov/pesticides/reregistration/web/pdf/dma_moa-2.pdf).

5. INDOOR AIR ASSESSMENT

Charge Question 5.1: The Draft Indoor Air Exposure Assessment

The Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h) quantitively assessed (Section 3.1.1) four TSCA conditions of use (listed below) resulting in residential (e.g., homes, mobile homes, apartments) exposure and one TSCA condition of use (last in the list below) in vehicles that are expected to be consistent contributors of formaldehyde exposure.

These are:

- Construction and building materials covering large surface areas, including wood articles; Construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles
- Floor coverings; Foam seating and bedding products; Cleaning and furniture care products; Furniture & furnishings including stone, plaster, cement, glass, and ceramic articles; metal articles; or rubber articles
- Paper products; Plastic and rubber products; Toys, playground, and sporting equipment
- Fabric, textile, and leather products not covered elsewhere

> Please comment on the metrics and data used by EPA to focus its risk assessment on these four TSCA conditions of use. In addition to the consideration of relatively high emission rate and persistence (rather than temporary transient emissions), please provide feedback on additional criteria or information EPA may want to consider in its identification of major contributors to indoor air concentrations of formaldehyde.

Response to Charge Question 5.1: The Draft Indoor Air Exposure Assessment

Identifying a final list of conditions of use (COUs) for assessment is admittedly a difficult task. The EPA identified four categories of COUs for analysis. Conditions of use were selected based on an assessment of emission rates, and published literature, as well as professional judgment.

The rationale for the grouping of uses into the four categories needs to be more clearly justified. For example, a wide range of uses were grouped into the first grouping. These include "floor covering, foam seating and bedding products, furniture and furnishings, cleaning and care products, textile finishing etc…"

It was not clear how specific metrics were used to select the COUs. For example, what emission rate cut-off was applied to highlight the four chosen COUs, and how was professional judgement solicited

and systematically used as a source of input. Emission rates by themselves may not be sufficient to rank COUs. For example, a longer exposure time to a lower emitting product may be as important as a shorter exposure than a high emitting product, this should be discussed.

Emission rate data are quantitative and well-described. The choices of using the mid-point of reported values and the average of the median values is likely to be insufficiently protective. The alternative use of higher values, such as the 95th percentile, is recommended as a more accurate representation of emissions that are of concern, although this might not affect the choice or the grouping of COUs.

EPA should specify whether CEM results were used to validate the choices of COUs. If not, this may be another input to provide confidence that the COU choices focus on the greatest exposure risk. Overall, while the EPA could have used different groupings, and provided additional information or analysis, their choices in this area are reasonable and adequate for the analysis of risk from indoor air. A larger concern is the need to explore a more comprehensive set of exposure scenarios as described in response to CQ 4.2.

Recommendations:

- **Further explain how EPA chose the four COUs used in its analysis, and whether CEM results were used to validate them.**
- **Use 95% percentile emission rate data instead of the less protective central tendency value.**

Charge Question 5.2

The CEM has primarily been used to estimate short-term chemical exposures from consumer products in previous TSCA existing chemical risk evaluations. As described in Section 2.1.1 of the Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h), the CEM was used to estimate long-term concentrations of formaldehyde in residential indoor air. Please comment on the strengths and limitations of using the CEM to estimate long-term indoor air exposures to formaldehyde resulting from TSCA conditions of use.

Response to Charge Question 5.2

The CEM has been widely used in EPA risk assessments and can be used here. However, in discussion of previous charge questions, Committee members suggested that the model would be improved if a probabilistic approach was taken. The Committee agreed with thd comments, as long as a model could be constructed and validated in a reasonable amount of time.

For CEM results to properly estimate long-term indoor air exposures, product specific decay rates need to be incorporated into the model. Without this component, confidence in the resulting exposure data is limited.

Recommendations:

- **Construct, validate and use a probabilistic consumer exposure model, and compare its results with the existing results. This comment may be essential to improve risk evaluations of other chemicals undergoing TSCA review.**
- **Incorporate product-specific decay rates into the model or models. This comment may be essential to improve risk evaluations of other chemicals undergoing TSCA review.**

Charge Question 5.3

The CEM was used to model the contribution of specific TSCA conditions of use to indoor air when products and articles containing formaldehyde are newly introduced to homes, mobile homes, and vehicles. Due to the uncertainty in model input assumptions related to a person's likelihood to move into newly constructed homes, what products they acquire while they live in the home, and the uncertainty in the rate formaldehyde may be released from those products, the Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h) did not quantify chronic cancer risks associated with specific indoor conditions of use conditions of use that contribute to indoor air exposures. Please comment on EPA's assumptions and conclusion not to assess chronic-cancer risks for formaldehyde in indoor air based on uncertainties in exposure estimates beyond 1 year. Please also comment on information or approaches that may increase confidence in modeled COU-specific estimates for long-term exposures relevant to cancer risks.

Response to Charge Question 5.3

Cancer risk assessment for any population from aggregate exposure assessment modeled over a lifetime is always an assessment rife with uncertainty. The establishment of the potency curve is defined by the upper bound of the predicted curve's probable uncertainty. Uncertainty is assumed as we define products and people's activity over future years. Existing or historically defined products, emissions, environmental scenarios, or people's activity profiles will certainly change with time. But the task at hand is to estimate risk with what is now known or, as TSCA directs**,** would be reasonably expected. It is the Committee's opinion that avoiding a quantified assessment creates an even bigger issue of confidence than doing the calculation with description of its inherent uncertainties.
As discussed in other charge questions, the Committee concluded that EPA has a systemic problem regarding their use of the available data and the inability to do aggregated exposure assessment. Formaldehyde is richly researched, but the exposure assessment task is conflicted by at least two big issues. EPA models do not calculate value distributions for factors key to the exposure assessment, beginning with anticipated media concentrations, nor utilize standard principles of probabilistic modeling. These models do not calculate aggregation of multiple COUs or exposure scenarios, etc. This is a serious limitation of technical capacity for the scientists preparing these assessments. These issues again are raised here and are addressed more comprehensively in Charge Question 7.1.
The Committee offers the following recommendations and supporting discussion:
Probabilities of occurrence (percentage of residences with flooring, or with new flooring, etc.) are valuable data (or assumptions derived from narrative) to calculate a distribution of exposures in homes that are likely to have air contamination from given sources. Monitoring study results could be utilized in even more powerful ways with such approaches.

Recommendation:

- **Design parametric distributions for assumptions such as the duration of exposure and values of indoor air concentrations, as well as off-gassing rates for different media, showing a projected decline over 1 year. Report these values along with the entire distribution curve and the rationale behind the curve designs.**

The absence of any estimate for relevant cancer risk, from even a single COU in any exposure scenario, creates an unfortunate loss of confidence, presumably with the public and certainly for the scientific community. EPA's explanation of why that can not be done further erodes public confidence in EPA's technical capacity. Confidence building begins with trust, and that begins with

"best scientific approaches." The public would like to know, even in the absence of aggregate exposure, what could the risk be for at least the single COUs for which acute exposure assessments have been fashioned. As recently presented, the EPA appeared to state, "There is a cancer risk but we do not know how small or big that risk might be." The Committee concluded that the EPA draft assessment has dismissed too much information and avoided too many difficult aspects of the assessment to inspire confidence.

Recommendations:

- **Present quantitative risk assessments for all described scenarios, along with detailed descriptions of the approach and limitations.**
- **Conduct exposure assessments for each Condition of Use (COU) and for metrics from all monitoring studies. Use these quantitative exposure assessments to provide a perspective on the relative contributions of individual COUs. Compare results from individual COUs to those from monitoring studies, which presumably reflect multiple COUs.**

The Committee saw value in recognizing the work of other authoritative organizations and discussion as to why EPA's assessment delivered different answers than achieved by other regulatory authorities, particularly the EU. This discussion would have demonstrated the Agency had been aware of these differences and possess several explanations…again improving confidence.

Recommendation:

- **Acknowledge and discuss quantitative evaluations conducted by other countries and authoritative organizations, comparing their conclusions to those reached by the EPA.**

The Committee assumed the EPA will not immediately have a probabilistic aggregate exposure model. Evaluation of exposure and risk assessments with exiting deterministic approaches could be valuable. The EPA could utilize more than one concentration for variations of key parameters within each assessment scenario (creating multiple assessment answers for a given COU/scenario). The Agency could present a narrative on the limitations and concerns for each of these assessments, however their existence could provide some public confidence that EPA is not being dismissive. Discussions and comparisons across the assessments in that appendix could serve to bring perspective to the challenges in data utility, differences in assumptions for exposure scenarios, etc.

Recommendation:

- **Present an appendix containing an assembly of exposure assessments and risk assessments created with existing deterministic approaches. Use available monitoring data for COU-specific and exposure scenario-specific situations, especially those affecting PESS and challenged communities, as well as common microenvironments, such as new vehicle exposure and risk.**

Charge Question 5.4

The Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h) characterizes the available indoor air monitoring data as representing aggregate exposure from all sources of formaldehyde in indoor air including TSCA conditions of use. Several sources of indoor air monitoring data were considered, and the American Healthy Homes Survey II (AHHS II) (QuanTech, 2021) was determined to be the source of the most current nationally representative indoor air data. Please comment on the strengths and limitations of AHHS II, its application for this formaldehyde risk evaluation, and the conclusions that the data represent aggregate sources of formaldehyde in American residences. Please comment on the appropriateness of the other indoor air monitoring data considered in the assessment and the extent to which the weight of evidence narrative is supported by current indoor air monitoring information for formaldehyde.

Response to Charge Question 5.4

Strengths

The Healthy Home Survey is a relatively new study, and as such is likely to represent contemporary formaldehyde-based products and COUs. This survey is reasonably representative of US population in primary residences[4] in the US. Very good statistical design and thorough reporting represent a large sample (1,131 homes) with weighting to show permanent residence representation of the monitored formaldehyde concentrations. Excellent discussions by the authors explain the findings.

> Homes from 4 regions of contiguous US are represented as homes constructed from before 1940 to 2005. The survey reports formaldehyde concentrations [vii] by age of home, household income, # children < 6yrs old, US location (NE, Midwest, South, West), and other characteristics which allow insight into issues such as socioeconomics, (renter/owner, household income) (with inferences as to household content of new formaldehyde-based products.

Limitations

The AHHS II most likely represents American residences, but ONLY permanent residences were monitored, excluding all other interior building spaces…offices, schools, hotels, retail and showroom spaces, warehouses, etc. Hence, this is applicable only to a part of the potential daily formaldehyde exposure, even from the same COU (e.g. flooring).

No sampling was conducted in Alaska. It should not be assumed that this study represents formaldehyde concentrations in air within residences of Alaska.

> *….and the conclusions that the data represent aggregate sources of formaldehyde in American residences*

This study very likely represents aggregate sources of formaldehyde in American residences (except

[4] The target population for AHHS was all permanently occupied, non-institutional housing units in the U.S. in which children may live. Thus, vacant housing and seasonal housing, such as vacation homes, were ineligible for the AHHS, as well as any housing where children cannot reside, such as group housing and senior housing. Hotels/motels and military housing were also ineligible because of anticipated difficulties gaining access, although children may sometimes reside in such housing.

possibly in Alaska). It also shows other findings of interest for formaldehyde assessments.

- Table 1 of the AHHS II Final Report discusses several interesting findings which are important to consider regarding EPA's assumptions throughout their evaluation. Among those:
    - Homes in the Midwest and South had significantly higher concentrations than in the Northeast or West.
    - Homes built before 1940 had about 1/3rd lower concentrations than more recent ones. Discussion of this in the report suggests that the newer construction materials are made of more formaldehyde-derived components rather than all wood as used in the older homes. However, after 60 years of off gassing, floors and original construction materials may not be the major contributor to the formaldehyde concentrations in these older homes.
    - Homes of non-smoking families had higher levels of formaldehyde air concentration—a surprising finding. This finding was discussed and logic for this finding was offered. But it points out the perils and possible fallacies in assumptions utilized in exposure assessment approaches. EPA has noted that air monitoring may connote the aggregated air concentration, including from sources not covered by TSCA, but these findings show that when the non-TSCA sources are present, one cannot assume that the overall air concentrations will be higher. This study deserves a more detailed utilization of its findings and "lessons" about the perils of assumptions and intuition about qualitative assessments. The items mentioned above cast further doubt onto some assumptions made by EPA in their assessments.

The appropriateness of the other indoor air monitoring data considered in the assessment

The two key automobile monitoring studies utilized by EPA (Lawryk et al., 1995 and Lawryk and Weisel, 1996) have some significant limitations. Newer and better studies are now available, particularly a publication by Wang et al[viii] 2023. They report concentrations of formaldehyde and other volatile organics off gassed from the components of relatively new cars. A detailed discussion can be located in CQ 4.1. Formaldehyde concentrations were sensitive to interior temperatures and were the dominant volatile among the chemicals analyzed. The study carefully documents the formaldehyde concentrations air inside vehicles under conditions very relevant to likely exposures to many Americans…short term high concentrations when first entering warm vehicles and continued off gassing over potentially hours of car-time per day. Over 15 million new cars were sold in the US during 2023, with expectations that even more will be sold in 2024. Such exposures could be repeated multiple times per day, every day. Concentrations will, diminish over time for each car, but that could take months or years before low concentrations are reached. The study predicts exposure via inhalation and dermal exposure.

Other monitoring studies are useful for the exposure assessment and also for consideration across all study findings. While not designed and reported as was AHHS II, these data are valuable for a broader range of building types…each of which provide opportunities of exposure to the population. The Committee's response to Charge Question 4.1 details their opinion that consideration of "residence" is far too limited to represent formaldehyde exposure opportunities. The Committee recommended other studies there.

Recommendation:

- **Use all available indoor air, vehicle, and contained space monitoring studies to fully assess such exposures.**

The extent to which the weight of evidence narrative is supported by current indoor air monitoring information for formaldehyde

The EPA makes note that monitoring studies, themselves, cannot drive the exposure assessment because air concentration contribution from individual COUs cannot be readily estimated. However, the quality of the monitoring studies provides a very high degree of confidence for the assessment for the overall, general considerations of air concentrations expected in primary residence in most parts of the US. There may be weight of evidence support for quantitative EPA risk assessment decisions with further consideration of the studies (described below). These studies also deserve further integrated discussion in the EPA report for their findings regarding indoor environments other than primary residences (see below). Those considerations will further define the weight of the evidence as needed for different purposes, for different exposure scenarios, for different population groups, for different PESS (or fenceline) scenarios. Thus, the weight of the evidence support can be different for each purpose and EPA can discuss those important purposes separately.

Recommendations:

- **Descriptions in the EPA report of the findings for each of these monitoring studies should be presented in more detail. For example, the final report of the AHHS II (March 2024), especially as focused on the formaldehyde air concentrations for different types of homes, different locations, different population groups, etc, …. will bring perspective to the utility of the study, to variation of air concentrations found within a study, etc. For formaldehyde we have a wealth of information. The findings of any one study can be compared to findings from the other studies…even if those findings were from studies designed differently or were older. These are important perspectives and the concordance or disagreement among studies when viewed this way will be important for supporting the weight of evidence narrative, or for defending EPA's reliance on one study in preference of others, or to understand why there may be differences among the studies. Indeed, the limitations of the AHHS II may be addressed by use of other studies and would argue for more inclusive consideration of these other studies. While AHHS II is an excellent study, it does have limitations, especially when considering air concentrations for indoor environments other than people's primary residences.**
- **All of these monitoring study reports could be represented on one graphical display of their findings in terms of the stats of Mean, 5th % ile, max, 95%ile etc. That display could provide perspective on whether or not there really is discord among these studies. It could be that results from different studies fall within a broad statistical distribution--essentially variability that could be expected given the different approaches etc. Where there are significant differences, the outlier study could be addressing different populations, different COUs or other conditions. Such studies might address scenarios not included in the other studies, etc. Taken together, the riches of these many studies should be embraced to bring information to the risk assessments and to expand the conversation here for weight of evidence (especially for selecting single air concentration values for use in the deterministic risk models used by EPA), confidence, and concordance with the modeled answers. Again, as in other Charge Question discussions, a more comprehensive statistical examination of the studies is recommended.**
- **European studies showed similar results in residential air concentrations of formaldehyde, but the exposure and risk assessments were quite different. The**

Committee recommended a thorough examination for what mathematics or approaches or assumptions led to these different answers.

Charge Question 5.5

The identified wood article-specific emission rates used in the Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h) predate EPA's 2016 final rule to reduce emission rates of formaldehyde from new composite wood products made after the March 2024 compliance date and will not represent current and future emissions of formaldehyde from these products. A supplementary assessment of wood articles assuming the new emission standards as described in Appendix D of the Draft Indoor Air Exposure Assessment (U.S. EPA, 2024h) was completed. Please comment on the strengths and weaknesses of this approach to better characterize future risks from formaldehyde products that reflect the new emissions standard.

Response to Charge Question 5.5

The wood article-specific emission rate used in the *Draft Indoor Air Exposure Assessment* (U.S. EPA, 2024h) and the supplementary assessment conducted by the EPA (U.S. EPA, 2024h) are valuable in establishing potential risk from formaldehyde emissions. Both identify risk to consumers from new wood products and over time. The supplementary assessment of wood articles, using the concentrations released based on new emission standards for new wood products (after March 2024) is very helpful in estimating the diminished risk from wood products produced after enactment of the new standards. As a focus for charge questions5.6 and 5.7, there may be differences in exposures due to ventilation and other sources of formaldehyde (Singer et al., 2009; Kashtan et al, 2024; Uchiyama et al., 2024).

Specifically in response to charge question 5.5, there are two aspects to consider: first, what risks will continue to exist from wood products manufactured before the EPA's 2016 final rule for new composite wood articles; and second, how much of a reduction in risk will be realized from formaldehyde products made according to the new standards.

EPA stated medium confidence in the overall findings for indoor air exposure based on WOSE (LL 134-138), yet there is low confidence for estimating emissions from wood products (LL 186-189), which is one of the primary sources of formaldehyde emission for indoor air. These and other items are considered in the specific recommendations and comments that follow.

Specific Recommendations and Comments Applicable to Historic and Post 2016 Final Rule (implementation March 2024):

Recommendations:

- **Add more explanation about the potential impacts of the recently implemented exposure standards for new composite wood products. Information on Table 2.1 is very helpful in distinguishing what materials can be considered under the Toxic Substances Control Act (TSCA) Conditions of Use (COU) and Table 3.5 (conclusions) will provide some of this information to clarify these potential outcomes associated with the newly implemented exposure standards.**

- **Additional details should discuss sources of uncertainty from the following:**
    - **Composite wood types are shown on Table 2-2 and reflect various wood types, including pressed wood, treated wood products, sealed, and other products, etc. Wood types in floors and furniture also vary, both in the pre- 2016 final rule standards and the post new standard implementation.**
    - **There is additional uncertainty from glues, and other products used in the home, in addition to formaldehyde emanating from the wood.**
    - **Products that predate the new emission standards clearly do not currently reflect the emissions for wood products on the market; however, there may be diminution of formaldehyde emission over time according to the specific product constituents and usage.**
- **Acknowledge that articles passively used can contribute to chronic exposure, which are key factors in aggregate exposure. Recognize that these factors may contribute to aggregate exposure (CQ 6) and note that some are outside the scope of this document. For example:**
    - **Estimates from consumer exposure are higher in residential environments compared to offices and business establishments. The Consumer Exposure Model should consider the usable lifespan of the wood products and potential difference in the retention of these products in different sites.**
    - **Potential compounds from wood stoves and other combustion sources are not included; see Section 3.2.2.1.**
    - **Hardwood floors are the highest emitters of formaldehyde as described in the Healthy Housing report .**
    - **Are museums, colleges, medical schools using formaldehyde products for preservation considered or are these beyond the scope? It is noted that schools are not included in the review materials, despite potential exposure for younger individuals or more concentrated exposure in university/medical school or museum settings.**
    - **Inhalation is the primary route of exposure, with dermal and oral routes secondary; however, this does not mean that the secondary routes have negligible effects, especially in aggregation with other sources (applicable to CQ 6).**

<u>Recommendations:</u>

- **Discuss estimates of predicted outcomes associated with the new emission standards as summarized in Appendix D.:**
    - **Despite medium confidence in the findings (due to chemical half-life not being considered in the CEM), how accurate are the overall estimates of declining risk of exposure under the new standards over time?**
    - **Other sources of formaldehyde, such as crafts that are not included in the new standards and therefore may impede progress towards reduced indoor formaldehyde emissions.**
    - **As mentioned in LL 254-263, it is important to consider Potentially Exposed or Susceptible Subpopulations (PESS) as these individuals may or may not benefit from the new standard, depending on use of new wood products.**
    - **Table 3.1 provides interesting and important information; how do these estimated exposures compare to levels of exposure that would be below concern or is there insufficient information to provide this estimate?**

- **Similarly, Table 3-2 summarizes the data for homes in a clear manner. The analyses in Appendix D predict reduced potential exposures to formaldehyde from wood floors and wood products. Does the improved insulation after 1990 (LL 226-220 and Section 3.1.1.1) affect these estimates or this adjustment is already incorporated into the one-year estimate?**
- **A figure or table showing the comparative difference in emissions would help clarify the potential effects of the new emission standards.**

In summary, the predicted benefit from the new emission standards suggests a significant improvement in the risk to consumers in residential and office buildings. There will be a time lag for realizing change due to both reduced new emitting wood products and the decreasing emissions from existing products. It is emphasized that a figure that contrasts changes in the concentrations and risk would be very useful. The American Healthy House Survey, III will be interesting and hopefully will reflect a reduction in the risk of exposure to formaldehyde from indoor air. Overall, it is hoped that there will be an actual improvement that reflects the predicted improvement in the near future.

Specific Comments
LL186-189: This sentence states a rationale for low confidence; however, the reasons need more explanation as there are a number of different issues included. For example, the conclusion of low confidence includes emission standards that have just been implemented. This is appropriate and certainly a reason for variability, but there could be a sentence referring to post-implementation emissions estimates in new products.

LL 398 and 782: Error messages for reference source.

Charge Question 5.6

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the chronic non-cancer inhalation hazard endpoints and PODs derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022 that have been peer reviewed by NASEM. Section 4.2.3 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the chronic inhalation POD to assess risks to people with exposure to formaldehyde through indoor air. Please comment on the strengths and uncertainties associated with OPPT's application of the chronic inhalation POD in this context.

Response to Charge Question 5.6

The Committee agrees with the limitations of the currently proposed chronic inhalation POD to assess risks to people with exposure to formaldehyde which have been discussed extensively in previous sections (charge questions: 3.3 and 4.4).

Several Committee members disagreed with the derived dose-response and POD the DRE uses for formaldehyde, and the majority of Committee members recommended incorporating NASEM and HSRB recommendations to revise the formaldehyde chronic non-cancer hazards reached by IRIS. Specifically, there is also agreement that the three observational studies relied upon by IRIS for chronic non-cancer hazards are not appropriate to determine a dose-response and a POD, as commented in charge question 1.2. Therefore, the POD that was selected is also not suitable to use in

this or any instance in this risk evaluation.

The Committee concurred with the recommendation that was made to explore a unified approach for the chronic and cancer risk assessments based on using the NOEL or NOAEL POD for irritancy effect via the relevant route of exposure since the acute irritating effects of formaldehyde, makes it unlikely for these long-term exposures over many hours, days, weeks, and months to occur, as commented in charge question 3.3. However, application of the unified approach to dose-response assessment would not necessarily be limited to the irritancy effect and would require evaluation and consideration of the evidence of systemic effects.

Indoor air concentrations are applicable to all age groups. For people who lack elevated workplace exposures, indoor air, as defined for this risk assessment, is the environment that best reflects formaldehyde exposures that could be a health risk. It should be noted that certain indoor settings may be more likely to be relevant at different life stages (e.g. schools). People spend a majority of their time in indoor air where the typical U.S. home concentration of formaldehyde is 23.2 ug/m^3 (18.6 ppb) (AHHS; QuanTech 2021). Thus, it appears unreasonable and unrealistic that EPA's chronic POD is 21 ug/m^3 (16.8 ppb), which was based on a study of pulmonary function in children. Canada has recommended exposure limits in indoor air for 2 types of exposure: (1) short-term exposure: 123 µg/m³ or 100 ppb based on a 1-hour average to protect against irritation of the eyes, nose, or throat and (2) long-term exposure: 50 µg/m³ or 40 ppb based on a minimum 8-hour average, to protect against respiratory symptoms in children with asthma.

If the EPA utilizes the study conducted by Krzyzanowski et al. (1990) to develop the POD, along with associated UFs, it could imply that EPA is suggesting that the typical home is hazardous to our and our children's health. Several Committee members do not think this POD is appropriate, and it may be that for this consideration EPA is not asking the right question to derive an appropriate POD and explain an adequate margin of exposure (MOE). Suitable questions to address would be, how does risk increase above the POD, who is most at risk, and how those risks estimate compare with real-world data on disease prevalence (e.g., reduced pulmonary function in children). At least two Committee members suggested that many homes, like schools have inadequate ventilation, such that emissions of formaldehyde from various sources that are being evaluated by the EPA and those that are not – such as releases from gas stoves, can be present in concentrations that are problematic for people living in homes without adequate ventilation (Uchiyama et al; 2024; Kashtan et al, 2024). At least two Committee members stated in regard to rates of disease, that tracking and compiling rates of asthma (new cases and exacerbations) are under-reported, particularly for people who live in places in the US that lack health care infrastructure and access to clinics (Pate et al., 2021). There are not adequate epidemiological estimates for rates associated with in-home exposures to formaldehyde for multiple reasons, many of which have been discussed. Committee members suggested that stating rates of formaldehyde-associated disease do not align with concentrations or predictions based on application of the chronic POD is problematic. However, other Committee members agreed with a public commenter regarding that links to asthma can be confounded by so many other exposures (e.g. pollen, dander, tobacco smoke, exhaust) that an observational epidemiology study should not be used for causality or to develop a POD.

One Committee member stated that using the MOA is important as stated, but using the MOA as the basis for harmonizing the cancer and non-cancer values as proposed is problematic because it results essentially in the use of a threshold value below which there is an assumption of no effect (as discussed in CQ 1.1). It is not consistent with the best available science. Some Committee members

agreed with this statement and other Committee members disagree. The data provide an understanding of the carcinogenicity and inhalation toxicity mode of action, as described in responses to charge questions 1.4, 3.3, and 4.4 as well as 3.4, 4.5, 5.7, and 6.6, and there is ample evidence that a unified POD for chronic effects including a carcinogenic response, such as was recommended by the World Health Organization (WHO 2010) for formaldehyde, would be health protective and would be consistent with the NAS report Science and Decisions, 2009 as described in response to charge question 3.3 but the Agency has not developed/presented an analysis according to the unified dose-response approach.

Recommendations:

- **Reevaluate the POD values and the studies they are based on by considering the most current NASEM and HSRB comments related to the 2022 IRIS assessment of formaldehyde.**
- **Utilize the publicly available RISK21 framework and webtool (www.risk21.org) to better communicate the data used in risk assessments and to establish protective margins of exposure. This approach has been detailed in previous Charge Question 1.4.**

Charge Question 5.7

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the cancer IUR derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022) that has been peer reviewed by NASEM. Section 4.2.3 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the cancer IUR to assess risks to people with exposure to formaldehyde through indoor air based on air monitoring data. Please comment on the strengths and uncertainties associated with OPPT's application of the cancer IUR in this context.

Response to Charge Question 5.7

As stated in charge question 5.6, indoor air is likely the dominant exposure to formaldehyde for most people where they spend a good portion of their time and the typical home concentration of formaldehyde (AHHS; QuanTech 2021) is 23.2 ug/m^3. Thus, EPA's cancer IUR would suggest that the formaldehyde exposure in typical home is hazardous to us and our children's health. It is accepted that many homes and indoor spaces do not have adequate ventilation, could have higher exposure depending on proximity to various conditions of use and could have higher than average formaldehyde concentrations. However, there are no adequate epidemiological estimates for rates of cancer or respiratory disease associated with in-home exposures to formaldehyde.

Limitations of the currently proposed cancer IUR have been discussed extensively in previous sections (charge questions 3.4 and 4.5). The Committee noted that the peer review by NASEM was limited to the Charge Questions supplied and was not a full review of the full body of literature relevant to the hazards and risks of formaldehyde, nor was NASEM charged with reviewing alternative scientific opinions. At least three Committee members acknowledged that NASEM (2023) generally supports the use of IUR in cancer risk estimate. The quote from NASEM (2023, Page 104): "Finding: The overall approach and conduct of the cancer dose-response analysis is consistent with EPA's state-of-practice methods for deriving inhalation unit risk estimates. The 2022 Draft IRIS Assessment adequately and transparently evaluates the scientific evidence, and generally documents

the dose-response analysis overall in a well-organized and transparent manner." Several Committee members disagreed with this position and suggested that the agency use a unified RfC approach based on the well-established mode of action that would be protective for any chronic response including carcinogenicity and not use the IUR as described in the 2022 IRIS document." The Committee agreed that since the IRIS Assessment is still in draft form, it is difficult to assess the use of any final proposed IUR in this Risk Assessment.

The proposed mode-of-action for formaldehyde-induced *carcinogenesis* is being based on a cytotoxicity/regenerative mechanism. Several Committee members recommended the consideration of formaldehyde as a *threshold* carcinogen, along with development of a cancer risk POD as opposed to using a linear, no-threshold (LNT) model under all scenarios, including indoor air. The overarching discussion for the cancer risk assessments emphasized reasons not to use the IUR approach from the draft 2022 IRIS assessment. Several committee members suggested using a RfC approach as described in the 2005 Cancer Guidelines when the chronic toxicity risk and potential carcinogenic risk can both be addressed from the understanding of the mode of action from the chemical-induced adverse effects and can be quantified in a dose response manner by using a quantitative key event dose response framework (QKEDRF). Such an approach has been described and used by OPP for the Dimethylarsinic Acid assessment and frequently by OPP for many chronic/carcinogenicity risk assessments. The Office of Water has also used this approach for chloroform, one of the first chemical regulated using this approach (Simon et al., 2014). However, one Committee member suggested that formaldehyde-induced DNA-protein crosslinks (DPC) are genotoxic, and, if not repaired efficiently could be mutagenic as well. The statement was countered by another Committee member who agrees that while this may be true in an *in vitro* setting, most of the time DPC are considered evidence of sufficient exposure and are part of the toxicity pathway leading to cell death or sufficient damage that results in regenerative cell replication, the rate limiting key event. Another Committee member pointed to a genotoxicity review that counters the opinion that exposure to formaldehyde would lead to mutations *in vivo* (Albertini and Kaden, 2017).

The Agency noted that the purpose of this evaluation is to establish an understanding of the margin of exposure to assure no appreciable risk of harm but does not define "appreciable". It is important to point out that there is evidence that formaldehyde could result in a carcinogenic response in the nasal tissues and also to show that the human exposure levels have a sufficient margin from the potential for the early key event of an adverse effect, and therefore would be protective. In addition, given the MOA evidence for a dose-response model of the key events, and the science supporting that air concentrations below that threshold do not significantly impact the formaldehyde concentrations in the cells of the body as supported by the extensive elegant adduct work by the Swenberg lab at UNC-Chapel Hill, NC (Edrissi et al.,2013; Rager et al., 2014; Yu et al., 2015; Lai et al.,2016 ; Edrissi et al., 2017; Liu et al., 2018; Leng et al., 2019), the body of scientific evidence does not support the elevated risks suggested by EPA in the Formaldehyde *Draft Human Health Risk Assessment*.

The overall topic of exogenous formaldehyde as a threshold-based toxicant is extensively discussed in charge question 4.5. A case can certainly be made for a threshold approach as discussed in previous sections (CQ 3.4 and CQ 4.5). Two Committee members supported an assertion that formaldehyde carcinogenesis is a threshold effect is indeed extraordinary and that the assertion that: "Protecting against formaldehyde concentrations at or above 2 ppm would prevent both noncancer and cancer impacts in people in all instances." EPA's proposed threshold concentration is also extraordinary and not consistent with other federal evaluations or the IARC analysis of formaldehyde (IARC

Monograph 88). For example, the OSHA standard is 0.75 ppm, and OSHA standards only consider risks above 10^{-3} to be significant, but it was explained that these are different protection goals and should not define the EPA evaluation of formaldehyde. It was then explained that using mode of action leading to the use of key events to establish a point of departure and RfC/RfD approach for risk assessment to protect against chronic toxicity and carcinogenicity is a common approach at the US EPA and many other regulatory agencies including the FDA, Health Canada, EFSA, ECHA, and many others. Although there are exceptions, the low dose linear model has dominated risk assessment for almost seven decades.

The low dose linear model has not been the default or standard since the publication of the IPCS papers starting in 2001 and the promulgation of the 2005 Cancer Guidelines which follows the IPCS Human Relevancy Framework. Thus, when a mode of action can be determined, and it is biologically plausible in humans the dose response for the key events can be used for setting protection goals. This is standard practice and is done routinely by the Office of Pesticide Programs. Many human health risk assessments can be found on regulations.gov that illustrate this approach. When a mode of action cannot be identified or when the chemical has a mutagenic mode of action as the molecular initiating event then the low dose linear model (Q* or slope factor approach) is the default precautionary approach. However, when a mode of action can be described with sufficient confidence then an RfC/D approach is appropriate. Also, numerous articles show this as standard practice all over the world https://doi.org/10.1016/j.yrtph.2022.105160 (Boobis et al., 2006; Meek et al., 2014; Elcombe et al., 2014; Collaborative AOP, 2024; Goetz et al., 2024; HED OPP, 2005; Heusinkveld et al., 2020; Luijten et al., 2020; Jacobs et al., 2020; Manibusan et al, 2020; Hilton et al., 2022).

Several Committee members assessed that cancer from formaldehyde is likely a threshold effect, only evident at the site of contact when formaldehyde concentrations are at or above 2 ppm, it might be worthwhile taking a unified approach to both cancer and noncancer effects. This is the type of approach taken by the WHO for formaldehyde in their Indoor Air Guidelines document (WHO, 2010). Protecting against formaldehyde concentrations at or above 2 ppm would prevent both noncancer and cancer impacts in people in all instances. However, some Committee members supported the assertion that, while cytotoxicity is an important MOA, there is ample evidence for genotoxicity and mutagenicity, as well as evidence that formaldehyde can cause acute and chronic myelogenous leukemia. If this is correct, then a no-threshold model is appropriate, and cancer and noncancer effects cannot be combined in a unified approach. Other Committee members disagree with the statement of "ample evidence for genotoxicity and mutagenicity, as well as evidence that formaldehyde can cause acute and chronic myelogenous leukemia."

Some Committee members noted that while IARC classified formaldehyde as a category 1 carcinogen, these data were more compelling for nasopharyngeal cancer than for myeloid leukemia.

Some Discussants did not entirely dismiss the EPA's findings on mutagenesis and myeloid leukemia, whereas a number of discussants fully disagreed with the Agency's findings. However, EPA should consider all available science (the "best science" approach) and carefully justify their conclusion. In a review of the *Draft Risk Evaluation for Formaldehyde*: Systematic Review Supplemental File, it was found that EPA literature review did not include search terms for mutation, genotoxicity, etc. and so did not identify any of the recent literature including the Albertini and Kaden (2017) paper on genotoxicity / formaldehyde and the equally important paper by Albertini and Kaden (2020) which discusses the likely origin of mutations observed in cells obtained after *in vivo* exposures (and concludes that most evidence to date does not reflect mutations occurring in the bone marrow, where

hematopoietic cancers originate. Similarly, there are few recent papers that are relevant and related to the myeloid leukemia question. Two articles released in 2024 carry significant relevance and merit review and inclusion within this risk-related article (Vincent et al. 2024; Cox et al. 2024).

Recommendation:

- **Review the literature supporting both threshold and non-threshold models of formaldehyde carcinogenicity, and on the basis of 'Best Available Science' and if appropriate, calculate a level of risk independent of the IRIS assessment.**

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6. AMBIENT OUTDOOR AIR ASSESSMENT

Charge Question 6.1

The Draft Ambient Air Exposure Assessment for Formaldehyde (U.S. EPA, 2024a) characterizes The available outdoor air monitoring data as representing aggregate exposure from all sources of formaldehyde in outdoor ambient air, including TSCA conditions of use, as well as other sources of formaldehyde. The EPA's Air Monitoring Technology Information Center (AMTIC) (U.S. EPA, 2024a) was determined to be the source of the most current nationally representative Outdoor ambient air data. Please comment on the strengths and limitations of AMTIC, its application for this draft formaldehyde risk evaluation, and the conclusions that the data represent aggregate sources of formaldehyde in the United States. Please also comment on the appropriateness of any other outdoor ambient air monitoring data that could be considered in the formaldehyde assessment of outdoor ambient air. Lastly, comment on the extent to which the WOSE narrative is supported by current outdoor ambient air monitoring information for formaldehyde.

Response to Charge Question 6.1

The plan of EPA in using this data is to obtain a representation, albeit at sites sparsely located across the United States, of the ambient formaldehyde concentration that is reflective of all sources of formaldehyde, from industrial releases to biogenic processes and secondary sources.

The Committee identified several strengths of AMTIC data, including:

1. The high quality of the observations
2. The representativeness of real-world conditions
3. The national coverage of the AMTIC dataset

The Committee identified several weaknesses of AMTIC:

1. The varied measurement methods and observation periods (e.g., 5 min to 24 hours)
2. The representativeness of all sources, including both TSCA COUs and other emissions sources

The Committee provided several comments on the application to the formaldehyde risk evaluation and conclusions that the AMTIC measurements represent aggregate sources of formaldehyde:

1. More information is requested to assess inferred annual average from AMTIC observations.
2. The committee provides recommendations for approaches to compare concentrations across AMTIC monitors and to associate variability in AMTIC observations with TRI facilities.
3. The Committee recommended working closely with the Office of Air and Radiation on

matters involving observations and modeling of formaldehyde.
4. Additional recommendations regarding assuming concentration values for measurements reported below the limit of detection.

The Committee identified satellite data as a potential source of additional data for assessing formaldehyde exposure, but several limitations were noted for satellite data products.
In assessing the extent to which the WOSE narrative is supported by current outdoor ambient air monitoring information for formaldehyde the Committee noted that the observations can contribute to evidence that the modeled exposures are reasonable. However, the conclusions are mostly qualitative because Committee members had not observed source-specific formaldehyde.

Recommendations:

- **Consult with the Office of Air and Radiation on issues related to ambient formaldehyde concentrations and contributions from specific sources.**
- **Provide more clarity about the form of the concentrations provided by the AMTIC dataset.**
- **Acknowledge formaldehyde's contributions to ozone and secondary organic aerosol.**
- **Include descriptions of data distributions to the extent that they may be incorporated in probabilistic analyses.**
- **Describe what measurement or modeled data would sufficiently support the risk evaluation, and what simplifications and uncertainties are acceptable.**
- **Provide information on the times of day when the observations are taken.**
- **Compare the observations with model products more precisely by considering location.**
- **Show more completely the implications of removing observations below the limit of detection and consider alternate approaches than removing this data altogether.**
- **Consider satellite data products but represent and recognize the various sources of uncertainties of this type of data.**

Strengths of AMTIC
The Air Monitoring Technology Information Center appears to be a great source of information on ambient formaldehyde concentration. As EPA has elaborated in the *Draft Ambient Air Exposure* to Formaldehyde Section 4.4, AMTIC data "has received a high-quality rating from the EPA's systematic review process," thus providing some degree of confidence that the values reported by the AMTIC monitors are trustable. In general, a strength of AMTIC left unaddressed is that monitored values should have lower uncertainty than modeled concentrations or contributions from specific sources.

Observations also do consider environmental chemistry, transport, and deposition, which includes contributions from anthropogenic and natural VOC emissions to HCHO, along with considering anthropogenic HCHO that is emitted and transformed in the atmosphere to other chemicals.

AMTIC is generally nationally representative (note comment from previous charge question about monitors only in lower 48 states shown in Figure 3-7) and looks to mostly be in urban areas (representative for population exposure), but it would be useful to identify and summarize the nearby formaldehyde sources (e.g., amount of TRI/NEI HCHO emissions within some distance of AMTIC observations versus outside this distance)

Recommendation:

- **Consult with the Office of Air and Radiation on issues related to ambient formaldehyde concentrations and contributions from specific sources.**

It is important to include information in consultation with Office of Air & Radiation related to EPA modeling activities related to regulating formaldehyde as a HAP and contributor to ozone and PM under the Clean Air Act. The Committee recommended participation from the Office of Air to the extent that they are included as co-authors on the ambient air documents.

Limitations of AMTIC

Recommendation:

- **Provide more clarity about the form of the concentrations provided by the AMTIC dataset.**

Ambient air quality standards include both a value & form of the standard, which differs by pollutant (e.g., day average, one hour peak, etc.). It is not clear to the extent that this format was incorporated by EPA in developing their documentation on formaldehyde.

As the Agency elaborates in Section 3.2.1 of the *Draft Ambient Exposure* and in Section 2.4.1 of the *Draft Human Health Risk Assessment*, AMTIC data are very heterogeneous in terms of the methodology used to measure the concentration (and, consequently the limit of detection), the reliability of the instruments used to measure the concentration, and the timing and duration of the measurement (5-minutes to 24 hours). It is also unclear exactly what is the form of the measurement provided by the AMTIC data: are the monitors reporting "average concentration over a specific time interval" or are they reporting "total" or "maximum concentration" over a specific time interval? The Agency does not provide describe the format of the concentration measurements. A committee member's inclination would be that the reported concentrations are averages but the statement in line 787 of the *Draft Ambient Exposure* that the formaldehyde concentrations "were not otherwise normalized by sample collection duration or methodology" appear to indicate that potentially the measurements were not provided in the form of averages. Providing more clarity and being more specific in this regard is of fundamental importance to be able to evaluate the results and conclusions reported by the Agency in the drafts.

One limitation is (as EPA states) that ambient data include everything—primary emissions and secondary formation from all use cases, included and not included in the risk assessment. This is considered a strength in terms of assessing what real people are exposed to, but it is a limitation for the somewhat arcane exercise here of attributing exposure to individual use cases.

Recommendation:

- **Acknowledge formaldehyde's contributions to ozone and secondary organic aerosol.**

A related limitation of AMTIC data that is not considered is formaldehyde's contribution to secondary pollutant species like ozone & secondary organic aerosol. While this is out of the scope of the risk evaluation, these downstream impacts are real and important to acknowledge.

Recommendation:

- **Include descriptions of data distributions to the extent that they may be incorporated in probabilistic analyses.**

The Committee recommended including descriptions of the distributions of the data to the extent that they may be incorporated in probabilistic analyses.

Application to risk evaluation

By comparing AMTIC monitoring values with the estimates of ambient formaldehyde concentrations that the Agency obtained using the IIOAC model and AirToxScreen allows the Agency to perform some sort of source apportionment and draw conclusions regarding the contribution of each source to the total ambient formaldehyde concentration. While in theory this plan appears reasonable, particularly considering a lack of better sources of information and more specialized monitoring data, there are questions about the implementation of the plan. While the AMTIC data has potential to shed some light, although probably more at a qualitative level rather than quantitative, on source apportionment, the current usage of these data does not allow development of well-founded conclusions.

Recommendation:

- **Describe what measurement or modeled data would sufficiently support the risk evaluation, and what simplifications and uncertainties are acceptable.**

It would be helpful for EPA to lay out in a perfect world which modeled or measured output would be sufficient for the risk evaluation. What simplifications/uncertainties are acceptable, and how do those relate to the measurement and modeling tools available?

Recommendation:

- **Provide information on the times of day when the observations are taken.**

It is unclear how representative the monitoring data are of annual averages. It would be beneficial to organize the data according to the time of day that the measurements encompass. An issue with taking the annual average (or average across many days) is that it does not consider short-term spikes. However, they could be identified by assessing the temporal variability in the data (for example, with a smoothing temporal filter) and identifying outliers. Identifying any temporal variability in outliers in observations nearby TRI sites could help to identify locations and times when air emissions happened.

Figure 3-7 in the *Draft Ambient Exposure* showcases a map of the AMTIC monitoring sites which appeared to indicate that most of monitors are located in urban areas rather than rural. From Table 3-1, it appears that the vast majority of the AMTIC monitors provide measures of formaldehyde concentration over a 5-minute interval. Given the transience of formaldehyde and its different half-life length in the presence of sunlight, it is important to know when, during a day, the 5-minute AMTIC monitors are collecting data. The Agency investigated variability in ambient formaldehyde concentration from AMTIC monitors based on methods of collection and duration of collection. As for what concerns collection, it appeared that the 5-minute monitors tend to report smaller concentration values than other durations of collections with an occasionally larger value. Again, given that formaldehyde tends to be unstable and react based on meteorological conditions, understanding the spatial distribution of the AMTIC monitors and the timing of the day these

measurements are taken is fundamental.

Recommendation:

- **Compare the observations with model products more precisely by considering location.**

Some information on the AMTIC ambient monitoring data, e.g. how/whether daily average and annual average formaldehyde concentration could be calculated, is not mentioned in the draft report on Ambient Exposure to Formaldehyde. It would be helpful if that information was reported in the above-mentioned document and if the information regarding the AMTIC monitoring data is consistent across documents.

Comparing values across monitors is rather difficult given the many confounding variables that might have an influence on the value reported by a monitor: the location of the monitor (is it rural versus urban?), the time of the day and the year the measurement is collected, the method of collection and the duration of collection, to just state a few. Simply averaging the available measurements reported by an AMTIC monitor over the course of a year without taking into account these confounding factors and creating plots of the distribution that lumps all the values together as in Figure 3.8 of the *Draft Ambient Exposure* without considering the spatial location of the monitors, and comparing it to the distribution of ambient formaldehyde concentration obtained from IIOAC is not quite fair as the comparison does not consider all the confounding factors that lead to differences between the AMTIC monitoring data and the IIOAC.

Given the spatial misalignment between the AMTIC monitoring data and the IIOAC data, a different approach would be to:

use the AMTIC monitoring data,

assume that the measurement represents a daily average concentration, regardless of the duration of collection, and

fit a spatial regression model that regresses the measured AMTIC observed concentration data at a given AMTIC monitor on the various confounding factors mentioned above (method of collection, duration of collection, time of collection, season of collection, rural versus urban, distance to nearest industrial facility, wind speed, wind direction, etc.) and a spatial random effect to account for the fact that there is also variation from monitor to monitor and concentrations from monitors nearby might tend to be similar.

The model can then be used to estimate the average daily "AMTIC" formaldehyde concentration at the same exposure points at a distance of 100m to 1000m from a TRI facility as used in the IIOAC exposure calculations. This would allow comparison of estimated ambient exposure from all sources (the "AMTIC" formaldehyde concentration) leveraging the AMTIC monitoring data with the IIOAC modeled concentration relative to the same locations, accounting for all the confounding factors that lead to differences among the AMTIC monitoring values besides the source of formaldehyde.

Alternatively, the Agency could calculate average AMTIC concentration, averaged over all the AMTIC monitor locations that are within a certain distance buffer from a TRI facility. These averages could be used to compare the IIOAC modeled concentration 100-1000 meters from a given TRI facility to this more localized average AMTIC concentration.

Comparing distributions lumped regardless of the spatial locations of the monitors and thus disregarding the actual spatial distribution of the concentrations is not meaningful. To understand this, imagine we reshuffle the average annual formaldehyde concentration at the AMTIC monitors but we do not reshuffle the IIOAC values. The overall distributions for formaldehyde concentration relative to AMTIC and IIOAC in Figure 2.10 of the *Draft Human Health Risk Assessment* wouldn't change but the spatial distribution of the AMTIC average annual formaldehyde concentration across the United States would have. This has important consequences when one wants to draw conclusions regarding what percentage of the total formaldehyde concentration that on average the population is exposed to is due to releases connected with the TSCA COUs. To draw conclusions on those percentages, one would have to calculate the ratio of the annual average formaldehyde concentration due to TSCA COUs at a location and the annual average formaldehyde concentration due to all sources at the same location!

Conclusion that the data represent aggregate sources of formaldehyde in the US

Recommendation:

- **Show more completely the implications of removing observations below the limit of detection and consider alternate approaches to removing this data altogether.**

The Committee does not support assigning zeros as concentration values for data falling below limits of detection (LOD) for environmental data where the data are being aggregated from methods that have a wide range of detection limits. There is also a need to understand the distribution of LODs. With such large data sets that represent large temporal and spatial settings, there is a non-negligible possibility that many LODs will fall well into the quantifiable concentration range of other methods. It is improper to assume that below LOD values represent the lowest values in a distribution. The SACC has spoken to this point in several previous DRE reviews, most notably those for chlorinated solvents.

Appropriateness of any other outdoor ambient air data

Recommendation:

- **Consider satellite data products but represent and recognize the various sources of uncertainties of this type of data.**

The Committee noted that there are differences in the interpretation of the word "data" among Committee members, with one Committee member using the word "data" to indicate "ground truth, based on observational methods that can be considered as the gold standard because they represent the most reliable method to measure a quantitative variable" while another Panel member intended "data" to indicate any quantitative value. The latter Committee member supported a more encompassing use of the word "data" because of a recognition that also observations based on lab-based methods contain uncertainties.

In the draft documents, EPA mentions that satellite data have measured formaldehyde concentrations across the United States, providing insights on temporal and geographic trends that help to characterize ambient formaldehyde concentrations (Wang et al., 2022; Harkey et al., 2021; Zhu et al., 2017). However, it did not appear that this data source was considered in the draft reports. According

to some Committee members, use of the remote sensing data would have been useful to understand spatial variability.

Another Committee member noted instead that while remote sensing data can provide potentially useful information, it was important to acknowledge that remote sensing data are not actual data nor a measurement of formaldehyde concentration, as instruments aboard satellites measure quantities related to refraction of light, not chemicals concentrations. Air pollutants concentrations, as many other variables derived from remote-sensing measurements, are inferred by solving what are called "inverse problems" through statistical models and algorithms. Thus, the remote-sensing derived formaldehyde concentration is a modeled concentration and not data. Because of how it is obtained, the satellite-based formaldehyde concentration is characterized by various forms of uncertainties: uncertainties connected to the correctness of the model used to retrieve ambient exposure formaldehyde concentration from the actual measurement of light reflectance performed by the remote sensing instrument, uncertainty connected to the method used to perform the estimation, and uncertainty in the measurement of light reflectance.

In addition to this issue, the same Committee member also noted the importance of the time of collection of the measurement. Satellites can be either stationary or orbiting. If ambient formaldehyde concentration is estimated using data collected from an orbiting satellite, then the concentration refers to the average concentration during the time of overpass of the satellite. In that sense, this data would be comparable to the 5-minutes AMTIC data, although again in this case it would refer to an estimate and not an actual measurement. Additionally, differently from the AMTIC data that provides information on ambient formaldehyde concentration at a specific location, formaldehyde concentration estimated by a satellite would refer to the average value of ambient formaldehyde concentration over a square grid cell. In the case of an orbiting satellite, data would be available only at the time of overpass, which often would happen at somewhat regular intervals over the course of a week, with a frequency that depends on the orbit of the satellite. In some cases, this might result in only two-three estimates of average ambient formaldehyde concentration over a few minutes relative to approximately the same grid cells. This would not provide enough "sample" estimates to derive estimates of annual average concentrations, which is what would be needed to characterize long-term exposure.

In the case of a stationary satellite, e.g. a satellite that does not move, the estimated ambient formaldehyde concentrations provided by the satellite data product would be available for a grid cell almost on a daily basis and could thus be used to derive estimates of average annual ambient concentrations of formaldehyde.

The Committee member also noted that remote sensing estimates are available only when measurements of light reflectance can take place. Measurements of light reflectance are not available in the presence of clouds. This would mean that estimates of formaldehyde concentrations derived from remote sensing instruments are not available in those locations/grid cells that are covered by clouds during the time of the satellite overpass, if the satellite is orbiting, or for hours/times of the day during which the clouds obscure the view of the satellite, if the satellite is stationary. Given the nature of formaldehyde and the reactivity of formaldehyde with sunlight, it could be argued that the estimates of ambient formaldehyde concentration obtained from satellites might tend to underestimate the actual ambient formaldehyde concentration.

In conclusion, while remote sensing might offer an additional source of information on formaldehyde

concentration, the Committee member highlighted the importance of validating the quality of the data and recognizing the different sources of uncertainties in this data set. While people are familiar with the idea that monitoring data has uncertainty coming from the instrument reliability and other sources of uncertainty, satellite data is often treated almost as monitoring data, even though it has many more sources of uncertainties as mentioned above.

Researchers have applied source apportionment with AMTIC observations using volatile organic carbon and other species measured simultaneously. This would offer an approach for identifying the sources that contribute to HCHO observations.

Extent to which WOSE narrative is supported by current outdoor ambient air monitoring information for formaldehyde

The findings derived from the draft report's outdoor ambient air monitoring data are predominantly qualitative, due to the absence of source-specific formaldehyde observations. Regarding the WOSE, although its elements such as AERMOD and AirToxScreen have undergone peer review and received support from prior Committees for different objectives, it does not imply that their application, if not done with great care, would automatically yield valid results when attributing sources of formaldehyde concentrations. Each individual comparison has merits, but there is no inherent merit in each additional comparison.

Minor/editorial comments
Doc 13, Table 2-4 is confusing—what does the count refer to? Also, this plot is not presented in [24]

Ambiguity between years used: Line 130-131 [24] 2015-2021 doesn't match line 144 and line 1370 of the *Draft Human Health Risk Assessment* (states 2015-2020)

780-790; repeat of 610-616.

Figure 3-7 in the *Draft Ambient Exposure Assessment* document; it is unclear how to interpret the concentric circles plotted on the map and how do they relate to legend.

Figure 3-9 in the *Draft Ambient Exposure Assessment document*, the Committee found this plot difficult to interpret with a different color for each sample collection duration, it is suggested to subdivide further by sample duration.

Charge Question 6.2

Considering the variable time increments and locations of the samples included in the AMTIC dataset, please comment on the Draft Ambient Air Exposure Assessment (U.S. EPA, 2024a) conclusion that AMTIC data represents long-term exposure concentrations. In your discussion, please discuss any adjustments to the monitoring data that could be completed to better align monitored concentrations with exposures and the timeframes associated with human health points of departure (e.g., acute noncancer or chronic noncancer and cancer outcomes) considered in the Draft Human Health Hazard Assessment (U.S. EPA, 2024f).

Response to Charge Question 6.2

As mentioned in the discussion of charge question 6.1, the AMTIC data set, while it represents a unique, invaluable information on ambient formaldehyde concentration has several limitations, most of which we have elaborated at length in the discussion to charge question 6.1.`

The Committee provided several comments on the conclusion that AMTIC represents long-term exposure concentrations and is better aligned with timeframes associated with human health points of departure:

1. The Committee recommended various post-processing approaches to better represent long-term exposure, and the Committee members noted that it is important to know the timing of the measurements during the day.
2. The Committee recommended sensitivity analyses addressing the decisions about removing data that falls below detection limits.
3. The Committee recommended two potential approaches to better align the data with human health considerations.

Recommendations:

- **Include additional data summaries and potential post-processing that would enable considering these data as representative of long-term formaldehyde exposure.**
- **Expand the discussion on data processing steps undertaken that are related to the limit of detection and perform additional sensitivity analyses.**
- **Include additional post-processing to better align calculated exposures with health points of departure.**

General Comments

Descriptions of the AMTIC data are somewhat inconsistent. The Methods Section 2.2.1 of the *Draft Ambient Air Exposure Assessment* for Formaldehyde says 234,000 entries (Jan. 2015 to December 2020) comprised the ambient air data set. On the other hand, Results section 3.2 of the same document says 306,529 samples before exclusion of "invalid" data (e.g. null or NA) or reported values that were below the limit of detection. Table 3-1 of the same document lists 233,961 samples of "all" monitoring data, so apparently there were 72,568 (306,529 -233,961) invalid entries. As a fraction of total data, these remaining entries appear to match what EPA refers to as "standardized concentration data" (Line 800). The Committee member recommended that the EPA make these statements clearer.

Conclusion that AMTIC represents long-term exposure concentrations

Recommendation:

- **Include additional data summaries and potential post-processing to enable considering the data as representative of long-term formaldehyde exposure.**

While the AMTIC monitoring data can be considered as providing information on the ambient formaldehyde concentration due to all sources, inclusive of industrial releases, biogenic processes, and secondary formation, it is hard to think of the raw data as representative of long-term exposure concentration.

The sampling duration, the differences in collection methods - each having its own detection limit and reliability characteristics - makes it difficult to state with confidence that each monitor provides a reliable estimate of the long-term exposure to ambient formaldehyde concentration experienced by the population living nearby the monitor. One Committee member believed that in order to state that, these data need to be statistically post-processed to obtain reliable daily average concentrations. The Draft Report for Human Health Risk Assessment discusses how nomenclatures such as "daily average" or "annual averages" are only allowed if more than 75% of the samples over the averaged timeframe are available. Based on Table 2-4 of the Draft Report for Human Health Risk Assess, the vast majority of the AMTIC samples do not sample long enough during a day to even be able to derive a daily average formaldehyde concentration! Only 3,843/233,961 =1.64% of the AMTIC monitors have enough data available during the course of a day to be able to estimate a daily average ambient formaldehyde concentration at the site, and only 0.03% of the AMTIC sites (64) have enough monitoring data available during the course of a year to be able to estimate the average annual ambient formaldehyde concentration due to all sources.

Given that average annual ambient formaldehyde concentration can be estimated only at a very small percentage of AMTIC sites, a Committee member believed that stating that the AMTIC data provide estimates of long-term average exposure to formaldehyde is not realistic, at least not under the current sampling scheme.

Because of the fate and highly transient and reactive nature of formaldehyde and the way formaldehyde behaves in presence of sunlight and other meteorological conditions, it is extremely important to know the timing of formaldehyde concentration measurements, both in terms of time of the day and time/day of the year during which the samples are collected. It would be useful to present which time of the day the measurements were taken along with information on the sampling duration that is already presented in the draft documents.

In order to confidently relate AMTIC data to human exposure, it is also important to have a better description of the spatial distribution of the AMTIC monitors, including urban/rural representativeness and a summary of distances from TRI emissions sites.

Recommendation:

- **Expand the discussion on data processing steps undertaken that are related to the limit of detection and perform additional sensitivity analyses.**

Since Table 3-1 of the *Draft Ambient Air Exposure Assessment* for Formaldehyde includes 233,961 (valid) samples and includes concentrations of "zero", the Committee member has deduced that the number 234,000 reported in Section 2.2.1 is apparently a rounded approximation of the number of samples before excluding values below the detection limit. The Committee member requests more clarity on why 15 percent of samples were excluded for being below the limit of detection as per section 2.2.1. EPA should provide an explanation/justification for this choice. After removing these non-detects ("filtering"), EPA is then left with usable concentration estimates from only 65 percent of the original entries, if the Committee Member's math is correct. Assuming all of the invalid and filtered data represent low concentrations (an assumption deemed reasonable by the Committee member), the "median" of the full data set could be closer to the (50-35)/60 =15/65 = 23%ile. Similarly, EPA's 95th percentile becomes the 96.8th percentile of the original 306,529 entries.

The Committee recommended that the EPA do at least one sensitivity analysis where they retain the non-detect samples and/or invalid entries but make assumptions about the values of the concentration, for example by setting the concentration to be equal to ½ of the detection limit. It would also be of interest to see which collection duration bins and geographic regions were more represented among the excluded data to identify the risk characterizations most likely to have been affected by this choice.

Comparing the "count" information Table 3-1 page 26, and Figure 3-6 page 27 in the *Draft Ambient Air Exposure Assessment* for Formaldehyde, it appears that the Fluxsense data first became available in 2019. Since the Fluxsense data are 5-minute samples, comparing the frequency diagrams for 2019 and 2020 to 2015-2020 could be like comparing apples and oranges. In that same vein, 2020 has a different frequency distribution shape than the preceding years. Were the Fluxsense frequency distributions similar in those two years (data count increased from 77,654 to 121,218, so maybe Fluxsense implementation occurred part way through 2019?)? Is 2019 versus 2020 an apples-to-apples comparison in terms of sample durations? Or was there a decrease in ambient air formaldehyde correlated to Covid-19 pandemic lockdowns? Answers to these questions could inform the relevance of the 2020 data as benchmark for future exposure estimates.
In Figure 3-7, page 28 in the *Draft Ambient Air Exposure Assessment* for Formaldehyde, the "relative" concentration at each monitoring site is not defined. Is this value a median, geometric mean, 95th percentile, or something else? Please explain.

Adjustments that could be completed to better align monitored concentrations with exposure & timeframes associated with human health points of departure

Recommendation:

- **Include additional post-processing to better align calculated exposures with health points of departure.**

Regarding aligning monitoring data to PODs, the Committee believed that data could be better aligned with the underlying studies and more realistic exposure scenarios for the acute POD could be derived. One member downloaded one AMTIC data file (for year 2019) to get a sense of the available metadata and noted that sample times are logged (among other things). These data could be aligned to time of the day and weighted in the assessment for the times of the day that people are most frequently outside (e.g., not 3 a.m.). Also, the acute POD is most directly related to 3-5 h exposures in the key studies. Moving average estimates of formaldehyde concentrations over a 4-hr period would better match the scenarios in the key acute studies.

Formaldehyde varies in predictable diurnal and seasonal patterns (higher in summer; higher at mid-day), which is important to take into consideration when calculating an annual average. There are benefits in using the simple approach applied, such as just taking the average, but regarding lines 1425-1432 in the *Draft Human Health Risk Assessment* for Formaldehyde, EPA could build seasonal trends (e.g., using the Komogorov-Zurbenko (KZ) filter, which sufficiently handles missing data, or other methods used by EPA in their trends assessments for criteria pollutants; cited below) from the available data based on time of the year and predict missing days to create updated annual means & modeled daily concentrations. Another Committee member is less supportive of this suggestion, as the member believed that, depending on the amount of actual monitored concentration data available during the course of a year, such an activity risks resembling more an attempt at extrapolation than an

act of prediction. Extrapolation and predictions are quite different concepts in statistics, and the former is always strongly discouraged in any statistical modeling textbook.

Wells, Benjamin, Pat Dolwick, Brian Eder, Mark Evangelista, Kristen Foley, Elizabeth Mannshardt, Chris Misenis, and Anthony Weishampel. "Improved Estimation of Trends in U.S. Ozone Concentrations Adjusted for Interannual Variability in Meteorological Conditions." *Atmospheric Environment* 248 (March 1, 2021): 118234. https://doi.org/10.1016/j.atmosenv.2021.118234.

Henneman, Lucas RF, Heather A Holmes, James A Mulholland, and Armistead G Russell. "Meteorological Detrending of Primary and Secondary Pollutant Concentrations: Method Application and Evaluation Using Long-Term (2000-2012) Data in Atlanta." *Atmospheric Environment* 119 (2015): 201–10. https://doi.org/10.1016/j.atmosenv.2015.08.007.

Hogrefe, Christian, Somaraju Vempaty, S.Trivikrama Rao, and P.Steven Porter. "A Comparison of Four Techniques for Separating Different Time Scales in Atmospheric Variables." *Atmospheric Environment* 37, no. 3 (January 2003): 313–25. https://doi.org/10.1016/S1352-2310(02)00897-X.

It is also important to consider when during the day samples are taken, since concentrations are expected to be higher during mid-day.

Wang, Peidong, Tracey Holloway, Matilyn Bindl, Monica Harkey, and Isabelle De Smedt. "Ambient Formaldehyde over the United States from Ground-Based (AQS) and Satellite (OMI) Observations." *Remote Sensing* 14, no. 9 (2022): 2191. https://doi.org/10.3390/rs14092191.

For chronic endpoints, it might be possible to use consecutively reported samples to generate additional multi-hour TWA concentrations. However, the lesser relevance of, for example, overnight ambient air, limits the duration of relevant moving-average windows.

Measurement locations, time of day, and other considerations are highly influenced by EPA regulations and policy, so there should be closer involvement between offices in optimizing observation locations, times of day, and times of year of measurements.

Charge Question 6.3

EPA's Human Exposure Model (HEM 4.2) and 6 years of Toxic Release Inventory data were used to evaluate national scale population impacts of exposures to industrial releases of formaldehyde in the outdoor ambient air, based on site-specific information including release location and census data. This is the first time EPA has used the HEM in a TSCA risk evaluation. Please comment on the application of the HEM for the purpose of identifying communities with elevated ambient air exposures to formaldehyde from industrial facilities and characterizing the exposed populations. In your response, please comment on the strengths and uncertainties associated with EPA's presentation of HEM results in Section 2.4.2.3 and Section 4.2.4.2 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g), including Figures 2-8 and 2-9 and Tables 4-2 and 4-3 of that assessment.

Response to Charge Question 6.3

The Committee recognized the utility of the HEM in developing the formaldehyde assessment but discussed a number of concerns regarding data choices and the need to acknowledge the limitations of

the datasets incorporated into the model. For example, the Committee is concerned that use of the Toxic Release Inventory (TRI) dataset will underestimate exposure. Discussion of e data in the models, model implementation and resulting exposure metrics informs comments about what is presented in Figures 2-8 and 2-9. The Committee is also concerned that important exposures are not captured in the current assessment given the models, methods and approaches used. Several editorial comments and clarifications are recommended.

Recommendations:

Data issues

- **Acknowledge the limitations of the 2020 Census data and discuss the implications of those limitations on the results of the outdoor air exposure assessment.**
- **More explanation/justification of using the Toxic Release Inventory (TRI) dataset instead of the much larger NEI dataset.**
- **Exploratory data analysis on the 6 years of TRI data to identify trends.**

Model implementation and uncertainties

- **Clarify the temporal scale of meteorological data used in AERMOD.**
- **Provide clear explanations of how the census block ambient concentrations are derived. This is fundamental to be able to understand and interpret the results presented in Figure 2-8. E.g. what procedure is used to aggregate the estimated annual exposure from the receptors to obtain the annual average concentration at the census block level.**
- **Given the large uncertainty surrounding the estimated annual average ambient formaldehyde concentration, the Committee strongly encourages the Agency to discuss the uncertainties inherent in these estimates. The committee also invites the Agency to provide ranges of concentrations for each census blocks rather than presenting only one estimated annual average formaldehyde concentration.**
- **It is unclear what is the benefit of showing whether a census block has an estimated ambient formaldehyde exposure annual concentration that is larger than a US-wide biogenic threshold? The Committee recommended an analysis to understand whether in a specific block the amount of formaldehyde concentration due to TRI releases is greater than the 95th percentile of formaldehyde concentration due to biogenic sources at that location. This would be more protective to the population as it sets a threshold that is location-specific, potentially lower than a nation-wide 95th percentile threshold.**

Figure 2-8

- **Clarify how the data presented were derived and provide better legend and caption for the figure. E.g., does Figure 2-8 represent a specific year or is it an annual average over the 6-years of data?**
- **Identify and discuss the extent that multiple facilities contribute to elevated concentrations in any location.**

Figure 2-9

- **Clarify how the data presented were derived and provide better legend/explanation for the figure. It is unclear how the total concentration, which is assumed to be the sum of fugitive and stack release has a median that is smaller than the median for one of the two terms that defines it. The spatial distribution of the concentrations is obscured because the concentrations for all the receptors are lumped together at each distance.**

Missing exposure scenarios

- **Model a mixed-use urban setting which appear to be missing in the draft assessment. This could be estimated with the IIOAC model or preferably the HEM model.**

Strengths

EPA Presentation
Draft Human Health Risk Assessment Section 2.4.2.3:
The description of the reasoning for using the HEM and its basic features are clear.

Lines 2566-2573 and Table 4-3 (pages 102-103): This is an interesting analysis of disparities in risk by various demographic variables. However, the limitations of the 2020 Census (as mentioned below) should be acknowledged.

Uncertainties
It is important to note uncertainties in Census data that the HEM is based on, especially in the 2020 Census, which has been shown to under-count certain groups (Hill et al 2022; US Census Bureau 2022, 2023, 2024).

A limitation of Integrated Indoor/Outdoor Air Calculator Model (IIOAC) and AMS/EPA Regulator Model (AERMOD) used in HEM is that daily meteorological conditions (e.g., which way the wind is blowing or an inversion) that might vary concentrations by multiple orders of magnitude are not considered. It is also not clear whether other factors such as building down-washing have been incorporated in the AERMOD modeling. Was AERMOD run with daily meteorology, or some other temporal scale?

More justification is needed for why the concentration contributions from TRI facilities are presented as a fraction of biogenic contribution from AirToxScreen.

In fgure 2-8 in Draft Human Health Risk Assessment, what do the dots represent? It appears as if concentrations are assigned to specific points, but this does not match the description of the figure. It would be helpful to identify/discuss the extent that multiple facilities contribute to elevated concentrations in any locations.

Toxic Release Inventory (TRI) emissions are used; what is the variability across those 6 years? (And is there any trend?). It is understood that these are annual reported values, but the biggest worry for most of these sites would be whether there is a large accidental (or planned) release that accounts for most of the reported annual emissions. There may be information from these facilities' air permits that might add more information about the periodicity and magnitude of non-continuous emissions from these facilities.

Table 4-2 in *Draft Human Health Risk Assessment*: the values are presented rounded to the unit digit and without uncertainty. EPA should consider rounding to a level with more confidence based on the uncertainty in exposure data and population data (Census data is also uncertain). A presentation of uncertainty limits (e.g., confidence intervals) should be included.

Table 2-1 in *Draft Human Health Risk Assessment*: National Emissions Inventory (NEI) has stack parameters for some sources—how representative are the parameters used for IIOAC and

AERMOD/HEM?

In theory the idea of using the HEM to obtain an idea of which communities in the United States are subject to elevated levels of ambient air exposure to formaldehyde from industrial facilities is a good one. There are concerns with the way the HEM is implemented to derive the results, as well as the choice of the threshold. First the HEM takes as input release of formaldehyde the maximum annual release reported by a TRI facility during the 6-year period 2016-2021.

It is unclear why the Agency decided to use the TRI data rather than the NEI data. A comparison of releases reported in the two databases shows that the TRI tends to have lower release values as Oil and gas drilling industries tend to have highest releases of formaldehyde, yet that sector does not have to report for TRI. By choosing to use release data from TRI, even if using the maximum release reported by a site, the ambient exposure estimated by the HEM is likely to be an underestimation.

Additionally, the number of TRI sites for which release data is available is dwarfed by the amount of release data available from NEI. Hence again the results reported by the HEM analyses are likely underestimating the ambient exposure to formaldehyde.

Having established the input release data, the HEM model estimates the ambient exposure at receptors placed on 11 rings at varying radial distances from the facility releasing formaldehyde up to a distance of 50km. It is unclear whether the HEM model uses actual meteorological data, with different meteorological conditions every year, or whether the same fixed meteorological conditions are used for every day in the year, as the Agency has done to derive the modeled concentrations using the IIOAC approach. It is also unclear if the results the Agency are presenting in Figure 2.8 refers to a specific year or refers to averages across the 6-year worth of data. Neither the caption to the figure nor the text explaining how the results in Figure 2.8 are derived in either the *Draft for Human Health Risk Assessment* nor the *Draft Ambient Air Exposure Assessment* are very specific in that regard. On the contrary, the level of details provided in the text is so summary and, in certain instances so confusing, that it makes it impossible for somebody to replicate the results the Agency has obtained.

Assuming the meteorological data for a given year have been used, the HEM model allows then to derive the estimated ambient formaldehyde daily concentration at each receptor point due to stack and fugitive releases. The latter are further averaged at each receptor site over the days in a year to obtain the average annual concentration due to stack, respectively, fugitive releases at each exposure point. The text is unclear about what procedure is exactly used to aggregate the estimated annual exposure from the receptors to obtain the annual average concentration at the census block level. Did the Agency overlay the boundaries of each census block in a map of the United States and selected all the receptor points surrounding TRI sites that fall in the census block? What approach did the Agency use? Was the annual average ambient concentration from the receptor points falling within a census block boundaries averaged or summed together? This is not clear from the text. The text uses the phrase “modeled total concentration”, which appeared to imply that the receptor average annual ambient concentrations were summed together, although this intuitively would lead to values much larger than the ones reported in Figure 2.8. Providing clear explanations of how the census block ambient concentrations were ultimately derived is fundamental to be able to understand and interpret the results presented in the figure.

Figure 2.8 demonstrated the modeled annual formaldehyde concentrations for each census block with the census block shaded in different colors to indicate its range and its relationship to the 95th

percentile of the biogenic threshold. It is unclear what is the benefit of showing whether a census block has an estimated ambient formaldehyde exposure annual concentration that is larger than a US-wide biogenic threshold. Both the ambient formaldehyde concentration and the concentration of formaldehyde related to biogenic sources/phenomena vary spatially, hence it appeared to evaluate that it would make more sense to understand whether in a specific block the amount of formaldehyde concentration due to TRI releases is greater than the 95th percentile of formaldehyde concentration due to biogenic sources at that location. This would be more protective to the population as it sets a threshold that is location specific.

Figure 2.9 attempted to compare the distribution of the ambient exposure concentration at the receptor points and evaluate the contribution of fugitive release versus stack release at different distances from a TRI sites. However, it is unclear how the total, which is assumed to be the sum of fugitive and stack release has a median that is smaller than the median for one of the two terms that defines it. Secondly, these results do not consider the spatial distribution as the concentrations for all the receptors are lumped together, so for example there could be a receptor at 10m from a TRI site for which the concentration due to stack release is larger than the concentration due to fugitive release and that might be true for all the receptors in a particular region of the United States because of meteorological conditions and of dispersal. Yet one would not be able to identify this type of pattern as here the results are collated over space.

None of these results address uncertainty in the estimated annual average ambient formaldehyde concentration. Given the large uncertainty surrounding this estimate the committee strongly encourages the Agency to discuss the uncertainties and think about providing ranges of concentrations for each census blocks rather than presenting only one estimated annual average formaldehyde concentration.

<u>Concerns that current approaches in the current draft miss important exposure scenarios</u>

In response to CQ 4.1, the need for additional exposure scenarios was discussed. Consideration of only the industrial and consumer product scenarios omits an important array of other exposure scenarios. Also, several Committee members (from CQ 4.1 and others) have challenged the EPA assertion that the calculations they've presented are representative of the US population with no PESS identified. Indeed, in CQ 4.1 high density, multi-use urban areas qualify as a PESS for several reasons including the probability that ambient air for residents near small businesses (auto body shops used as an example, but also including furniture repair and construction, metal and duct fitting shops and others). The perimeters discussed in EPA evaluations are too far to apply to these emissions where the human target lives only 10 meters away.

The EPA studied the air pollution provided from auto body shops (EPA 2005), noting 287,000 tons of volatile organic compounds are emitted each year including volatile organic compounds.
This reality provides daily opportunities for exposure to the surrounding populations in mixed-use urban areas. Exposure opportunities are greatest for the nearby residents, school children and public in nearby spaces—indoor and outdoor. Note: Photographs were presented during the public peer review meeting but are not provided here.
Again, this is a single source of formaldehyde, composed of multiple COUs in a complex scenario. Any single COU contribution may be small, if calculated at all, but in combination creates a significant exposure opportunity on a daily basis…presumably 6 days per week…repeatedly to the same people.

EPA has calculated ambient air concentrations in the IIOAC model to represent exposure farther than 100 meters from the source of contamination (*Draft Ambient Air Exposure Assessment*). Obviously, there are no football-field sized spaces between the auto body shop's rooftop vents and the homes and a preschool in these pictures. Ambient air concentrations of formaldehyde as calculated by EPA with these factors and assumptions are unlikely to represent daily exposures for these urban populations. Modeling for this mixed-use urban setting could be estimated with the IIOAC model or preferably the HEM model. Literature is available on this issue with a variety of monitoring information studies. Detailed information about formaldehyde-based products in car repair and painting shops is available in the publication and references therein by Granadero et al., as a start.

Notes

Note regarding photographs: The autobody shops do not appear to be in violation of any workplace regulations and were chosen for presentation only to visualize the close proximity between the potential source of formaldehyde emission and nearby residents experiencing that exposure opportunity, daily. This situation is normal in lower socioeconomic, mixed-use urban settings in many, many cities across the US. It is highly unusual in high socioeconomic urban settings, suburban and rural areas. As such, lower socioeconomic, urban, mixed-use communities may be considered PESS for this exposure scenario. The adjacent residences and other businesses may be considered as frontline exposure groups.

Editorial Comments

Please clarify the difference between Figure Appendix B-2 and Figure 3-5 in *Draft Ambient Air Exposure Assessment for Formaldehyde*.

The Draft Human Health Risk Assessment (LL 1546-1547: page 65) contains an incomplete sentence, "Across the country, a total population of 105,463 people (based on 2020 Census data) live in census blocks shown with ambient air [something missing here?]"

Draft Human Health Risk Assessment, Figure 2-8: Recommend adding explanation of the white space/missing data to figure legend.

Draft Human Health Risk Assessment, Section 4.2.4.2

- Line 2470 (page 99): Recommend adding text to explain that risk estimates above the MOE indicate no increased risk.
- Lines 2506-2510 (page 101): The text, "within the same order of magnitude greater than" is not easy to understand. Recommend adding the range of estimated values so the meaning is clear.
- Draft Human Health Risk Assessment Table 4-2 (on page 102):
- Recommend adding "estimated" to the text within the table. E.g., Change the header above the content of Table 4-2 to read: Number of People within 50 km of any Facility in Different Ranges for Lifetime Estimated Cancer Risk. Also, recommend adding the "Total population within model domain" row to the top of the table in addition to the current location near the bottom of the table.

Charge Question 6.4

As described in the Draft Ambient Air Exposure Assessment (U.S. EPA, 2024a) and the Draft Human Health Risk Assessment (U.S. EPA, 2024g), EPA recognizes that exposure to formaldehyde is the result from many sources. Please comment on the use of 2019 AirToxScreen to describe different sources of formaldehyde and associated contributions to the overall exposure profile of formaldehyde in ambient air. In your response, discuss contribution secondary formation and natural sources of formaldehyde in relation to contributions formaldehyde from TSCA conditions of use.

Response to Charge Question 6.4

The key points brought up by the Committee for charge question 6.4 during the discussion include:

1. It is unclear why biogenic and secondary formaldehyde are used as baseline comparisons for IIAOC and point source formaldehyde.
2. Comparisons between AirToxScreen and observations are difficult to interpret because of the issues with observations being made at different locations and different times of year and day. The Committee recommended reconciling these datasets in time and space prior to performing any comparison.
3. The Committee recommended close collaboration with other EPA offices regarding modeling formaldehyde.

Recommendations:

- **Describe more clearly the reasoning for using biogenic and secondary formaldehyde as a baseline point of comparison for point-source formaldehyde.**
- **Describe more clearly the differences between the concentrations obtained by the various models, incorporating recommendations from CQ6.1 and 6.2 related to the spatial and temporal alignment of the exposure products.**
- **Explore more fully the secondary formation contribution and consider its role in ambient formaldehyde exposure.**
- **Address concerns related to comparing AirToxScreen output and IIOAC.**

Use of 2019 AirToxScreen to describe different sources of formaldehyde and associated contributions to the overall exposure profile of formaldehyde in ambient air

As described in the two Draft reports (*Draft Ambient Air Exposure and Draft Human Health Risk Assessment*), the Agency uses the 2019 version of AirToxScreen to be able to perform some form of source apportionment by estimating the ambient formaldehyde concentration at each census tract and breaking down the total ambient formaldehyde concentration at a census tract into the contribution due to as many as 38 sources, which can be more broadly grouped as point sources, biogenic sources and secondary formation.

To estimate ambient formaldehyde concentration at a given census tract, AirToxScreen starts with information on the estimated amount of formaldehyde released by industries as reported in the 2017 NEI database and disperse it over space using the approaches for pollution dispersion encoded in the

CMAQ and AERMOD models. Both of these models estimate dispersion of particles also accounting for meteorology.

Recommendation:

- **Describe more clearly the reasoning for using biogenic and secondary formaldehyde as a baseline point of comparison for point-source formaldehyde.**

The Agency used biogenic & secondary HCHO as its baseline assessment. However, the reasoning was not made clear. There is a discernible rationalethat formaldehyde is present in the air without the TSCA use cases, but it is unclear whether all risk in the ambient air is discounted relative to biogenic or secondary HCHO. The Committee was not convinced this discounting was appropriate.

It appeared arbitrary to compare the HEM model results with the 95th percentile biogenic contribution (line 568, 592-600 in the *Draft Ambient Air Exposure Assessment for Formaldehyde*). This approach is not protective of public or environmental health. Why did EPA select biogenic and not secondary sources, or why not all sources? Biogenic contributions and secondary contributions vary in space, and the Committee recommended comparing each facility's contribution from HEM/AERMOD with the biogenic or total formaldehyde spatially.

Recommendation:

- **Describe more clearly the differences between the concentrations obtained by the various models, incorporating recommendations from charge questions 6.1 and 6.2 related to the spatial and temporal alignment of the exposure products.**

The Committee noted a disconnect between results from three data sets. IIOAC results yield concentrations up to 6μg/m^3, while AirToxScreen showed contribution of up to only 0.88μg/m^3, and HEM with a maximum concentration of 8.9μg/m^3. The disagreements were not fully addressed by the discussion of the HEM spatial scale being at census blocks, whereas AirToxScreen generates estimates at census tracts, and IIOAC at a specific distance from sources. However, the Committee believed that there is more going on here to lead to an order of magnitude difference in concentrations, including that AirToxScreen is based on a combination of a chemical transport model (CMAQ)—to capture "background" contributions and chemistry—and AERMOD, which captures local contributions. The method to combine CMAQ and AERMOD may contribute to the order of magnitude difference in concentrations by AirToxScreen.

The EPA used only AirToxScreen to estimate overall contributions from various sources, but spatial extent and contributions from various source categories would be useful too. The Committee recommended that the Agency harmonize the modeled concentrations and observations in space and time.

Figure 3.3 page 22, in the *Draft Ambient Air Exposure Assessment* showed the resulting 2019 average annual formaldehyde ambient concentration as estimated by AirToxScreen when all sources are considered and broken down by sources, across all sites. While the plot is helpful to appreciate the range of annual average concentration across the various census tracts in the United States, to adequately perform source apportionment it is necessary to calculate, at each census tract, the ratios of the estimated formaldehyde concentration that can be attributed to a specific type of source in that census tract, e.g. secondary formation, to the estimated concentration due to all sources at the same

census tract. The current figure does not show these ratios, thus not allowing one to draw any conclusion. Taking the ratio of the mean average annual formaldehyde concentration due to point sources, averaged across all census tracts, and divide it by the mean average annual formaldehyde concentration due to all sources, averaged across all census tracts, as currently reported in the *Draft Ambient Air Exposure* Assessment is incorrect as it completely ignores the fact that these 3 average annual concentrations (due to point sources, biogenic sources, secondary formation) are not independent of each other.

In general, when looking at the overall distribution of formaldehyde concentration due to secondary production, one can see that those concentrations tend to be larger than the rest of the concentrations. Discuss contributions of secondary formation and natural sources of formaldehyde in relation to contributions of formaldehyde from TSCA conditions of use

Recommendation:

- **Explore more fully the secondary formation contribution and consider its role in ambient formaldehyde exposure.**

In relation to secondary formaldehyde percentages, the committee offers the following reference: Zhang, H., J. Li, Q. Ying, B. B. Guven, and E. P. Olaguer (2013), Source apportionment of formaldehyde during TexAQS 2006 using a source-oriented chemical transport model, J. Geophys. Res. Atmos., 118, 1525–1535,doi:10.1002/jgrd.50197. This reference noted that 10-30% of secondary formaldehyde comes from industrial sources. Those would clearly represent a TSCA use, even if NOT specified in the currently listed COUs. This study and those that can be found from a forward search of the literature to identify more recent related research can be used to estimate secondary formaldehyde arising from industrial sources. The problem will be identifying the spatial distribution of the secondary formaldehyde as there are many environmental factors that contribute to atmospheric formaldehyde formation.

It is unclear how well observations reflect total HCHO from AirToxScreen. According to Figure 3-8 on page 29 of the *Draft Ambient Air Exposure Assessment for Formaldehyde*, it appeared that AirToxScreen estimated lower concentrations and with a smaller spread, but it is difficult to draw any conclusion because there are different numbers of observations, suggesting that we are not comparing at the same location. In general, it would be better to do more direct comparisons e.g., comparisons made only at areas with IIOAC modeled locations or only at AMTIC monitoring sites.

Note that similar to HEM/AERMOD, no photodegradation is considered in IIOAC, but it is considered by the CMAQ modeling used to assess the impacts of some sources in AirToxScreen.

Recommendation:

- **Address concerns related to comparing AirToxScreen output and IIOAC.**

To perform some form of source apportionment and estimate the contribution of formaldehyde from TSCA COU's to the total formaldehyde concentration due to all sources, the Agency plans to compare the estimated formaldehyde concentration as obtained using the IIOAC approach, which considered all the formaldehyde released from TSCA COU's, to the estimated formaldehyde concentration obtained using AirToxScreen. While in theory this appeared to be an approximative way to perform some form of source apportionment, as already commented in charge question 6.1

above, the problem is in the implementation. Concentrations estimated by the IIOAC method and AirToxScreen are not comparable for multiple reasons:

(i) Spatial misalignment: The two estimated concentrations do not refer to the same spatial locations. The IIOAC estimates of formaldehyde concentrations only refer to concentrations at selected locations within a certain distance (100m to 1,0000m) from TRI facilities, while the AirToxScreen concentrations refer to all census tracts centroids.
(ii) Different input sources: The IIOAC method uses as input the formaldehyde releases from TRI facilities while AirToxScreen uses as input the formaldehyde releases provided in the NEI database. There are sizeable differences between the two databases in terms of amount of data and even magnitude of the releases, with the largest releases not included in the TRI dataset.
(iii) Static versus changing meteorology: he Estimates of formaldehyde concentration obtained by the IIOAC method are not derived using actual meteorological conditions, but they are derived using a fixed meteorological condition that is maintained constant for every day of the year. This can be deduced by the fact that the daily average ambient formaldehyde concentration is the same as the annual average ambient formaldehyde concentration. As elaborated in response to charge question 6.1, given the high reactivity of formaldehyde and the way it behaves under different meteorological conditions, not allowing the meteorological conditions to change from day to day or even from season to season is not realistic and might yield estimated of formaldehyde concentration due to TSCA COU's that are too high or too low.

To draw conclusions on the contribution of TSCA COU'S to the total formaldehyde ambient concentration due to all sources, the issues noted above should be addressed. Once they are addressed, a calculation of the ratio of the estimated formaldehyde concentration due to TSCA COU's at a given location and the estimated formaldehyde concentration due to all sources (and estimated by AirToxScreen) at the same location or at least in a neighborhood of the same location would allow to quantify the percentage of formaldehyde concentration at a given location that is contributed by TSCA COU's. Repeating such calculation for each location, it will make evident the variability in the contribution of TSCA COU's to the formaldehyde due to all sources across space. This variability is to be expected given the different meteorological conditions over space as well as the variability in the density of industrial facilities releasing formaldehyde across space.

Editorial Comment

Figure 3-4 in page 23 of the *Draft Ambient Exposure Assessment* document: are the census blocks points or the geographic boundaries? The document should also clarify the convention regarding the areas presented in white. These areas are only assumed to be zero since they are outside 50-km from TRI facility.

Charge Question 6.5

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the chronic inhalation hazard endpoints and PODs derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022) that have been peer reviewed by NASEM. Section 4.2.4 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the chronic inhalation POD to assess risks to people with exposure to formaldehyde in outdoor air. Please comment on the strengths and uncertainties associated with OPPT's application of the chronic non-cancer inhalation POD for

evaluation of formaldehyde risks through outdoor air.

Response to Charge Question 6.5

The robust discussion and recommendations surrounding the chronic POD generated for charge questions 1.2, 3.3, and 4.4 captured all the Committee's comments for question 6.5. Outdoor air exposure is experienced by essentially all ages, life stages, and occupations, with astronauts and submariners being among the few exceptions. Although most individuals are exposed to outdoor air, this exposure generally reduces their average personal exposure to formaldehyde over time (USEPA, 2024, Figure 4-12). The exposure concentrations vary widely, and the highest risk scenario presumes that people are constantly near a facility emitting formaldehyde. As shown in Tables 16-21 and 16-22 of the Exposure Factors Handbook (US EPA 2011), typical relative to time spent at work or otherwise indoors, the time spent outdoors is small (36-132 minutes per day for children; 281 minutes per day for adults 18-64, and 298 minutes per day for adults >64 years old). Additionally, acute, and chronic exposures from industrial releases of formaldehyde which can be attributed to the Toxic Substance Control Act (TSCA)'s conditions of use (COUs) based on the Integrated Indoor-Outdoor Air Calculator (IIOAC) modeling are less than the formaldehyde concentration in a typical home.

Charge Question 6.6

The Draft Human Health Hazard Assessment (U.S. EPA, 2024f) relies on the cancer IUR derived in the draft IRIS assessment on formaldehyde (U.S. EPA, 2022) that has been peer reviewed by NASEM. Section 4.2.4.1 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) outlines the use of the cancer IUR to assess risks to people with exposure to formaldehyde in outdoor air. Please comment on the strengths and uncertainties associated with OPPT's application of the cancer IUR for evaluation of formaldehyde risks through outdoor air exposure.

Response to Charge Question 6.6

The robust discussion surrounding the cancer IUR generated for charge questions 3.4, 4.5, and 5.7 captured all of the Committee's comments for question 6.6. One Committee member asserted that without a clear distinction between threshold and non-threshold carcinogens for formaldehyde, it is neither feasible nor suitable to carry out formaldehyde cancer risk assessment and management decisions. The same Committee member suggested the need for establishing a clear distinction between the types of carcinogens pertaining to formaldehyde when the Agency evaluates the relevance of using the cancer IUR for assessing the risks associated with outdoor air exposure to formaldehyde. This comment is also relevant to CQ 4.5 and 5.7 as well as CQ 6.6.

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6. AGGREGATE EXPOSURE

Charge Question 7.1

Section 4.3 of Draft Human Health Risk Assessment (U.S. EPA, 2024g) qualitatively considered the combined exposures that may result from multiple sources releasing formaldehyde to air in

specific indoor or outdoor environments. For example, EPA's HEM analysis estimated exposures and risks from formaldehyde released to ambient air from all TRI facilities present in a particular location. EPA also used monitoring data to estimate aggregate exposures and risks from all sources of formaldehyde in a range of indoor and outdoor settings. Please comment on the strengths and uncertainties of EPA's approaches for estimating aggregate exposure and risk from multiple sources of formaldehyde through a specific pathway (i.e., indoor, or outdoor air).

Response to Charge Question 7.1

The strengths and uncertainties of the approach for estimating aggregate exposure and risk in the *Draft Human Health Risk Assessment* were noted as follows.

The concept of "estimating aggregate exposure and risk from multiple sources of formaldehyde through a specific pathway" is an appropriate approach which facilitates consideration of multiple contributions to the pathway of exposure, hence consideration of either aggregated exposure estimates from many individual products through common exposure scenarios or using monitoring data specific to that pathway. Indeed, if both the monitoring data and the modeled estimations are considered, confidence in the range of pathway concentrations is improved as well as providing some indication of relative contribution across many products contributing to the aggregated concentration.

However, EPA's consideration of simply "indoor" and "outdoor" and "residence" is too broad and omits very important pathways and vast numbers of exposed people. The Committee recommended that the concept can be focused to key microenvironments with both pulses of high exposure as well as long term exposure (vehicle interiors) (Reddam, 2021), and conditions of outdoor emissions from general business in densely populated, mixed use urban areas [The latter example appears to qualify as a PESS scenario and is discussed in previous Charge Questions].

In most deliberations about COUs or exposure scenarios or values for the parameters of the exposure assessment, "indoor" was not really considered…rather "residence" or manufacturing facility were the focus. But other indoor areas should also be included as they become the venue for potential exposures and may involve a broad part of the US population. [retail spaces, warehouses, show rooms, hotel conference and guest rooms, schools, libraries, etc.] Such exposure would result from a combination of products in those indoor spaces. Products in such spaces could off gas formaldehyde, as there are broad areas of flooring, constantly renewed furniture, and decorative settings (with glues, paints). Some have multiple electronic items, arts, fabrics, etc. on hand. Vehicles should be considered separately, as discussed in other Charge Questions.

- Example: page 11, lines 348-358, discussion refer to automotive care products. Exposure assessments for each product in this category are considered "in residential settings", "based on consumer use activities". While that is a legitimate approach, other considerations of use profile and an aggregation of exposures across many products used in business are absent. The existing exposure assessment for car wax considered a few minutes of a consumer who bought the product and polished their car. But what about businesses who purchase boxes of this product and use it frequently during the day (either themselves or nearby workstations) along with many other vehicle care and repair products (paints, greases, etc.). These exposures are greater in terms of magnitude of exposure per unit time (dermal and inhalation), greater in duration of exposure, and far greater in terms of repetitive exposure (perhaps daily). In terms of "bystander" exposure, other workers in these businesses will also

be exposed. Also, these businesses must exhaust the workspaces, which then provides daily air-borne exposures to nearby residents in urban areas. Monitoring data from industrial facilities with perimeters of 100 meters or further would not be representative for this urban ambient air estimation. However, this scenario is widespread in the cities of lower socio-economics where densely populated areas include both residential and business properties, schools, playgrounds, clinics, etc side-by-side. These are challenged neighborhoods—easily viewed as PESS communities for this exposure scenario. Indoor exposure within these businesses, however, would occur throughout the country, potentially in such small and medium size businesses. These exposures are the product of aggregation from multiple products…predictable combinations which has been the subject of EPA research in the past. The same aggregation provides constant exposure to workers inside these businesses.

When a probabilistic aggregation is modeled, two additional analyses can be made. First, the comparison of modeled aggregate exposure can be compared to the exposure predicted from the relevant monitoring studies. Significant differences can be explored…either in understanding the strengths and weaknesses of the monitoring study or in the aggregate model (or its inputs for the parameters). Next, in the model, the relative contribution from each of the sources can be calculated. Together, the confidence can be increased for both the calculated overall population risk in different settings (multiple venues of indoor and outdoor) and the decision-making for risk mitigation among the TSCA covered products.

Reviewers found that it is not possible to answer this charge question solely based on the text of Section 4.3. Sections 2.3 and 2.4 of the *Draft Human Health Risk Assessment* (U.S. EPA, 2024g) describe the data sources and approaches used by EPA for indoor and outdoor air exposure assessment. Tables 2.1 and 2.2 document numerous data sources of indoor air monitoring in homes and mobile homes and some types of commercial buildings (school buildings, government buildings). These data will represent an aggregate of indoor sources. For outdoor air, EPA again describes multiple sources of data both measured and modeled reflecting a range of ambient conditions near facilities (AMTIC) and attributed to various point and mobile sources (AirToxScreen).

Strengths include the consideration of multiple data sources in each setting. For indoor air in Section 2.3.1, "EPA identified over 800 monitoring studies, 290 of which are specific to the indoor air environment and associated with the 12 TSCA COUs subject to this risk evaluation (see Appendix A of the *Draft Indoor Air Exposure Assessment for Formaldehyde* (U.S. EPA, 2024j))." For outdoor air in Section 2.4, EPA discusses several EPA datasets and modeling resources that capture formaldehyde concentrations near facilities (AMTIC) as well as models representing general population exposures at the census tract level (AirToxScreen). From Section 2.4.2.1, "EPA's modeling evaluated industrial releases of formaldehyde that are associated with COUs from two separate databases (TRI and NEI). EPA compared releases and modeled concentrations from the two databases and found results were within the same estimated distribution range."

The Committee specified the need to quantify aggregate exposure. While we do not have sampling data for every possible exposure scenario, EPA should build on the considerable strengths of the datasets and models they have and develop a quantitative estimate of aggregate exposure for the indoor and outdoor air pathways.

While it is a strength that Section 4.3. page 111 of the *Draft Human Health Risk Assessment* acknowledges how aggregate exposure is from "multiple sources, across multiple routes, across groups of people or pathways", there appeared to be very limited information and action towards aggregate assessments. This section also stated very good examples of what these aggregate scenarios could be (i.e. stating people could be exposed through indoor and outdoor air and occupational exposure) however, it did not seem to follow these with actual analyses that assessed these aggregate exposures. EPA "…concluded that there is too much uncertainty in the individual analyses underlying exposure and risks from individual pathways to support a quantitative aggregate analysis." Although there might be some uncertainty, there are steps that could be taken to conducted aggregate exposure assessments across pathways (e.g., simulations and other statistical modeling). Otherwise, there is a potential for underestimation, and this would be detrimental for the general population, especially those in the susceptible subpopulation.

The EPA considered that exposure can occur through multiple sources and provided scenarios in which people could have exposure through multiple sources. Regarding uncertainties in this approach, given that EPA already used monitoring data to estimate risk associated with formaldehyde across individual routes of exposure (as noted on lines 2766-2768, page 111), the EPA could, at the bare minimum, added these risk estimates together to get a crude estimate of potential additive effects. The EPA's assumption that risks are not additive across routes was not justified based on the qualitative information provided.

Although there are undoubtedly uncertainties associated with an approach to crudely estimate additive effects, the calculations could be conducted under a range of scenarios. Simulations may be one approach that could aid in these types of calculations and could reduce the uncertainty. In the draft risk evaluation, EPA considered sentinel exposures by considering populations who may have upper bound exposures (e.g., workers; draft HHRA lines 2792-2794, page 11). However, it's possible that people who are exposed to both indoor and outdoor air are also experiencing upper bound exposures. The qualitative approach appeared to lack consideration for these individuals.

The concept of "estimating aggregate exposure and risk from multiple sources of formaldehyde through a specific pathway" is an appropriate approach which facilitates consideration of multiple contributions to the pathway of exposure, hence consideration of either aggregated exposure estimates from many individual products through common exposure scenarios or using monitoring data specific to that pathway. Indeed, if both the monitoring data and the modeled estimations are considered, confidence in the range of pathway concentrations is improved as well as providing some indication of relative contribution across many products contributing to the aggregated concentration.

However, EPA's consideration of simply "indoor" and "outdoor" and "residence" is too broad and omits very important pathways and vast numbers of exposed people. The concept can be focused to key microenvironments with both pulses of high exposure as well as long term exposure (vehicle interiors), and conditions of outdoor emissions from general business in densely populated, mixed use urban areas, relevant to PESS scenarios.

In most deliberations about COUs or exposure scenarios or values for the parameters of the exposure assessment, "indoor" was not really considered. Rather, "residence" or manufacturing facility were the focus. But other indoor areas should also be included as they become the venue for potential

exposures and may involve a broad part of the US population such as retail spaces, warehouses, show rooms, hotel conference and guest rooms, schools, libraries, etc. Such exposure would result from a combination of products in those indoor spaces. Those products could off gas formaldehyde including flooring, furniture, and decorative settings (with glues, paints), multiple electronic items, vehicles, arts, furnishings, etc.

For example, page 11, lines 348-358 of the *Draft Human Health Risk Assessment,* in the discussion regarding automotive care products, exposure assessments for each product in this category are considered "in residential settings", "based on consumer use activities". While that is a legitimate approach, other considerations of use profile and an aggregation of exposures across many products used in business are absent. The existing exposure assessment for car wax considered a few minutes of a consumer who bought the product and polished their car. But what about businesses who purchase boxes of this product and use it frequently during the day (either themselves or nearby workstations) along with many other vehicle care and repair products (paints, greases, etc.)? These exposures are greater in terms of magnitude of exposure per unit time (dermal and inhalation), greater in duration of exposure, and far greater in terms of repetitive exposure (perhaps daily). In terms of "bystander" exposure, these businesses must exhaust the workspaces, which then provides daily air-borne exposures to nearby residents in urban areas. This scenario is widespread in the cities of lower socio-economics where densely populated areas include both residential and business properties, schools, playgrounds, clinics, etc. side-by-side. These are challenged neighborhoods—easily viewed as PESS communities for this exposure scenario. These exposures are the product of aggregation from multiple products, predictable combinations which has been the subject of EPA research in the past. The same aggregation provides constant exposure to workers inside these businesses.

Additional uncertainties of the EPA's approach regarding aggregate assessment are as follows:
The proper identification and treatment of PESS is critically relevant to proper quantitative aggregate exposure assessment. EPA did not include females of reproductive age as a PESS even though males of reproductive age are included. EPA stated that they will apply an uncertainty factor of 3X for chronic inhalation but has not proposed additional uncertainty factors specific to lifestage, including early life or pregnancy despite evidence demonstrating that these are vulnerable life stages. Formaldehyde exposure before pregnancy has been associated with increased time to conception, and women exposed to mixtures of chemicals that included formaldehyde in high amounts showed evidence of menstrual cycle disturbances (Hassani et al, 2014), which is indicative of the lifestage susceptibility for "women of reproductive age."

Further, the initial identification of PESS should not be contingent on chemical-specific data. Rather, chemical-specific evidence, intrinsic and extrinsic susceptibility factors should be used to identify PESS, and separately, account for the elevated risks for each group. When such data are absent, the application of generic adjustment factors (beyond the 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated (Varshavsky et al.).

We also know that PESS are co-exposed to numerous chemicals, further justifying quantitative aggregate and cumulative assessment. A 2021 study used the TRI database to identify co-exposures to formaldehyde and 15 other chemicals with a shared adverse health outcome (respiratory carcinogens). The authors identified over 600 communities in the US with combined exposures to formaldehyde and at least one other respiratory carcinogen (Pullen et al, 2021). Assessment of formaldehyde without considering other carcinogens for which co-exposures occur in the human population will underestimate risk because co-exposures to formaldehyde and multiple other carcinogens are

prevalent in US communities and are known to increase the likelihood of developing cancer (NRC, 2016).

Accounting for background sources is an additional important aspect of aggerate quantification. EPA did not to account for multiple background sources of exposure in the *Draft Risk Evaluation for Formaldehyde* stating that all possible pathways of exposure to the general population, including secondary formation, uses as preservatives, and baby products could not be considered because they constitute "non-TSCA" uses (U.S. EPA, 2024 Draft Human Health Risk Assessment for Formaldehyde, page 9). The National Academies of Science Engineering and Medicine recommended consideration of background exposures when conducting a risk evaluation for both individual chemicals and categories of chemicals through a cumulative risk assessment, citing that background exposures at "even small doses may have a relevant biological effect" (NRC, 2009). By not estimating total exposure from all potential pathways, EPA is significantly underestimating the risks of harm of formaldehyde in the general population.

In order to comply with TSCA, some committee members recommended evaluating formaldehyde and other carcinogens that are currently undergoing risk evaluation as a class of chemicals and conduct a cumulative risk assessment. It is the charge of TSCA and the policy of the United States that the EPA should regulate "chemical substances." – not substance—substances and mixtures which present an "unreasonable risk of injury to health or the environment, and to take action with respect to chemical substances and mixtures which are imminent hazards." TSCA grants EPA broad authority to review "categories of chemicals" when conducting risk evaluations and that "[a]ny action authorized or required to be taken by [EPA] under any provision of [TSCA] with respect to a chemical substance or mixture may be taken by [EPA] in accordance with that provision with respect to a category of chemical substances or mixtures" (15 U.S.C. § 2625(h).

Risk estimates

Regarding risk estimates, for quantitative aggregation, the human health risk assessment should include acute non-cancer, chronic non-cancer, and cancer risk estimates for each condition of use. The figures in the human health risk assessment document do not provide detailed tables with the quantitative risk values requisite for clear and transparent risk communication. EPA has presented these in previous TSCA risk evaluations, and the Committee recommended them to be a standard part of evaluations so that an explanation for EPA's conclusions are more robust.

EPA states that its risk determinations for formaldehyde are made by placing the risk estimates and comparisons to benchmark values for each exposure scenario in a broader context of total formaldehyde exposure. An explanation or scientific rationale for what is meant by "pragmatic and holistic evaluation" and "case-by-case and context driven," is missing. Also absent is why levels of naturally occurring formaldehyde are relevant to the determination of unreasonable risk from manufacture and processing of formaldehyde and use of formaldehyde in industrial, commercial and consumer products.

There is also missing rationale for comparisons made including: 1) Maximum concentrations of formaldehyde in outdoor air used to determination of unreasonable risk from workplace exposures and; 2) Formaldehyde concentrations in homes used to determination of unreasonable risk from workplace exposures. The fact that many formaldehyde-exposed workers also experience high formaldehyde exposures in their homes or from outdoor air is not relevant to a determination of the reasonableness of their workplace exposures, except in the context of assessing aggregate exposures

from the various settings in combination.

Use of the Central Tendency Exposure Estimates

Also relevant to aggregate assessment is the use of central tendency vs. high-end exposure estimates to inform risk characterization. Use of high-end exposure estimates is consistent with the best available science, EPA's practice in previous TSCA risk evaluations, and with the requirements of TSCA. However, in this RE, EPA states that it used central tendency exposure estimates for both chronic non-cancer and cancer risk determinations for occupational, consumer exposure and indoor air. No statement for rationale of this decision is provided other than the following:

> "The basis for chronic non-cancer and cancer risk estimates for indoor air were designed to estimate concentrations at the central tendency because this represents the most common scenario in an indoor environment (p. 14 of Unreasonable Risk Determination)."

In choosing to rely on the central tendency, EPA does not consider whether there is unreasonable risk to individuals with greater exposures, disregarding the exposure levels of 50% of the population. Further, it fails to meet its obligation under TSCA to identify any unreasonable risks to PESS, defined as "a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly" (U.S.C. §2602(12).

POD and MOE in Risk Determinations

EPA recommended to utilize epidemiological dose-response data to generate quantitative estimates of non-cancer risks from formaldehyde exposures. In the *Draft Risk Evaluation of Formaldehyde*, EPA continues to rely on the outdated methods for non-cancer dose-response analysis and risk characterization employed in previous TSCA risk evaluations. EPA's methods for non-cancer risk evaluation do not provide a quantitative estimate of risk. Instead, they rely on calculation of a margin of exposure ("MOE"), defined as: Margin of Exposure = non-cancer point of departure/ Human exposure (page 80, Draft Human Health Risk Assessment for Formaldehyde).

The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals impacted, and it perpetuates an outdated scientific notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population (Woodruff et all 2023; McGartland et all, 2017). The National Academies and the World Health Organization have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population and have been demonstrated in published case studies (NRC 2009; WHO 2017; Chiu et al. 2018; Nielson et al., 2023; Blessinger et al. 2020; Ginsberg et al., 2012).

The EPA should apply these methods to chronic non-cancer hazards identified in the draft IRIS assessment for which PODs were derived from animal data. In the case of formaldehyde, the draft IRIS assessment identified epidemiological studies with suitable data for POD estimation for multiple endpoints, including allergies, current asthma, and reproductive toxicity. The EPA recommended to use the dose-response data from these studies to estimate dose-response functions that can be used to quantify risks of non-cancer effects at exposure levels relevant to the TSCA formaldehyde risk evaluation, as it has done previously for multiple pollutants and chemicals, including lead, mercury,

arsenic, PFAS, and particulate matter.

Use of Less Certainty

Regarding the use of the phrase "less certainty," the EPA has applied a justification that it has "less certainty of the contribution to the unreasonable risk" to numerous exposure scenarios where formaldehyde exposures exceeded the level at which the EPA determined humans experience adverse reductions in lung function – which indicates high certainty of an unreasonable risk, rather than "less certainty." A rationale of this justification and an explanation of the departure from previous TSCA risk evaluations is missing.

Recommendations:

- **Accurately characterize real-world formaldehyde exposures and risks by including potentially exposed or susceptible subpopulations in risk evaluations.**
- **Revise the risk evaluation to reflect quantitative non-cancer risk estimates using high-end exposure and risk estimates. Remove any scientifically unsupported justifications that downplay or disregard risk. Adopt best available scientific methods, such as quantitative aggregate and cumulative risk assessments, to better reflect real-world exposure scenarios**.

Charge Question 7.2

Section 4.3 of the Draft Human Health Risk Assessment (U.S. EPA, 2024g) qualitatively considered the aggregate exposures individuals may experience from multiple exposure scenarios. For example, individuals exposed to formaldehyde through work or through use of consumer products are expected to also have exposure to formaldehyde through outdoor air or through indoor air at home. EPA concluded that there is too much uncertainty in exposure and risk estimates for individual sources to support quantitative aggregation across more than one exposure scenario. Please comment on the extent to which qualitative approach is supported by the available information. In your response, specifically describe the data that could potentially support an alternative approach and how that approach could be implemented.

Response to Charge Question 7.2

Committee members generally disagreed with EPA's conclusion that there is too much uncertainty to support quantitative aggregation across multiple exposure sources. The lack of an attempt to quantify appeared to result from a lack of technical tools, an approach using exposure scenario categories that are far too broad, and dismissal of valuable information. Committee members noted that the lack of any sort of quantitative analysis was likely leading to an underestimate of risk for those who are potentially the most exposed (i.e., those who are experiencing exposure across multiple exposure routes). The Committee concluded that an aggregate exposure assessment will more accurately capture exposures in homes and the workplace. Further, the best available science also supports evaluating cumulative and aggregate exposures from a health protective lens. Of course, even the best-informed modeled assessment of exposure and risk to the most documented population group will have statistical uncertainty across a distribution of possible answers, but the qualitative "discussion" of exposure and risk, along with the single source calculations, yields only a quagmire of

answers that invite challenges and dissent. One Committee member recommended that EPA consider using the term 'limited aggregate exposure' as opposed to 'aggregate exposure,' as there are sources of formaldehyde exposure that were not included in this risk evaluation (i.e., occupational exposure to formaldehyde in embalmers and medical pathologists and technicians).

Several Committee members noted that there was a substantial amount and diversity of available data to support a probabilistic approach to explore aggregate exposure across scenarios. There appear to be numerous data sources that could be used for these types of calculations. For example, EPA could use the monitoring data with explanations as to the limitations and range of resulting plausible exposure values. Similarly, Tables 2.1 and 2.2 document numerous data sources of indoor air monitoring in homes and mobile homes and some types of commercial buildings (school buildings, government buildings). These data will represent an aggregate of indoor sources. Regarding outdoor air, EPA describes multiple sources of data (both measured and modeled) reflecting a range of ambient conditions near facilities (AMTIC) and at the census tract level attributed to various sources (AirToxScreen) which could be used for aggregate analysis (see Figure 2-10 in Section 2.4).

If a quantitative probabilistic approach is not possible, some members noted that another alternative approach for the current risk assessment would be to conduct screening-level sensitivity analysis. This sensitivity analysis could develop exposure and risk estimates for worker and consumer conditions of use with medium or high confidence that would be reasonably expected to co-occur and include ambient exposures using AirToxScreen and AMTIC.

Furthermore, the Committee strongly recommended that the EPA add vehicle air as a microenvironment relevant for all populations using existing information about peaks of initial minutes of air concentrations as well as durable, frequent exposures to lesser ambient (in this microenvironment) concentrations throughout voyage periods. Assume at least 2 years of off gassing into the car interior with concentrations diminishing over time. Updated references were provided in CQ 4.1. [5]

One member further strongly recommended adding challenged urban communities as a unique community exposure scenario for ambient air representation. This would apply to mixed use urban conditions of comingling of residential, public, and commercial space nearby constant emissions from businesses utilizing formaldehyde-based products and necessary venting of those indoor business spaces into close proximity of the broad population groups. This also was discussed in previous Charge Questions.

As discussed in previous Charge Questions, individuals who use the formaldehyde-based products in their employment or business are absent in the EPA assessment. These products are used in greater quantities, perhaps daily, in those scenarios. A greater number of individuals could experience the exposure from those uses in businesses ranging from painting, construction, car maintenance and

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[5] Wang, H., Guo,D., Zhang, W.,Zhang,R., Gao, Zhang,X., Liu,W., Wu,W., Sun,L., Yu, X., Zhao,J., Xiong,J. Huang, S., Wolfson, J.M., Koutrakis, P., Observation, prediction, and risk assessment of volatile organic compounds in a vehicle cabin environment. April 12, 2023, Cell Reports Physical Science , Vol 4, Issue 4. (available via ScienceDirect Observation, prediction, and risk assessment of volatile organic compounds in a vehicle cabin environment - ScienceDirect)

repair, furniture customizing and repair, duct work, computer maintenance and many others. The Committee strongly recommended their exposure and risk be considered.

As discussed in previous Charge Questions, the committee noted that EPA did not include the transportation and distribution system in its entirety, with all potential exposures for people working in the transport of consumer products including workers in giant warehouses (distribution centers). The initial periods of off gassing of the products being transported (wood and particle board, furniture, etc.) would occur shortly after production where the products enter this prompt transport, distribution, storage system.

Committee members acknowledged that while this may not be possible in the current risk assessment, for future risk assessments reviewers recommended that EPA provide a competent, state-of-the-art, versatile, exposure and risk model with *at least* the following capabilities: 1) Probabilistic capability for overall algorithm calculations as well as for most (if not all) factors within the algorithms; 2) Visibility and access for changing values and or distribution shapes of data for algorithmic values (utilizing at least 7 basic approaches to data probability distribution); 3) Aggregation across multiple exposure opportunities introduced in time-dependent continuums across people's lifetime, and for different population groups, as chosen by the assessor; 4) Ability to set model factors such that the assessor can consider different environmental scenarios setting up exposure opportunities; 5) Based on person-oriented modeling framework with options for data utility, periods of analysis, output reports on data utilization, chosen assessment metrics, etc. [6] [7] [8] These and additional features are

[6] Price, P., Chaisson, C., A Conceptual Framework for Modeling Aggregate and Cumulative Exposures to Chemicals, Journal of Exposure Analysis Environ Epidemiol. Nov; 15(6):473-81. DOI:10.1038/sj.jea.7500425 A conceptual framework for modeling aggregate and cumulative exposures to chemicals - PubMed (nih.gov)

[7] Price, Paul & Chaisson, Christine & Koontz, Mike & Wilkes, Charles & Ryan, P. & Macintosh, David & Georgopoulos, Panos. (2003). Construction of a Comprehensive Chemical Exposure Framework Using Person Oriented Modeling 2003, The LifeLine Group, full-text PDF available ResearchGate (PDF) Construction of a Comprehensive Chemical Exposure Framework Using Person Oriented Modeling (researchgate.net).

[8] Jayjock, M., Chaisson, C., Arnold, S., Dederick, E., Modeling framework for human exposure assessment. *J Expo Sci Environ Epidemiol* 17 (Suppl 1), S81–S89 (2007). https://doi.org/10.1038/sj.jes.7500580

discussed in the literature with examples provided in the references. [9] [10] [11] [12] Recommendations for the development of these tools is offered here also. Software design benefits greatly from review by programming experts, exposure and risk scientists, and the public prior to adoption and creation. While the resulting code does not have to be open-source (would not recommend open-source), the algorithms, data application, statistical applications, answer reporting options, record keeping methods, flexibility and other features would benefit from such pre-programming review. In addition, it is recommended that such software be programmed and reviewed by professional model developers with maintenance plans to support the model, improve it (with estimated updating plans) and/or archive key modules as needed.

Such models do exist, and some are currently freely available to EPA.[13] The exposure and risk assessment models utilized by the Office of Pesticide Programs have operated since the mid-1980s on these principles (in the models used for quantifying exposure and risk to pesticides on foods). Those models produce aggregated exposure and risk assessments for people eating those foods. This is analogous to the model (and full distributions of values for some parameters) suggested for the activity related exposures and risks as in the TSCA formaldehyde assessment. A few examples of that comparison are presented in the Table below:

Pesticide on Crops	Chemical in Goods, Environment, etc
Not everyone eats every crop per day—probability of eating the food from that crop…unto itself or as an ingredient in a complex food (e.g. cookies). Probability is considered…which differs for different age groups and subpopulations.	Not everyone is exposed via the same scenario every day (i.e. vehicle, car wax), but some may be exposed frequently (industry workers, school environments). Probabilities for each exposure scenario for different populations can be estimated.

[9] Price, P., G. Glen, H. Hubbard, K. Isaacs, AND K. Dionisio. Developing a rich definition of the person/residence to support person-oriented models of consumer product usage. 2017 Annual Meeting of the Society of Risk Analysis, Arlington, VA, December 10 - 14, 2017. CEMM@EPA.gov

[10] Dionisio KL, Frame AM, Goldsmith MR, Wambaugh JF, Liddell A, Cathey T, Smith D, Vail J, Ernstoff AS, Fantke P, Jolliet O, Judson RS. Exploring consumer exposure pathways and patterns of use for chemicals in the environment. Toxicol Rep. 2015 Jan 2;2:228-237. doi: 10.1016/j.toxrep.2014.12.009. eCollection 2015.PMID: 28962356

[11] Susan F. Arnold , Paul S. Price [b], Arnold, S.F., Price, P.S., Modeling mixtures resulting from concurrent exposures to multiple sources, 2007, Toxicology and Applied Pharmacology. September 121-124, Volume 223, Issue 2

[12] Brandon, N., Price, P.S. Calibrating an agent-based model of longitudinal human activity patterns using the Consolidated Human Activity Database. 2020 J Expo Sci Environ Epidemiol. Jan;30(1):194-204. doi: 10.1038/s41370-019-0156-z. Epub 2019 Jul 10.PMID: 31292521

[13] LifeLine ™ Software, Tutorial, Databases. 2023 Available from University of Arizona Southwest Environmental Health Sciences Center, LifeLine™ Community Based Assessment Software Tools | Southwest Environmental Health Sciences Center (arizona.edu)

Different concentrations of the pesticide may reside on the food item due to processing, washing, etc. Percent reductions or concentrations in food item residue estimated.	Concentration of the chemical may be different (though presenting the same function) under different labels or intent of use.
Different ages come into contact with the pesticide in different ways. (baby foods vs juices vs whole fruits vs processed foods, etc.)	Different exposure scenarios from the same product are age dependent. (baby crawling and sitting on carpet vs adult just walking across it.) Different durations of exposure or concentrations of exposure may exist in one scenario under different circumstances.
Different physiological factors…age and gender specific	Different physiological factors…age and gender specific
Different dietary preferences for different ages, subpopulations, etc.	Different durations of exposure, use of products for different subpopulations, ages, PESS, etc.
Etc.	Etc.

For future risk assessments, one Committee member directed the EPA to their own General Principles for Performing Aggregate Exposure and Risk Assessments (https://www.epa.gov/sites/default/files/2015-07/documents/aggregate.pdf) and the resources including exposure assessment tools for both aggregate and cumulative exposure: https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-aggregate-and-cumulative). One reviewer also suggested that EPA may consider using software developed by LifeLine to facilitate an aggregative quantitative analysis.

One Committee member also suggested using quantitative assessments from other global assessments. It appears that authoritative organizations used comparable data but reached significantly different conclusions using different statistical approaches and much more scientifically competent models. Those assessments are visible to US decision-makers, stakeholders, and the public, and thus it is recommended that they be recognized formally with discussions as to why the EPA was more confident in their own assessments than in those from other countries.

Recommendations:

- **Estimate aggregated exposures and risks using available monitoring data from all available studies, noting the differences in the media and scenarios represented and the concordance (or not) with exposure and risk assessments done by EPA's existing CEM model.**
- **Expand the scenarios to be considered, especially for a range of enclosed spaces: vehicles, schools, public buildings, retail, storage, transportation, distribution, and multiple housing types with uncertainties.**
- **Expand the scenarios to include workplaces that use the formaldehyde containing products in their businesses, considering the workers, customers, bystanders, and exterior venting in urban areas where the daily venting is less than 100 meters from the public and/or other buildings.**
- **Provide statistical tools and competent aggregate exposure and risk assessment models to the scientific staff. Those models should, at a minimum, reflect the aggregate risk assessment principles published by the EPA.**

- **Recognize exposure and risk assessments developed by other regulatory authorities and compare those with the calculations derived by the EPA scientists, discussing areas of agreement and significant differences.**

REFERENCES

Endnotes:

[1]Page 15, lines 634-641 of Occupational Exposure Assessment for Formaldehyde.

[2]Page 111, lines 2765-2768 of Draft Human Health Risk Assessment for Formaldehyde.

[3]See CQ 4.1 response re: Formaldehyde from off gassing of components of new vehicles—inhalation and dermal exposure potential.

[4]The target population for AHHS was all permanently occupied, non-institutional housing units in the U.S. in which children may live. Thus, vacant housing and seasonal housing, such as vacation homes, were ineligible for the AHHS, as well as any housing where children cannot reside, such as group housing and senior housing. Hotels/motels and military housing were also ineligible because of anticipated difficulties gaining access, although children may sometimes reside in such housing.

[5]Wang H, Guo D, Zhang W, Zhang R, Gao Y, Zhang X, Liu W, Wu W, Sun L, Yu X, Zhao J, Xiong J, Huang S, Wolfson JM, Koutrakis P. 2023. Observation, prediction, and risk assessment of volatile organic compounds in a vehicle cabin environment. Cell Rep Phys Sci 4(4): Available via ScienceDirect: https://www.sciencedirect.com/science/article/pii/S2666386423001431.

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[8]Jayjock M, Chaisson C, Arnold S, Dederick E. 2007. Modeling framework for human exposure assessment. J Expo Sci Environ Epidemiol 17(Suppl 1):S81–S89. doi: 10.1038/sj.jes.7500580. Available at: https://pubmed.ncbi.nlm.nih.gov/18004418/.

[9]Price P, Glen G, Hubbard H, Isaacs K, Dionisio K. 2017. Developing a rich definition of the person/residence to support person-oriented models of consumer product usage. 2017 Annual Meeting of the Society of Risk Analysis, Arlington, VA, December 10-14, 2017. Available at: CEMM@EPA.gov.

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