PUBLIC HEALTH DIVISION
Office of the State Public Health Director
Tina Kotek, Governor

800 NE Oregon Street
Portland, OR 97232
Voice: (971) 673-1222
FAX: (971) 673-1299
TTY: 711

DATE: March 12, 2024

TO: Hearing Attendees and Commenters –
OAR chapter 333, division 56 - "Permitting human pathological waste removal from a health care facility" (SB 189, 2023)

FROM: Brittany Hall, Hearing Officer

SUBJECT: Presiding Hearing Officer's Report on Rulemaking Hearing and Public Comment Period

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Hearing Officer Report

Date of hearing: February 15, 2024, via Microsoft Teams

Purpose of hearing and public comment period: To receive testimony and comments regarding the Oregon Health Authority (OHA), Public Health Division's proposed permanent amendments to Oregon Administrative Rules in chapter 333, division 56 in response to the passage of Senate Bill 189 during the 2023 legislative session.

Senate Bill 189 (Oregon Laws 2023, chapter 269), which took effect September 24, 2023, permits pathological waste removal from a health care facility "in accordance with rules adopted by the Oregon Health Authority" (OHA). To ensure that health care facilities that wish to do so may release pathological waste, OHA temporarily amended Oregon Administrative Rules 333-056-0020 and 333-056-0045, effective September 24, 2023, through March 21, 2024 (Temporary Administrative Order PH 45-2023). To continue to comply with the statute, OHA must amend those rules permanently, permitting removal of pathological waste from health care facilities while minimizing potential health hazards.

These rules define health care facility and freestanding birthing center in accordance with ORS 442.015 and allow human pathological waste (defined by reference to ORS 459.386), such as removed anatomical parts, to be received by the donor or their representative for the purposes of cremation, interment, or other final disposition in accordance with ORS chapter 97. Minor changes are made to the rule related to the release of placentas without changing the substance of the rule.

Hearing Officer: Brittany Hall

Testimony received: Three individuals provided testimony at the hearing. Oral testimony was followed by submission of written comments and supplemental information by two of the individuals.

Other Comments: Three individuals or organizations submitted written comments to OHA within the period allotted for public comment, which closed at 5:00 PM on February 21, 2024. Written comments and supplemental information are attached to this report as **EXHIBIT 1**.

1. In oral testimony and written comments, OHA heard concern about the reference in statute and proposed rules to ORS chapter 97. "Chapter 97 is the authority statute for the care and disposition of deceased people. It is not intended to be the authority for the disposition of body parts of live people. The definition of human remains per Chapter 97 states: 'Human remains' or 'remains' means the body of a deceased person in any stage of decomposition or after cremation or reduction. Chapter 97 and it's supporting OAR's do not address body parts or tissues of live people, nor do they provide criteria for disposition of these tissues."

It was suggested that text similar to the following be inserted into the rules: "Pathological waste released under OAR 333-056-00XX is exempt from being considered infectious waste, pathological waste or deceased, for the purposes of performing cremation, burial, reduction or other accepted means of disposition under ORS chapter 97."

OHA also heard concern that "the pathological items being potentially released to Oregon citizens are by definition 'pathological waste,' which crematories are prohibited by DEQ from cremating." (OAR chapter 340, division 230).

It was suggested that in order to address the Department of Environmental Quality (DEQ) crematory permit, something similar to the following text be inserted into the rules: "Pathological waste released under OAR 333-056-00XX is exempt from being considered infectious waste or pathological waste with regard to the DEQ and similar entities' (eg LRAPA in Eugene) crematory permits."

Agency response:
OHA appreciates the potential for confusion caused by a reference to ORS chapter 97, which deals with disposition of "human remains," in ORS chapter 459 and our associated rule, which deals with "pathological waste."

OHA has no authority to change either statute or rules promulgated by the Department of Environmental Quality (DEQ). Specifically, OHA may not change the definition of "human remains" in ORS 97.010. Similarly, for the purpose of the Oregon Administrative Rules (OARs) currently being amended (OARs 333-056-0020 and 333-056-0045), both "infectious waste"

and “pathological waste”—including the exception newly granted in ORS 459.400—are defined in statute, which we have no authority to change.

In light of these comments, we have called the issue to the attention of colleagues within DEQ. We defer to them as to whether DEQ might attempt to address this, perhaps by amending its regulations regarding incinerators (OAR 340-230-0210).

2. In oral testimony and written comments, OHA heard the concern about “the potential risks posed by the improper handling and disposal of dangerous substances, particularly formalin, which is used to fix tissue. Formalin, a solution containing 4% formaldehyde, is widely recognized for its carcinogenic properties and suspected role in genetic defects and organ damage.” Further concern was expressed about “the release of human pathological waste to the public without proper guidance for disposal. The absence of stringent regulations may prompt individuals to resort to improper disposal methods, such as burying or consuming the waste, thereby posing significant health risks, including cancer and genetic defects. These foreseeable scenarios not only jeopardize public health but also escalate long-term liabilities for both facilities and the state.” Comments urged that public safety be prioritized “by implementing strict regulations and promoting responsible disposal practices.”

Agency response:
Formalin-fixed tissue renders pathologic waste non-infectious. The points about health hazards associated with exposure to formalin are well taken.

Existing federal and state law address the issue of discharging hazardous substances into the environment. To remind involved parties, we have added the following to OAR 333-056-0045:

“(7) Nothing in this rule exempts facilities from other state or federal laws, including but not limited to the Resource Conservation and Recovery Act, regarding handling of pathological waste.”

EXHIBIT 1

SB 189 rulemaking testimony
Wally Ordeman on behalf of the Oregon Funeral Directors Association
Marc Lund on behalf of crematory operators and cemeterians

Thank you for the opportunity to offer testimony regarding the establishment of OAR's related to SB 189. For the record my name is Wally Ordeman and I'm the Executive Director for the Oregon Funeral Directors Association and a funeral home owner from Albany.

While the proposed rules address the "front end" of releasing tissues and body parts to Oregon's citizens, we feel that they don't go nearly far enough to address those entities that will likely be accepting these tissues. Namely funeral homes, crematories and cemeteries. Our testimony addresses two main concerns.

1. The references in the statute and proposed rules to ORS chapter 97.
2. The fact that DEQ permits issued to crematories expressly forbid the cremation of "pathological waste."

Chapter 97 is the authority statute for the care and disposition of deceased people. It is not intended to be the authority for the disposition of body parts of live people. The definition of human remains per Chapter 97 states: "Human remains or "remains" means the body of a deceased person in any stage of decomposition or after cremation or reduction." Chapter 97 and it's supporting OAR's do not address body parts or tissues of live people, nor do they provide criteria for disposition of these tissues.

We suggest an insertion into the rules something similar to this: "Pathological waste released under OAR 333-056-00XX is exempt from being considered infectious waste, pathological waste or deceased, for the purposes of performing cremation, burial, reduction or other accepted means of disposition under ORS chapter 97."

In addressing our item number 2, it appears that the pathological items being potentially released to Oregon citizens are by definition "pathological waste," which crematories are prohibited by DEQ from cremating.

340-230-0210
Crematory Incinerators: Design and Operation

(3) As defined in OAR 340-230-0030(10), crematory incinerators may only be used for incineration of human and animal bodies, and appropriate containers. No waste, including infectious waste as defined in OAR 340-230-0030, may be incinerated unless specifically authorized in the Department's Air Contaminant Discharge Permit.

OAR 340-230-0030 (9)(c)

(9) "Infectious Waste" means waste as defined in ORS Chapter 763, Oregon Laws 1989, that contains or may contain any disease producing microorganism or material, and includes, but is not limited to the following:

(c) "Pathological waste", which includes biopsy materials and all human tissues, anatomical parts that emanate from surgery, obstetrical procedures, autopsy and laboratory procedures and animal carcasses exposed to pathogens in research and the bedding and other waste from such animals. "Pathological wastes" does not include teeth or formaldehyde or other preservative agents.

In addressing the DEQ crematory permit we suggest:
An insertion into the rules similar to: “Pathological waste released under OAR 333-056-00XX is exempt from being considered infectious waste or pathological waste with regard to the DEQ and similar entities’ (eg LRAPA in Eugene) crematory permits.

Without revisions to the proposed OAR language as suggested previously, the death care industry is very uncomfortable with the vulnerability this places on all involved in death care. There doesn’t seem to be a clear roadmap, and the proposed OAR’s don’t provide enough direction either. Our hope is that language can be added that provides peace of mind to the industry, and by association the clientele they serve.

MCB
OREGON MORTUARY & CEMETERY BOARD
Regulating Death Care Facilities & Practitioners in Oregon.

OHA, Public Health Division
Brittany Hall, Administrative Rules Coordinator
800 NE Oregon Street, Suite 930
Portland, OR 97232

Re: SB 189 Administrative Rulemaking

Sent via email to publichealth.rules@odhsoha.oregon.gov

Dear Ms. Hall:

First, I wanted to thank you, Stephen Ladd-Wilson & Dr. Paul Cieslak for including me as a participant of the Rules Advisory Committee for SB 189.

Second, while the intent of this legislation and subsequent administrative rules are well-intentioned and respectful of diverse cultures and customs, there appears to be some unintended consequences that could significantly impact the laws and rules that our agency currently relies upon for guidance and enforcement.

Based upon the Notice of Proposed Rulemaking, the following language was presented:

> *(1) Notwithstanding any other provision in OAR chapter 333, division 56 or ORS 459.386 to 459.405, a health care facility is authorized to release pathological waste other than a placenta to the donor of the pathological waste or to an authorized representative of the donor, if the recipient attests in writing that the pathological waste will be disposed of by cremation, interment, or other means in accordance with ORS chapter 97, and the facility complies with sections (4) and (5) of this rule.*

To provide some context, the relevant sections in ORS 97 reference the disposition of human remains and does not mention pathological waste.

Specifically, "human remains" is defined as "the body of a deceased person in any stage of decomposition or after cremation or reduction." *ORS 97.010(24)*

The proposed administrative rule language above references ORS 97 (disposition of human remains) and seems to apply the same requirements to pathological waste – which would significantly impact what the industry is currently allowed/required to do. The language almost seems to restore pathological waste to human remains since pathological waste is being required to "be disposed of by cremation, interment or other means in accordance with ORS chapter 97," and it is my understanding based upon recent conversations that was not the intent of this administrative rule section.

It would be beneficial to make the distinction that pathological waste does not become human remains again – if a distinction is not made, this administrative rule section could create a great deal of confusion and would most likely require our agency to initiate legislation and administrative rulemaking to address this significant adjustment.

This administrative rule section could be rewritten to require that the pathological waste received by the donor or authorized representative is properly disposed of (without reference to ORS 97) – either by cremation, interment or other lawful means.

Finally, it is my understanding that the Oregon Funeral Directors Association (OFDA) will be submitting testimony that addresses the potential issue with cremating pathological waste in violation of DEQ permit requirements, so I will allow their testimony to speak for itself.

I hope that I've clearly illustrated a potentially significant issue that most likely would impact our agency and licensees.

If you have any questions, please feel free to ask.

Thank you.

Cordially,

Chad William Dresselhaus

Chad Dresselhaus
Executive Director

pathology consultants PC

February 19, 2024

Oregon Health Authority
Public Health Division
800 NE Oregon St. Suite 772
Portland, OR 97232

Re: Human Pathological Waste; Senate Bill 189- Known Health Hazards Associated with Formalin

To Whom It Concerns:

I am writing to bring to your attention a matter of utmost importance regarding the release of human pathological waste to the public. As Chief Financial Officer at Pathology Consultants, I am deeply concerned about the potential risks posed by the improper handling and disposal of dangerous substances, particularly formalin, which is used to fix tissue.

Formalin, a solution containing 4% formaldehyde, is widely recognized for its carcinogenic properties and suspected role in genetic defects and organ damage. Studies conducted by the IRIS Toxicological Review and EPA's risk assessment have unequivocally linked inhalation of formaldehyde to leukemia and various cancers affecting the head and neck.

Due to the known health hazards associated with formalin, our laboratory is required to monitor formalin exposure to maintain accreditation. Formalin exposure is monitored and tracked for employees who are working with the substance. This is not a requirement for the general public who would be exposed to formalin fixed tissue if it was released to them.

Moreover, the health hazards associated with formalin fixed tissue extend beyond inhalation risks. Direct contact with the skin can cause irritation, while ingestion may lead to allergic reactions and severe health complications. It is imperative to emphasize that disposal regulations strictly prohibit burning, burying, flushing into waterways, or disposing of formalin fixed tissue into sewer systems.

My primary concern lies in the release of human pathological waste to the public without proper guidance for disposal. The absence of stringent regulations may prompt individuals to resort to improper disposal methods, such as burying or consuming the waste, thereby posing significant health risks, including cancer and genetic defects. These foreseeable scenarios not only jeopardize public health but also escalate long-term liabilities for both facilities and the state.

In light of these concerns, I urge policymakers to prioritize public safety by implementing strict regulations and promoting responsible disposal practices. The proposed legislation allowing the unregulated release of toxic materials to the public is inherently dangerous and fiscally irresponsible. It disregards the potential health hazards associated with formalin fixed tissue and neglects the long-term liabilities stemming from improper waste disposal.

Denis M. McCarthy, M.D., President | Lauren A. Hammock, M.D. | J. Robert McFarlane III, M.D.
Deven L. Smith, M.D. | Brittany L. Pakalniskis, M.D. | Lyle C. Lawnicki, M.D. | Misty M. Payne, M.D. | Colin NewBill, M.D. | Claire Murphy, M.D.
P.O. Box 72059, Springfield, OR 97475-0285 | 541.222.6915 (ph) | 541.222.6908 (fax) | www.pathconsultantspc.com

It is my sincere hope that you will carefully consider the implications of this matter and take proactive measures to safeguard the well-being of our community. I am available to provide any additional information or assistance you may require on this critical issue.

Thank you for your attention to this urgent matter.

Sincerely,

Jasmine Reiber | Chief Financial Officer

pathology

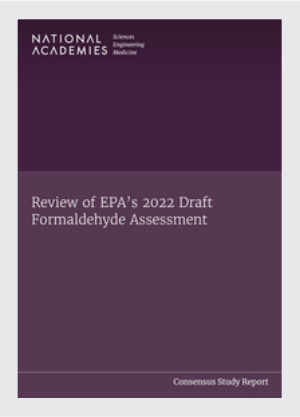
consultants PC

541.222.6956 | 541.326.0924 fax

Post Office Box 72059 | Springfield, OR 97475-0285

jreiber@pathconsultants.com

Enclosures: Review of EPA's 2022 Draft Formaldehyde Assessment (2023) and World Health Organization Environmental Health Criteria 89 Formaldehyde



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DETAILS

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CONTRIBUTORS

Committee on Review of EPA's 2022 Draft Formaldehyde Assessment; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

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Committee on Review of EPA's 2022 Draft Formaldehyde Assessment

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

Consensus Study Report

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COMMITTEE TO REVIEW EPA'S 2022 DRAFT FORMALDEHYDE ASSESSMENT

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RAKESH GHOSH, University of California, San Francisco
SABINE S. LANGE, Texas Commission on Environmental Quality
ANDREW F. OLSHAN, University of North Carolina at Chapel Hill
IVAN RUSYN, Texas A&M University
LIANNE SHEPPARD, University of Washington School of Public Health
KATYA TSAIOUN, Johns Hopkins Bloomberg School of Public Health
JOSEPH WIEMELS, University of Southern California
LAUREN ZEISE, California Environmental Protection Agency
YILIANG ZHU, University of New Mexico

Staff

KATHRYN GUYTON, Study Director
BRENNA ALBIN, Senior Program Assistant
NATALIE ARMSTRONG, Associate Program Officer
ELIZABETH BOYLE, Senior Program Officer
ANTHONY DEPINTO, Associate Program Officer
DARLENE GROS, Senior Program Assistant
KATHERINE KANE, Senior Program Assistant

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KATHERINE KANE, Senior Program Assistant
LAURA LLANOS, Finance Business Partner
THOMASINA LYLES, Senior Program Assistant
RAYMOND WASSEL, Scholar and Director of Environmental Studies

Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

A. JOHN BAILER, Miami University
RICHARD CORLEY, Greek Creek Toxicokinetics Consulting, LLC
SUSAN FELTER, Procter & Gamble
PENNY FENNER-CRISP, Private consultant
JULIE B. HERBSTMAN, Columbia University Mailman School of Public Health
JULEEN LAM, California State University East Bay
MALCOLM MACLEOD, University of Edinburgh
SUE JINKS-ROBERTSON (NAS), Duke University School of Medicine
MOSHE OREN (NAS, NAM), Weizmann Institute of Science
JOE RODRICKS, Ramboll

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of this report was overseen by **DANNY REIBLE,** Texas Tech University (Monitor), and **DON MATTISON,** University of South Carolina (Coordinator). They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Acknowledgments

Many people were critical in helping the committee accomplish its charge. The committee gratefully acknowledges the participants at its information-gathering sessions, who provided insights and viewpoints pertinent to the committee's task (see Appendix B). We thank Lisa Bero, Professor of Medicine and Public Health, University of Colorado, for her presentation at the committee's first information-gathering session. Importantly, the committee heard from more than 40 individuals who shared their perspectives during the public comment periods of the information-gathering sessions, as well as in written input provided for the committee's consideration. The committee is very grateful for these valuable contributions to its work.

In addition, we are grateful to the U.S. Environmental Protection Agency (EPA) for sponsoring the study, and to the following EPA staff for their presentations to the committee: Andrew Kraft and Thomas Bateson, Office of Research and Development.

Gratitude is also extended to the staff of the National Academies of Sciences, Engineering, and Medicine who contributed to producing this report, especially the outstanding and tireless study staff: Brenna Albin, Natalie Armstrong, Elizabeth Boyle, Anthony DePinto, Darlene Gros, Kathryn Guyton, and Katherine Kane. Thanks also go to the staff of the Division on Earth and Life Studies Executive Office and other Academies staff who provided additional support.

Preface

This report documents the lengthy history of the Integrated Risk Information System (IRIS) Program's assessment of the health risks of formaldehyde, which dates to 1989. The predecessor of the 2022 Draft Assessment is an IRIS assessment completed in 2010 and reviewed by the National Academies in 2011. The 2011 National Research Council (NRC) report on the 2010 Draft Assessment called for substantial revisions to the assessment and to the processes used to develop it. The 2011 NRC report included the recommendation that completion of the formaldehyde assessment not await the possible development of these revisions and their finalization. Over the ensuing twelve years and in response to additional recommendations of the National Academies, the methods used by the IRIS Program have evolved. These evolving methods increasingly reflect the state of practice for carrying out systematic reviews, evidence integration, and quantitative risk estimation for human health risk assessments of environmental contaminants. The 2022 Draft Assessment reviewed by this committee was prepared across this decade of rapid change. Consequently, there was no static benchmark for evaluating the methods used. The committee took a broad view of the state of practice as it evaluated the 2022 Draft Assessment, recognizing that the methods used for that assessment would not correspond in all respects to the state of practice in 2023. Overall, the committee found that the methods used for the assessment were appropriate and reflect EPA's current practices in some components of the IRIS process.

Not surprisingly, given its length and complexity, there are opportunities to strengthen and clarify the 2022 Draft Assessment. The committee offers numerous recommendations to that end. The committee was asked to prioritize its recommendations in tiers. Tier 1 represents important recommendations that would address critical scientific concepts, issues, or narrative in the assessment. Currently the methods for the 2022 Draft Assessment are located in several places throughout its three documents, which together consist of more than 2000 pages. Perhaps the most critical area for structural and editorial revision is to bring greater clarity as to the methods used and to facilitate their consideration by readers. The committee's single Tier 1 recommendation calls for the changes needed to make the assessment's methods sufficiently accessible for its users, and to facilitate access to related sections across the different elements of the assessment for the different outcomes analyzed. In accordance with its statement of task, the committee did not conduct an independent hazard assessment or recommend alternative toxicity values.

Tier 2 recommendations are suggested revisions intended to strengthen or clarify the scientific concepts, issues, or narrative in the assessment, while Tier 3 recommendations are considerations that might inform future evaluations of key science issues. The committee has made many Tier 2 and Tier 3 recommendations regarding methods, the assessment narrative, and the dose-response assessment. We point to opportunities to harmonize the assessment narrative across health outcome domains and to bring greater consistency by structuring them more carefully around a common review framework. We also urge rigorous editing to enhance the overall quality of the assessment.

Quoting the website for the IRIS Program:

> EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment.

The 2022 Formaldehyde Draft Assessment, which addresses a widely used, high-volume production chemical, needs to be completed to support EPA in accomplishing this mission.

Finally, the committee urges closure on the Draft Assessment. The committee members have a long perspective on the Formaldehyde Draft Assessment and the changes in the IRIS Program's methods over the last decade. The assessment has been revised and improved substantially, and its findings on hazard and quantitative risk are supported by the scientific evidence identified. A confined set of revisions will enhance clarity and transparency. The committee's recommendations should be undertaken expeditiously to complete a revised assessment document that can be implemented without delay.

Jonathan M. Samet, M.D., M.S
Committee Chair
Committee to Review EPA's 2022 Draft Formaldehyde Assessment

Contents

APPENDIXES

Acronyms and Abbreviations

ADAF	age-dependent adjustment factor
ADME	absorption, distribution, metabolism, and excretion
ALS	amyotrophic lateral sclerosis
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	biologically based dose response
BMC	benchmark concentration
BMCL	benchmark concentration lower bound
BMD	benchmark dose
BMDL	benchmark dose lower bound
BMDS	benchmark dose software
BMR	benchmark response
CDC	Centers for Disease Control and Prevention
CFD	computational fluid dynamics
CIIT	Chemical Industry Institute of Toxicology
cRfC	candidate reference concentration
DDCs	DNA–DNA crosslinks
DPCsX	DNA–protein crosslinks
ED	effective dose
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FEF25-75	forced expiratory flow 25%–75%
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GLP	Good Laboratory Practices
GM	geometric mean
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HEC	human equivalent concentration
hm-DNA	hydroxymethyl-DNA
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
ISA	integrated science assessment
IUR	inhalation unit risk

LOAEL	lowest observed adverse effect level
MeSH	medical subject headings
MOA	mode of action
MSW	Multistage Weibull
NAM	new approach method
NASEM	National Academies of Sciences, Engineering, and Medicine
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NRC	National Research Council
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation (now the NIEHS Division of Translational Toxicology's Integrative Health Assessments Branch)
ORD	Office of Research and Development
osRfC	organ- or system-specific reference concentration
OVA	ovalbumin
PBPK	physiologically based pharmacokinetic
PECO	population, exposure, comparator, and outcome
PEFR	peak expiratory flow rate
POD	point of departure
POD_{ADJ}	adjusted point of departure
QSAR	quantitative structure–activity relationships
RfC	reference concentration
RfD	reference dose
ROB	risk of bias
ROC	Report on Carcinogens
SAR	structure–activity relationships
SCC	squamous cell carcinoma
SEER	surveillance, epidemiology, and end results
SEM	systematic evidence map
TCEQ	Texas Commission on Environmental Quality
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
UFA	interspecies uncertainty factor
UFD	database uncertainty factor
UFH	uncertainty factor for variability across the human population
UFL	LOAEL-to-NOAEL uncertainty factor

UFS	subchronic to chronic or lifetime exposure uncertainty factor
URT	upper respiratory tract

Summary

Formaldehyde is widely present in the environment. It is one of the highest production chemicals by volume, used in many manufactured goods: wood products (e.g., cabinets, furniture, plywood, particleboard, laminate flooring, etc.), permanent press fabrics, and household products (glues, paints, caulks, pesticides, cosmetics, detergents etc.). It is also formed by combustion sources and present in smoke from cigarettes and other tobacco products, and in emissions from gas stoves and open fireplaces. Additionally, it is naturally produced in humans through one-carbon metabolism.

The U.S. Environmental Protection Agency (EPA) Office of Research and Development's Integrated Risk Information System (IRIS) Program conducts comprehensive scientific reviews that lead to the development of reference concentrations (RfCs) for noncancer outcomes and inhalation unit risk (IUR) values for cancer outcomes for inhaled chemicals. In 1989, the IRIS Program listed formaldehyde as a probable human carcinogen and provided a cancer unit risk estimate (URE). In 1990, a noncancer reference dose (RfD) was provided by the IRIS Program. In 2010, EPA updated its draft IRIS assessment of formaldehyde, which underwent review by an ad hoc National Research Council (NRC) committee. The resulting report was released in 2011. Thereafter, in 2012, EPA began working on a revised draft assessment, convened workshops in 2014, and completed a revised draft assessment in 2017. In 2018, work was suspended on the draft assessment, according to the IRIS website (US EPA 2022). The draft assessment was updated beginning in 2021 before being released in April 2022 as the 2022 *Draft IRIS Toxicological Review of Formaldehyde: Inhalation* (hereafter referred to as the "2022 Draft Assessment"; the 2010 version is referred to as the "2010 Draft Assessment"). The timeline of EPA's development of the formaldehyde Draft Assessment in the context of reports from the NRC (in 2011 and 2014) and the National Academies of Sciences, Engineering, and Medicine (NASEM) (in 2018 and 2022) is shown in Figure S-1. These reports encouraged the IRIS Program to adopt systematic review methods, to develop a staff handbook with general guidance on the methods used in IRIS assessments, and to develop an a priori protocol for each major IRIS assessment.

In line with its statement of task, the committee considered that any Tier 1 recommendations would be important to address to improve critical scientific concepts, issues, or narrative in the 2022 Draft Assessment. Tier 2 and Tier 3 recommendations could also trigger additional work on the Draft Assessment, including document editing to better clarify and support the assessment's conclusions. The committee did not conduct an independent hazard evaluation or dose-response assessment, and therefore does not recommend alternative hazard identification conclusions or toxicity values. The committee also was not charged with commenting on other interpretations of scientific information relevant to the hazards and risks of formaldehyde, nor did its statement of task call for a review of alternative opinions on EPA's formaldehyde assessment. Any other topics that do not fall within the committee's charge were beyond the purview of this study.

To address its task, the committee organized its review of EPA's hazard identification and dose-response analyses of noncancer and cancer outcomes around the agency's overview of its approach to developing the 2022 Draft Assessment (Figure S-2).

STUDY CHARGE, SCOPE, AND APPROACH

The committee's statement of task is provided in Box S-1. As a comparison for the methods of the 2022 Draft Assessment and their documentation, the committee relied on general principles for conducting a systematic review and for ensuring transparency. To better understand the state

of practice applied in preparing the Draft Assessment, the committee sought the protocols for EPA's reviews of noncancer, cancer, and mechanistic evidence so they could be evaluated against accepted systematic review methods that existed at the time the Draft Assessment was prepared. The committee also relied on EPA's responses to queries it posed to the agency.

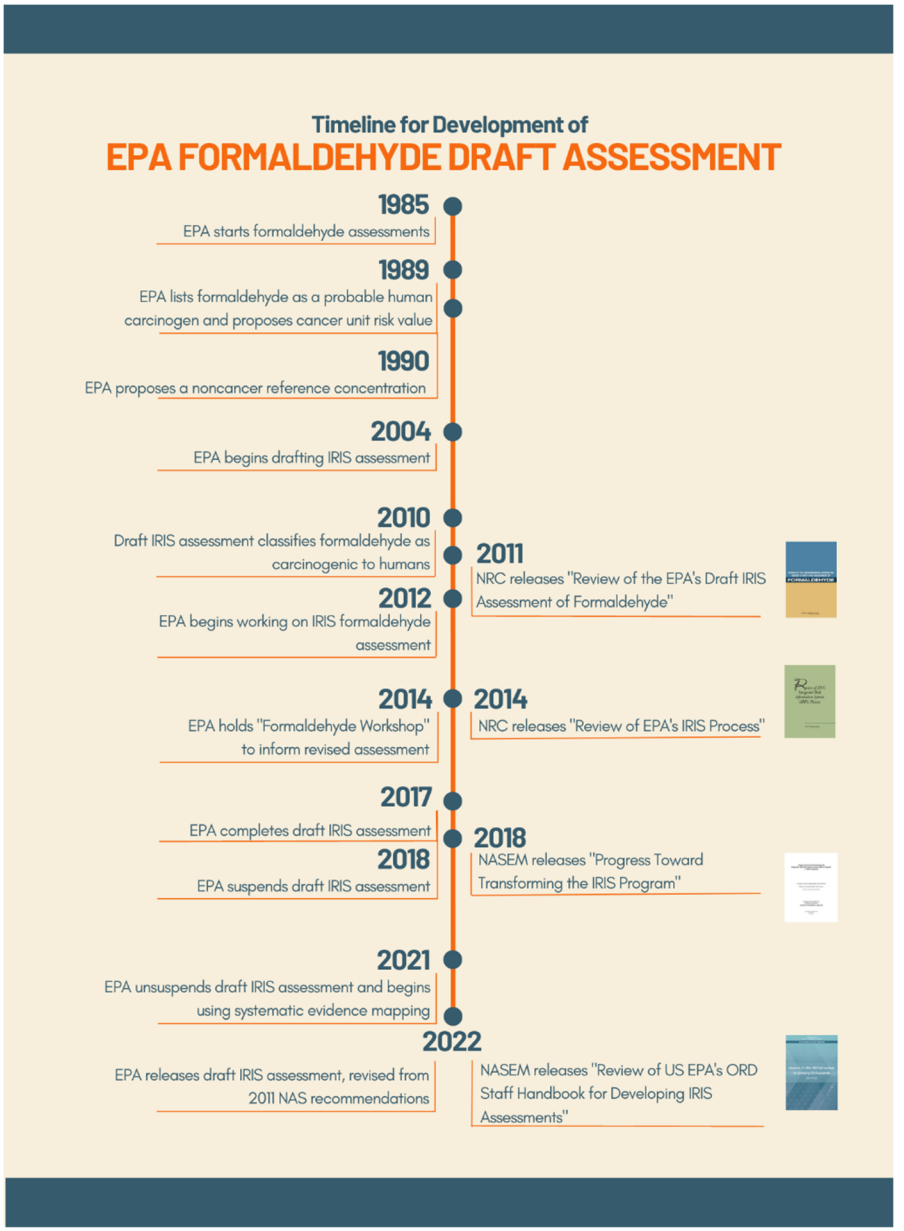

FIGURE S-1 Timeline of development of EPA's formaldehyde Draft Assessment.

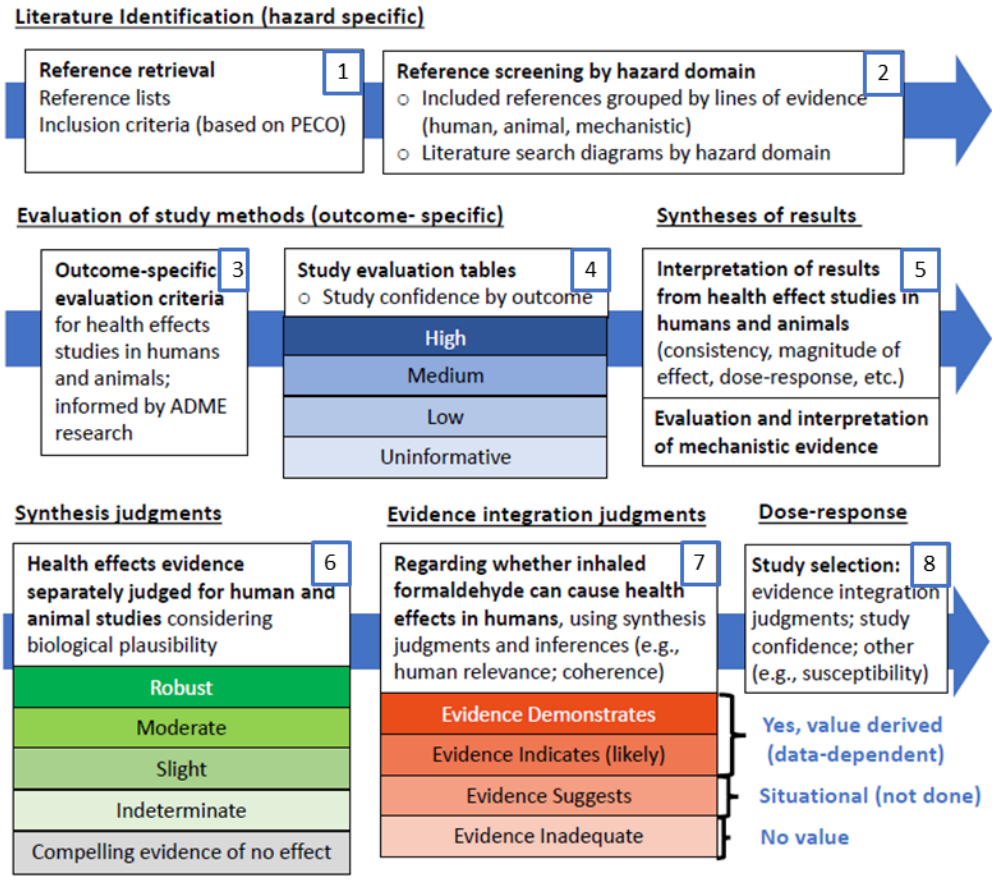

FIGURE S-2 Systematic review approach used by EPA to complete the 2022 Draft Assessment
NOTE: Modified from EPA's presentation to the committee on October 12, 2022.

The committee provided critiques and suggestions on EPA's methods for each step in the assessment (documentation of methods, evidence identification, study evaluation, evidence synthesis, evidence integration, and dose-response assessment). For each step, the committee considered the alignment of the 2022 Draft Assessment methods with the contemporaneous state of practice and prior advice to EPA from the National Academies. Transparency in EPA's systematic review methods implies that the committee should be able to replicate each step based on the information included in the assessment documents or in publicly available supplemental materials. Accordingly, the committee used a case study approach to provide a detailed evaluation of the transparency and replicability of the 2022 Draft Assessment methods, relying on the documentation provided by EPA in the 2022 Draft Assessment and in the written responses to the committee's queries.

BOX S-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will conduct a scientific review of EPA's draft document referred to as the Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde, plus appendices. The committee will assess whether EPA's draft document adequately and transparently evaluated the scientific literature, used appropriate methods to synthesize the current state-of-the science, and presented conclusions regarding the hazard identification analysis and dose-response analysis of formaldehyde that are supported by the scientific evidence. The committee will not conduct its own hazard assessment of formaldehyde, nor will the committee address the broader aspects of the IRIS Program.

Recommendations about the IRIS assessment will be prioritized as follows:

- Tier 1: recommended revisions that are important for EPA to consider and address to improve critical scientific concepts, issues, or narrative in the assessment.
- Tier 2: suggested revisions that are encouraged to strengthen or clarify the scientific concepts, issues, or narrative in the assessment but are not critical. Other factors, such as agency practices and resources, might need to be considered by EPA before undertaking the revisions.
- Tier 3: considerations that might inform future evaluations of key science issues or inform development of future assessments.

The committee also reviewed the hazard and dose-response conclusions for noncancer outcomes (covering sensory irritation, pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity) and for cancer outcomes. This aspect of the committee's review addressed each step of EPA's assessment methods for each outcome as used to develop evidence integration judgments and derive risk estimates for formaldehyde. In line with its overall charge, the committee focused its review on whether the 2022 Draft Assessment adequately and transparently evaluated the available studies and data, and used appropriate methods in reaching hazard identification conclusions and dose-response analyses that are supported by the scientific evidence. In its review, the committee also considered the recommendations of prior NRC and NASEM committees, including the 2014 NRC committee that reviewed the formaldehyde assessment of the National Toxicology Program 12th Report on Carcinogens. In accordance with its statement of task, the committee did not conduct an independent assessment of formaldehyde's hazards or risks.

SUMMARY OF THE COMMITTEE'S FINDINGS AND RECOMMENDATIONS

The committee provides a number of Tier 1, 2, and 3 recommendations to improve the 2022 Draft Assessment. Key recommendations are provided in this section, and others are presented in the context of the detailed discussion within the main chapters.

RESPONSIVENESS TO PRIOR RECOMMENDATIONS AND DOCUMENTATION OF METHODS

Overall, the committee found that the 2022 Draft Assessment is responsive to the broad intent of the 2011 NRC review of EPA's 2010 Draft Assessment and the 2014 NRC review of the IRIS process. Yet, while the steps in the systematic review process used in preparing the Draft

Assessment are generally consistent with those outlined in the 2014 NRC report, the assessment does not satisfactorily follow recommendations for problem formulation and protocol development. EPA did not develop a set of specific protocols for the 2022 Draft Assessment in a fashion that would be consistent with the general state of practice that evolved during the prolonged period when the assessment was being developed. Instead, EPA described the assessment methods across the three documents that together make up the 2022 Draft Assessment: the Main Assessment (789 pages), accompanying Appendices (1059 pages), and an Assessment Overview (192 pages). The committee concluded that prepublished protocols are essential for future IRIS assessments to ensure transparency for systematic reviews in risk assessment.

The committee's review of the 2022 Draft Assessment documents the challenges faced by users of the assessment in navigating the voluminous documentation and understanding the methods used and evidence assessed. Revision is needed to ensure that the methods used for each outcome can easily be found. This can be accomplished by providing a linked roadmap and merging the descriptions of the methods used for each outcome in a single location.

Recommendation 2.1 (Tier 1): **EPA should revise its assessment to ensure that users can find and follow the methods used in each step of the assessment for each health outcome. EPA should eliminate redundancies by providing a single presentation of the methods used in the hazard identification and dose-response processes. A central roadmap and cross-references are also needed to facilitate access to related sections across the different elements of the assessment (e.g., Appendixes, Main Document) for the different outcomes analyzed. Related Tier 2 recommendations would amplify the impact of this Tier 1 recommendation in improving the assessment.**

Recommendation 2.2 (Tier 2): In updating the assessment in line with the Tier 1 Recommendation 2.1, EPA should further clarify the evidence review and conclusions for each health outcome by giving attention to the following:

- **Using a common outline to structure the sections for each health outcome in order to provide a coherent organization that has a logical flow, by**
  - **adding an overview paragraph to guide readers at the start of sections for each of the various health domains, and**
  - **including hyperlinks to facilitate crosswalking among sections within the document;**
- **Moving lengthy, not directly used information to an appendix;**
- **Including a succinct executive summary in the Main Assessment; and**
- **Performing careful review and technical editing of the documents for consistency across the multiple parts of the 2022 Draft Assessment, including across the Assessment Overview and Appendices. (The Assessment Overview could be entirely removed if the above recommendations were carried out.)**

The sections that follow address the specific steps depicted in Figure S-2.

EVIDENCE IDENTIFICATION (STEPS 1 AND 2)

Generally, the committee found the literature searches to be adequate. EPA appears to have sufficiently harmonized the approaches for the pre- and post-2016 literature searches that were conducted using two different methods, and the approaches used were consistent with the state of practice at the time. Although the search strategies are adequately documented, the origins of the

various population, exposure, comparator, and outcome (PECO) statements are less clear. In particular, across noncancer outcomes, the rationale for excluding studies on the basis of the populations, exposures, and outcomes studied is not well documented. For allergy and asthma, for example, the age cutoffs are not stated and clearly applied, and it is unclear whether a broader set of immunopathologies was considered before the focus was narrowed to prevalent allergies and prevalent asthma. For sensory irritation, the rationale for excluding outdoor air studies is unclear. For respiratory pathology, the search terms and inclusion and exclusion criteria used to search human and animal evidence are discrepant.

Recommendation 2.3 (Tier 2): EPA should expand the text explaining the choices of the elements of the PECO statements.

STUDY EVALUATION (STEPS 3 AND 4)

EPA provides overall and outcome-specific evaluation criteria that are generally consistent with the common domains for risk-of-bias analysis. However, the information is presented in several different locations in the documents, and in some cases is inconsistently presented and integrated across the documents. As a result, for several noncancer outcomes, the committee was challenged to reconstruct the study evaluation approach and how the criteria were applied for study evaluation.

The considerations listed for study confidence classification and evaluation of each study by at least two independent experts are adequate. However, the committee's evaluation revealed some inconsistencies in how evaluation criteria are described and applied. Such inconsistency was broadly evident in the committee's review of EPA's evaluation of human and animal studies across noncancer outcomes (including for sensory irritation, pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity). In multiple instances, individual ratings of confidence for noncancer studies may merit more careful reassessment, whereas others are merely described inconsistently.

Overall, while outcome-specific criteria for evaluating the human and animal studies were generally appropriate, the committee could not satisfactorily identify the final criteria that were applied, as well as the judgments made in determining overall study confidence for both human and animal studies. Inconsistencies between the stated criteria and the rationale for conclusions on study confidence were evident.

Recommendation 2.4 (Tier 2): EPA should thoroughly review the 2022 Draft Assessment documents to address issues of consistency and coherence so as to ensure that its methods can be applied and replicated with fidelity. The reviews for each outcome in Chapters 4 and 5 provide more specific guidance.

EVIDENCE SYNTHESIS (STEPS 5 AND 6) AND INTEGRATION (STEP 7)

For evidence synthesis, the strength-of-evidence categories and how they were applied to the overall evidence judgments are generally clear and appropriate for the human and animal evidence streams.

While drawing on long-established methods for inferring causation, the 2022 Draft Assessment deviates in several respects, including (1) blurring of the boundary between evidence synthesis and integration, and (2) the choice of terminology used to describe the strata in the four-level

schema for classifying strength of evidence. Additionally, in some instances the narratives concerning the evidence integration step are too terse to fully explain why EPA came to specific confidence conclusions.

Recommendation 2.5 (Tier 2):

- **The 2022 Draft Assessment should be edited to more sharply demarcate the synthesis and the integration of evidence discussions.**
- **EPA should expand the narrative descriptions of the evidence integration step, or should follow published methodology while providing detailed explanation of any adaptations.**

Regarding mechanistic evidence, the committee found that EPA is thorough and transparent in identifying the relevant information. However, the definition of "impactfulness" and how this concept was applied are not well described. Similarly, the term "other inferences" is used in the sections on integration of cancer evidence, but is not explained.

Recommendation 2.6 (Tier 2): To increase the transparency of the evaluation of mechanistic data, EPA should clarify key terms (e.g., "impactfulness," "other inferences") and their application to specific studies. "Impactfulness" can be defined (in Table F-12 and elsewhere), and "other inferences" can be explained in discussing the approach to evidence integration in the Preface on Assessment Methods and Organization.

Regarding toxicokinetics, EPA used the data in the evidence synthesis step and applied the available models to derive candidate RfCs for respiratory tract pathology in animals in a manner consistent with its state-of-practice methods. Transparency could be enhanced by explicitly identifying the models used to derive flux values in the summary tables, and by improving documentation of the dosimetry approaches in the tables and text.

For noncancer outcomes comprising effects on pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity and sensory irritation, EPA presents hazard identification conclusions supported by the available scientific evidence from humans, experimental animals, and mechanistic studies. The assessment could be strengthened by clarifying the basis for summary judgments, such as by referencing the specific studies relied upon in reaching conclusions.

Recommendation 4.7 (Tier 2): EPA should clarify the basis for its synthesis judgments and provide additional information about the studies on which they are based, such as the formaldehyde levels observed, as well as the exposure ranges or other measure of variability. The study summary tables (Tables 1-6 to 1-9) should be updated to provide an organized distillation of the points made in the evidence synthesis text.

With respect to cancer hazard identification, EPA used its state-of-practice methods to synthesize the current state of the science and presents hazard identification conclusions supported by the available scientific evidence from humans, experimental animals, and mechanistic studies. For lymphohematopoietic cancers, EPA was responsive to previous recommendations from the NRC and focused on the most specific diagnoses of myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma. Clarifications are needed with respect to the summary statements, and some terminology (e.g., "other inferences") needs to be defined, as noted above.

Recommendation 5.1 (Tier 2): While the narrative describing the application of criteria for each site is well done, EPA should enhance clarity by providing explicit statements in section 1.2.5 summarizing synthesis judgments for each criterion (consistency, strength, temporal relationship, exposure-response relationship, etc.).

DOSE-RESPONSE ASSESSMENT (STEP 8)

The committee found the considerations for selection of dose-response studies to be reasonable, although the discussion in multiple places in the documents made it difficult to determine what the considerations were and how they were applied.

EPA provides criteria for study inclusion in the dose-response assessment, but does not include any discussion of how these criteria were applied to the specific studies chosen for dose-response. Using the Hanrahan et al. (1984) study as a test case, there are inconsistencies between the characteristics of the study and EPA's criteria for selecting studies for dose-response analyses. Similar inconsistencies were identified across the noncancer outcomes considered by the committee.

Recommendation 4.6 (Tier 2): EPA should clarify and clearly state the criteria used to select the studies for dose-response analysis of noncancer endpoints.

Recommendation 4.16 (Tier 2): EPA should carefully address the following points regarding the derivation of the RfC:

- **Fully disclose data extracted from original study reports using HERO or other means.**
- **Cite relevant guidance documents regarding the use of a mean versus median and arithmetic mean versus geometric mean to estimate a lowest observed adverse effect level or no observed adverse effect level.**
- **In reanalyzing data from published studies, the use of raw data is preferred. Aggregated data may be used when appropriate. At a minimum, group size, group mean, and a measure of variance (e.g., group standard deviation or standard error of the mean) for each exposure level are needed to capture data variation in a reanalysis of dose-response.**
- **Avoid fitting a dose-response model that has as many parameters as the number of distinct aggregated data points taken from the published literature. Report and consider only models that meet the goodness-of-fit criterion EPA accepts.**
- **To ensure that the resulting benchmark concentration lower bound is not artificially overestimated, better account for within-group variability in the dose-response analysis of Hanrahan et al. (1984) to address limitations arising from reliance on only secondary, aggregated rates per exposure group that were extracted from the plot of the originally fitted model.**
- **Be more explicit as to how the final RfC was chosen (in Figure 2-2 of the 2022 Draft Assessment and elsewhere).**

Regarding the dose-response assessment for cancer endpoints, the committee found that EPA used approaches consistent with its state-of-practice methods to derive the inhalation unit risk estimates. The analyses generally followed the process outlined in the 2022 IRIS Handbook and were consistent with the 2005 Guidelines for Carcinogen Risk Assessment. As documented in Appendix

D and in sections on cancer dose-response analyses, the decision points and analyses were also responsive to the recommendations of the 2011 NRC committee.

The derivation of the unit risk is documented in approximately 200 pages in total across the three documents in the 2022 Draft Assessment, and some redundancies are evident within and across the documents. The sections documenting the derivations based on epidemiological evidence are transparent, and overall are well written and accessible.

Specific recommendations regarding the cancer dose-response assessment concern the criteria for study selection, the procedure and justification for pooling the data from two animal studies into one analysis, the discussion of uncertainties and variabilities, and the characterization of inhalation unit risk estimate, as detailed below.

Recommendation 5.4 (Tier 2): While the criteria for selecting the Beane Freeman et al. (2013) study can reasonably be discerned from the 2022 Draft Assessment, EPA should provide clearer statements of the criteria and comparison of studies with such criteria, in tabular format, to improve transparency and clarity. EPA should add to such a table other studies that evaluated the same cancer outcome so it is apparent why the selected study was superior for the purposes of dose-response analysis.

EPA identified three high-confidence and three medium-confidence long-term (>2-year) animal studies of formaldehyde in F344 rats for the purposes of dose-response analysis. The rationale for selecting some but not all of the studies and the procedure for combining data from two selected studies are not clearly presented. In joint analysis of the combined data, the description for the models used is not sufficiently transparent, particularly regarding the estimation of some key parameters.

Recommendation 5.8 (Tier 2): EPA should describe more clearly the procedure and justification for pooling the data from two animal studies into one analysis, and clarify that combined and corrected incidence data are contained in the Bermudez memorandum, which is not readily accessible to the public. The individual animal data for time-to-tumor occurrence used in the model should be provided in an appendix.

Recommendation 5.9 (Tier 2): To enhance transparency, EPA should provide additional detail on the modeling, including constraints imposed on model parameters, the results of model fitting (goodness-of-fit test), and the approach used to define lag parameters. The relationship between administered dose and the DNA–protein crosslinks and flux dose metrics should also be provided. Given the uncertainties in the dose surrogates, a dose-response analysis and benchmark concentration calculations using administered concentrations should be provided as a point of comparison.

Recommendation 5.10 (Tier 2): EPA should organize the discussion of uncertainties and variabilities in a manner that is easier to follow, such as by models or by process (models, benchmark concentration estimation, lower dose extrapolation, or extrapolation from animal data to humans).

Recommendation 5.12 (Tier 2): EPA should discuss the extent to which the inhalation unit risk estimates based on animal squamous cell carcinoma data and mechanistic data provide supporting evidence for the inhalation unit risk based on the human nasopharyngeal carcinoma data.

Recommendation 5.15 (Tier 2): In the discussion of uncertainties and confidence in the inhalation unit risk for myeloid leukemia, EPA should include the unknown dose rate-response relationship, the choice of statistical model and method, and the lack of understanding of mechanism. The three estimates in Table 2-35 should be presented as alternative, low-confidence inhalation unit risk estimates for myeloid leukemia without selection of a preferred estimate. EPA should not characterize the combining of other/unspecified leukemia with myeloid leukemia as "the best approach."

THE PATH FORWARD

EPA's 2022 Draft Assessment has been revised over a period spanning more than a decade and has been improved substantially. During that time, the methods used by the IRIS Program have evolved, prompted in part by the recommendations of the 2011 NRC report and subsequent reports of the National Academies. The 2011 report recognized that a period of change in methods used by the IRIS Program would begin if its recommendations and suggestions were followed, and cautioned that revisions to the 2010 Draft Assessment should not await finalization of any new methods.

The 2022 Draft Assessment was developed over a period of evolving methods within EPA and externally. The revised 2022 Draft Assessment follows the advice of prior National Academies committees, and its findings on hazard and quantitative risk are supported by the evidence identified.

In addressing its charge, the committee had to be able to identify the methods used, compare them against the state of practice for the IRIS Program, and assess their replicability. The committee did not find it easy to fulfill its charge given the organization and scope of the three documents, together totaling more than 2,000 pages, and the presentation of the review methods in several locations across the three documents. The IRIS Program did not consolidate protocols for the various outcome reviews, as would be current practice. Many of the committee's findings and recommendations relate to the fragmented description of methods across the documents and insufficient clarity in their presentation.

In the chapters that follow, the committee reviews in detail EPA's methods and conclusions and provides detailed recommendations for improving the clarity, accuracy, and usability of the final assessment. A major focus of the committee's recommendations is revisions needed to provide a clearer description of the methods used in order to facilitate their consideration by readers. At present, the description of methods in several places throughout three lengthy documents is perhaps the most critical area for structural and editorial revisions. Other recommendations point to opportunities to harmonize the assessment narrative across health outcome domains and to bring greater consistency by structuring them more carefully around the assessment's overall review framework. Implementation of the committee's recommendations would strengthen EPA's conclusions on the many noncancer outcomes reviewed, as well as the cancer hazard identification and dose-response conclusions. Revisions are needed to achieve the overall objective of making the assessment's methods sufficiently accessible for its users, and to facilitate access to related sections across the different elements of the assessment for the different outcomes analyzed.

The committee notes that according to the IRIS Program's website:

> EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment.

The 2022 Draft Assessment, which addresses a widely used, high-volume production chemical, needs to be completed to support EPA in fulfilling its mission. The committee acknowledges the significant effort made by EPA to improve the assessment since the 2010 Draft Assessment was reviewed. This report provides a number of specific Tier 1, 2, and 3 recommendations to guide the assessment's finalization, and the committee encourages EPA to implement all of the needed changes. A confined set of revisions will enhance clarity and transparency. Overall, the committee's judgment is that EPA should undertake its recommendations expeditiously to complete a revised assessment document that can be implemented without delay.

1
Introduction

Formaldehyde, a one-carbon molecule, is a flammable, colorless gas that has a distinct, strong odor. It is endogenously produced in humans through one-carbon metabolism and is also widely present in the environment. It is one of the higher-production chemicals by volume and is used in many manufactured goods: wood products (e.g., cabinets, furniture, plywood, particleboard, laminate flooring, etc.), permanent press fabrics, and household products (e.g., glues, paints, caulks, pesticides, cosmetics, detergents, etc.). It is also formed by combustion sources and is present in cigarette smoke and in emissions from electronic cigarettes, as well as in emissions from gas stoves and open fireplaces.

This report reviews an assessment of the human health risks of formaldehyde that has been carried out by the Integrated Risk Information System (IRIS) Program of the U.S. Environmental Protection Agency (EPA) (EPA, 2022a). According to its website (EPA, 2022b), the IRIS Program was established in 1985 to:

> provide an internal database of human health assessments for chemicals found in the environment. The goal of the IRIS Program was to foster consistency in the evaluation of chemical toxicity across the Agency.

For the selected chemicals, the IRIS Program carries out hazard assessments and provides toxicity values. The program is housed within EPA's Office of Research and Development (ORD). The program's website states (EPA, 2022b, 2023):

> EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment.

EPA's first evaluation on the health effects of formaldehyde was under its Office of Pesticides and Toxic Substances (OPTS, 1987). The IRIS Program first reviewed the evidence on formaldehyde and proposed a cancer unit risk estimate (URE) in 1989 and a noncancer reference dose (RfD) in 1990 (NCEA, 1989). The RfD of 0.2 mg/kg/day is based on reduced weight gain and histopathology from a two-year oral bioassay in rats (Til et al., 1989). For carcinogenicity, the weight-of-evidence characterization was B1-probable human carcinogen, based on limited evidence in humans and sufficient evidence in animals, along with supporting mechanistic data (in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes, such as acetaldehyde). An inhalation URE of 1.3E-5 per ug/m^3 was based on squamous cell carcinomas in male F344 rats (Kerns et al., 1983). The carcinogenicity of formaldehyde was subsequently evaluated by the International Agency for Research on Cancer (IARC), the National Toxicology Program's Report on Carcinogens (NTP ROC), and in 2014 by a National Research Council (NRC) ad hoc committee (see Figure 1-1) (NRC 2014b).

In 1981 and affirmed the following year, IARC classified formaldehyde as "possibly carcinogenic to humans" (Group 2B), based on recently released findings of nasal cancer in animal studies and short-term studies showing genotoxicity (IARC, 1982a,b). With the growing evidence of nasal cancer from occupational studies, in 1987 and 1995 IARC reclassified formaldehyde as "probably carcinogenic to humans" (Group 2A) based on "limited" evidence of cancer in humans

and "sufficient" evidence in experimental animals (IARC, 1987, 1995). In 2004 (published 2006), IARC classified formaldehyde as "carcinogenic to humans" (Group 1) based on sufficient evidence for nasopharyngeal carcinoma (IARC, 2006). In 2009 (published in 2012), the IARC classification of formaldehyde in Group 1 was reaffirmed, and formaldehyde was also determined to cause leukemia (IARC, 2012).

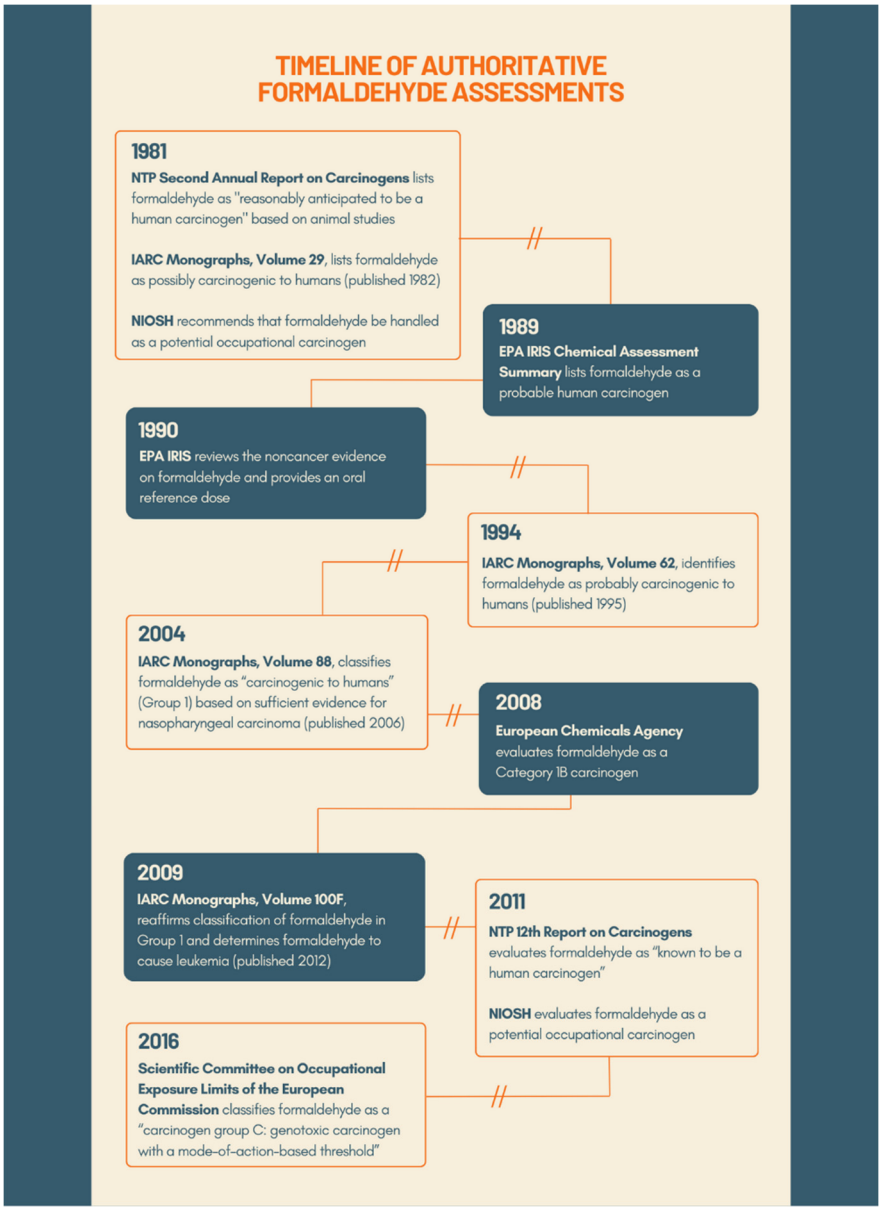

FIGURE 1-1 Timeline of authoritative formaldehyde assessments.

A similar pattern of higher levels of hazard identification classification for formaldehyde can be seen in determinations of another authoritative program in the area of carcinogenicity assessment—the NTP ROC. In 1981, formaldehyde was designated in the ROC as a "reasonably anticipated human carcinogen" (NTP, 1981). More recently, in 2011, the NTP ROC evaluated formaldehyde as "known to be a human carcinogen" (NTP, 2011), a finding that was reaffirmed by an ad hoc NRC committee in 2014 (NRC, 2014b).

The timeline of EPA's development of the *Draft IRIS Toxicological Review of Formaldehyde: Inhalation* (hereafter referred to as the 2010 or 2022 Draft Assessment) in the context of reports from the NRC (2011, 2014a) and the National Academies of Sciences, Engineering, and Medicine (in 2018 and 2022) is shown in Figure 1-2.

In 2010, EPA updated its formaldehyde Draft Assessment, which underwent review by an ad hoc NRC committee. The resulting report was released in 2011 (NRC, 2011). Thereafter, EPA began working on a revised Draft Assessment in 2012, convened workshops in 2014, and completed a revised Draft Assessment in 2017. In 2018, work was suspended on the Draft Assessment, according to the IRIS website (EPA, 2022b). The Draft Assessment was updated beginning in 2021 before being released in April 2022. The 2022 Draft Assessment consists of three documents: the Main Assessment (789 pages), accompanying Appendices (1059 pages), and an Assessment Overview (192 pages).

The 2011 NRC review committee identified numerous specific and general problems with EPA's 2010 Draft Assessment. To summarize, the committee found that the 2010 Draft Assessment lacked clarity, and the assessment methods were not well documented, leading to issues with transparency in how the conclusions of the assessment were drawn. The committee noted that poor documentation of methods was a finding of other NASEM committees that had reviewed IRIS assessments. The 2010 Draft Assessment was characterized as not prepared in a coherent, consistent fashion, with clear linkages to an underlying framework. The committee also concluded that the Draft Assessment did not contain sufficient documentation of methods and criteria for identifying evidence from studies, for evaluating studies, for assessing the weight of evidence, for selecting studies for derivation of toxicity and risk estimates, and for characterizing uncertainty and variability. Specifically, the 2011 NRC report contained the following general recommendations:

- First, rigorous editing is needed to reduce the volume of the text substantially and address the redundancies and inconsistencies; reducing the text could greatly enhance the clarity of the document.
- Second, Chapter 1 of the draft assessment needs to discuss more fully the methods of the assessment. The committee is recommending not the addition of long descriptions of EPA guidelines but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
- Third, standardized evidence tables that provide the methods and results of each study are needed for all health outcomes; if appropriate tables were used, long descriptions of the studies could be moved to an appendix or deleted.
- Fourth, all critical studies need to be thoroughly evaluated for strengths and weaknesses by using uniform approaches; the findings of these evaluations could be summarized in tables to ensure transparency.
- Fifth, the rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly.

- Sixth, the weight-of-evidence descriptions need to indicate the various determinants of "weight." The reader needs to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.

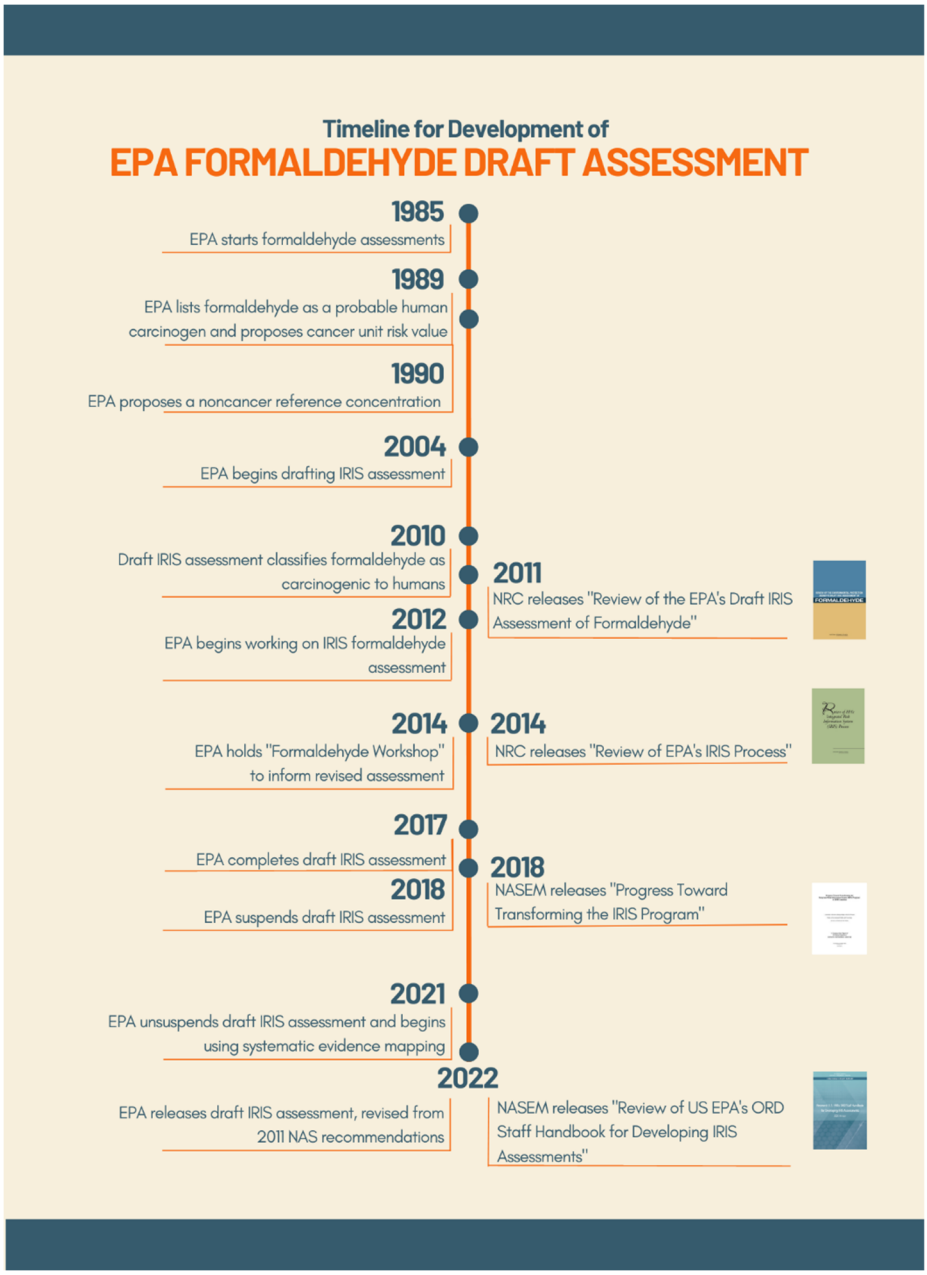

FIGURE 1-2 Timeline of development of EPA's formaldehyde Draft Assessment.

The report's last chapter, titled "A Roadmap for Revision," offered suggestions for changing the IRIS process to bring it closer to the state of practice for systematic review and evidence integration.

Several subsequent ad hoc NRC (in 2014) and NASEM (in 2018 and 2022) committees provided a series of recommendations in their reports (NRC, 2014a; NASEM, 2018, 2022) that encouraged the IRIS Program to adopt systematic review approaches, to create a staff handbook with general guidance on the methods for the IRIS assessments, and to develop an a priori protocol for each major IRIS assessment. The 2014 NRC committee defined systematic review as encompassing problem formulation, protocol development, evidence identification, evidence evaluation, and evidence integration to inform hazard identification and dose response. The committee provided specific recommendations on each step of the process.

The 2014 committee noted the substantial improvements made in the IRIS process and offered recommendations for building on that progress, including the creation of a handbook to "provide a single detailed guidance document for all those involved in the development of IRIS assessments." The 2018 NASEM committee also noted the substantial progress made in the IRIS process and presented findings around adherence to the 2014 recommendations. The 2018 committee observed that guidance for conducting newly planned IRIS assessments is contained in protocols that may overlap with the handbook's description of standard operating procedures. EPA noted that, although not provided to the 2018 committee, a handbook was under development. The version of the handbook released in 2020 was reviewed in a 2022 NASEM report, which highlighted opportunities to improve the handbook's scientific rigor and clarity. The report included a recommendation that a time-stamped, read-only final version of the protocol be released before further IRIS assessments were conducted. The 2022 committee recommended clarifying that the protocol would constitute a complete account of planned methods. EPA released an updated version of the handbook in December 2022 which included the recommendations from the NASEM committee.

THE COMMITTEE, ITS TASK, AND ITS APPROACH

EPA requested that NASEM convene a committee to review the 2022 Draft Assessment (EPA, 2022a), which was released for the committee's evaluation in April 2022. Reflecting its task (Box 1-1), the committee included expertise in public health risk assessment, systematic review methods, biostatistics, environmental epidemiology, toxicology, carcinogenesis (leukemogenesis), reproductive effects, developmental effects, neurotoxicology, respiratory effects (including asthma), biological modeling, exposure assessment, and dose-response analysis (see Appendix A for biographical information on the committee members).

The committee's charge was to review the 2022 Draft Assessment prepared by EPA, and not to conduct its own formaldehyde assessment. The committee also was not charged with commenting on other interpretations of scientific information relevant to the hazards and risks of formaldehyde, or with reviewing alternative opinions of EPA's assessment. Any other topics not falling within the committee's charge were excluded from the committee's purview.

To address its task, the committee held nine meetings, including three open sessions with public comment periods. Appendix B provides the agendas for the open sessions and a list of the more than 40 public commenters who provided oral input, as well as web links to the presentations, the recordings, and the documents provided by EPA that were reviewed by the committee.

The first open session was convened on October 12, 2022, and included a presentation and question-and-answer session with Professor Lisa Bero, chair of the 2022 NASEM ad hoc committee that reviewed the 2020 draft of the IRIS handbook; a presentation and question-and-answer session with EPA staff on the 2022 Draft Assessment; and a public comment period. The second

BOX 1-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will conduct a scientific review of EPA's draft document referred to as the Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde, plus appendices. The committee will assess whether EPA's draft document adequately and transparently evaluated the scientific literature, used appropriate methods to synthesize the current state-of-the science, and presented conclusions regarding the hazard identification analysis and dose-response analysis of formaldehyde that are supported by the scientific evidence. The committee will not conduct its own hazard assessment of formaldehyde, nor will the committee address the broader aspects of the IRIS Program.

- Recommendations about the IRIS assessment will be prioritized as follows:
- Tier 1: recommended revisions that are important for EPA to consider and address to improve critical scientific concepts, issues, or narrative in the assessment.
- Tier 2: suggested revisions that are encouraged to strengthen or clarify the scientific concepts, issues, or narrative in the assessment but are not critical. Other factors, such as agency practices and resources, might need to be considered by EPA before undertaking the revisions.
- Tier 3: considerations that might inform future evaluations of key science issues or inform development of future assessments.

open session was convened on December 22, 2022, to provide additional opportunity for public comment. The third open session, held on January 30, 2023, provided an opportunity for the committee to ask questions of EPA staff, as well as to hold a public comment period. In addition to requesting answers to its questions in writing from EPA, the committee had requested an opportunity for EPA to provide any additional clarifications on the answers it had prepared for the committee, which EPA did following the session. Written materials from EPA were made publicly available via the meeting website (see links in Appendix B). In addition to the opportunities provided for oral remarks during the three public meetings, stakeholders were encouraged to submit written comments or other materials relevant to the committee's charge at any time during the course of the study. Written input provided by members of the public is available upon request via the study's public access file.

In line with its statement of task, the committee considered that addressing any Tier 1 recommendations would be important to improve critical scientific concepts, issues, or narrative in the 2022 Draft Assessment. Tier 2 and Tier 3 recommendations could also trigger additional work on the Draft Assessment, including document editing to better clarify and support the assessment's conclusions.

To address its statement of task, the committee organized its review of EPA's hazard identification and dose-response analyses of noncancer and cancer outcomes around EPA's overview of its approach to developing the 2022 Draft Assessment (Figure 1-3). This framework follows the most recent version of the IRIS handbook, as reviewed by the 2022 ad hoc NASEM committee; it also parallels the framework proposed for the IRIS process in the 2014 NRC report.

As a comparison for the methods of the 2022 Draft Assessment and their documentation, the committee relied on general principles for conducting a systematic review and for ensuring transparency. To better understand the state of practice applied in preparing the Draft Assessment, the committee sought the protocols for EPA's reviews of noncancer, cancer, and mechanistic evidence so they could be evaluated against accepted systematic review methods that existed at the time the Draft Assessment was prepared. The committee also relied on EPA's responses to the questions it had posed.

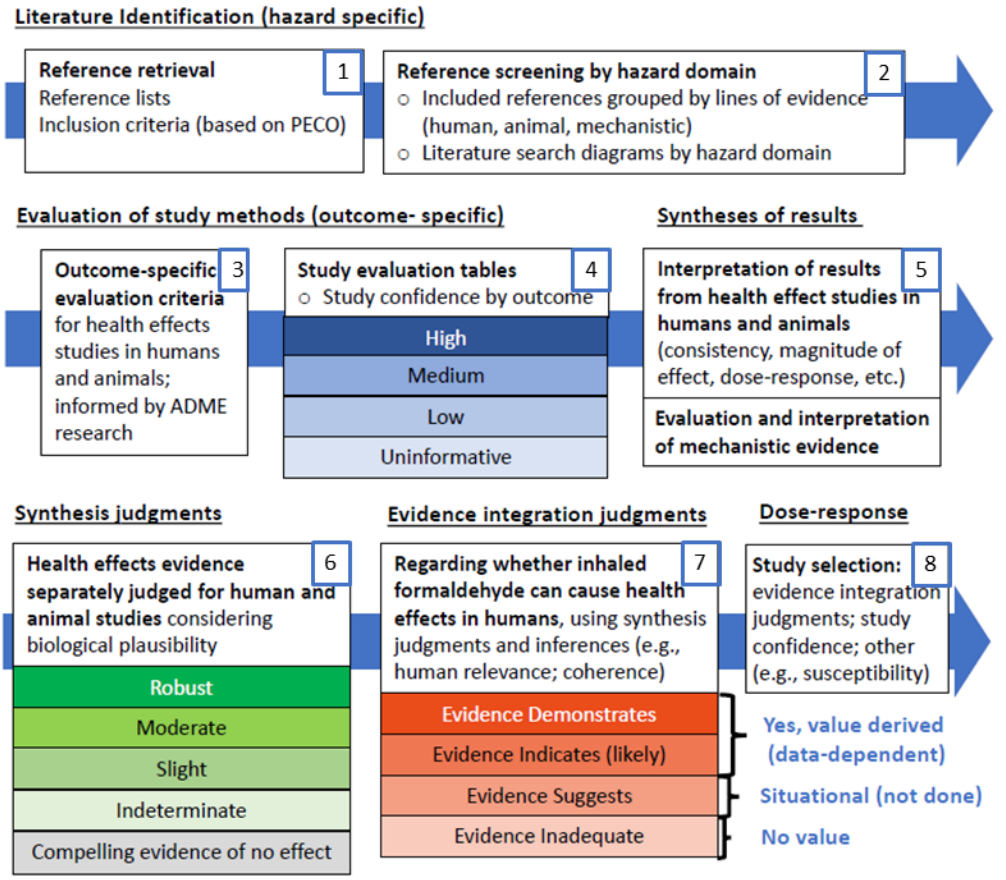

FIGURE 1-3 Systematic review approach used by EPA to complete the 2022 Draft Assessment.
NOTE: Modified from EPA's presentation to the committee on October 12, 2022.

The committee provided critiques and suggestions on EPA's methods for each step in the assessment (documentation of methods, evidence identification, study evaluation, evidence synthesis, evidence integration, and dose-response assessment). For each step, the committee considered the alignment of the 2022 Draft Assessment methods with the contemporaneous state of practice and prior advice to EPA from the National Academies. Transparency in EPA's systematic review methods implies that the committee should be able to replicate each step based on the information included in the assessment documents or in publicly available supplemental materials. Accordingly, the committee used a case study approach to provide a detailed evaluation of the transparency and replicability of the 2022 Draft Assessment methods, relying on the documentation provided by EPA in the 2022 Draft Assessment and in the written responses to the committee's questions EPA's response to the committee's questions[1].

[1] See https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D3A22C29743668E583CD8759F633481333EE3E7ECF54?noSaveAs=1, Tables 2 and 3 (accessed July 23, 2023).

The committee also reviewed the hazard and dose-response conclusions for noncancer outcomes (covering sensory irritation, pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity) and for cancer outcomes. This aspect of the committee's review addressed each step of EPA's assessment methods for each outcome as used to develop evidence integration judgments and derive risk estimates for formaldehyde. In line with its overall charge, the committee focused its review on whether the 2022 Draft Assessment adequately and transparently evaluated the available studies and data, and used appropriate methods in reaching hazard identification conclusions and dose-response analyses that are supported by the scientific evidence. In its review, the committee also considered the recommendations of prior NRC and NASEM committees, including the 2014 NRC committee that reviewed the formaldehyde assessment of the National Toxicology Program (NTP) 12th Report on Carcinogens. In accordance with its statement of task, the committee did not conduct an independent assessment of formaldehyde's hazards and risks.

ORGANIZATION OF THE REPORT

This report is organized into five chapters and five appendices. Chapter 2 addresses the assessment development methods and organization of the 2022 Draft Assessment. It covers the state of practice, drawing on relevant reports from the NRC (in 2011 and 2014) and NASEM (in 2018 and 2022), addresses the responsiveness of the 2022 Draft Assessment to the recommendations provided by the NRC (2011), and provides illustrative examples of the transparency and replicability of EPA's assessment using a case study approach. Chapter 3 reviews EPA's analysis of toxicokinetics. Chapters 4 and 5 review hazard and dose-response for noncancer and cancer outcomes, respectively. For each outcome considered in Chapters 4 and 5, the adequacy of the following aspects is addressed: the literature identification; study evaluation criteria; synthesis and judgments, including any mode-of-action considerations; overall hazard conclusions; and dose-response evaluation. Appendix A contains biographical information on the committee members. Appendix B includes the meeting agendas for the open sessions and a list of the more than 40 public commenters who provided oral input, as well as web links to the presentations and recordings, as well as the documents provided by EPA that the committee reviewed. Appendices C and D contain the committee's case studies. Appendix E gives examples of issues identified by the committee that should be addressed as EPA revises and finalizes the Draft Assessment.

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2
Methods and Organization

This chapter addresses the methods used by EPA for the systematic reviews in the 2022 Draft Assessment (EPA, 2022a), for synthesis within evidence streams and evidence integration across streams, and for the selection of studies used to derive the reference concentration (RfC) and unit risk estimates. The chapter provides the committee's assessment of these methods and addresses the organization of the 2022 Draft Assessment. Subsequent chapters provide the committee's scientific review of the hazard identification conclusions and risk analyses of formaldehyde presented in the Draft Assessment for noncancer and cancer outcomes.

The committee's approach to assessing the methods underlying the 2022 Draft Assessment encompassed several steps. First, the committee considered whether the methods used were aligned with the general state of practice for systematic review, evidence synthesis, and hazard identification (i.e., evidence integration). Second, the committee considered whether the methods used responded to the advice provided by the National Academies in the reports that offered advice for the IRIS Program and were incorporated in the development of the 2022 Draft Assessment. Finally, the committee reviewed the documentation of the methods in the Draft Assessment and its appendices. To evaluate whether the 2022 Draft Assessment was transparent enough to support replicability and evaluation of the process by an independent third party, the committee conducted a case study for the outcome of sensory irritation. The committee applied the documented steps of the assessment framework as contained in the three volumes of the 2022 Draft Assessment (i.e., the Assessment Overview, the Main Assessment, and Appendices), to test for replicability. It also completed a related case study for sensory irritation involving the calculation of reference concentrations based on two epidemiological studies.

THE STATE OF PRACTICE FOR SYSTEMATIC REVIEW

According to the Institute of Medicine report *Finding What Works in Health Care: Standards for Systematic Reviews* (IOM, 2011, p. 2), systematic review is "a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies." Systematic review allows for transparency of processes and methods used in an assessment and also provides structure for expert judgment. Expert judgment is integral to the systematic review process, from question formulation, protocol development, study selection, and evaluation through determination of the strength of evidence of each evidence stream. It is particularly influential at the evidence integration step. Throughout the IRIS assessment process, multidisciplinary expertise is needed from individuals able to view evidence holistically and reach judgments regarding its fit within the review schema. Expert judgment is needed to reconcile conflicting evidence and uncertainties, and to reach consensus and closure across the steps of the assessment process.

Comparison of the methods used for the 2022 Draft Assessment against a single gold standard approach are complicated by the protracted period over which the review was conducted—from 2012 to 2022. During this decade, the state of practice for systematic review related to environmental exposures was evolving, with national and international working groups developing guidance and tools for systematic reviews relating to environmental health. In addition to efforts at EPA, systematic review approaches were being advanced by the Navigation Guide group at the University of California, San Francisco; the Office of Health Assessment and Translation (OHAT)

of the National Toxicology Program (NTP); the Texas Commission on Environmental Quality (TCEQ); the European Food Safety Authority (EFSA); and a collaboration of the World Health Organization and the International Labour Organization (Woodruff and Sutton, 2014; Schaefer and Meyers, 2017; Descatha et. al., 2018; A. J. Morgan et al., 2018; NTP, 2019). The International Agency for Research on Cancer (IARC) Monographs Preamble approach for evidence integration, which has been adopted for many systematic review frameworks, was also updated during this period (IARC, 2019; Samet et al., 2020).

The 2011 National Research Council (NRC) committee anticipated the evolution of systematic review methods for environmental health and advised EPA that "although the committee suggests addressing some of the fundamental aspects of the approach to generating the draft assessment later in this chapter, it is not recommending that the assessment for formaldehyde await the possible development of a revised approach" (NRC, 2011, p. 151).

The 2014 NRC report *Review of EPA's Integrated Risk Information System (IRIS) Process* provides a framework for the IRIS process, showing where systematic review fits into the process and documenting the parallel, but separate, reviews for the three relevant evidence streams: human, animal, and mechanistic. The framework describes the flow of evidence utilization through the steps of evaluation of studies, evidence integration for hazard identification, and derivation of toxicity values. The report was intended to provide overall guidance as EPA moved forward with changes to the IRIS process (NRC, 2014).

Consequently, the procedures used by the IRIS Program were evolving over the period during which the 2022 Draft Assessment was being developed. The IRIS Handbook (EPA, 2022b), which would provide detailed and codified guidance for developing IRIS assessments and make the IRIS process transparent to stakeholders, was also being prepared during this time (Figure 2-1). The use of prereviewed—that is, publicly released—protocols to document the methods to be used in an IRIS systematic review began in 2018 (EPA, 2018), and the IRIS Handbook was released in draft in 2020 and finalized in 2022 following a review by the National Academies of Sciences, Engineering, and Medicine (NASEM). Further, work on the 2022 Draft Assessment was suspended in 2018 after the draft's completion in 2017. When EPA resumed work on the draft in 2021, systematic evidence mapping was used to identify newer publications that would potentially be "impactful" if added to the evidence gathered through 2017.

Thus, this committee's evaluation of the methods used by EPA for hazard assessment and for dose-response assessment is complicated by the 11-year timeframe of the draft's development, the fluidity of the IRIS Handbook over time, and the continued evolution of systematic review methods for environmental agents generally.

RESPONSE TO THE 2011 NRC REPORT

The 2011 NRC committee reviewed EPA's 2010 Draft Assessment (NRC, 2011). That committee's report identified many issues with the methods used and the organization and transparency of the assessment. Subsequent NRC and NASEM committees reviewed the procedures used by the IRIS Program and provided advice on how EPA could resolve many of these issues, recommending the incorporation of systematic review methodology and greater transparency of methods for evidence synthesis and integration (NRC, 2014; NASEM, 2018).

The overall approach to revising the 2010 Draft Assessment was motivated by the general and specific comments of the 2011 NRC report. Appendix D of the 2022 Draft Assessment provides a 37-page response to the comments in the 2011 NRC committee's report, responding to both the specific and general comments in the 2011 report while also pointing out that the 2022 Draft

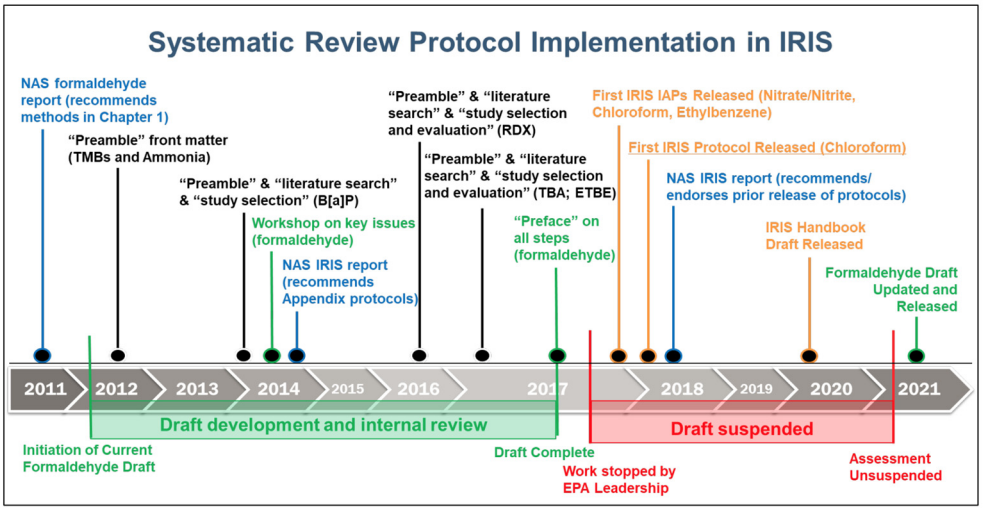

FIGURE 2-1 Timeline of protocol implementation in the IRIS program.
SOURCE: EPA's responses to committee's questions (see https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D3A22C29743668E583CD8759F633481333EE3E7ECF54?noSaveAs=1 [accessed May 11, 2023]). Abbreviations: B[a]P = benz[a]anthracene; EPA = Environmental Protection Agency; ETBE = ethyl tertiary butyl ether; IAP = IRIS assessment plan; IRIS = Integrated Risk Information System; RDX = hexahydro-1,3,5-trinitro-1,3,5-triazine; TBA = tert-butyl alcohol.

Assessment "is a completely different document." Given the scope of the revisions and methodological changes, the present committee did not review specific changes in the 2022 Draft Assessment against the recommendations in the 2011 NRC report, although it did find Appendix D to be responsive to the methodological concerns raised in that report.

For example, the committee that prepared the 2011 NRC report recommended that EPA use biologically based dose-response (BBDR) models for formaldehyde (Conolly et al., 2004) in its cancer assessment and discuss the strengths and weaknesses of using the BBDR models. The 2022 Draft Assessment presents rat and human risk estimates based on BBDR modeling to estimate points of departure from the animal nasal cancer data, and EPA explored uncertainties that occur when these models are used for low-dose risk estimation. Ultimately, EPA chose not to use the full rat and human BBDR models to estimate unit risks because its analysis showed instability of estimates in the human extrapolation modeling provided by Conolly et al. (2004). The cancer unit risks are based on human epidemiology data instead.

Finding: The 2022 Draft Assessment responds to the broad intent of the 2011 NRC report.

RESPONSE TO THE 2014 NRC REPORT

The 2014 NRC report provided general guidance on the IRIS Program, offering a framework for its review processes. The report assessed scientific, technical, and process changes made by EPA in response to the 2011 NRC recommendations. The 2014 NRC committee noted that EPA was making significant progress, and was incorporating systematic review principles as it implemented changes to the IRIS process. The 2014 NRC report highlighted the standards detailed in

the above mentioned Institute of Medicine report *Finding What Works in Health Care: Standards for Systematic Review* (IOM, 2011), providing specific recommendations for each step of the systematic review process.

The methods used in the 2022 Draft Assessment encompass eight steps that generally align with the processes described in the 2014 NRC report: evidence identification, evidence evaluation, evidence synthesis, and evidence integration to inform hazard identification and dose-response estimation.

Finding: The 2022 Draft Assessment is responsive to the broad intent of the 2011 NRC review of EPA's 2010 Draft Assessment and the 2014 NRC review of the IRIS process.

ALIGNMENT OF THE 2022 DRAFT ASSESSMENT METHODS WITH THE STATE OF PRACTICE

The following sections provide the committee's critique of EPA's methods for each aspect of the systematic review. Figure 2-2 shows an overview of the EPA process; the committee's review is framed by these steps, numbered for convenience from 1 to 8. In discussing the steps, the committee provides a brief description of the current state of practice and prior advice to EPA from NRC/NASEM to frame the review that follows.

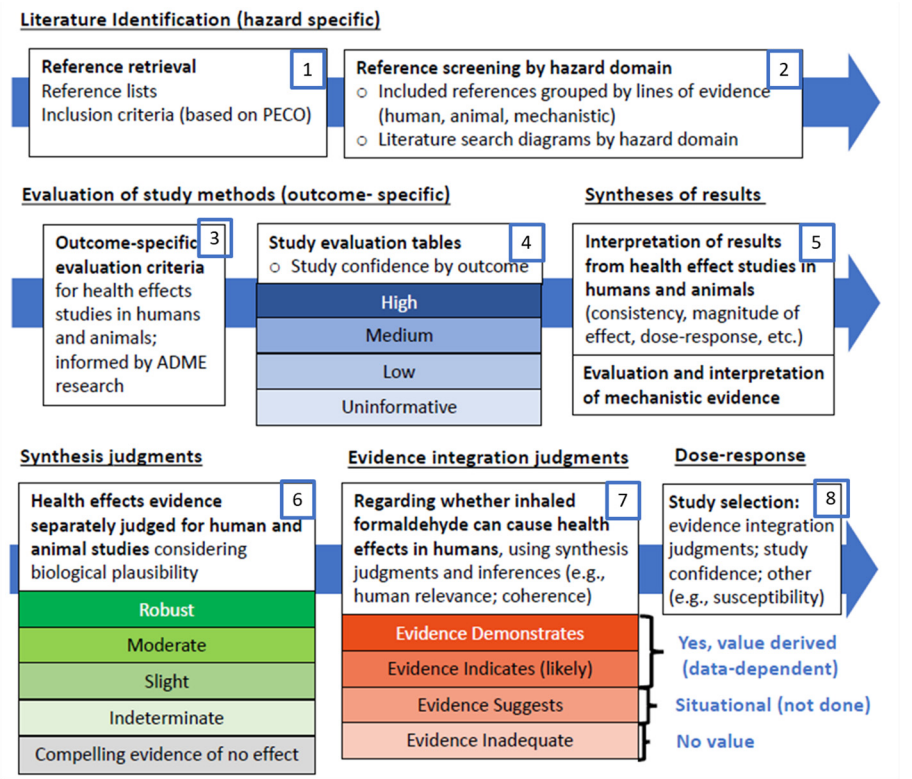

FIGURE 2-2 Systematic review methods used by EPA to complete the 2022 Draft Assessment. NOTE: Modified from EPA's presentation to the committee on October 12, 2022.

DOCUMENTATION OF METHODS

State of Practice

A human health risk assessment of a chemical includes an initial scoping and problem formulation step to inform the development of the research questions and the best evidence-based approach for answering them (NRC, 2009). Problem formulation entails stakeholder engagement as well as a broad literature search, which then can inform more specific research questions. The research questions inform the development of the assessment methods, which are typically documented in a protocol that is established before the assessment begins. The protocol provides comprehensive documentation of inclusion and exclusion criteria for compiling evidence, as well as the methods for the subsequent steps of the systematic review. These steps include evaluating the internal validity of individual studies using appropriate risk-of-bias tools, synthesizing evidence within an evidence stream, and integrating evidence across evidence streams to reach overall hazard conclusions and support the selection of studies for dose-response analyses. The protocol needs to include a level of detail sufficient to support replication of the approach followed.

Documenting planned methods and any deviations from them allows for tracing of every step of the study compilation, study evaluation, and evidence synthesis and integration processes (Figure 2-2). This level of documentation is the foundation for transparency and has been recommended for systematic reviews in clinical fields since at least 2011 (Cochrane Collaboration, 2011; IOM, 2011). It remains the state of practice, although it had not been adopted for systematic reviews in environmental health until 2014, when the Navigation Guide published a protocol for a review of triclosan (Johnson et al., 2016). The IRIS Handbook specifies the publication of an assessment plan, which describes what the assessment will cover, and a systematic review protocol, which describes how the assessment will be conducted (EPA, 2022b).

Prior Advice to EPA from the National Academies

The 2011 NRC committee recommended that the revised EPA assessment include a full discussion of the methods used, including the following elements:

- Clear, concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
- Thorough evaluation of all critical studies for strengths and weaknesses using uniform approaches; the findings of these evaluations could be summarized in tables to ensure transparency.
- Clear articulation of the rationales for selection of studies that are used to calculate RfCs and unit risks.
- Indication of the various determinants of "weight" that contribute to the weight-of-evidence descriptions, so that the reader is able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.

The 2014 NRC committee called for the development of a protocol outlining the methods for identifying and evaluating studies, for integrating evidence to reach hazard conclusions, and for supporting dose-response analyses.

The IRIS Handbook was developed over the last decade. The NASEM committee that reviewed the 2020 version of the IRIS Handbook recommended creation of a time-stamped, read-

only final version of the protocol before the assessment was performed. The 2022 NASEM committee also recommended clarifying that the protocol would constitute a complete account of planned methods (NASEM, 2022).

Approach to Documentation of Methods in the 2022 Draft Assessment

To conduct the case study on sensory irritation (Box 2-1), the committee followed methods that are described across several different documents, as the 2022 Draft Assessment does not document methods in specific protocols for the various outcomes. Instead, EPA describes the assessment methods generally in the preface to the Main Assessment and the Assessment Overview. Specific methods for health outcome are described in the Main Assessment and the Appendices of the 2022 Draft Assessment. EPA notes that presenting "the assessment methods within the assessment documents rather than in a separate protocol is consistent with the practices within the IRIS Program at the time the formaldehyde assessment was being developed during 2012–2017" (EPA, 2023, p. 2).

BOX 2-1
Sensory Irritation and the Study by Hanrahan et al. (1984)

This case study was conducted to test the replicability of EPA's approach to carrying out the eight steps of its IRIS assessment framework (Figure 2-2), as applied in the 2022 Draft Assessment (EPA, 2022a). For this case study, the committee evaluated the various steps of the assessment for a single study and endpoint. The purpose was to determine the utility of EPA's documentation of each step and not to attempt to "validate" the review outcome for human sensory irritation.

For the case study, the committee identified where the descriptions for the eight steps of the assessment are provided and evaluated their application to the Hanrahan et al. (1984) study. For sensory irritation, the committee found the population, exposure, comparator, outcome(s) (PECO) statement and associated literature search to be adequately documented (Steps 1 and 2). The committee carefully identified the criteria for study evaluation, finding inconsistencies across the several descriptions included in the 2022 Draft Assessment (Step 3). These inconsistencies complicated the committee's completion of Step 4—classification of study confidence by outcome. Overall, the committee found some inconsistencies between the presented human sensory irritation outcome—specific evaluation criteria and how they were applied to the Hanrahan et al. study, as well as how study limitations were presented for other sensory irritation studies. For Steps 5 and 6 (synthesis of results and synthesis judgments), EPA was clear about the basis for the strength-of-evidence determination, and it was applied in a way that was consistent with the stated framework. For evidence integration (Step 7), the conclusion was supported by the evidence presented. With regard to the dose-response analysis (Step 8), the committee had difficulty following EPA's reasoning in selecting the Hanrahan et al. study. This study was reported four decades ago as a two-page publication that does not meet the current norm for documentation and data access. The committee finds that the 2022 Draft Assessment does not adequately acknowledge the full scope of uncertainty associated with the Hanrahan et al. dose-response relationship.

The committee acknowledges that different groups of expert reviewers may come to different places in a multistep review process, and the committee cannot replicate EPA's process with complete fidelity. Nonetheless, the committee did identify inconsistencies between EPA's evaluation of the Hanrahan et al. (1984) study and EPA's stated criteria for study evaluation. Within the specified methods for synthesis and integration, the 2022 Draft Assessment reaches justified conclusions within the framework. A full description of the committee's case study for the Hanrahan et al. paper with the human sensory irritation endpoint is included in Appendix C.

The committee asked EPA about the use of protocols and documentation of methods in the 2022 Draft Assessment. EPA provided a table outlining where procedures that map to the steps shown in Figure 2-2 are described in the 2022 Draft Assessment. In response to the committee's questions, EPA pointed to the descriptions of its methods in the "Preface on Assessment Methods and Organization" and the additional and more detailed health effect–specific methodological considerations provided in the Appendices.

Finding: EPA did not develop a set of specific protocols for the 2022 Draft Assessment in a fashion that would be consistent with the general state of practice that evolved during the prolonged period when the assessment was being developed. Instead, EPA described the assessment methods across the three documents that together make up the 2022 Draft Assessment: The Main Assessment (789 pages), accompanying Appendices (1059 pages), and an Assessment Overview (192 pages).

Conclusion: Prepublished protocols are essential for future IRIS assessments to ensure transparency for systematic reviews in risk assessment.

Finding: The committee's review of the 2022 Draft Assessment documents the challenges faced by users of the assessment in navigating the voluminous documentation and understanding the methods used and evidence assessed. EPA needs to revise the Draft Assessment to ensure that the methods used for each outcome can easily be found by providing a linked roadmap and merging the descriptions of the methods used for each outcome in a single location.

Recommendation 2.1 (Tier 1): **EPA should revise its assessment to ensure that users can find and follow the methods used in each step of the assessment for each health outcome. EPA should eliminate redundancies by providing a single presentation of the methods used in the hazard identification and dose-response processes. A central roadmap and cross-references are also needed to facilitate access to related sections across the different elements of the assessment (e.g., Appendixes, Main Document) for the different outcomes analyzed. Related Tier 2 recommendations would amplify the impact of this Tier 1 recommendation in improving the assessment.**

Recommendation 2.2 (Tier 2): In updating the assessment in line with the Tier 1 Recommendation 2.1, EPA should further clarify the evidence review and conclusions for each health outcome by giving attention to the following:

- **Using a common outline to structure the sections for each health outcome in order to provide a coherent organization that has a logical flow, by**
  - **adding an overview paragraph to guide readers at the start of sections for each of the various health domains, and**
  - **including hyperlinks to facilitate crosswalking among sections within the document;**
- **Moving lengthy, not directly used information to an appendix;**
- **Including a succinct executive summary in the Main Assessment; and**
- **Performing careful review and technical editing of the documents for consistency across the multiple parts of the 2022 Draft Assessment, including across the Assessment Overview and Appendices. (The Assessment Overview could be entirely removed if the above recommendations were carried out.)**

EVIDENCE IDENTIFICATION (STEPS 1 AND 2)

Aspects of EPA's approach relevant to evidence identification are presented in Figure 2-3.

State of Practice

Evidence identification involves developing a PECO (population, exposure, comparator, outcome[s]) statement to guide the search strategy. As the next step, a trained librarian or informationist should search multiple databases to identify a broad pool of articles to be screened for inclusion. Abstract screening is typically then conducted by at least two reviewers working independently, and decisions are made as to whether to include or exclude each article. These decisions should be documented and made in accordance with criteria for inclusion and exclusion that are established a priori.

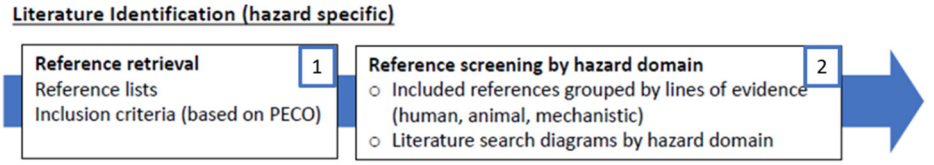

FIGURE 2-3 Aspects of EPA's approach relevant to evidence identification.

Prior Advice to EPA from the National Academies

The 2014 NRC committee advised EPA to include a section on evidence identification that "is written in collaboration with information specialists trained in systematic reviews and that includes a search strategy for each systematic-review question being addressed in the assessment. Specifically, the protocols should provide a line-by-line description of the search strategy, the date of the search, and publication dates searched and explicitly state the inclusion and exclusion criteria for studies" (NRC, 2014, p. 59). Additionally, the 2014 committee recommended that evidence identification involve a predetermined search of key sources, follow a search strategy based on empirical research, and be reported in a standardized way that would allow replication by others, and that the search strategies and sources be modified as needed on the basis of new evidence on best practices. The 2014 committee also recommended that contractors who perform the evidence identification for a systematic review adhere to the same standards and provide evidence of experience and expertise in the field.

Approach to Evidence Identification in the 2022 Draft Assessment

The steps EPA followed in conducting the literature search and the PECO assessment for inclusion and exclusion of studies are described in the Main Assessment as well as in the Appendices. For each outcome, the literature search strategy is documented, and inclusion and exclusion criteria are provided that are based on the PECO statement and are detailed in a table. EPA updated its literature searches annually through September 2016, after which systematic evidence mapping was used to search studies from 2017 through 2021 when work on the assessment was resumed.

Finding: EPA's literature search strategies for the 2022 Draft Assessment are adequate and consistent with the state of practice at the time. EPA appears to have sufficiently harmonized the methods for the pre- and post-2016 literature searches that were conducted using two different methods and were consistent with the state of practice at the time. Although the search strategies are adequately documented, the origins of the various PECO statements are less clear. In particular, across noncancer outcomes, the rationale for study exclusion on the basis of the populations, exposures, and outcomes is not well documented. For the literature searches, EPA used four databases, curated reference lists in published reviews, and "other national or international health assessments of formaldehyde," consistent with prior NASEM guidance (See Appendix C). As an example, see the literature search documentation for sensory irritation (pp. A-231–232).

Recommendation 2.3 (Tier 2): EPA should expand the text explaining the choices of the elements of the PECO statements.

STUDY EVALUATION (STEPS 3 AND 4)

In this step of the IRIS process (see Figure 2-4), the human and animal studies selected for inclusion are assessed for study quality, including risk of bias.

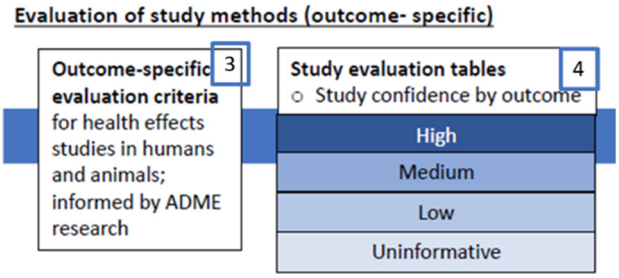

FIGURE 2-4 Aspects of EPA's approach to study evaluation.

State of Practice

The state of practice for study evaluation is that each selected study be assessed for risk of bias using a tool that evaluates whether a study may be affected by systematic errors that impact internal validity and cause the results to deviate from the truth. The potential for error in a study can be assessed, but quantitative estimation of the magnitude of any bias may not be possible. Classes of bias include selection bias, information bias (such as misclassification of exposure or outcome), confounding, selective reporting of study findings, missing data, and inappropriate statistical analysis (Frampton et al. 2022). Two reviewers independently evaluate each study, and any disagreements in rating of the evaluation domains are resolved by consensus, as is described in the IRIS Handbook.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) is an example of a transparent framework for developing and presenting evidence summaries that provides a systematic approach for making clinical practice recommendations (Guyatt et al., 2008a,b, 2011). GRADE is the most widely adopted tool for classifying the quality of evidence and for making recommendations, and is officially endorsed by more than 100 organizations worldwide.

While GRADE was developed for randomized controlled trials, since 2011 work has been in progress to adapt it for epidemiological and animal studies. Examples include the ROBINS-I tool for nonrandomized (epidemiological) studies (Sterne et al., 2016); its use is explained in Schünemann et al. (2019). Hooijmans' SYRCLE risk-of-bias tool is typically used to grade risk of bias in animal studies of interventions (Hooijmans et al., 2014). OHAT has adopted these tools for toxicological applications in the OHAT risk-of-bias tool (NTP, 2015), which is based on GRADE. Tools and criteria that guide judgments for each bias domain and for each outcome are preestablished during the protocol development stage, thereby calibrating how judgments are made so that decisions will be transparent and replicable.

Prior Advice to EPA from the National Academies

The 2011 NRC review of EPA's 2010 Draft Assessment provided considerations for a template for evaluating epidemiologic studies (NRC, 2011, p. 158). The elements include many of the sources of bias that are commonly addressed in risk-of-bias tools, including selection bias, information bias, and confounding (Box 2-2).

Approach to Study Evaluation in the 2022 Draft Assessment

EPA assessed the risk of bias for included studies using a domain-based approach. The domains included were related to study factors that influence internal validity, that is, whether the study is potentially affected by bias, which can lead to under- or overestimation of risk. The domains used for study evaluation are described in the Assessment Overview and the preface of the Main Assessment and in Appendix A. The descriptions are somewhat different in each location. For example, the Assessment Overview does not describe domains used but provides considerations when different types of research studies, observational epidemiologic studies, controlled human exposure studies, animal toxicological studies, and mechanistic studies are being reviewed. The preface of the Main Assessment (Figure II) describes four domains that are used to summarize the study quality of epidemiological studies, including the potential for selection bias, information bias, and confounding, along with other considerations.

BOX 2-2
Considerations for a Template for Evaluating Epidemiologic Studies

- Study population characteristics and the generalizability of findings to other populations.
- Approach used for exposure assessment and the potential for information bias, whether differential (nonrandom) or nondifferential (random).
- Approach used for outcome identification and any potential bias.
- Appropriateness of analytic methods used.
- Potential for confounding to have influenced the findings.
- Precisions of the estimates of effect.
- Availability of an exposure metric that is used to model the severity of an adverse response associated with a gradient of exposures.

SOURCE: NRC, 2011, p. 158.

Finally, in Appendix A, Section A.5.1 (pp. A-232 to A-233) five domains are described for epidemiological studies:

- *Population selection*: Recruitment, selection into study, and participation independent of exposure status, reported in sufficient detail to understand how subjects were identified and selected.
- *Information bias*: A validated instrument for data collection described or citation provided. Outcome ascertainment conducted without knowledge of exposure status. Timing of exposure assessment appropriate for observation of outcomes. Information provided on the distribution and range of exposure with adequate contrast between high and low exposure.
- *Potential for confounding*: Important potential confounders addressed in study design or analysis. Potential confounding by relevant coexposures addressed.
- *Analysis*: Appropriateness of analytic approach given the design and data collected; consideration of alternative explanations for findings; presentation of quantitative results.
- *Other considerations not otherwise evaluated*: Sensitivity of study (exposure levels, exposure contrast, duration of follow-up, sensitivity of outcome ascertainment).

Appendix A, Sections A.5.2 – A.5.9, includes the study-specific evaluations and provides study tables (e.g., Table A-34), with one row per study that considers six domains for noncancer endpoints: (1) consideration of participant selection and comparability, (2) exposure measure and range, (3) outcome measure, (4) consideration of likely confounding, (5) analysis and completeness of results, and (6) size. For studies of cancer outcomes, the domains are the same, except that instead of size, sensitivity is considered.

For noncancer outcomes, EPA documents how judgments are made for each domain, in a generic sense, by providing some description of classification of studies as having a high, medium, or low level of confidence or not being informative in tables documenting risk-of-bias decisions. These tables have two columns for exposure and for study design and analysis (see, e.g., Table A-33). The descriptions in the table cells sometimes mention risk-of-bias domains described elsewhere in the document. However, the documentation is not specific to each domain as a heading in the tables (because there are only two table headings rather than six for the high, medium, low, not informative classification). For cancer outcomes, the risk-of-bias domains are described generally for each outcome, but there is no clear description of how judgments were made concerning the classification of studies as having high, medium, or low confidence or not being informative for each risk-of-bias domain.

Animal studies are also evaluated in terms of domains that would influence internal validity or study sensitivity. Tables in Appendix A describe these domains, as does the text in the sections that precede the tables. For example, Section A.5.1 describes considerations for five general study quality categories: exposure quality, test animals, study design, endpoint evaluation, and data considerations and statistical analyses. The criteria for the epidemiology studies follow the same tabular organization described above (see Table A-57). For animal respiratory pathology, Section A.5.5 addresses additional factors for evaluating these studies, emphasizing certain aspects that would decrease study confidence and noting factors that are of less concern (e.g., methanol coexposure for portal-of-entry effects). Footnotes to the study results tables (e.g., Table A-59) provide characteristics of robust (++), adequate (+), or poor (gray shading) determinations for the individual evaluation domains. Some criteria are found only in the footnotes (e.g., protocol description, protocol relevance to humans), while others are included in different domains from those in the general categories presented in A.5.1 (“General Approaches to Identifying and Evaluating Individual Studies”).

Overall, while outcome-specific criteria used to evaluate studies were generally appropriate, the committee found it difficult to fully understand the final criteria that were applied, as well as the judgments made on overall study confidence for both human and animal studies. Comparable tables for different outcomes may not have sufficiently parallel descriptions.

Finding: EPA provides overall and outcome-specific evaluation criteria that are generally consistent with the common domains for risk-of-bias analysis and their application in practice. However, the criteria are found in several different locations in the documents and in some cases are inconsistently presented and integrated across the documents. As a result, the committee was challenged to reconstruct the study evaluation approach and how the criteria were applied for study evaluation.

Finding: The considerations listed for classification of study confidence and evaluation of each study by at least two independent experts are adequate. However, the committee's case studies (see Box 2-1 and Appendix C) revealed inconsistencies in how evaluation criteria were described and applied in EPA's evaluation of human and animal studies.

Recommendation 2.4 (Tier 2): EPA should thoroughly review the 2022 Draft Assessment documents to address issues of consistency and coherence so as to ensure that its methods can be applied and replicated with fidelity. The reviews for each outcome in Chapters 4 and 5 provide more specific guidance.

EVIDENCE SYNTHESIS (STEPS 5 AND 6)

Evidence synthesis involves separately interpreting the results from human, animal, and mechanistic studies and reaching judgments as to the strength of evidence in each evidence stream. Biological plausibility is an overarching consideration (Steps 5 and 6; see Figure 2-5).

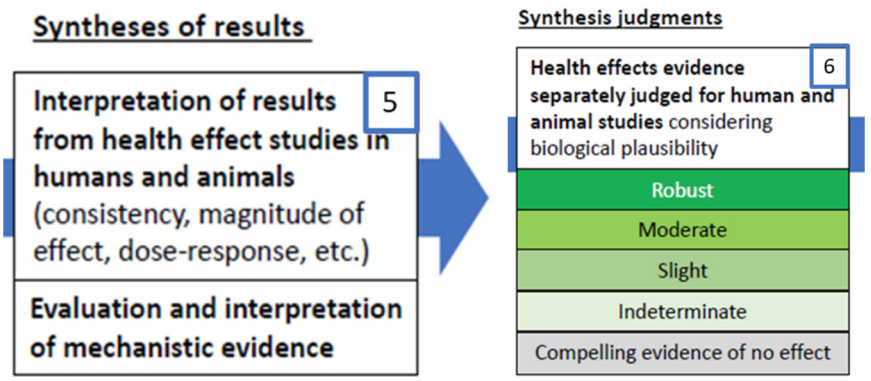

FIGURE 2-5 Aspects of EPA's approach relevant to syntheses of results and synthesis judgments.

State of Practice

Evidence synthesis is a process of bringing together data from a set of included studies with the aim of drawing conclusions about a body of evidence (Higgins et al., 2019). The process consists of summarizing study characteristics, quality, and effects, and combining results and exploring differences among the studies (e.g., variability of findings and uncertainties) using qualitative and/or quantitative methods. GRADE is the approach used most commonly in the clinical field for evidence synthesis, and several groups, including the National Academies (NASEM, 2017), are working to adapt it to environmental hazard assessments. The approaches developed by R. L. Morgan and colleagues (2016, 2019) and the Navigation Guide group (Woodruff and Sutton, 2014) are similar to the original GRADE approach, but use slightly different criteria for setting initial levels of certainty and for upgrading and downgrading certainty. The Navigation Guide was designed for human nonrandomized studies, whereas OHAT extended the approach to animal studies. Although there are slight differences in the environmental health field regarding evidence synthesis, there is some convergence on common baseline methods, such as the GRADE approach, to bring consistency. Moreover, the committee emphasizes that all of the above-mentioned methods have undergone pilot testing, stakeholder vetting, and peer review and have been made public.

Approach to Evidence Synthesis in the 2022 Draft Assessment

EPA applies a set of considerations and a framework for assessing the strength of evidence in each of the evidence streams within an outcome class, which are described in the preface of the Main Assessment (p. xxxiii). The primary considerations for assessing the strength of evidence for health effects studies in humans and, separately, in animals fall into six categories: (1) risk of bias, sensitivity (across studies); (2) consistency; (3) strength (effect magnitude) and precision; (4) biological gradient/dose-response; (5) coherence; and (6) mechanistic evidence related to biological plausibility. In Table III, EPA describes the information most relevant for informing causality during evidence synthesis for all categories other than risk of bias, sensitivity (across studies). In Table IV, EPA notes what information would increase or decrease the strength of evidence for animal or human data streams.

The Main Assessment presents a set of guidelines on how the literature for a particular endpoint and evidence stream should be considered in assigning a particular level of strength of evidence. The framework for strength-of-evidence judgments is provided for each evidence stream, with considerations for human evidence being discussed in Table VI and for animal evidence in Table VII. These tables describe the considerations required to make that overall evidence determination, using the categories robust, moderate, slight, indeterminate, or compelling evidence of no effect. The synthesis framework is applied to the endpoint and evidence stream-specific synthesis judgments.

Finding: In general, the strength-of-evidence categories are appropriate for the human and animal evidence streams and consistent with the state of practice.

EVIDENCE INTEGRATION (STEP 7)

In this step in the IRIS process (see Figure 2-6), the evidence synthesized within the human, animal, and mechanistic streams receives an overall evaluation for the strength of evidence that an agent has caused one or more noncancer or cancer outcomes. This step completes the hazard as-

sessment, and classifies the relationship between exposure and health effect into one of four categories: (1) evidence demonstrates, (2) evidence indicates (likely), (3) evidence suggests (but is insufficient to infer), and (4) evidence inadequate.

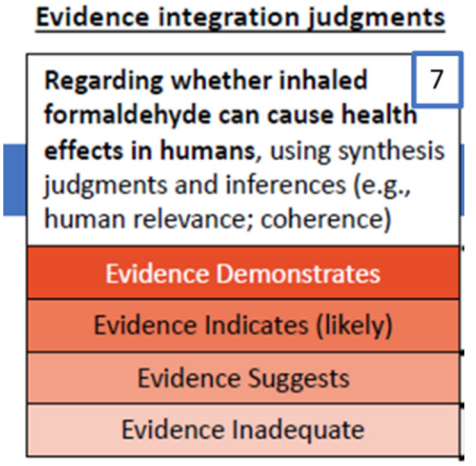

FIGURE 2-6 Aspects of EPA's approach relevant to evidence integration judgments.

State of Practice

The state of practice for evidence integration dates to landmark publications in the 1960s, including the 1964 report of the U.S. Surgeon General's Advisory Committee on Smoking and Health (*Smoking and Health: Report of the Advisory Committee to the Surgeon General*) and a paper by Sir Austin Bradford Hill (1965). Both offered comparable guidelines for the evaluation of strength of evidence for causation (summarized in Box 2-3). Application of these guidelines is not algorithmic, but rather involves the expert judgment of one or more reviewers or a panel. Typically, a narrative review is provided that aligns the evidence with the guidelines, providing insights as to how the evidence fulfills the elements of the guidelines.

BOX 2-3
Guidelines for Causal Inference from the 1964 *Smoking and Health: Report of the Advisory Committee to the Surgeon General* and from Hill (1965)

U.S. Surgeon General Report	Hill
Strength of association	Strength
Consistency of association	Consistency
Specificity of association	Specificity
Temporal relationship of association	Temporality
Coherence of association	Biological gradient
	Coherence
	Experiment

SOURCE: Glass et al., 2013.

Additionally, the state of practice includes a hierarchical classification of the strength of evidence for causation. Four- and five-level schemes are generally employed, as with the Surgeon Generals' reports on smoking and health, IARC's Monographs on carcinogenicity, and EPA's Integrated Science Assessments (ISAs) for the criteria air pollutants (Figure 2-7).

As mentioned, the GRADE framework, developed collaboratively by the GRADE Working Group and adopted by the Cochrane Collaboration for clinical evidence (Guyatt et al., 2008b), is being adapted to decision making in environmental health (Cochrane Collaboration, 2011; R. L. Morgan et al., 2019). In this framework, the quality (termed certainty) of evidence is ranked for each outcome. An overall GRADE certainty rating can be applied to a body of evidence across outcomes, usually by taking the lowest quality of evidence from all the outcomes that are critical to decision making.

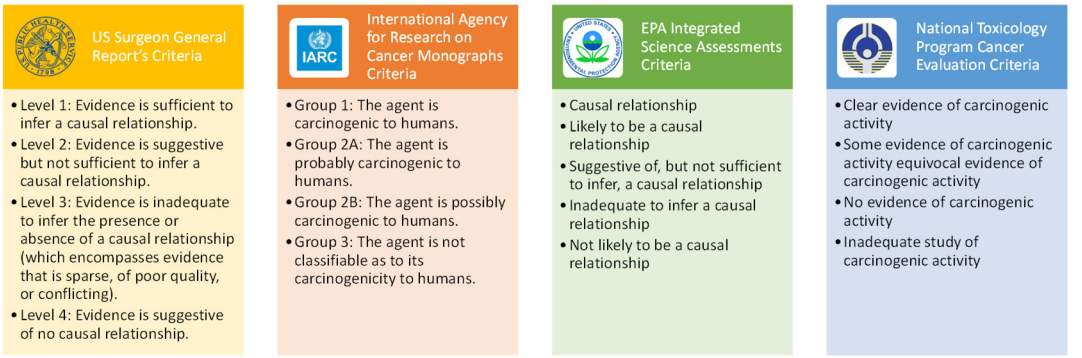

FIGURE 2-7 Hierarchical classifications of the strength of evidence for causation: Surgeon General, International Agency for Research on Cancer, Environmental Protection Agency (EPA) Integrated Science Assessments, and National Toxicology Program.
SOURCE: Warren et al., 2014; EPA, 2015; IARC, 2019; NTP, 2023.

Several other systematic review frameworks (e.g., Navigation Guide, OHAT) are consistent with the GRADE approach and yield hierarchical classifications in line with those given in Box 2-4 (NASEM, 2017). The judgments using GRADE or other frameworks cannot be implemented mechanically; a considerable amount of expert judgment is of necessity required for each decision. Two persons evaluating the same body of evidence might reasonably come to different conclusions about its certainty. What GRADE and other frameworks do provide is a reproducible and transparent framework for grading the certainty of evidence (Mustafa et al., 2013).

The NRC committee that conducted the 2014 review of the IRIS Program recommended that EPA maintain its current process of guided expert judgment but make its application of the process more transparent or adopt a structured process for evaluating evidence and rating recommendations. The 2014 committee also recommended that EPA develop templates for structured narrative justifications of the evidence-integration process and conclusions.

Approach to Evidence Integration in the 2022 Draft Assessment

EPA described evidence integration as a two-step process (Figure III of preamble to the Main Assessment, p. xxxvii). The distinction between the evidence synthesis step (step 6) and the first step of the evidence integration step (step 7) is that in the latter, mechanistic evidence is considered

in making human and animal study judgments. As mentioned above, Tables VI and VII in the preamble provide the criteria for classifying human and animal evidence into five categories, ranging from robust to compelling evidence of no effect. Table V gives examples of how to interpret mechanistic evidence, with columns for mechanistic inferences considered and potential specific applications within the assessment. The description of the approach for considering strength of evidence emphasizes having a set of studies evaluated as having high or medium confidence, along with consideration of the number of studies and coherence of research, providing mechanistic evidence.

The second step of evidence integration brings together the strength of evidence for the human and animal streams and consideration of mechanistic evidence. The description of this step also mentions the coherence of the evidence streams and information on susceptible populations. This second step leads to an overall four-level classification of strength of evidence as (1) demonstrates, (2) indicates, (3) suggests, or is (4) inadequate that a toxicant, in this case inhaled formaldehyde, can cause adverse health effects in humans. Table VIII in the Preamble provides an algorithmic approach to use of the two evidence streams in tandem to perform the four-level classification. Cancer outcomes entail an additional step of using the cancer descriptors from EPA's *Guidelines for Carcinogen Risk Assessment* to translate the four categories to the five levels of those guidelines (Table IX of the preamble, pp. xlvii–xlviii).

For each outcome considered, overall classification of the strength of evidence is supported by a table titled "Evidence Integration Summary for…." The table's two columns are labeled "Evidence judgment" and "Hazard determination," and its three rows are for human evidence, animal evidence, and "other inferences." See, for example, Table 1-4, pp. 1–33, the evidence integration summary for sensory irritation. The "Evidence judgment" column gives the synthesis classification (e.g., robust), and the "Hazard determination" column gives the strength of evidence for the existence of a hazard (e.g., demonstrates). A brief narrative supports the table. The summary and evaluation of the hazard evaluation, Section 1.4, explores susceptibility and compiles the synthesis and hazard identification conclusions from all the evaluated outcomes.

The approach used in the 2022 Draft Assessment for determining the strength of evidence for the existence of a hazard draws on long-standing methods: summarizing evidence within different streams and applying long-used guidelines for evaluating evidence for a causal association. Transparent application of this approach involves carrying out the earlier steps of evidence identification and evaluation with a documented approach and synthesizing and integrating evidence with a specified and replicable protocol.

Finding: In general, the IRIS Program's approach to evidence integration is appropriate and grounded in methods used by EPA and many other entities for reaching causal conclusions. Expert judgment is involved in this phase of the assessment, and the IRIS Program appears to draw on appropriate multidisciplinary groups to evaluate the evidence.

Finding: The committee identified aspects of the process for further consideration and reformulation. First, the IRIS Program's schema blurs the distinction between evidence synthesis and integration, combining them into a single step, as exemplified by the summary tables for each health outcome that include both "evidence judgment" and "hazard determination." (e.g., Table 1-4). A clear distinction between synthesis and assessment of the overall strength of evidence would be preferable conceptually and more consistent with the state of practice.

Recommendation 2.5 (Tier 2):

- **The 2022 Draft Assessment should be edited to more sharply demarcate the synthesis and the integration of evidence discussions.**

- **EPA should expand the narrative descriptions of the evidence integration step, or should follow published methodology while providing detailed explanation of any adaptations.**

Given the reliance on expert judgment for both the evidence synthesis and evidence integration aspects of hazard identification, expanded narrative descriptions would be useful for documenting the rationale for the classifications made. The tables are useful but terse, as is the accompanying text.

The committee notes that the terminology adopted for the four-level characterization of the strength of evidence for the existence of a hazard includes descriptors that are not inherently hierarchical. The terms used in the 2022 Draft Assessment—demonstrates, indicates, suggests, or is inadequate—are aligned with the IRIS Handbook, but are not obviously hierarchical, nor are they consistent with terms used elsewhere within EPA, (e.g., in the Integrated Science Assessments) or outside of EPA (e.g., the reports of the Surgeon Generals' on smoking and health). The terms also are used inappropriately, as in the inherent proposition that it is the evidence itself that "demonstrates" or "indicates." The use of these terms represents an unnecessary source of inconsistency with the state of practice.

Use of Mechanistic Evidence

Toxicological assessments have typically relied on evidence from human observational (epidemiological) or experimental and animal studies. However, mechanistic data have been used to modify or strengthen conclusions based on human or animal studies for several decades. In 1982, for instance, the Preamble to the IARC Monographs introduced the possibility of "upgrading" overall classifications based on results from short-term genotoxicity assays, and in 1991, an IARC expert group proposed principles and procedures for mechanistic "upgrades" and "downgrades" based on the extent of mechanistic understanding. Current evidence integration frameworks, including that of IARC (2019), include approaches for drawing hazard identification conclusions without evidence from human observational or experimental animal evidence. Mechanistic evidence has increased in volume and complexity over the past several decades, and is the predominant form of evidence for some agents. This shift in the mix of available evidence to support hazard conclusions has been supported by advances in molecular biology, automation, and ultrasensitive analytical methods, resulting in a large influx of in vitro and computational studies that provide insights into mechanisms of toxic response. Indeed, the number of in vitro and computational studies is growing exponentially, supported by the many agency roadmaps for transitioning away from animal-based toxicology studies, including EPA's own New Approach Methods (NAM) work plan (EPA, 2021). Yet despite recommendations from the National Academies that date back to 2007 (NRC, 2007, 2009; NASEM, 2017), there are few examples of the use of EPA's NAM data to inform risk assessment decision making. Recently, a committee of the National Academies urged the EPA to create a framework for assessing and gaining trust in new approach methods, recommending that these methods be transitioned from laboratory evaluation to inclusion in systematic-review-based risk assessments (NASEM, 2023).

EPA's inclusion of mechanistic evidence as a separate evidence stream is appropriate, but EPA faced substantial challenges in considering this evidence, especially in the context of systematic review. First, generally accepted frameworks for systematically identifying, screening, and evaluating mechanistic data have only recently been advanced, tested, and formalized (Smith et al., 2016). Second, the available studies are voluminous and variable in quality. As of this writing, the risk-of-bias and study quality tools, developed and validated in intervention research and being adapted and validated for observational and animal toxicological studies, are in their infancy for

application to mechanistic evidence. This presented a particular challenge in 2011, when work on the formaldehyde assessment started. EPA has pioneered the use of mechanistic evidence and the committee evaluated the use of this evidence in the formaldehyde assessment with these challenges in mind.

In the 2022 Draft Assessment, EPA classifies mechanistic studies as in vitro or as results of modeling, and assesses them as a separate evidence stream (e.g., Section F.2.4, "Literature Inventory"). The literature search approach was developed as outlined in the health effect-specific population, exposure, comparator, and outcome (PECO) for the pre-2016 literature searches (Appendix A, Section A.5). EPA used the systematic evidence map methodology to identify the most recent relevant publications that might alter conclusions about hazards or toxicity values— that is, studies it considered "impactful"— for literature published from 2016 to 2021. Studies identified in the systematic evidence map as possibly impactful were incorporated into the updated 2022 Draft Assessment. EPA stated that it used a literature search approach identical to that outlined in the health effect–specific PECOs for the earlier searches (Appendix A, Section A.5). The searches were conducted in the same databases with the exception of ToxNet, which ceased to exist in 2019. For the 2022 Draft Assessment, EPA used a process that relied on information gathered from the literature inventory and expert judgment by two reviewers. The new term "impactfulness" was introduced in the 2022 Draft Assessment and defined as follows:

> More apical endpoints and those most directly related to the mechanistic uncertainties identified in the 2017 draft as most relevant to drawing hazard or dose-response judgments were considered more impactful. The specifics of this consideration vary depending on the health outcome(s) of interest. In some cases, this relevance determination relates to the potential human relevance of the endpoints, while in others this relates to an ability to infer adversity.

Finding: Overall, the committee found that EPA has been thorough and transparent in identifying the scientific literature with regard to mechanistic evidence." However, the definition of "impactfulness" and how this concept was applied are not well described. Similarly, the term "other inferences" is used in the sections on integration of cancer evidence, but the term is not explained.

Recommendation 2.6 (Tier 2): To increase the transparency of the evaluation of mechanistic data, EPA should clarify key terms (e.g., "impactfulness," "other inferences") and their application to specific studies. "Impactfulness" can be defined (in Table F-12 and elsewhere), and "other inferences" can be explained in discussing the approach to evidence integration in the "Preface on Assessment Methods and Organization."

Finding on Evidence Integration

Finding: Evidence integration is the critical last step in hazard identification, and transparency is essential, requiring a sufficiently comprehensive narrative documenting the decision-making process. In completing its determination of hazard identification in the 2022 Draft Assessment, EPA drew on long-standing approaches for inferring causation, including the Bradford Hill considerations, first enumerated in a 1965 publication (Hill, 1965). Nonetheless, the 2022 Draft Assessment deviates from those long-established approaches in several respects, including (1) blurring of the boundary between evidence synthesis and integration, and (2) the choice of terminology used to describe the strata in the four-level schema for

classifying the strength of evidence. Additionally, in some instances the narratives concerning the evidence integration step are too terse to explain fully why EPA came to its confidence conclusions.

DOSE-RESPONSE ASSESSMENT (STEP 8)

The final step in EPA's process is the selection of studies for derivation of RfCs and cancer unit risk values. This component of EPA's process is depicted in Figure 2-8.

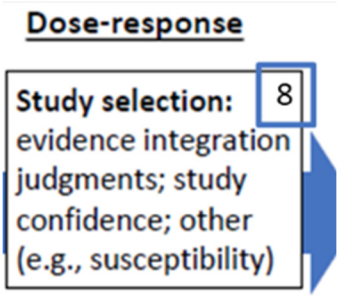

FIGURE 2-8 Dose-response assessment in EPA's systematic review approach.

State of Practice

Dose-response analysis and derivation of RfCs—estimates of the amount of a substance in the air that a person can inhale daily over a lifetime without experiencing an appreciable risk of adverse health effects—are typically conducted for high-quality studies in which the exposure is associated with the outcome. Study selection is critical for RfC estimation, and the rationale for selection should be described clearly within the assessment. Then modeling can be used to estimate an effective dose (ED) for cancer effects or a benchmark dose (BMD) for noncancer effects. If the effects are nonmutagenic, a BMD approach can be applied for both cancer and noncancer effects (EPA, 2005a). When modeling is not possible because of a lack of data, a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) is used. Next, a unit risk for cancer effects or an RfC is calculated. This is often done by applying uncertainty factors to the BMD or the benchmark dose lower bound (BMDL) or the NOAEL or LOAEL. While the NOAEL–LOAEL approach is still used, the BMD approach is preferred because it uses dose-response information more fully and reduces uncertainty (NRC, 2014).

Approach to Dose-Response Assessment in the 2022 Draft Assessment

EPA used its causal judgments to determine when to complete a dose-response assessment. For each noncancer outcome for which EPA judged that the "evidence demonstrates," or "evidence indicates," a dose-response assessment was conducted. Similarly, for each cancer outcome for which the weight of evidence led to a determination of "carcinogenic" or "likely to be carcinogenic," a dose-response assessment was carried out. Then a study was selected for dose-response and RfC derivation. The approach to dose-response analysis differed for noncancer and cancer outcomes, according to methods that are fully described in EPA guidance documents.

EPA presents the considerations for study inclusion for dose-response assessment in the preface of the Main Assessment, Table X. The categories are overall confidence conclusion, study confidence, population, and exposure information. Each category includes one or more considerations important for study selection. Additional considerations for study selection are described in the preface and in Section 2.1. These considerations include the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels analyzed, as well as a requirement that the study be of medium or high quality. To determine whether EPA's choice of studies to use in deriving the RfC had an impact, the committee conducted a case study comparing RfCs derived from Hanrahan et al. (1984) and Liu et al. (1991) (Box 2-5).

BOX 2-5
Point-of-Departure Analysis Using Two Studies: A Case Study

The committee replicated the estimation of the candidate reference concentration for sensory irritation from the Hanrahan et al. (1984) study and also used their method to estimate a candidate value based on the study by Liu et al. (1991) (see Appendix C). One intent of this case study was to assess how considering the Liu et al. study along with the Hanrahan et al. study would affect the candidate reference concentration for sensory irritation, in accordance with the recommendation of the 2014 National Research Council (NRC) report to use data from multiple studies when possible. In the case study, the committee fit models to data derived from the two reports (see Appendix C). For that purpose, assumptions were required that are documented in the case study, given the lack of access to the primary data.

The committee was able to replicate EPA's methods. Estimates from the committee's models from the Hanrahan et al. study were close to those in the 2022 Draft Assessment. Benchmark concentration (BMC_{10}) estimates based on the combined data from the two studies were somewhat lower—by about 20 percent—than those based on the Hanrahan et al. study alone. The committee notes the complementarity of the two studies and the broadening of the range of exposures considered in the combined analysis. Based on this case study, the committee developed Recommendations 2.7 and 2.8 (see below). More detail on this point-of-departure case study is provided in Appendix D.

Finding: The committee found EPA's considerations for study inclusion to be reasonable, although the discussion of those considerations in multiple places in the documents made it more difficult to determine what the considerations were and how they were applied.

Finding: Although EPA provides criteria for study inclusion in the dose-response assessment, it does not include any discussion of how these criteria were applied to the specific studies chosen for dose-response. Using the Hanrahan et al. (1984) study as a test case, there are inconsistencies between the characteristics of the study and EPA's criteria for studies that would be selected for dose-response analysis.

Recommendation 2.7 (Tier 2): EPA should consider using information from studies that are complementary to each other to derive benchmark concentrations for outcomes of interest (see also Appendix D). For example, multiple studies can be complementary by widening the exposure scale, broadening the age groups, and including vulnerable or susceptible groups.

Recommendation 2.8 (Tier 2): Given that EPA has requested additional information from some study authors, the authors of the Liu et al. (1991) study could be approached for additional information that would help EPA reconstruct an overall dose-response graph (see also Appendix D).

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3
Toxicokinetics

This chapter provides a brief overview of EPA's evaluation of the toxicokinetics of inhaled formaldehyde in humans and other mammals. This is followed by the committee's analysis of the use of formaldehyde toxicokinetic data, pharmacokinetic models, and biologically based dose-response (BBDR) models in the 2022 Draft Assessment (EPA, 2022). The committee's analysis focuses on the toxicokinetic evidence and modeling approaches presented in the 2022 Draft Assessment that were used to support EPA's key conclusions and derivation of toxicity values. This chapter focuses on inhalation since this route of exposure is the primary focus of the 2022 Draft Assessment.

OVERVIEW OF INHALED FORMALDEHYDE TOXICOKINETICS IN THE 2022 DRAFT ASSESSMENT

The 2022 Draft Assessment provides an extensive evaluation of the toxicokinetics of formaldehyde (Section 1.2.4 and Appendix A, Section A.2). Formaldehyde is a naturally occurring, volatile, water soluble, one-carbon aldehyde. Upon inhalation, formaldehyde rapidly undergoes hydration on contact with the moist mucus layer found in the respiratory tract. Hydration of formaldehyde in water or following addition of alcohol yields methanediol (formaldehyde hydrate), or hemiacetals and acetals, respectively. Once in the respiratory tract epithelium, formaldehyde can undergo metabolism, including enzymatic reactions with the respiratory tissue and nonenzymatic reactions with glutathione and macromolecules, including proteins and DNA.

DISTRIBUTION OF INHALED FORMALDEHYDE

The 2022 Draft Assessment considers factors that influence the distribution of inhaled formaldehyde at the point of entry in the respiratory tract. EPA also reviewed available dosimetry models evaluating the initial delivery of formaldehyde to the upper respiratory tract (URT). A detailed description of dosimetry modeling efforts in humans, monkeys, and rats is provided in Appendix B, Section B.2.2 of the 2022 Draft Assessment.

Factors considered by EPA that could influence the distribution of inhaled formaldehyde include species differences in airway anatomy and physiology, especially the roles of nasal turbinate structure and nasal breathing in rodents versus oronasal breathing in humans. At low inhaled concentrations (<20 ppb), absorption of formaldehyde is nearly complete in the human URT, with limited amounts of formaldehyde reaching the lung. Formaldehyde demonstrates a perpendicular concentration gradient within the epithelium lining the respiratory tract (Overton, 2001). Highest concentrations are anticipated to occur near the airway lumen. As formaldehyde diffuses through the epithelium, a portion of the initially absorbed formaldehyde is lost to hydration, local tissue metabolism, and chemical reactions between formaldehyde and macromolecules. Other factors can also influence the toxicokinetics of formaldehyde. For example, reflex bradypnea occurs in rodents following formaldehyde inhalation, resulting in reduced minute volume (Chang and Barrow, 1984; Chang et al., 1981). This physiologic response to inhaled irritants does not occur in humans or nonhuman primates.

METABOLISM, BINDING, AND REMOVAL OF INHALED FORMALDEHYDE

The 2022 Draft Assessment provides a discussion of the fate of formaldehyde following inhalation. Formaldehyde is metabolized in the URT by glutathione-dependent class III alcohol dehydrogenase (ADH3) and to a lesser extent by S-formyl-glutathione dehydrogenase to formic acid. Formaldehyde can bind noncovalently to glutathione, tetrahydrofolate, or albumin in nasal mucus. It can also bind covalently to macromolecules, forming DNA–protein crosslinks (DPCs); DNA–DNA crosslinks (DDCs); hydroxymethyl–DNA (hm-DNA) adducts; and protein adducts, including N6-formyllysine (Edrissi et al., 2013a,b). Repeated (28-day) exposure of rats to lower formaldehyde concentrations (up to 300 ppb) did not result in formation of either DNA monoadducts (N^2-HOMe-dG) or DPCs in the URT or bone marrow (Leng et al. 2019). At higher exposure concentrations, a concentration-dependent increase in DPC formation is observed in the nasal cavity of animals following formaldehyde inhalation.

A key question addressed by EPA concerns the systemic delivery of inhaled formaldehyde to distant sites. Blood formaldehyde levels of approximately 0.1 mM remain unaltered following formaldehyde inhalation, suggesting that inhaled formaldehyde is not significantly absorbed into blood (Casanova et al.,1988; Heck et al., 1985; Kleinnijenhuis et al., 2013). Because formaldehyde is present in tissues endogenously, EPA also considered how inhaled (exogenous) formaldehyde and endogenous formaldehyde could contribute to adduct formation. Studies (Lu et al., 2010a,b, 2011; Moeller et al., 2011; Yu et al., 2015; Lai et al., 2016) distinguishing DNA monoadducts (e.g., N^2-HOMe-dG) or DPCs formed from endogenous or exogenous formaldehyde were used to support EPA's conclusion that exogenous formaldehyde is not distributed to the bone marrow or other distant tissues.

> Finding: EPA concluded that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to systemic sites; thus, inhaled formaldehyde is not directly interacting with tissues distal to the portal of entry to elicit effects. EPA's conclusions regarding systemic delivery of inhaled formaldehyde are based on its expert judgment, with the support of available scientific evidence.

> Finding: Despite the lack of evidence regarding systemic delivery of formaldehyde to distant sites, the biological basis for observed systemic effects (described in Chapters 4 and 5) remains unclear. Additional research is needed to address this apparent discrepancy.

DOSIMETRY MODELS

Numerous mathematical models of inhalation dosimetry have been developed for formaldehyde and were examined by EPA for applicability. The models were developed to recapitulate key toxicokinetic observations from experimental animal studies. Several physiologically based pharmacokinetic (PBPK) models describe the disposition of inhaled formaldehyde reacting with upper-respiratory-tract tissue, resulting in the formation (and repair) of DPCs (Conolly et al., 2000; Subramaniam et al., 2008; Klein et al., 2011). Several computational fluid dynamics (CFD) airflow and material transport models account for species differences in airway anatomy and physiology (Hubal et al., 1997; Kimbell et al., 2001). Some CFD models account for the influence of endogenous formaldehyde on the toxicokinetics of inhaled formaldehyde (Schroeter et al., 2014; Campbell et al., 2020). These models predict that the uptake of low concentrations of formaldehyde will be reduced by the presence of endogenous formaldehyde. Other CFD models are coupled with time-dependent PBPK models that describe boundary conditions at the air–tissue interface (Corley et

al., 2015). These boundary conditions account for tissue reactions, first-order and saturable metabolism, and other factors that influence formaldehyde toxicokinetics.

Collectively, EPA used these dosimetry models to show that inhaled formaldehyde is not deposited uniformly throughout the nose; rather, some regions in the nasal cavity receive a higher delivery of formaldehyde compared with other nasal regions. Sites within the nasal epithelium with higher formaldehyde flux to the tissues are also areas where DPCs form and tumors are most likely to arise. Models predict that localized deliveries of formaldehyde to portions of the human nose are comparable to those seen in rats exposed at similar concentrations (Kimbell et al., 2001). The available models suggest further that total nasal deposition is lower in humans or nonhuman primates than in rats, leading to greater penetration of inhaled formaldehyde to the lower respiratory tract.

BBDR models have also been developed for formaldehyde (Conolly et al., 2003, 2004) and were extensively evaluated by EPA. These models incorporate dosimetric and mechanistic data into a single computational model. They have two main subunits: species-specific CFD models to describe formaldehyde delivery in the respiratory tract, and a two-stage clonal growth model for formaldehyde carcinogenesis. The human version of the model (Conolly et al., 2004) incorporates a typical path model (Overton et al., 2001) of the lower respiratory tract that allows for the prediction of formaldehyde delivery to the entire human respiratory tract. A detailed National Research Council (NRC) analysis of the use of these models by EPA is available in an earlier formaldehyde assessment (NRC, 2011).

EPA'S USE OF TOXICOKINETIC DATA AND DOSIMETRY MODELS

The committee first examined EPA's broad use of toxicokinetic data in the 2022 Draft Assessment. The committee also considered whether toxicokinetic data or toxicokinetic models influenced EPA's derivation of either its evidence integration judgments for noncancer health effects and the reference concentration (RfC), or its estimation of inhalation unit risk (IUR) for cancer incidence.

Findings: The committee found that EPA used toxicokinetic data as follows:

- EPA used these data to support its assumption that "inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to systemic sites. Thus, EPA assumed that inhaled formaldehyde does not directly interact with tissues distal to the portal of entry to elicit effects. EPA's conclusions regarding systemic delivery of inhaled formaldehyde are based on its expert judgment, with the support of the available scientific evidence.
- EPA concluded that studies examining potential associations between levels of formaldehyde or formaldehyde by-products (e.g., formate) measured in distal tissues and health outcomes were not relevant to inhaled formaldehyde. This conclusion is consistent with EPA's state-of-practice methods and supported by the available scientific evidence.
- EPA concluded that formaldehyde toxicokinetics show significant route-to-route difference (e.g., inhalation versus oral). With few exceptions (e.g., genotoxicity), EPA focused solely on inhalation studies. The committee supports this decision, and found it to be consistent with EPA's state-of-practice methods.
- EPA used toxicokinetic data as a primary consideration informing causality during its evidence synthesis step, as "an explanation for any observed differences in responses

across route of exposure, other aspects of exposure, species, or life stages." Toxicokinetic data were used to examine consistency across studies and to evaluate biological gradient/dose-response data. Overall, the committee found that the portions of the 2022 Draft Assessment describing the toxicokinetics of formaldehyde and associated computational models are well organized and extensive. The 2022 Draft Assessment accurately reflects current understanding of the toxicokinetics of inhaled formaldehyde. The literature review in the 2022 Draft Assessment appears to be up to date and includes relevant studies published as of the assessment's release date. The use of these data in the synthesis step is consistent with EPA's state-of-practice methods.

EPA used the available models to derive the candidate RfCs (cRfCs) for respiratory tract pathology seen in animals. Dosimetry modeling was used to estimate a human equivalent concentration and account for toxicokinetic differences between animals and humans. These cRfCs were applied to lesion data from two studies (Battelle Columbus Laboratories, 1982; Kerns et al., 1983). In its dosimetry modeling efforts, EPA initially used a CFD model (Kimbell et al., 2001) to determine average flux values in the anterior region of the rat nasal cavity that corresponded to the rat benchmark concentration lower bound (BMCL) derived from the incidence of squamous metaplasia seen in a study. Human CFD models were then used to estimate the exposure concentration at which any region in the human nose (see Appendix B, Section B.1.3) is exposed to this same level of formaldehyde flux using an inspiratory rate of 15 L/min. EPA also applied a second CFD model (Schroeter et al., 2014) to estimate formaldehyde flux at different sites (e.g., squamous epithelium) in the rat nasal cavity. Unlike the Kimbell et al. (2001) model, this revised CFD model considers endogenous formaldehyde production in nasal tissues. EPA estimated the extent to which the results change if flux estimates from Schroeter et al. (2014) are used; See, for example, EPA Summary Table 2-5, "Summary of Derivation of the Point of Departure (POD) for Squamous Metaplasia Based on Observations in F344 Rats," from Kerns et al. (1983).

Finding: The use of these models is appropriate and consistent with EPA's state-of-practice methods.

Recommendation 3.1 (Tier 2): To enhance transparency, the summary tables (i.e., Tables 24, 43, and 44) should explicitly identify the models used to derive flux values. Table 44 should clearly indicate whether the BBDR models used here are equivalent to Models 1 and 2 identified in Table 43 and the text. Table 46 should indicate which flux model was used.

EPA also used an alternative method to derive cRfCs for respiratory tract pathology seen in animals (see Chapter 4). This alternative method relied on an assumption of concentration equivalence and was applied to lesion data from Wistar rats (Woutersen et al., 1989). EPA used it because CFD models have not been developed for this strain of rat. In this method, allometric principles are applied. EPA applied additional duration adjustments (6/24) × (5/7) for continuous daily exposure to generate the final human equivalent concentration (HEC). EPA provides extensive discussion of alternative models (e.g., Corley et al., 2015) it considered, and provides its rationale for not using these alternative models in the assessment.

EPA used the available models to derive cRfCs for nasal cancers seen in animals (see Chapter 5). These cRfCs were estimated based on points of departure (PODs) obtained from a pathology study of hyperplasia, labeling studies of proliferating cells, and BBDR modeling results using the Conolly et al. (2003) model (see Section 2.2.1 of the 2022 Draft Assessment). URT cancer risk was extrapolated from the incidence of nasal squamous cell carcinoma in experimental studies

performed on F344 rats. EPA evaluated and compared results from several methods used to model these data, including a BBDR model, statistical time-to-tumor models, and statistical benchmark dose modeling using data on DPCs and formaldehyde flux as dose metrics. Additional analyses and comparisons considered the impact of endogenous formaldehyde concentration on dosimetric estimates. EPA considered these efforts to be secondary or supportive calculations since human data were available. EPA evaluated the BBDR model that includes a CFD component (Conolly et al., 2003) for extrapolation of the rat nasal cancer risk to human exposure scenarios. EPA's analysis of this model led to the conclusion that the BBDR model for humans (Conolly et al., 2004) was not robust at any formaldehyde exposure concentration. EPA was also concerned that this model presumes that formaldehyde-induced mutagenicity, modeled as proportional to DPC concentration, is not relevant to formaldehyde's carcinogenicity. EPA used the rat BBDR model (Conolly et al., 2003) to derive multiple PODs and corresponding HECs, but not to extrapolate to human exposure scenarios. DPC tissue concentrations used in the rat BBDR model (Conolly et al., 2003) were calculated using a PBPK model (Conolly et al., 2000). A second set of CFD and PBPK models (Schlosser et al., 2003) were used to predict formaldehyde flux and DPC concentrations in the rat and human nasal cavities. These alternative model estimates are provided in the Assessment Overview of the 2022 Draft Assessment (Table 2-22, "Benchmark Concentrations and Human Equivalents Using Formaldehyde Flux and DPC as Dose Metrics"). As mentioned earlier for squamous metaplasia of the nasal cavity, EPA employed a similar method using CFD models (Kimbell et al., 2001; Schroeter et al., 2014) to predict formaldehyde flux to the rostral portion of the rat nasal cavity (see EPA Summary Tables 2-21 and 2-22).

Finding: The 2022 Draft Assessment generally provides a thorough discussion of the strengths and weaknesses of the available models, including an extensive discussion of how EPA used them in the assessment.

Recommendation 3.2 (Tier 2): To increase transparency, EPA should provide additional clarification regarding its decision not to use the BBDR model to extrapolate rat nasal carcinogenicity to humans. Criteria used by EPA to determine whether the models would be adequately robust for this purpose are not readily available in the 2022 Draft Assessment. Likewise, EPA should provide additional support for its decision not to use the BBDR model (Conolly et al., 2004) for this extrapolation because of the model's conclusion that formaldehyde-induced mutagenicity, modeled as proportional to DPC concentration, is not relevant to formaldehyde's carcinogenicity.

Finding: Documentation of the dosimetry methods used is variable in the 2022 Draft Assessment, especially with regard to some summary tables (e.g., Table 2-27). Discussion of the comparison of and basis for unit risk estimates for nasopharyngeal cancer in humans and nasal squamous cell carcinomas in rats mentions the use of CFD and PBPK models without identifying the specific models that were used.

Recommendation 3.3 (Tier 2): To increase transparency, EPA should address these shortcomings by updating tables and text to better document its dosimetry methods.

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4
Noncancer Health Effects

EPA assessed multiple noncancer health effects associated with formaldehyde exposure. These effects can be characterized as either portal-of-entry or systemic effects: *portal-of-entry* effects are those that arise from direct interaction of inhaled or ingested formaldehyde with the affected cells or tissues, while *systemic* effects are those that occur beyond tissues or cells at the portal of entry.

This chapter addresses EPA's assessment of the selected noncancer health effects of formaldehyde. In line with its overall charge, the committee focused its review on whether the 2022 Draft Assessment (EPA, 2022) adequately and transparently evaluates the available studies and data, and uses appropriate methods in reaching hazard identification conclusions and dose-response analyses that are supported by the scientific evidence. The committee focused on health outcomes that led to derivation of a candidate reference concentration (cRfC).

The sections that follow address the following outcomes: sensory irritation, pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity. The committee's review encompassed consideration of whether EPA identified the appropriate studies; whether, according to its state-of-practice methods, it conducted the hazard identification appropriately; and whether suitable studies were advanced for calculation of the cRfC for each outcome. Each section provides a brief introduction to the health effect, steps used by EPA to identify the relevant literature, outcome specific criteria used to evaluate studies, an overview of EPA's synthesis and integration judgments, EPA's overall conclusions, and whether EPA used appropriate dose-response evaluations to derive cRfCs. A brief overview of the methods used by EPA to identify points of departure (PODs) and cRfCs is also provided. To complete this task, the committee broadly reviewed relevant portions of the Main Assessment, associated Appendices, and the Assessment Overview. Table 4-1 documents the specific materials considered for each health outcome.

Tier 2 and 3 recommendations specific to each outcome are provided in the sections below. The committee's discussion of cross-cutting issues related to the methods used by EPA for its assessment of these outcomes is presented in Chapter 2. Although the committee was not charged with providing a comprehensive list, Appendix E gives specific examples of these issues to illustrate the committee's recommendation and to serve as a guide to EPA's revision. Thus, in implementing the Tier 2 and 3 recommendations provided for each outcome, EPA should take account of the additional relevant findings, recommendations, and detailed issues included in Chapter 2 (for general methodological issues), in the section below on EPA's approach to dose-response, and in Appendix E.

NONCANCER PORTAL-OF-ENTRY EFFECTS

Portal-of-entry effects occur following *direct* interaction of inhaled formaldehyde with the respiratory tract or other tissues. Noncancer portal-of-entry effects include sensory irritation, decreased pulmonary function, respiratory tract pathology, and allergies and asthma. Although it is a portal-of-entry effect, the committee's discussion concerning asthma is included in the evaluation of systemic effects, reflecting the broader inflammatory consequences of asthma.

TABLE 4-1 Documents Reviewed by the Committee during Its Evaluation of the EPA's Assessment of Noncancer Health Outcomes in the 2022 Draft Assessment (EPA, 2022)

Noncancer Health Effect	Main Assessment	Appendices	Assessment Overview
Sensory irritation	Section 1.2.1 (pp. 1–11 to 1–34), Section 1.4.2 (pp. 1–555), Section 2 (pp. 2–1 to 2–10; 2–25 to 2–42)	Section A.5.1 (pp. A-231 to A-261), A.5.2 (pp. A-261 to A-298) Section B.1.1 (pp. B-1 to B-11)	Section 3.1 (pp. 29–38) Section 3.7 (pp. 89–95)
Pulmonary function	Section 1.2.2 (pp. 1–93 to 1–126)	Section A.5.3 (pp. A-313 to A-351)	Section 3.2 (pp. 50–59)
Respiratory pathology	Section 1.2.4 (pp. 1–148 to 1–195	A.5.5 (pp. A-388 to A-427)	Section 3.4 (pp. 64–75)
Allergy and asthma	Section 1.2.3 (pp. 1–77 to 1–149)	A5.4 (pp. A-336 to A-388) A5.6 (various pages)	Section 3.3 (pp. 47–64)
Reproductive and developmental toxicity	Section 1.3.2 (pp. 1–382 to 1–433)	A.5.8 (pp. A-630 to A-665)	Section 3.6 (pp. 77–88)
Nervous system toxicity	Section 1.3.1 (pp. 1–341 to 1–382)	Section A.5.7 (pp. A-588 to A-629)	Section 3.5 (pp. 75–77)

SENSORY IRRITATION

Sensory effects of formaldehyde, which has a strong odor, have been studied for several decades, although only a handful of studies have been published more recently. Sensory irritation encompasses eye, nose, and throat symptoms, and evidence concerning this outcome is based on experimental and observational studies in humans. According to EPA, sensory irritation in animals following formaldehyde inhalation is well established. The primary mechanism involved in sensory irritation is stimulation of the branch of the trigeminal nerve present in the respiratory mucosa. Oxidative stress at low formaldehyde concentrations may also contribute to sensory irritation. Using a systematic approach to identify and evaluate relevant studies, EPA identified three studies for POD analysis to derive cRfCs, and chose one study, representing an organ- or system-specific cRfC, for consideration of the overall formaldehyde RfC.

Literature Identification

In the Main Assessment and Appendices, EPA documents the steps it followed to formulate a population, exposure, comparator, and outcome (PECO) statement; develop inclusion and exclusion criteria; and conduct its literature search. EPA updated its literature searches annually through September 2016, after which systematic evidence mapping was used to search studies through 2021. For its literature search, EPA used four databases, and curated reference lists in published reviews and other national or international health assessments of formaldehyde (see Appendix A, Section A-231), although the flow diagram shows that only two databases were used (Figures A-22 and A-263). Search terms included *formaldehyde*, *paraformaldehyde*, *formalin*, *irritation*, *irritant*, and *irritants* (Table A-31).

Recommendation 4.1 (Tier 2): To maximize transparency and facilitate replication, EPA should clarify the Medical Subject Headings (MeSH) terms used, list and justify any MeSH terms that were excluded (e.g., eye, ear, nose, or skin), provide the list of

national and international reviews and assessments used to identify additional references, and provide more specific links to the Health & Environmental Research Online (HERO) database where the screening decisions are documented (see Appendix A, Section A-232, line 4).

Finding: EPA excluded outdoor exposure studies (Table A-32) without providing adequate justification. This exclusion was broadly applied to multiple health outcomes (e.g., sensory irritation [see Table A-32], pulmonary function [see Table A-42], and nervous system effects [see Table A-83]). In the Main Assessment (p. xxv) EPA states:

Publications were typically excluded if they contained no information about formaldehyde exposure or were descriptions of analytic methods using formaldehyde. Ambient levels of formaldehyde in outdoor air are significantly lower than those measured in the indoor air of workplaces or residences, and the exposure range was narrow in many epidemiological studies of ambient exposure (<0.005 mg/m^3) limiting their sensitivity to find any associations with health outcomes even if they existed.

Excluding outdoor studies from the 2022 Draft Assessment may skew the evidence pool in the direction of higher exposure studies relative to the levels commonly experienced by the general population. The committee also found unconvincing EPA's argument that studies with lower exposure levels may have a limited ability to detect associations between formaldehyde exposure and health effects.

The committee notes further that the assertion that outdoor levels of formaldehyde are universally below 0.005 mg/m^3 may not correctly represent true population exposures for all geographies and time periods. For example, the Hanrahan et al. (1984) study, which is a pivotal sensory irritation study for this assessment, reported mean outdoor levels of 0.04 ppm (0.05 mg/m^3) with high variation (standard deviation [SD] = 0.03 ppm). The committee noted that additional studies reported ambient levels at or above 0.005 mg/m^3, as summarized in Table 4-2.

Recommendation 4.2 (Tier 2): EPA should include the body of evidence from outdoor exposure studies at the preliminary stage to derive a more holistic and objective assessment of the scientific literature.

Finding: In the Main Assessment (Figure 2-3), the box representing typical formaldehyde levels depicts a sharp delineation between lower outdoor and higher indoor levels. In real-world exposure scenarios, that is unlikely to be the case; rather, a continuum of concentrations with overlapping outdoor and indoor levels is a more likely scenario (Table 4-2). Figure 2-3 could show representative ranges of outdoor and indoor formaldehyde concentrations levels more accurately (see Appendix E).

Study Evaluation

Outcome-specific criteria used to evaluate human studies of formaldehyde-induced sensory irritation included participant selection; information bias; potential for confounding; statistical analysis; and other considerations, such as exposure levels, contrast, duration of follow-up, and sensitivity of outcome assessment (Appendix A, Section A-233). Figure A-22 states that a total of 38 observational studies and 20 randomized controlled trials on humans were included for sensory irritation. Selection bias receives some attention in the evaluation, given the cross-sectional nature of some of the key observational studies.

TABLE 4-2 Formaldehyde Levels in Outdoor Air Reported in Selected Studies

Author (Year)	Study Year	Country	Originally Reported Levels	Reported Levels Converted to mg/m^3
Dziarzhynskaya et al. (2021)	2009–2018	Minsk, Belarus (city limits)	Max: 12.3 µg/m^3 Mean: 3 µg/m^3	Max: 0.123 Mean: 0.003
Chang et al. (2017)	2006–2008	Seoul, S Korea (city limits)	Mean: 81.57 (SD, 51.88) µg/m^3 GM: 67.36 µg/m^3[a]	Mean: 0.082 (SD, 0.052) GM: 0.067[a]
Delfino et al. (2003)	1999–2000	Los Angeles, CA, USA	Min: 4.27 ppb Max: 14.02 ppb Mean: 7.21 ppb	Min: 0.005 Max: 0.018 Mean: 0.009
Li et al. (2014)	2012	Ziyang, China (suburb)	Min: 0.19 ppb Max: 16.30 ppb Mean: 2.98 (SD, 1.65) ppb	Min: 0.0002 Max: 0.021 Mean: 0.004 (SD, 0.002)
Li et al. (2010)	2008	Beijing, China (near Olympic Stadium)	Min: 1.33 ppb Max: 19.54 ppb Lowest median (of the 4 measurement periods): 5.14	Min: 0.002 Max: 0.025 Lowest median: 0.007
Hak et al. (2005)	2002	Milan, Italy (city outskirts)	30-minute means across instruments ranged between 1 and 13 ppb	Range of means between 0.001 and 0.017
Kleindienst et al. (1988)[b]	1986	North Carolina, USA (semirural)	Min: 1 ppb Max: 10 ppb	Min: 0.001 Max: 0.013
Lawson et al. (1990)	1986	Glendora, CA, USA (urban)	Min: 6 ppb Max: 20 ppb	Min: 0.008 Max: 0.025
Grossmann et al. (2003)	1998	50 km from Berlin, Germany (rural)	Min: 0 ppb Max: 7.7 ppb	Min: 0 Max: 0.01

NOTES:
[a] GM = geometric mean.
[b] See also Table 6 of this article for additional studies on formaldehyde.
[c] SD, Standard deviation.

Finding: The outcome-specific criteria EPA used to evaluate the human studies were generally appropriate but the application of the specified criteria across studies appears inconsistent, and it is not clear if the same set of quality criteria was applied uniformly across studies. The potential for selection bias is addressed for each of the studies. Determining the potential for selection bias in a study is challenging as the specific selection fractions that lead to potential bias are generally unknown. Cross-sectional studies are generally at risk for selection bias. The potential for selection bias may also be signaled by a low response rate and nonrepresentativeness of a study population on exposure and outcome frequency. The committee could not find a consistent approach in how EPA evaluated the potential for selection bias, for example, across the range of observed response rates.

Finding: The 2022 Draft Assessment described specific aspects of exposure assessment that EPA considered when evaluating individual studies, such as having a measurement protocol, duration of exposure measurement period, number of samples obtained, consideration of temperature and humidity, and percentage of measurements below the limit of detection

(Appendix A, Section A-236). The text does not clarify whether systematic or random contributors to inaccuracy were assessed in evaluating information bias in individual studies, nor does it describe how the assessment took account of multiple sources of information bias.
Finding: The 2022 Draft Assessment lacks clarity as to how the availability and characteristics of outcome assessment questionnaires were used to rate the confidence level of a study. For example, Mueller et al. (2013) provide a reference for their questionnaire, and EPA assessed this study as having a *high* confidence level. However, Green et al. (1989) do not provide a reference for their outcome assessment questionnaire, yet EPA categorized it as well as having a *high* confidence level (Main Assessment: Table 1-1, pp. 1–18). EPA categorized several studies (Hanrahan et al., 1984; Liu et al., 1991; Sexton et al., 1986) as having *medium* confidence because of concerns regarding the questionnaires used to assess symptoms without adequate explanation of their deficiencies.

Recommendation 4.3 (Tier 2): EPA should explicitly state what constitutes an adequate assessment of outcomes when a questionnaire is not cited, and explicitly provide the criteria used to determine the adequacy of a questionnaire. Information on these aspects of outcome assessment would facilitate replication of the EPA approach. It would be preferable for EPA to use age categories generally instead of ambiguous descriptors.

Finding: Some studies are potentially affected by multiple limitations. The approach used to classify the level of confidence for such studies is unclear. If there are three sources of potential bias with no apparent directionality (i.e., either over- or underestimation) for each bias, how will the quality of that study be determined? The committee considered as an example the evaluation of the study by Main and Hogan (1983). In Table 1-2, two problems with this study are identified, with one box fully colored. The classification scheme in Figure II would suggest this study is of *medium* confidence, but it is classified as having *low* confidence, presumably because the fully colored box for "other" signifies a greater "degree of limitation." Additional explanations related to Figure II would make it easier to understand individual study confidence determinations, such as when there is only one potential source of bias, and that bias is likely to overestimate the exposure effect.

Recommendation 4.4 (Tier 2): To increase transparency, EPA should document how it assessed the potential for different types of biases, the directionality of resulting biases, and the number of biases, and state how each combination should be interpreted in terms of *high, medium, low*, or *not informative* study confidence.

Finding: The considerations listed for classification of study confidence and evaluation of each study by at least two independent experts is consistent with EPA's state-of-practice methods.

Recommendation 4.5 (Tier 3): In the population selection criteria, the potential for selection bias could be assessed by considering the proportion of the eligible population invited to participate in the study and the proportion of the eligible population that was ultimately included in the analysis. EPA should state the criteria used to assess selection bias in the text, tables, and figures.

Evidence Synthesis and Judgment

The 2022 Draft Assessment concludes that there is robust evidence for sensory irritation from controlled human exposure studies, as well as epidemiological studies. It also concludes that robust evidence exists from animal studies, and there are established mechanisms. The 2022 Draft Assessment indicates further that there is robust evidence for a specific mode of action (MOA) underlying the association between inhalation of formaldehyde and sensory irritation. Formaldehyde exposure directly or indirectly stimulates trigeminal nerve endings in the respiratory epithelium, which has been highlighted as the dominant pathway for causing this outcome. The supporting evidence is based largely on animal studies, but EPA's interpretation is that the suggested MOA identified in animals is also relevant to humans.

Finding: EPA provides a reasonable basis, one that is consistent with its state-of-practice methods, for labeling as robust the evidence relating formaldehyde exposure and sensory irritation.

Overall Conclusions About the Hazard Descriptor

EPA's judgment was that, taken together, the *evidence demonstrates* that inhalation of formaldehyde causes sensory irritation. This judgment was based on four *high*- and *medium*-confidence studies of symptom prevalence in humans in residential settings, numerous *high*- and *medium*-confidence acute controlled human exposure studies, and numerous *high*- and *medium*-confidence occupational studies.

Finding: EPA's overall hazard conclusions are supported by the scientific evidence and are consistent with EPA's state-of-practice methods.

Dose-Response Evaluation

In section 2.1.1 of the Main Assessment (p. 2-2), EPA states that only *high*- and *medium*-confidence studies were chosen for POD analysis. This section also reports that emphasis was placed on the characteristics of the study population, the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels. Human epidemiological studies that evaluated groups most representative of the general population were preferred, as were studies that reported complete results and are unlikely to have alternative explanations.

Recommendation 4.6 (Tier 2): EPA should clarify and clearly state the criteria used to select the studies for dose-response analysis of noncancer endpoints.

EPA excluded three of the six studies selected for POD derivation: one (Liu et al., 1991) that reported partial results, another (Mueller et al., 2013) that did not observe an exposure–response relationship, and a third (Lang et al., 2008) for which the adverse response level was difficult to define. For the remaining three studies, EPA derived a POD. EPA stated that of these three studies, it had less confidence in those of Kulle et al. (1987) and Andersen and Molhave (1983), which were controlled exposure studies for which the PODs were an order of magnitude higher than that for the study by Hanrahan et al. (1984), which was the final selection.

Finding: EPA's favoring of well-conducted and -reported epidemiologic studies over controlled human exposure studies was justifiable for sensory irritation.

PULMONARY FUNCTION

Pulmonary function is an important health outcome given the association of level of lung function with mortality, chronic respiratory disease, and coronary heart disease. Small declines in pulmonary function can have a large impact on public health, regardless of whether individual declines are clinically significant (ATS, 2000). Thus, EPA evaluated studies reporting changes in pulmonary function following formaldehyde exposure with changes in spirometric measure outcomes, including FEV_1 (forced expiratory volume in 1 second), FVC (forced vital capacity), their ratio (FEV_1/FVC), maximum midexpiratory flow or forced expiratory flow 25–75 percent (FEF_{25-75}), and peak expiratory flow rate (PEFR). EPA's review and evaluation focused on experimental and observational studies in humans. Animal studies were not considered because "there were few directly relevant studies in the peer-reviewed literature and the extensive literature on these endpoints in humans was considered adequate to draw a hazard conclusion" (Main Assessment, p. 93, lines 8–11). Thus, animal studies of analogous endpoints were not searched for or cited in the hazard evaluation. However, animal study evidence was used to provide mechanistic support.

Formaldehyde exposure levels differed, mainly as a result of study design. Occupational exposures tended to have time-weighted average (TWA) concentrations above 0.2 mg/m^3, with some intermittent peaks at >1 mg/m^3, while students in anatomy labs had exposures between 0.1 and >1 mg/m^3. Exposures in community settings (residences, schools) were often below 0.1 mg/m^3. In controlled human exposure settings, formaldehyde exposures ranged between 0.61 and 3.7 mg/m^3.

Literature Identification

Table A-41 in Appendix A summarizes the search terms used for PubMed and Web of Science. Table A-42 (p. 314) summarizes the PECO inclusion and exclusion criteria. Only human studies with indoor inhalation exposure and formaldehyde measurements were included. Outcomes were restricted to FVC, FEV_1, FEF, and PEFR.

A total of 53 studies were identified and evaluated for consideration (Appendix A, p. 313, line 15). This total apparently represents studies rather than individual publications since some studies are described in multiple publications (e.g., Broder et al., 1988a,b,c). Among these 53 studies were 42 observational epidemiology and 11 controlled human exposure studies (Appendix A, Figure A-23). Publication dates for these studies ranged between 1975 and 2015.

Finding: The inclusion and exclusion criteria listed in Appendix A, Table A-42 are consistent with EPA's state-of-practice methods.

Study Evaluation

Methodological issues considered in the evaluation of studies are provided in the Main Assessment (p. 95), as well as in the Assessment Overview (Section 3.2.2). They include pulmonary function measures (with a table of definitions [Table 1-5]); a preference for studies that follow American Thoracic Society (ATS) guidelines or provide detailed protocol and reference equation information; and a preference for pulmonary function measures normalized by race or ethnic origin, gender, age, and height. EPA mentions smoking as a potential confounder and the need to consider a referent group when evaluating change across a work shift or laboratory session. Appendix A presents a table (Table A-43) of criteria used to categorize study confidence for epidemiological studies as *high, medium, low*, and *not informative*. This table considers two aspects: (1) exposure, and (2) study design and analysis. Neither the Main Assessment nor the Assessment

Overview references Table A-43. Table A-44 provides EPA's evaluation of all epidemiological studies of pulmonary function, organized by study type and then alphabetically by author. Some studies have multiple confidence ratings— for example, for preshift versus cross-shift outcomes, longitudinal versus cross-lab change, or comparison with community referents versus change during embalming. Table A-45 covers the controlled human exposure studies. This table is organized by confidence level and then year of publication, with the confidence categories being *medium* (randomized, with results fully reported) (five publications), *low* (incomplete reporting of results or blinding not described, with multiple exposure levels) (four publications), and *low* (no randomization, with blinding not discussed) (two publications).

Evidence Synthesis and Judgments

Section 1.2 of the Main Assessment, "Synthesis of Evidence for the Effects on the Respiratory System," addresses synthesis between and within evidence streams for all noncancer outcomes. Section 1.2.2, "Pulmonary Function," begins with an overview providing brief comments on aspects of the literature identification and inclusion, followed by brief summaries of the evidence synthesis, mechanistic support, and hazard evaluation. Detailed synthesis information begins with the unnumbered subsection on PDF p. 96 "Pulmonary Function Studies in Humans." The synthesis discussion is blended with the study evaluation tables (Tables 1-6 to 1-9) also presented in this section, and the subsection is organized by exposure duration (acute, intermediate, and long-term) and study design features: for acute, controlled human exposure and observational within the work shift or anatomy lab section; for intermediate, anatomy labs; and for long-term, occupational and then residential. Appendix A provides several figures (A-24 to A-26) that show results from studies describing change in pulmonary function measures during a work shift or anatomy lab session, with one figure for each outcome measure (FEF, FEV_1, FVC, etc.). This topic ends with Table A-46, summarizing each of those studies. The following narrative provides specific comments relevant to the synthesis discussion for each study grouping presented in the Main Assessment.

Acute controlled human exposure studies. This subsection notes that while formaldehyde exposure has not been shown to induce pulmonary function deficits in nonexercising healthy volunteers, small but statistically significant deficits have been observed in studies with two or more 15-minute exercise regimens, although not in studies with shorter exercise segments. The overview at the beginning of Section 1.2.2 (Main Assessment, p. 93) indicates that the controlled human exposure studies "consistently did not observe changes."

Acute epidemiological studies: Changes in pulmonary function across a work shift or anatomy course lab session. This subsection considers studies of work shift changes among multiple occupations (plywood workers, chemical industries, funeral workers), as well as students in anatomy lab sessions. The workers were assumed to have had prior formaldehyde exposure, while the students were not. The text states that many of the studies "observed pulmonary function declines over the course of the workday or lab." Most studies did not consider change in an unexposed referent group; studies that did include a referent group showed a change in pulmonary function on average in that group, although studies varied with respect to the direction observed, and this additional potentially insightful detail is not provided.

Intermediate-duration exposures (<1 year) among anatomy/pathology students. The discussion of the three panel studies published by two sets of authors highlights that there were different results for spirometry measures (FVC, FEV_1, FEV_1/FVC, and FEF_{25-75}) in one study versus change in PEFR measures in two other studies. Interpretation of those studies was challenged by intermittent exposures, student absences, and decreasing formaldehyde concentrations over the quarter.

These studies are not mentioned further in any of the summaries (i.e., the beginning of Section 1.2.2 of the Assessment Overview or the integrated summary of evidence in the Main Assessment).

Long-term formaldehyde exposure in occupational settings. This subsection addresses two types of study design: cross-sectional (or prevalence) studies and longitudinal studies. Note that the reference to cross-sectional studies (Main Assessment, p. 102) points to studies under the "prevalence studies" heading in Table 1-7; it is left to the reader to make this connection. EPA concludes that overall, these studies show evidence of decrements in pulmonary function associated with formaldehyde exposure, particularly given that many studies could be biased toward no association.

For the cross-sectional studies, challenges are highlighted in the text: selection bias (healthy worker effect and survivor [lead time] bias), a community-based reference group in one study, higher prevalence of other exposures affecting pulmonary function in the referent group). Nonetheless, EPA notes that most studies observed associations of formaldehyde with deficits in pulmonary function before the work shift at the beginning of the work week.

The discussion of the longitudinal results from three studies with lead authors Nunn, Alexandersson, and Lofstedt (p. 1–47, PDF p. 106), highlights that the four- to six-year duration of these studies, their small sample sizes, and the potential for exposure-related loss to follow-up leading to selection bias are challenges, but notes that nonetheless, some pulmonary function declines were reported. Three studies are mentioned briefly, and then an additional two reference studies are covered (Lee and Fry, 2010; Redlich et al., 2014). They report a formaldehyde-associated age-related decline in FEV_1 among nonsmokers that was 50 percent greater compared with the expected rate of age-related decline. The remainder of the discussion concerns duration of work in an exposed job and its association with pulmonary function. EPA concluded that results "seem to support a conclusion that occupational exposure may result in declines of FEV_1 and FEF over time" (PDF p. 53 of the Assessment Overview), but did not deem them to be consistent across studies.

Residential exposures among adults. This section addresses four studies (covered in seven publications), noting the challenge of comparing them given their different approaches to pulmonary function assessment and reporting. Overall, EPA concluded that "adults in general did not experience declines in pulmonary function at average formaldehyde levels less than 0.05 mg/m^3" (PDF p. 117). Much of the discussion in this subsection focuses on Krzyzanowski et al. (1990) because it was rated as having *high* confidence.

Residential and school exposures among children. This discussion also focuses on Krzyzanowski et al. (1990), whose results for children aged <15 years show a decrease in PEFR associated with increased formaldehyde exposure. Results from this paper are reproduced in Figure 1-6, which shows the modeled decrease in PEFR per unit of formaldehyde exposure; the figure would benefit from a more in-depth discussion given the later use of this study for dose-response analysis. The general discussion highlights the low exposures in these studies and the small exposure contrast in one, although it was difficult to determine the exposure concentration reported by Wallner et al. (2012).

> Finding: Within study groupings, EPA equates a lack of statistical significance with a lack of decline in pulmonary function (e.g., reference to Lofstedt PDF p. 98, line 19), and makes statements that are poorly supported by the evidence (e.g., reference to the size of differences and lack of precision on PDF p. 101, line 7).

> Finding: Evidence is presented inconsistently across the six sections describing results from different exposure durations and study populations.

Finding: Overall, while EPA's distillation and synthesis of the pulmonary function evidence is challenging to follow, the judgments presented in the Main Assessment are supported by the scientific evidence and consistent with EPA's state-of-practice methods.

Finding: Given the wording in Section 3.2.3, it is difficult to understand the basis for some of the evidence synthesis judgments as presented in the Assessment Overview. For example, EPA does not provide the specific evidence and decision frameworks used to support the following statement: "overall the longitudinal analyses appear to be inconsistent, but while hindered by a lack of sensitivity, seem to support a conclusion that occupational exposure may result in declines of FEV1 and FEF over time" (p. 53, line 17). Further, some aspects of the study synthesis discussion are not clearly defined. For example, what does it mean that studies observed "inconsistent responses" (Assessment Overview p. 52, line 10)? Does this mean that reported results are in different directions, or that some results are statistically significant, while others are not?

Recommendation 4.7 (Tier 2): EPA should clarify the basis for its synthesis judgments and provide additional information about the studies on which they are based, such as the formaldehyde levels observed, as well as the exposure ranges or other measure of variability. The study summary tables (Tables 1-6 to 1-9) should be updated to provide an organized distillation of the points made in the evidence synthesis text.

Recommendation 4.8 (Tier 2): If the Assessment Overview is retained (see Recommendations 2.1 and 2.2 in Chapter 2), EPA should harmonize its presentation of evidence synthesis with the presentation in the Main Assessment. In particular, the evidence synthesis section of the Assessment Overview could be updated to build upon the first three paragraphs of the "Integrated Summary of Evidence for Pulmonary Function" section in the Main Assessment (PDF p. 134).

EPA's synthesis also considers the MOA evidence for decrements in pulmonary function. As summarized in Figure 1-7, the most plausible mechanisms are indirect activation of sensory nerve endings in the lower respiratory tract and/or increases in airway eosinophils. There are also possible changes in the upper respiratory tract that may contribute to this outcome. Table 1-10 summarizes the studies that provide the most informative mechanistic evidence regarding decrements in pulmonary function following formaldehyde exposure.

Finding: The MOA considerations and mechanistic evidence are clearly presented and appropriately documented.

Overall Conclusions About the Hazard Descriptor

EPA concluded that, based on *moderate* human evidence, long-term inhalation of formaldehyde is likely causal for decreases in pulmonary function (i.e., EPA applied the *evidence indicates* rating). EPA deemed Krzyzanowski et al. (1990) to have the strongest design and methods, providing evidence supported by a more limited study in schools conducted by Wallner et al. (2012). The narrative and table also mention "several studies of workers with long-term exposure to >0.2 mg/m^3" without giving references. EPA also concluded that the *evidence is inadequate* to determine the causal effect of formaldehyde exposure on acute and intermediate-term time scales. This judgment does not give much weight to the evidence that pulmonary function decrements

occurred in controlled human exposure settings among participants who exercised at least 30 minutes (Green et al., 1987, 1989), or that some individuals exhibited clinically significant deficits (Green et al., 1987).

Finding: EPA's evidence integration judgments are supported by the scientific evidence and are consistent with EPA's state-of-practice methods.

Dose-Response Evaluation

EPA's confidence in the human study used to derive the POD (Krzyzanowski et al., 1990) was high. This cross-sectional study of residential exposure found a linear relationship between higher formaldehyde exposure and decreased PEFR among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb). EPA applied benchmark dose modeling to calculate the concentration at which a 10 percent decrement in pulmonary function would be expected; EPA considered a 10 percent decrement to be the benchmark response (BMR). A benchmark concentration $(BMC)_{10}$ (0.033 mg/m^3) and benchmark concentration lower bound $(BMCL)_{10}$ (0.021 mg/m^3) were subsequently determined from the regression coefficient from a random effects model of PEFR among children reported by the study authors. A single uncertainty factor to account for variability among humans (UF_H) of 3 was applied to the $BMCL_{10}$ to derive a cRfC of 0.007 mg/m^3.

Finding: EPA's derivation of BMCL was based on nonasthmatic children and nonmorning exposures. This practice was inconsistent with EPA's state of the practice of using more vulnerable subpopulations for risk estimation.

Recommendation 4.9 (Tier 2): EPA should provide additional justification for why the most vulnerable subpopulations were not used for risk estimation, and should consider using the data from children with asthma that are provided in Krzyzanowski et al. (1990).

RESPIRATORY PATHOLOGY

Formaldehyde's effects on the respiratory tract have been studied extensively. Animal studies show that inhaled formaldehyde at 2 ppm or higher is cytotoxic and that increases in epithelial cell proliferation occur after chronic formaldehyde inhalation in mice, rats, and nonhuman primates (Kerns et al., 1983; Monticello et al., 1996). Formaldehyde-induced airway lesions in animals include rhinitis, epithelial dysplasia, and squamous metaplasia. These lesions demonstrate concentration, time, and site dependence, as well as an anterior-to-posterior severity gradient (Kerns et al., 1983; Monticello et al., 1996).

Literature Identification

PubMed search terms related to respiratory tract pathology in humans included *hyperplasia*, *metaplasia*, *nasal mucosa*, *occupational diseases*, *respiratory tract diseases*, *rhinitis*, and *mucociliary*. Some broad terms (e.g., the MeSH term *pathology*) were not used in the search for human literature.

A total of 1009 citations were screened (title and abstract) for assessment of respiratory tract pathology in humans, and 12 studies were ultimately included in the review (Appendix A, p. A-390). A total of 1678 citations were screened (title and abstract) for the assessment of respiratory

tract pathology in animals, and 41 toxicology studies were ultimately included in the review (Appendix A, p. A-393).

Finding: For human studies, the comparator of the PECO is defined as *evaluated outcome associations with formaldehyde exposure*; it is unclear what specific comparisons were made. The comparator in the PECO statement used for screening the animal studies is undefined.

EPA's review focused on histopathological endpoints and signs of pathology in nasal tissues.

Finding: It is unclear why EPA did not consider more distal effects in the respiratory tract since studies performed in nonhuman primates have reported changes in the respiratory epithelium of the trachea and major bronchi (Monticello et al., 1989). The exclusion criteria for human respiratory tract pathology included exclusion of studies reporting rhinitis. This exclusion is surprising since rhinitis was a search term used to find human studies. Moreover, it is unclear whether this exclusion criterion resulted in exclusion of studies with histologic evidence of inflammation.

Recommendation 4.10 (Tier 2): EPA should provide an explicit description of the comparator used in screening human and animal studies, and resolve discrepancies between search terms and inclusion and exclusion criteria.

Study Evaluation

Outcome-specific criteria used to evaluate human studies of formaldehyde-induced respiratory pathology included assessment of the exposure, participant selection and comparability, possibility of confounding, analysis and completeness of results, and study size (Appendix A, Table A-57). EPA evaluated whether studies describing histologic results provided an explanation of how tissues were evaluated and scored. EPA downgraded cross-sectional studies among occupational cohorts since workers may have been less sensitive to the irritant properties of formaldehyde then the general population. EPA considered gender and smoking were considered by EPA to be potential confounders for pathological endpoints.

Outcome-specific criteria used to assess the animal studies included sample size, inadequate reporting of lesion incidence and/or severity, combining of multiple lesions, inadequate sampling of the respiratory tract, and short (<1 year) exposure duration or follow-up. EPA also evaluated the source of the formaldehyde (e.g., commercial grade, paraformaldehyde, or formalin). Coexposure to methanol (found in some formalin products) was not considered to be a major confounding factor for identifying effects of inhaled formaldehyde on respiratory pathology. According to EPA, "a sample size of less than 10 was considered a significant limitation"; however, this criterion was applied to the Holmstrom et al. (1989) study even though this study had 16 animals/group.

Finding: EPA's outcome-specific criteria are generally appropriate and consistent with its state-of-practice methods. It is unclear whether the downgrade for cross-sectional studies among occupational cohorts is relevant for histopathologic outcomes. Evidence supporting consideration of gender as a confounder is not provided. For animal studies, sample size limitations were applied inconsistently. In general, EPA was also inconsistent in providing a rationale for each study quality domain (Appendix A, Table A-59), reducing transparency.

Recommendation 4.11 (Tier 2): EPA should provide a consistent rationale for each study quality domain used in the assessment.

Evidence Synthesis and Judgments

EPA identified no *high*-confidence and four *medium*-confidence human occupational studies. Histological changes in the respiratory tract seen in the latter four studies were associated with formaldehyde exposures ranging from 0.1 to 2.5 mg/m^3 (Table 1-25). EPA downgraded occupational studies for this outcome. EPA's rationale for this downgrade was that survivor bias impacted studies, specifically, "current workers who likely were less sensitive 'survivors' of the long-term respiratory irritant effects of formaldehyde, which would cause survival bias and an attenuation of comparisons between exposed and comparison groups" (pp. 1–153). Although this downgrade was applied, EPA did not critically evaluate whether a healthy worker survivor effect was present in these studies.

EPA's evaluation of animal studies focused on the incidence of hyperplasia and metaplasia after formaldehyde inhalation. Only studies judged by EPA to be of *high* and *medium* confidence are included in the synthesis and evidence tables in the Main Assessment. Long-term studies were also deemed more relevant for the assessment. EPA concluded that "a clear relationship between formaldehyde exposure duration and the development of squamous metaplasia and, to a lesser extent, hyperplasia" (pp. 1–161) could be drawn from the experimental animal studies. EPA characterizes formaldehyde-induced squamous metaplasia in the rat nasal cavity as minimally adverse, with no clear discussion of this determination.

EPA identified a single study conducted in rhesus monkeys as having *medium* confidence. This study reported hyperplasia and metaplasia in the larynx, trachea, and carina after a 6-week exposure to 7.4 mg/m^3 formaldehyde (Monticello et al., 1989). EPA concluded that these data may suggest that the "monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air" (pp. 1–160). Although this conclusion is plausible, a more likely explanation relates to differences in breathing patterns between rodents and nonhuman primates (obligatory nasal versus oronasal).

EPA reviewed mechanistic data extensively and found robust data for several endpoints, including the binding of formaldehyde to macromolecules, alterations in mucociliary function, epithelial damage or dysfunction in the upper respiratory tract, increased cell proliferation in the upper respiratory tract, and trigeminal nerve stimulation. These data were used to support EPA's conclusion that epithelial cell injury results in squamous metaplasia in the upper respiratory tract.

Finding: The judgments presented in the Main Assessment are supported by the scientific evidence and consistent with EPA's state-of-practice methods.

Overall Conclusions About the Hazard Descriptor

EPA concluded that there was *robust evidence* that inhaled formaldehyde exposure can induce histopathologic lesions in the nasal cavity and other portions of the upper respiratory tract. Lesions were dependent on both the formaldehyde concentration and, to a lesser extent, duration of exposure. This conclusion was based on numerous *high*- and *medium*-confidence studies of chronic and subchronic exposure duration of multiple experimental animal species. EPA also concluded that the data provide *moderate evidence* that inhaled formaldehyde induces histopathological lesions in the human upper respiratory tract. This determination was based on four *medium*-confidence human epidemiological studies (Ballarin et al., 1992; Boysen et al., 1990; Edling et al.,

1988; Holmstrom et al., 1989). These studies showed that participants exposed to average formaldehyde levels between 0.05 and 0.6 mg/m^3 had higher average histopathology scores than those of their respective comparison group. Overall, the strength of the evidence for hyperplasia and squamous metaplasia includes *robust* evidence from animal studies and *moderate* human evidence from observational epidemiological studies, and strong support for a plausible MOA based primarily on mechanistic evidence from experimental animals. EPA's overall conclusion is that the *evidence demonstrates* that inhalation of formaldehyde causes respiratory tract pathology in humans given the appropriate exposure circumstances.

> Finding: The evidence integration judgments made by EPA are supported by the scientific evidence and consistent with EPA's state-of-practice methods.

Dose-Response Evaluation

EPA's confidence in the two studies used to derive PODs was high. Four human studies EPA judged as having *medium* confidence provided additional support. The PODs derived by EPA were based on lesions seen at Level 1 in the rat nasal cavity. EPA used lesion incidence data (Woutersen et al., 1989; Kerns et al., 1983) to model the dose-response relationship. EPA found that the 24-month data for Level 1 (Table 1-26) could not be modeled because of the steep dose-response relationship seen in the Kerns et al. (1983) study, so it modeled the 18-month incidence data and obtained a $BMCL_{10}$ of 0.448 mg/m^3 (Table 2-5).

EPA used a computational fluid dynamic (CFD) model (Kimbell et al., 2001) to estimate formaldehyde flux at the Level 1 cross section of the F344 rat nose. EPA found that the average flux in the Level 1 region corresponding to the $BMCL_{10}$ of 0.448 mg/m^3 determined for the Kerns et al. (1983) study was estimated to be 685 pmol/mm^2-hr. A human CFD model (Kimbell et al., 2001) was then used to estimate the formaldehyde exposure concentration (0.484 mg/m^3) that would result in a similar formaldehyde flux in the human nose (Table 2-5; Appendix B, Section B.1.3). This value was subsequently adjusted for continuous exposure (6 hours/24 hours) × (5 days/7 days) to provide a human POD_{ADJ} of 0.086 mg/m^3.

A human POD_{ADJ} of 0.094 mg/m^3 was obtained for squamous metaplasia at nasal Level 1 using lesion incidence data from Woutersen et al. (1989). Since a CFD model for Wistar rats was unavailable, EPA based the POD for the Woutersen et al. (1989) study on parts per million equivalence (pp. 2–19).

EPA's confidence in the POD calculation based on Woutersen et al. (1989) was *medium*, while confidence based on Kerns et al. (1983) was *low*. EPA stated that it assigned lower confidence to the POD derived from Kerns et al. (1983) because the calculation involved an extrapolation well below the tested formaldehyde concentrations, and the BMC was based on the 18-month exposure rather than the 24-month exposure, where responses were greater in magnitude. EPA did not explain why its confidence in the POD based on the Woutersen et al. (1989) study was *medium*.

An uncertainty factor $(UF)_A$ interspecies uncertainty of 3 was used to account for animal-to-human variation; a UF_H of 10 was used to account for human variation; and a UF_S subchronic uncertainty factor of 3 was applied to account for extrapolation to chronic exposure in the Kerns et al. (1983) study. Incidence data for squamous metaplasia at Level 1 from the Kerns et al. (1983) study are reported in Table 1-26. EPA's rationale for including a UF_S of 3 rests on its inability to model the 24-month data from the Kerns et al. (1983) study, prompting use of the 18-month data. EPA acknowledges that "a lower POD would have been expected if the 24-month data could have been modeled" (p. 74), and EPA states further that "while exposure duration is important to the development of this lesion, such effects appear to be more dependent on exposure concentration"

(p. 75). In addition, an 18-month study in rats is a chronic-duration study that would not typically necessitate the use of a subchronic UF.

Two cRFCs were calculated for respiratory tract pathology. The first was estimated using data from Woutersen et al. (1989), had a composite UF of 30 ($UF_A = 3$, $UF_H = 10$), and was 0.003 mg/m^3. The second cRFC was estimated using data from Kerns et al. (1983), had a composite UF of 100 (as discussed above), and was 0.0009 mg/m^3. EPA chose the organ-specific RfC for respiratory tract pathology of 0.003 mg/m^3 based on the Woutersen et al. (1989) study. EPA considered the completeness of the database for respiratory tract pathology to be high.

Finding: EPA's dose-response evaluation was well documented and transparent. Steps used are consistent with EPA's state-of-the-practice.

NONCANCER SYSTEMIC EFFECTS

The potential systemic effects of formaldehyde that are evaluated in the 2022 Draft Assessment include immunotoxicity (allergy and asthma), reproductive toxicity, and neurotoxicity. As noted in Chapter 3 of the present report, systemic bioavailability of inhaled formaldehyde beyond the respiratory tract is unlikely. Thus, systemic responses are unlikely to arise from the direct delivery of formaldehyde to a distant site in the body by mechanisms that could result in injury at sites distal from the respiratory tract.

ALLERGY AND ASTHMA

Formaldehyde's capacity to induce irritation and immune response–driven pathologies in nasopharyngeal and pulmonary organs is related in part to activation or suppression of immune function. As a respiratory toxicant, formaldehyde causes bronchial constriction, but it may also directly impact immune cells in the upper airway, cause formation of modified proteins that are antigenic, and exacerbate existing immune-related pathologies in exposed individuals. Immune-related diseases that are potentially linked to formaldehyde have a variety of mechanisms and pathologies that can be confused without careful diagnosis or validated assessments. Formaldehyde is a very common skin allergen that causes allergic contact dermatitis at a prevalence of 8 percent of the U.S. population (Silverberg et al., 2021). Because EPA was conducting an inhalation-specific assessment, this immune-toxic feature of skin contact formaldehyde is not reviewed in the 2022 Draft Assessment, apart from the capacity of inhaled formaldehyde to aggravate dermatologic conditions. Although EPA reviewed formaldehyde's impact on lower respiratory tract infections, it does not discuss it in detail, concluding that studies related to this outcome did not provide meaningful evidence for determination of a cRfC.

The primary diagnoses EPA chose to define as immune-related health effects following formaldehyde inhalation are *allergy* and *asthma*. This decision led to the convocation of two expert panels (one on allergy and one on asthma) to help EPA define the relevant symptoms, physiology, biomarkers of disease, and specific diagnoses to include for search terms. This approach was unique to this outcome domain because the mechanisms of toxicity for relevant immunopathophysiologies were deemed beyond EPA's expertise. Since these diseases can be misidentified by self-report, biomarker classifications of disease were favored in evaluating strength of evidence; validated (by the American Thoracic Society) questionnaire information was also favored for *high*-confidence determinations. Animal studies were viewed as indeterminate for allergy and asthma because of the unsuitability of animal models for evaluation of pathophysiology and mechanisms of these outcomes from formaldehyde exposures.

Finding: Allergies and asthma as systemic immunopathologies related to inhaled formaldehyde are well documented in the 2022 Draft Assessment. It is unclear whether additional systemic immune-mediated diseases (e.g., contact allergy, immunodeficiencies, lupus, rheumatoid arthritis) were also considered and rejected because of a lack of relevance or information.

Recommendation 4.12 (Tier 2): EPA should provide a comprehensive description or listing of immunopathologies that were considered as potentially related to formaldehyde before the decision was made to limit the focus to prevalent allergies and prevalent asthma.

Literature Identification

EPA's literature search strategy is described in detail in the 2022 Draft Assessment, and was informed by consultation with the outside experts. Table A-48 in Appendix A describes the PECO criteria. The experts advised EPA on study inclusion/exclusion criteria, diagnosis instruments used for immune outcomes, confidence assessments for specific studies, ages of participants, and disease mechanisms. The use of validated questionnaire instruments (e.g., International Study of Arthritis and Allergies in Children [ISAAC]; Asher et al., 1995) and diagnostic tests (e.g., skin prick) to specify diagnostic quality as criteria to enhance confidence determinations compared with studies without such validated instruments was appropriate. Studies on asthma involving very young (<5 yrs) and elderly (>75 yrs) subjects were excluded or downgraded since outside experts stated that respiratory conditions other than asthma may be the basis of symptoms in these age groups. Thirty-six studies (27 observational and 9 randomized controlled trials) were chosen for toxicological review pertaining to immune conditions.

Finding: The considerations and methods adopted by EPA were appropriate given the often poor specificity of diagnostic classifications in the published literature on these conditions. Study choice decision metrics are adequately described.

Finding: The terms "very young" and "very old" (as exclusion criteria) are not defined, and several studies of school-age children were used to inform the strength-of-evidence determination. While age cutoffs of <5 and >75 years are cited in the Assessment Overview and Appendices as exclusion criteria, the Main Assessment does not describe age cutoffs, and it is unclear how these cutoffs were made actionable in study choice as some studies of infants and children <5 feature in asthma evaluations in particular. "Infants" (again, a specified age needs to be given each time this word is used) were deemed to have nonspecific symptoms (wheeze and infection) compared with adults and were not considered in the formulation of PODs or synthesis judgments. Likewise, the "elderly" (assumed to mean >75, but again, age needs to be specified each time the word is used) were not considered because of the potential interference of alternative-mechanism diseases such as chronic obstructive pulmonary disease (COPD). In general, EPA divided evaluations into "child" and "adult" studies, but age cutoffs for these categories need to be stated and applied consistently.

Finding: EPA's decision to exclude food allergy in response to airborne formaldehyde while including eczema is not explained. The rationale for excluding formaldehyde-specific immunoglobulin E (IgE) as an endpoint (because of its rarity in evaluation) is explained appropriately.

Finding: The inclusion/exclusion criteria for animal studies are described in confusing terms. While the search terms emphasize biological mechanisms as relevant (biomarkers such as immunoglobulin G (IgG), IgE, cytokines, hypersensitive reactions), EPA also states that studies "describing the development of immunological or allergy animal models" were not included (Appendix A, p. A-337). The 2022 Draft Assessment documents that animal models are generally helpful only in immediate pathological response to formaldehyde rather than the development of disease states that recapitulate human diseases, but a clear reason for excluding animal models of "the development of immunological or allergy" outcomes is not provided.

Recommendation 4.13 (Tier 2): EPA should explicitly state its rationale for age-based exclusions and define the terms "very young" and "very old," better justify the rationale for excluding allergic contact dermatitis and food allergy as outcomes of interest, and provide the rationale for excluding animal models of "the development of immunological or allergy" outcomes (unless such studies do not exist or are inadequate).

Study Evaluation

EPA chose to adhere to the recommendations of the outside experts in applying evidence status to those studies that (1) had more robust measures of disease (using appropriate biomarkers and validated questionnaires), (2) included higher exposure levels, or (3) included a prospective study design. The one prospective study (in which formaldehyde exposures preceded disease [Smedje and Norback, 2001]) that was based on low exposure values (many were below the analytical chemical limit of detection) was elevated to *medium* confidence given its longitudinal, prospective nature. Children were deemed to be "more sensitive" at lower exposures given observed effects, and were carried through the evaluation to yield distinct POD and cRfC values separate from those for adults.

Finding: The outcome-specific criteria used to evaluate human studies were generally appropriate and in line with expert recommendations. However, EPA's approach appears to contradict the expert panel's advice that children's allergic symptoms are more liable to misdiagnosis than those of adults, particularly for asthma in infants and young children.

Recommendation 4.14 (Tier 2): EPA should include a specific statement on the age at which asthma diagnosis is considered valid to justify the age exclusions for young children, as well as the category of "the elderly."

Evidence Synthesis and Judgments

EPA concluded based on a *moderate* level of human evidence (and *slight* in animals) that inhalation of formaldehyde causes an increased risk of prevalent allergic conditions and asthmatic symptoms and decreased control of asthmatic symptoms, with evidence from occupational studies in the range of exposure values >0.1 mg/m^3 and from schools and homes at 0.03–<0.1 mg/m^3. EPA made these judgments after carrying out the synthesis of substantial evidence on allergic conditions, asthma, and lower respiratory tract infections (in young children), with a large number of *medium*-confidence studies being used to justify them. These studies included 8 studies on allergies in children and/or adults (one *high*- and three *medium*-confidence) and 15 studies on asthma in children or adults (2 *high*- and 13 *medium*-confidence), which together provide a preponderance of evidence that formaldehyde influences these phenotypes in humans. Two studies on asthma

control (in known asthmatic subjects; pp. 1–112 of the Main Assessment) provided *high* and *medium* confidence, respectively, with Venn et al. (2003) showing strong trends. The section on "Controlled Acute Exposure" describes studies of short-term acute exposures to humans.

> Finding: While EPA accorded some studies of acute exposures *high* confidence, those studies were not deemed generalizable to other populations (pp. 1–114) because of brief exposures not relevant to the chronic-exposure scenario. A short and useful section (pp. 1–122) considers effect modification by tobacco smoke, family history of atopy, and known atopy status.

Regarding animal studies, the synthesis was indeterminate for allergy and asthma outcomes based on the lack of appropriate models that recapitulate the symptoms and physiology of human allergy and asthma conditions. Most of the animal data is based on the ovalbumin (OVA) allergen model, which does not recapitulate the entirety of human pathophysiology. The animal model data did aid in advancing understanding of MOA.

> Finding: EPA's use of animal data and the resulting synthesis judgments are appropriate, described thoroughly, and consistent with EPA's state-of-practice methods. The relative risk size of 1.2 for exposures of around 0.04–0.06 mg/m^3 is small, but these conditions are common, making this an important outcome. A specific study (Matsunaga et al., 2008) suggests higher risks, including a two-fold higher risk for eczema, and a three-fold higher risk for allergy-like symptoms from a childhood classroom study that is helpful for determining a POD.

In the section "Evidence on MOA for Immune-related Conditions," EPA concludes that a definitive MOA could not be identified, but components of the MOA are clear. Formaldehyde is responsible for airway inflammatory changes and remodeling that can contribute to respiratory immune-related conditions. The mechanisms for allergic sensitization are less clear. Reliable human data on changes in production of antibodies to formaldehyde and its protein-adducting metabolites is lacking. Figure 1-12 describes the cascades of immune alterations leading to effector-level changes that result in the pathologic observed formaldehyde hazards. Many of the pathway components have uncertain interrelationships, and the evidence is at *moderate* to *slight* levels. These immune mechanisms are complex and largely beyond the scope of the 2022 Draft Assessment, and are described in light of several *high*- to *medium*-confidence studies in relation to formaldehyde MOA. These animal studies provide strong evidence for some aspects of formaldehyde's relevant activities—for example, bronchoconstriction and eosinophil activation via inflammatory mediators such as tachykinins, antibodies, Th2-related cytokines, and white blood cell changes. Summaries of these changes are provided in Tables 1-22 and 1-23, with extensive discussion in Appendix A, Section A.5.6.

> Finding: EPA provides an appropriately nuanced discussion of the complex MOA for immune-related conditions and identifies many gaps in knowledge, consistent with its state-of-practice methods.

Overall Conclusions About the Hazard Descriptor

Overall, based primarily on *moderate* human evidence as well as *slight* animal evidence from mechanistic studies supporting biological plausibility (including molecular and cellular inflammatory changes and evidence of hypersensitivity), EPA concluded that the *evidence indicates* that

inhalation of formaldehyde likely causes increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms, given appropriate exposure circumstances.

Finding: EPA's hazard determination judgments are appropriate given the scientific evidence described and are consistent with EPA's state-of-practice methods.

Dose-Response Evaluation

EPA deemed six studies on allergic conditions, six studies on asthma, and two studies on control of asthma in asthmatic persons eligible for POD derivation. Two studies with the highest confidence from each of these three categories were ultimately selected for POD identification. No observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) values were chosen from the highest-quality study in children (as a more sensitive population [Annesi-Maesano et al., 2012]) and the highest-quality study in adults (Matsunaga et al., 2008).

The study in children (Annesi-Maesano et al., 2012) used to derive an allergy POD also provided the NOAEL for asthma along with a second study in children, and the asthma control PODs both pertain to asthma in children. EPA's final judgments on confidence in these PODs were *high* for allergy in children and *medium* for asthma control. No judgments or statements about PODs were derived from studies in adults, who, as noted, are generally less sensitive than children. EPA provides reasoning for not providing a POD for adults given the lack of quantification in the studies evaluated, wide confidence intervals, and dichotomous analyses with variable exposure levels. EPA provides no POD evaluation for contact exposures to formaldehyde.

Uncertainty factors were applied to the PODs to derive cRfCs. Because NOAELs were used for most of the PODs, a LOAEL-to-NOAEL UF (UF_L) of 1 was applied. A UF_H of 3 was generally applied, since most studies assessed exposures and outcomes in potentially sensitive populations such as children or pregnant women. All other uncertainty factors were applied at 1 (apart from a UF_S of 3 that was applied for the one study in which exposure was measured during pregnancy [Matsunaga et al., 2008]).

Finding: EPA's conclusions and its choice of UFs are consistent with its state-of-practice methods, given the confidence levels and quality of the chosen studies. It is appropriate that asthma control PODs pertain to asthma in children, as no studies of asthma control in adults were of high enough quality.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The 2011 National Research Council (NRC) committee that reviewed EPA's assessment of formaldehyde-associated reproductive and developmental toxicity (NRC, 2011) disagreed with EPA's determination that the epidemiologic evidence indicates a convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes in women. The 2010 Draft Assessment was based on a single occupational study (Taskinen et al., 1999), and the 2011 NRC committee concluded that the pattern of association based on a small number of studies was suggestive, but not convincing (NRC, 2011).

EPA's 2022 Draft Assessment considers a range of developmental and female and male reproductive toxicity endpoints in relation to formaldehyde inhalation exposure. A total of 20 studies involved residential and occupational exposures for females and males. The human endpoints of interest spanned a wide range, including fecundity (probability of conception), spontaneous abortion, gestational age, birthweight, congenital malformations, and postnatal growth. Semen quality

parameters were also examined. A total of 30 animal studies included female reproductive toxicity (e.g., ovarian and uterine pathology, ovarian weight, hormonal changes), effects on the male reproductive system, and developmental toxicity (e.g., decreased survival, decreased growth, increased structural anomalies, and development endpoints). Formaldehyde exposure levels in human occupational studies were relatively high (>0.1 mg/m^3). Formaldehyde exposure levels in animal studies of *medium* or *high* confidence were also high (>5 mg/m^3).

Literature Identification

The steps EPA followed in conducting its literature search and PECO assessment for inclusion and exclusion of studies are described in the Main Assessment and the Appendices. The initial search was conducted in October 2012, with yearly updates through September 2016. A systematic evidence map identified literature from 2017 to 2021. Inclusion and exclusion criteria for human and animal studies are summarized in Appendix A, Tables A-89 and A-90, respectively. The text indicates that 20 human and 35 animal studies were identified for inclusion.

Finding: EPA's process for literature identification, PECO assessment, and study inclusion/exclusion was generally transparent and in line with EPA's state-of-practice methods for the female and male reproductive and developmental outcomes. However, search terms related to birth defects and teratology, such as *congenital anomalies*, were not included in the search.

Study Evaluation

EPA's evaluation of human studies of female reproductive or developmental toxicity resulted in two *medium*-confidence occupational studies of spontaneous abortion, two *low*-confidence studies of congenital malformations, two *medium*-confidence studies of decreased birthweight and head circumference, and five *low*-confidence studies of fecundability and spontaneous abortion. *Low*-confidence animal studies of female reproductive or developmental toxicity had mixed findings for several outcomes. For male reproductive toxicity, the evaluation included one *medium*-confidence human occupational study of sperm motility and other outcomes, and one *low*-confidence human study of sperm count and morphology. Multiple *high*-or *medium*-confidence animal studies using mice or rats contributed to an assessment of histopathological lesions of the testes or epididymes, sperm count, testosterone levels, and organ weight change.

Finding: EPA's outcome-specific criteria for evaluating human studies are consistent with EPA's state-of-practice methods. A summary of key assessment factors specific to human reproductive and developmental outcomes is not provided.

Finding: For human studies, EPA applied the appropriate general criteria for study quality (e.g., epidemiologic biases), consistent with its state-of-practice methods, as were the conclusions for individual studies (e.g., one *medium*-confidence study for effects on time to pregnancy and two *medium*-confidence studies for effects on spontaneous abortion).

Finding: For animal studies, EPA applied the appropriate criteria for study quality (e.g., test substance, dose(s), test animals, evaluation endpoints), consistent with its state-of-practice methods, as were the conclusions for individual studies (e.g., two *medium*-confidence studies and three *high*-confidence studies for male reproductive effects). Potential updates for two

high-confidence studies (Ozen et al., 2002, 2005) and one *medium*-confidence study (Sapmaz et al., 2018) are detailed in Appendix E. However, the potential reassignment of these three studies would not affect synthesis judgments and the next assessment steps since all *medium*- and *high*-confidence studies were considered in the next steps.

Evidence Synthesis and Judgments

The discussion of reproductive and developmental toxicity in the 2022 Draft Assessment is based on an evaluation of all female reproductive and developmental outcomes combined into a single group. With this treatment as a single group, the mix of human evidence, including *medium*-confidence studies (with uncertainty due to random error or bias), would place the evidence within the *moderate* level based on the framework for strength-of-evidence judgments. The justification for combining outcomes was that it would be difficult to distinguish underlying pathogenic events that could yield a delayed recognized pregnancy or fetal loss. Although this rationale may apply generally for delayed time to pregnancy and spontaneous abortion, the broader category of female reproductive and developmental toxicity also encompasses human studies of other "later" developmental outcomes, such as congenital malformations and birthweight.

Finding: Within EPA's framework for synthesizing results from human studies and making judgments, the conclusion of moderate evidence for female reproductive or developmental toxicity is justified. However, combining all reproductive and developmental outcomes in a single group is an oversimplification. EPA could consider separating its evidence synthesis section into early and late events.

Assessment of animal studies revealed *indeterminate* evidence for developmental toxicity and separately, *indeterminate* evidence for female reproductive toxicity. All evaluated studies had *low* confidence with methodological limitations, the majority of which were due to a lack of information about test substance or use of formalin, which can contain methanol, a known developmental and reproductive toxicant. For developmental effects, EPA found no direct evidence of biological plausibility; however, oxidative stress and/or hormone disruption are noted as possible indirect linkages. For female reproductive effects, EPA notes that the biological plausibility of neuroendocrine-mediated mechanisms involving the hypothalamic–pituitary–gonadal–axis is consistent with the alterations of reproductive hormones identified in the *low*-confidence rodent formaldehyde studies.

Finding: The conclusion of indeterminate evidence for developmental toxicity and female reproductive toxicity in animals is consistent with EPA's state-of-practice methods.

For male reproductive toxicity, EPA judged the evidence from human studies to be *slight*. There was one *medium*-confidence study, but the sparseness of the available evidence for multiple reproductive and developmental outcomes and the associated uncertainty provided a reasonable basis for the strength-of-evidence judgment as *slight*.

Finding: The conclusion of slight evidence for male reproductive toxicity in humans is consistent with EPA's state-of-practice methods.

For animal studies of male reproductive toxicity, EPA judged the evidence to be *robust* based on six *medium*- or *high*-confidence studies conducted by three research teams using five cohorts of rats or mice. The text on p. 82 of the Assessment Overview discusses six *medium*- or *high*-

confidence studies, but Table A-36 in Appendix A lists only five studies because one row combines two studies. Nonetheless, it is reasonable to conclude that these six studies were well conducted, although all used high formaldehyde concentrations (>5 mg/m3). The studies found adverse testes and epididymis histopathology, decreased sperm count, altered sperm motility and morphology, and decreased serum testosterone. In addition, several *low*-confidence studies produced consistent results on male reproductive toxicity, although they were also conducted with very high formaldehyde levels (most above >12 mg/m^3). Evidence on the MOA for formaldehyde and male reproductive toxicity is lacking, but indirect effects of oxidative stress and heat shock protein induction were noted in testes or epididymes of exposed rats in the *medium*- and *high*-confidence studies.

Finding: Information provided in the text and tables for animal studies of male reproductive toxicity is inconsistent (see Appendix E).

Overall Conclusions About the Hazard Descriptor

The judgment that the evidence *indicates that* inhalation of formaldehyde *likely* causes increased risk of developmental or female reproductive toxicity in humans (given the appropriate exposure circumstances) was based on *moderate* human evidence and *indeterminate* animal evidence for developmental or female reproductive toxicity.

Finding: The conclusion that the evidence *indicates that* inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans is consistent with EPA's state-of-practice methods.

The judgment that the evidence *indicates that* inhalation of formaldehyde *likely* causes increased risk of reproductive toxicity in men (given the appropriate exposure circumstances) was based on *slight* human evidence and *robust* animal evidence for male reproductive toxicity.

Finding: The conclusion that the evidence *indicates that* inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men is consistent with EPA's state-of-practice methods.

Dose-Response Evaluation

For female reproductive and developmental toxicity, dose-response estimation was based on a single *medium*-confidence study with a time-to-pregnancy endpoint (Taskinen et al., 1999). The 8-hour time-weighted average (TWA) for the intermediate (middle) exposure group was selected as a NOAEL. A UF_H of 10 was applied to the developmental toxicity POD.

Finding: The rationale for study selection, the POD determination, uncertainty factors, and cRfC derivation, including confidence levels, were consistent with EPA's state-of-practice methods.

For male reproductive toxicity, dose-response estimation was based on two *high*-confidence studies in rats exposed to paraformaldehyde for 13 weeks that assessed relative testes weight and serum testosterone endpoints. For decreased testes weight (Ozen et al., 2002), a LOAEL of 12.3 mg/m^3 was adjusted for continuous exposure based on the experimental paradigm to yield a POD_{ADJ} of 2.93 mg/m^3. A final uncertainty factor of 3000 was applied to the male reproductive toxicity testes weight POD. For decreased serum testosterone and decreased mean seminiferous tubule diameter likely associated with decreased serum testosterone (Ozen et al., 2005), a $BMCL_{1SD}$

of 0.208 mg/m^3 was calculated, resulting in a POD_{ADJ} of 0.05 mg/m^3. A final uncertainty factor of 300 was applied to the male reproductive toxicity decreased testosterone POD.

The final uncertainty factors were derived for the two male reproductive endpoints using the following assumptions. First, a UF_A of 3 was applied to both endpoints to account for residual toxicodynamic uncertainties in interspecies extrapolation. Second, a UF_S of 10 was applied to both endpoints to approximate the potential effect of chronic exposure because the studies were conducted over a subchronic duration. Third, a UF_L of 10 was applied to the relative testes weight endpoint, which was based on a LOAEL. Fourth, a UF_H of 10 was applied to both endpoints to account for the limited variability in susceptibility factors encompassed by these typical studies of inbred laboratory animal populations.

Finding: The rationale for exclusion of studies from the dose-response assessment is consistent with EPA's state-of-practice methods and includes analysis of pooled tissues, short exposure duration, single exposure level, and nonpreferred endpoint assessment.

NERVOUS SYSTEM

The 2010 Draft Assessment suggested that the available human studies demonstrated potentially concerning nervous system effects following formaldehyde exposure. However, the 2011 NRC committee concluded that EPA's conclusion regarding nervous system effects was overstated and based on insufficient evidence. In developing the 2022 Draft Assessment, EPA searched for evidence of neurotoxicity in both humans and animals. Outcomes in humans included neurobehavioral (e.g., effects on learning and memory), neurochemical, and neuropathologic effects. Relevant outcomes in animal studies included motor activity, anxiety, habituation, learning and memory, and chemical sensitization.

Literature Identification

The steps EPA followed to conduct its literature search and PECO assessment for inclusion and exclusion of studies are documented in the Main Assessment and the Appendices. A total of 4338 articles were screened for inclusion in the assessment of these outcomes, with 147 being considered for hazard identification (40 human, 60 animal, and 47 in vitro and noninhalation studies) (Appendix A, Figure A-25, p. A-591).

Finding: The process for literature identification and inclusion/exclusion criteria for the review of nervous system effects was transparent.

Finding: EPA elected to exclude headache as a human health outcome for evaluation because of the subjectivity of outcome reporting (Appendix A, Table A-83). Considering that other endpoints included in this assessment, such as sensory irritation, depend on subjective self-reporting, excluding headache based on this criterion is inconsistent.

Recommendation 4.15 (Tier 3): EPA should include studies with headache as an outcome to maintain consistency with other health effect categories. Alternatively, a stronger rationale should be provided for exclusion of headache other than its perceived subjectivity. Headache could be combined with other self-reported neurotoxicity outcomes.

Study Evaluation

Human studies of nervous system outcome-specific criteria were evaluated for strengths and limitations based on principles of epidemiologic study quality, including methods for exposure assessment; windows of exposure; sample size; and potential for selection bias, information bias, and confounding (Tables 1-44 and 1-45; Appendix A, Tables A-84 and A-85). EPA rated some human studies examining neurobehavioral outcomes such as memory impairment and deficits in concentration (Bach et al., 1990; Kilburn et al., 1985, 1987) as having overall *low* confidence. EPA also examined whether there were associations between formaldehyde and amyotrophic lateral sclerosis (ALS) or mortality from neurological disease. These studies estimated formaldehyde exposure based on estimated job exposures. For these included studies, occupational formaldehyde exposure was based on self-report or job exposure matrix (JEM) estimations of level and probability of exposure according to occupational history from tax records. Furthermore, three of the included studies dichotomized formaldehyde exposure into ever versus never exposed, although each attempted to account for duration and timing of exposure.

Finding: Overall, criteria for evaluating human studies were consistent with EPA's state-of-practice methods. However, it is not clear whether the study quality criteria were applied uniformly across studies.

In evaluating animal studies, EPA considered several factors, including possible confounding due to coexposure to methanol, especially when high exposures (>10 mg/m^3) were involved; the potential influence of irritation or changes in olfaction on behavioral measures, with preference given to behavioral studies with a period of latency between exposure and endpoint testing of at least 2 hours; blinding of the outcome assessors for nonautomated assessments; and a preference for outcomes that were deemed sensitive and specific for nervous system effects (Appendix A, Table A-86). Duration of exposure was also considered; however, studies of short-term or even acute duration were not considered to be less informative. Three animal studies (Aslan et al., 2006; Sarsilmaz et al., 2007; Sorg et al., 1998) were deemed to have *medium* confidence.

Finding: Where explanations are provided for confidence assessments for more recently published literature, EPA gives no details about the basis for confidence decisions for controlled exposure studies in humans (Appendix A, Table A-85).

Finding: Regarding human studies, study quality criteria (i.e., selection bias, sample size, exposure assessment, and confounding) were consistent with EPA's state-of-practice methods. However, the reasons for final conclusions on study confidence are not always clear, and there are inconsistencies in the explanations for the confidence ratings. Potential updates to specific studies (e.g., Bellavia et al., 2021; Kilburn, 2000; Pinkerton et al., 2013; Schenker et al., 1982; see also Seals et al., 2017 and Peters et al., 2017) are detailed in Appendix E.

Finding: Regarding animal studies, study quality criteria were consistent with EPA's state-of-practice methods.

Evidence Synthesis and Judgments

EPA summarizes its evidence synthesis for nervous system effects of formaldehyde in Table 1-50. For ALS, EPA determined that the human evidence was *slight*, that the animal evidence was

indeterminate, and that an effect of formaldehyde on ALS would be surprising in terms of biological plausibility because of a lack of systemic distribution (and a lack of relevant mechanistic studies in humans). For developmental neurotoxicity, the human evidence was *indeterminate*, and the animal evidence was considered *slight*, although some evidence of relevant molecular and neurochemical changes in animals provided biological plausibility. For several types of neurobehavioral effects, the human evidence was considered *indeterminate* or *slight*, and the animal evidence was considered *slight*, with some animal evidence that provided potential biological plausibility.

> Finding: With human studies having *medium* and *high* confidence for ALS and *low* or *not informative* confidence for neurobehavioral outcomes (e.g., memory, mood changes), along with *medium* confidence for animal studies on developmental neurotoxicity, the basis for the overall evidence judgment is not well articulated.

The 2022 Draft Assessment concludes that the underlying MOA for neurotoxicity for inhaled formaldehyde exposures is unknown. Although the text acknowledges that it is not likely that inhaled formaldehyde would be transported directly to the central nervous system, there are several potential indirect mechanisms for formaldehyde to impact the nervous system. Most notable is repeated sensory responses, which is recognized as a neurogenic pathway for immune and respiratory outcomes. However, the inflammatory responses could also elicit nervous system outcomes.

> Finding: The 2011 NRC committee found the discussion of the neurogenic MOA in the 2010 Draft Assessment to be vague and speculative. In the 2022 Draft Assessment, EPA provides a much more thorough overview of potential MOAs without speculative conclusions.

Overall Conclusions About the Hazard Descriptor

The 2022 Draft Assessment notes that evidence on noncancerous nervous system effects is weak and lacking, and thus concludes that the *evidence suggests, but is not sufficient to infer* that inhaled formaldehyde may lead to adverse neurological outcomes in humans. This assessment is based on limited animal studies having *medium* confidence and several human studies having *medium* and *high* confidence for ALS and *low* or *not informative* confidence for neurobehavioral outcomes (e.g., memory, mood changes).

> Finding: The conclusion that the *evidence suggests but is insufficient to infer* significant long-term neurotoxicity from inhaled formaldehyde in humans is consistent with EPA's state-of-practice methods, given the number of studies with final assessments of confidence in the *not informative* to *low* range, and very few being assessed as having *medium* or *high* confidence.

Dose-Response Evaluation

EPA did not derive a POD or cRfC for nervous system effects following formaldehyde inhalation.

DERIVATION OF THE RfC

Section 2.1 of the Main Assessment broadly defines EPA's approach to the dose-response assessment of noncancer effects due to formaldehyde inhalation. The dose-response assessment followed the selection of studies and endpoints receiving EPA's rating of *evidence demonstrates* or *evidence indicates*. EPA identified three human studies for sensory irritation, one human study

for pulmonary function, two human studies for allergic conditions, two human studies for current asthma, two human studies for asthma control, one human occupational study for a developmental outcome, two animal studies for respiratory tract pathology, and two animal studies for male reproductive toxicity.

These individual studies were then considered for risk estimation in four steps: (1) conducting dose-response modeling when data are adequate and deriving a POD; (2) deriving a cRfC; (3) selecting an organ- or system-specific RfC (osRfC); and (4) selecting an overall RfC. In keeping with prior recommendations from the NRC (NRC 2010, 2011), EPA developed multiple cRfCs.

To determine a POD for each selected study/endpoint, EPA either determined a NOAEL/LOAEL based on reported study data or reanalyzed dose-response data using its Benchmark Dose Software (BMDS) when the exposure-response data were deemed adequate for such reanalysis. EPA often lacked the raw data and extracted secondary data, such as exposure-group or model-predicted means. In the case of benchmark dose (BMD) analysis, EPA then estimated the benchmark concentration lower bound (BMCL) and used it as a POD.

Following its guidelines for derivation of the RfC (EPA's *Review of the Reference Dose and Reference Concentration Processes* [EPA, 2002, Section 4.4.5]), EPA applied up to five uncertainty factors to the PODs. These uncertainty factors were UF_A for interspecies uncertainty, UF_H for variability across the human population, UF_L for LOAEL-to-NOAEL uncertainty, UF_S for uncertainty in subchronic to chronic or lifetime exposure extrapolation, and UF_D for database uncertainty. The results of EPA's derivation of cRfCs for noncancer endpoints are summarized in Table 4-3.

EPA then determined an osRfC for each organ/system by qualitatively weighing the confidence and uncertainty of each cRfC. EPA finally chose an overall RfC by qualitatively weighing uncertainty and variability across all osRfCs. EPA used graphic tools (e.g., Figures 2-2 and 2-3) to aid in the final RfC determination.

Finding: The Main Assessment and Appendices reflected EPA's efforts to follow its various guidelines and are generally consistent with its 2022 IRIS Handbook. The committee identified concerns with the dose-response approach taken for some studies (e.g., Hanrahan et al., 1984, as detailed in Table 4-3 and footnotes). Other occasional issues concerning consistency and accuracy were sometimes the result of omissions or inadequate documentation. More than a dozen specific examples are detailed in Appendix E, which provides additional suggestions regarding EPA's consideration of the following studies: Kulle et al. (1987); Andersen and Molhave (1983); Krzyzanowski et al. (1990); Dannemiller et al. (2013); Woutersen et al. (1989); Ozen et al. (2002, 2005); and Kerns et al. (1983).

Recommendation 4.16 (Tier 2): EPA should carefully address the following points regarding the derivation of the RfC:

- **Fully disclose data extracted from original study reports using HERO or other means.**
- **Cite relevant guidance documents regarding the use of a mean versus median and arithmetic mean versus geometric mean to estimate a lowest observed adverse effect level or no observed adverse effect level.**
- **In reanalyzing data from published studies, the use of raw data is preferred. Aggregated data may be used when appropriate. At a minimum, group size, group mean, and a measure of variance (e.g., group standard deviation or standard error of the mean) for each exposure level are needed to capture data variation in a reanalysis of dose-response.**

TABLE 4-3 Selected Noncancer Studies/Endpoints and Derived Points of Departure (PODs) and Candidate Reference Concentrations (cRfCs)

Study/Reference	Endpoint	POD (mg/m^3)	EPA BMDS Modeling or Reanalysis	Uncertainty Factor (UF^a)	cRfC[b] (mg/m^3)	Basis of osRfC
Sensory Irritation						
Hanrahan et al. (1984)	Prevalence of eye irritation	**Benchmark concentration $(BMC)_{10}$ = 0.19[c]**	Yes	Uf_H = 10	**Q**	**Yes**
Kulle et al. (1987)	Prevalence of eye irritation	**BMC_{10} = 0.85**	Yes	Uf_H = 10	**Q**	
Andersen and Molhave (1983)	Prevalence of eye irritation	**BMC_{10} = 0.37**	Yes	Uf_H = 10	**Q**	
Pulmonary Function						
Krzyzanowski et al. (1990)	Peak expiratory flow rate	**BMC_{10} = 0.033** **Benchmark concentration lower bound $(BMCL)_{10}$ = 0.021**	No	Uf_H = 3	**0.007**	**Yes**
Immune System: Allergic Conditions						
Annesi-Maesano et al. (2012)	Rhinoconjunctivitis prevalence (children)	**NOAEL = 0.024 LOAEL = 0.040**	No	Uf_H = 3	**0.008**	**Yes**
Matsunaga et al. (2008)	Atopic eczema	**NOAEL = 0.046 LOAEL = 0.062**	No	Uf_H = 3 Uf_S = 3	**0.005**	
Immune System: Current Asthma						
Krzyzanowski et al. (1990)	Prevalence of current asthma (children)	**NOAEL = 0.062** **LOAEL = 0.092**	No	Uf_H = 10	**0.006**	**Median of three current asthma and asthma control studies**
Annesi-Maesano et al. (2012)	Prevalence of current asthma (children)	**NOAEL = 0.042** **LOAEL = NA**	No	Uf_H = 3;	**0.014**	
Immune System: Asthma Control						
Venn et al. (2003)	Asthma control (children) (3-day residence exposure)	**NOAEL = 0.027** **LOAEL = 0.041** **$BMCL_{05}$ = 0.013**	Yes[d]	Uf_H = 3	**0.004**	

continued

TABLE 4-3 *continued*

Study/Reference	Endpoint	POD (mg/m^3)	BMDS Modeling or Reanalysis	Uncertainty Factor (UF^a)	cRfC[b] (mg/m^3)	osRfC
Dannemiller et al. (2013)	Asthma control (children)	**NOAEL = 0.042**[e] **LOAEL = NA**			**ND**	
Respiratory Pathology (animal studies)						
Kerns et al. (1983)	Level I sagittal section squamous metaplasia: nasal turbinates, Fischer 344 rats	**$BMCL_{10}$ = 0.484 (HEC)** **$BMCL_{10}$ = 0.086 (HEC, adjusted for continuous exposure)**	Yes	Uf_A = 3 Uf_H = 10 Uf_S = 3	**0.0009**	
Woutersen et al. (1989) (28-month exposure)	Squamous metaplasia: nasal turbinates, Wistar rats	**$BMCL_{10}$ (HEC, adjusted for continuous exposure) = 0.094**	Yes	Uf_A = 3 Uf_H = 10	**0.003**	**Yes**
Developmental Toxicity (occupational cohort)						
Taskinen et al. (1999)	Time to pregnancy	**NOAEL = 0.106 LOAEL = 0.278**	No	Uf_H = 10	**0.01**	**Yes**
Male Reproductive Toxicity (animal studies)						
Ozen et al. (2002) (13-week exposure)	Relative testes weight	**LOAEL = 12.3 POD_{ADJ} = 2.93**	**No**[f]	Uf_A = 3 Uf_H = 10 Uf_S = 10 Uf_L = 10	**0.001**	**Yes**
Ozen et al. (2005)	Serum testosterone, Wistar rats	**BMC = 0.284**[g] **BMCL = 0.208 POD_{ADJ} = 0.05**	**Yes**	Uf_A = 3; Uf_H = 10; Uf_S = 10	**0.0002**	

NOTES:

[a.] All UFs not reported have a value of 1.

[b.] Q = the committee had concerns about EPA's approach to deriving the POD; ND = EPA did not derive a cRfC.

[c.] EPA extracted means of the original dose-response model of Hanrahan et al. (1984) to refit a logistic regression model with only eight data points (one per exposure level). The resulting model failed to recapture the data variation within each exposure group, leading to artificially smaller standard errors associated with the refitted model and an inappropriate BMCL.

[d.] EPA derived BMCL using models reported in Venn et al. (2003).

[e.] Dannemiller et al. (2013) report a geometric mean of 54.0 and 34.4 ppb in the "very poor control" group and "all others" group, respectively. EPA was not explicit as to whether the NOAEL of 0.042 (mg/m^3) was based on the geometric mean = 34.4 ppb, or whether EPA obtained raw data to derive the arithmetic mean (Table 2-4). The reference in the last row of Table 2-4 should be Dannemiller et al. (2013).

[f] EPA fit an exponential model for relative testes weight (Appendix B, Table B-13 and Figure B-15). EPA used both standard deviation (1 SD and 10% range of data variation as the BMR levels and derived $BMCL_{1sd} = 0.204$ and $BMCL_{10RD} = 3.24$ (mg/m^3), but decided to report the LOAEL from the Ozen (2002) without explanation.
[g] BMR level was defined by serum testosterone weight shift more than 1 SD relative to the comparison group.
Abbreviations: BMC= benchmark concentration; BMCL= benchmark concentration lower bound; BMDS= benchmark dose software; BMR= benchmark response; cRfC= candidate reference concentration; HEC= human equivalent concentration; LOAEL= lowest observed adverse effect level; NOAEL= no observed adverse effect level; osRfC= organ or system-specific reference concentration; POD= point of departure; POD_{ADJ} = adjusted point of departure; RfC= reference concentration; SD= standard deviation; UF= uncertainty factor.

- **Avoid fitting a dose-response model that has as many parameters as the number of distinct aggregated data points taken from the published literature. Report and consider only models that meet the goodness-of-fit criteria EPA accepts.**

Recommendation 4.16 (Tier 2) *(continued)***: EPA should carefully address the following points regarding the derivation of the RfC:**

- **To ensure that the resulting benchmark concentration lower bound is not artificially overestimated, better account for within-group variability in the dose-response analysis of Hanrahan et al. (1984) to address limitations arising from reliance on only secondary, aggregated rates per exposure group that were extracted from the plot of the originally fitted model.**
- **Be more explicit as to how the final RfC was chosen (in Figure 2-2 of the 2022 Draft Assessment and elsewhere).**

Additionally, EPA should address the following points (Tier 3):

- Handle dose-response modeling of correlated data (e.g., Andersen and Molhave, 1983; Kulle et al., 1987) by standard statistical methods, employing a two-step process that involves first fitting a dose-response model for correlated data using standard statistical methods, and then deriving BMC and BMCL using the fitted model.
- Develop methodology that goes beyond a qualitative display of the variability and uncertainty of cRfCs or osRfCs. The current EPA method has limited reproducibility because of the lack of detail. A meta-analysis approach offers a viable option.

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5
Cancer

This chapter provides the committee's assessment of the hazard identification and dose-response analysis for cancer endpoints in the 2022 Draft Assessment (EPA, 2022a). The 2022 Draft Assessment presents an evaluation of the evidence for cancer hazard and separately for dose-response in two parts: for the respiratory system and for nonrespiratory sites. This separation is appropriate and concordant with previous National Research Council (NRC) reports, which separately consider the portal-of-entry and systemic effects of formaldehyde (NRC 2011, 2014). These past reports define *portal-of-entry* effects as those arising from direct interaction of inhaled or ingested formaldehyde with the affected cells or tissues, and *systemic* effects as those that occur beyond tissues or cells at the portal of entry.

HAZARD IDENTIFICATION

The 2022 Draft Assessment includes detailed evaluation of the evidence from human, animal, and mechanistic studies that pertain to several specific cancer sites (Appendix A, Section A.5.9). Following systematic identification and evaluation of the relevant literature, EPA determined that for the portal-of-entry effects, cancers of the upper respiratory tract (i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer) would be evaluated in detail. For systemic effects, EPA was determined that cancers of the lymphohematopoietic system (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia) would also be evaluated in detail. EPA determined further that the evidence regarding the potential for formaldehyde exposure to cause cancers at other sites (i.e., lung, brain, bladder, colon, pancreas, prostate, skin) and non-Hodgkin lymphoma was highly limited, and therefore did not systematically evaluate these cancers.

In the past 20 years, several authoritative agencies and organizations have classified formaldehyde according to whether it poses a cancer hazard (Table 5-1). Unequivocal independent conclusions that formaldehyde is carcinogenic in humans have been reached by the International Agency for Research on Cancer (IARC) (2006, 2012), the National Toxicology Program (NTP) (2011), and the NRC (2014). The European Union (EU) Committee on Occupational Exposure Limits[1] concluded that formaldehyde poses a human cancer hazard, but with a threshold-based dose-response relationship. Two previous assessments have classified formaldehyde as a presumed[2] or potential (NIOSH, 1988) human carcinogen. The 2022 Draft Assessment concludes that the *evidence demonstrates* that formaldehyde inhalation causes cancer in humans and identifies nasopharyngeal and sinonasal cancers, as well as myeloid leukemia, as types of cancers with this level of evidence.

> Finding: The overall organization of the information on cancer effects of formaldehyde is appropriate and commensurate with prior recommendations from the NRC. The focus on respiratory tract cancers and cancer of the lymphohematopoietic system, but not other cancer types, is appropriate and justified.

[1] Commission Directive (EU) 2017/164. 2017. Establishing a fourth list of indicative occupational exposure limit values pursuant to Council Directive 98/24/EC, and amending Commission Directives 91/322/EEC, 2000/39/EC and 2009/161/EU. *Official Journal of the European Union* L27:115–120.
[2] Commission Regulation (EU) No 605/2014. 2014. *Official Journal of the European Union* L167:36–49.

TABLE 5-1 Cancer hazard classifications of formaldehyde

Agency	Year	Cancer Hazard Statement	Source
EPA	2022	The *evidence demonstrates* that formaldehyde inhalation causes [cancer] in humans	2022 Draft Assessment (EPA, 2022a)
European Commission, Scientific Committee on Occupational Exposure Limits (SCOEL)	2017	Carcinogen group C: genotoxic carcinogen with a mode-of-action-based threshold	SCOEL et al. (2016, p. 9)
National Research Council (NRC)	2014	"the committee concludes that formaldehyde should be listed in the [Report on Carcinogens] as 'known to be a human carcinogen'"	NRC (2014, p. 19)
European Union Harmonised classification under the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) (i.e., Annex VI of Regulation [EC] No. 1272/2008)	2014	Carcinogen Category 1B, presumed to have carcinogenic potential for humans (classification is largely based on animal evidence)	European Commission, Commission Regulation (EU) No. 605/2014, L167, p. 43
International Agency for Research on Cancer (IARC)	2012	Carcinogenic to humans (Group 1)	IARC (2012, Volume 100f, p. 430)
National Toxicology Program (NTP)	2011	Known to be a human carcinogen	NTP (2011)
IARC	2006	Carcinogenic to humans (Group 1)	IARC (2006)
National Institute for Occupational Safety and Health (NIOSH)	1981 1988	Potential occupational carcinogen	NIOSH 1981, 1988

LITERATURE IDENTIFICATION AND EVALUATION OF STUDY METHODS

While the 2022 Draft Assessment has been in development over several decades, most critical studies of cancer in humans and animals were published eight or more years ago. Studies on the potential mechanisms of formaldehyde carcinogenicity represent a dynamic body of literature. Methods and procedures for literature identification and evaluation of each study are presented in several parts of the 2022 Draft Assessment. Chapter 4.1 of the Assessment Overview presents a summary of the process, Sections 1.2.5 and 1.3.3 of the "Toxicological Review of Formaldehyde: Inhalation" provide more granular detail with references to the Appendix for additional information about respiratory tract and nonrespiratory tract cancers. The Appendix provides specific details about the population, exposure, comparator, and outcome (PECO) questions raised and associated inclusion and exclusion criteria for the human and animal studies of health effects, the bibliographic databases, search terms, and specific strategies used to search them (Appendix A, Sections A.4.7, A.5.5, and A.5.9). In addition, Appendix A, Section A.5.9 provides literature flow diagrams that summarize the results of the sorting process using the defined criteria and indicating the number of studies that were selected for consideration in the assessment through 2016. Because the completed 2017 draft assessment was suspended by EPA until 2021, EPA used a systematic evidence map (SEM) to conduct additional searches for any new (January 2016–May 2021) publications to be considered in updating the 2017 draft. The methods and results of this SEM process are provided in Appendix F. With respect to cancer endpoints and mechanistic evidence, several additional studies were identified, and were categorized as "possibly impactful" or "not impactful."

Finding: With respect to cancer hazard evaluation, EPA adequately and transparently evaluated the scientific literature using methods consistent with its state-of-practice methods. Sections of the 2022 Draft Assessment describing the methods used for identifying and evaluating studies of formaldehyde and cancer in humans and animals, as well as mechanistic evidence, are voluminous and extensive but well organized. EPA did not have the final version of the IRIS Handbook while it was developing the 2022 Draft Assessment, and also had the additional challenge of a four-year hiatus during which no work could be performed on this assessment. Nonetheless, the overall process used and choices made are consistent with EPA's state-of-practice methods and responsive to the recommendations of the 2011 NRC committee.

STUDY EVALUATION

EPA's evaluation of the studies identified through its literature searches was separated into several domains. Individual observational epidemiological studies were evaluated for several aspects of bias and sensitivity. An overall confidence classification (*high*, *medium*, or *low* confidence or *not informative*) was then developed by integrating the judgments for each category of bias and sensitivity for each study or for a specific analysis within a study, as detailed in Appendix A, Table A-28. Experimental animal studies were evaluated and assigned confidence ratings based on expert judgment regarding each study's experimental details related to predefined criteria within five study feature categories: exposure quality, test subjects, study design, endpoint evaluation, and data considerations and statistical analysis. Explanation of these criteria is provided in Appendix A, Table A-29. Given the volume and diversity of endpoints of individual mechanistic studies, these studies were not evaluated systematically; instead, the focus was on those studies pertaining to specific well-established key events for formaldehyde-induced cancer: genotoxicity and cell proliferation. Despite the heterogeneity of mechanistic studies conducted over the years, EPA carefully considered, where appropriate, exposure assessment, study design, outcome ascertainment, and comparison groups for potential sources of bias and their potential impact. Evaluation of exposure in individual studies was considered especially relevant, and detailed description of the approaches to and criteria for exposure assessment are provided for observational epidemiological and animal studies.

Finding: EPA followed a transparent and reasonable approach in evaluating the studies relevant to cancer in humans and in animals, and in providing mechanistic evidence to support its analysis. EPA followed the state of practice for literature review at the time the assessment was being conducted in evaluating studies of cancer outcomes in humans and in animals. For mechanistic evidence, EPA used a narrative review approach for summarizing the voluminous evidence on mechanistic events that are known to be associated with cancers of the upper respiratory tract and lymphohematopoietic cancers. Studies supporting and refuting the proposed mechanistic hypotheses were evaluated in a balanced and transparent manner.

SYNTHESES OF RESULTS AND SYNTHESIS JUDGMENTS

Synthesis of various lines of evidence (human, animal, and mechanistic) on the cancer-related effects of formaldehyde has previously been conducted by various authoritative agencies and organizations. Because numerous other agencies evaluated the same domains and synthesized results and judgments, a summary of the synthesis judgments in the 2022 Draft Assessment and

other published cancer hazard evaluations is provided in Tables 5.2–5.4. Overall, the synthesis judgments in the 2022 Draft Assessment are consistent with those of other authoritative agencies and organizations, while considering more endpoints and additional studies that have become available over time.

Cancers of the Upper Respiratory Tract

For upper respiratory tract cancers, the 2022 Draft Assessment first presents a synthesis for human, animal, and mechanistic evidence separately, and then overall for evidence integration.

For studies of human health effects, evidence is synthesized for cancer types based on the anatomical location of diagnoses commonly reported on death certificates because the histological type of each cancer is reported infrequently on death certificates.

- For ***nasopharyngeal cancer in humans***, the 2022 Draft Assessment evaluates 20 primary epidemiological studies—12 case-control and eight cohort study designs. The text explains confidence level determinations for each individual study (Appendix F, Table 1-32). Two additional possibly impactful studies for this cancer type were identified through systematic evidence mapping (Table F-8), and both provided additional analyses of the studies that had already been evaluated. Overall, the consistency of the observed association was judged on the basis of 17 studies that were deemed informative (with various levels of confidence). The Draft Assessment states that 14 of the 17 studies reported increased risks of nasopharyngeal cancer with at least one metric of formaldehyde exposure, often with both clear statistical significance and exposure-response relationships. Also, EPA notes that results showing increased risks were consistently reported in populations from both high-risk areas (e.g., with endemic Epstein-Barr infection) and low/medium-risk areas, as well as across study populations with different proportions of histological cancer subtypes. The studies that did not report increased risks of nasopharyngeal cancer were deemed to have *low* confidence, and EPA discusses the basis for the confidence determinations for those studies. The overall synthesis judgment for consistency of the findings was that the majority of studies from different populations, in different locations and exposure settings, and using different study designs reported increased risks of nasopharyngeal cancer associated with formaldehyde exposure. In addition, EPA implies that the strength of the observed association, and the temporal and exposure-response relationships was also evident despite the variable magnitude of the relative risk estimates. Discussion of why potential impacts of selection bias, information bias, confounding bias, and chance could be excluded in the overall evidence synthesis is also provided. In the overall synthesis of epidemiological evidence, EPA concludes that the available human studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of nasopharyngeal cancer.

TABLE 5-2 Formaldehyde Cancer Conclusions by Site: Evaluations of Epidemiological Data by EPA, the National Research Council (NRC), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP)

Assessment	Nasopharyngeal Cancer	Sinonasal Cancer	Myeloid Leukemia	Oro-/Hypo- Pharyngeal Cancer	Multiple Myeloma	Hodgkin Lymphoma
EPA (2022a, Draft Assessment)	The evidence demonstrates that formaldehyde inhalation causes nasopharyngeal cancer in humans, given appropriate exposure circumstances.	The *evidence demonstrates* that formaldehyde inhalation causes sinonasal cancer in humans, given appropriate exposure circumstances.	The *evidence demonstrates* that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances.	The available *evidence suggests*, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/ hypopharyngeal cancer in humans, given appropriate exposure circumstances.	The available *evidence suggests*, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma, given the appropriate exposure circumstances.	The available *evidence suggests*, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma, given the appropriate exposure circumstances.
NRC (2014)	"the committee concludes that the relationship is causal …" (p. 14)	the relationship between formaldehyde and sinonasal cancer is causal …" (p. 14)	"the committee concludes that there is a causal association between formaldehyde exposure and myeloid leukemia …" (p. 16)	Not specifically discussed	"A single, large, high-quality study (Beane Freeman et al., 2009) found evidence of increased risk of Hodgkin lymphoma and multiple myeloma in those who had a history of high peak exposures. Those findings do not appear to be supported by other epidemiologic evidence and, in the committee's view, constitute insufficient evidence of effects" (p. 120)	
IARC (2012, Volume 100F)	"Formaldehyde causes cancer of the nasopharynx …" (p. 430)	"Also, a positive association has been observed between exposure to formaldehyde and sinonasal cancer." (p. 430)	"Formaldehyde causes … leukaemia." (p. 430)	"the results are inconsistent" (p. 409)	"the results are inconsistent" (p. 409)	"the results are inconsistent" (p. 409)
NRC (2011)[a]	"it would be consistent with EPA guidelines to draw a causal conclusion for NPC [nasopharyngeal cancer] and formaldehyde on the basis of the combination of the	"The committee concluded that EPA's causal determination regarding sinonasal cancer is consistent with its cancer guidelines." (p. 85)	Declined to opine on whether the relationship was causal based on EPA guidelines: "The committee recommends that EPA revisit arguments that support determinations of causality for specific LHP	"little evidence about any upper respiratory cancer site other than NPC or sinonasal cancer was offered." (p. 86)	Declined to opine. (see myeloid leukemia entry for explanation).	Declined to opine. (see Myeloid leukemia entry for explanation).

continued

TABLE 5-2 *continued*

Assessment	Nasopharyngeal Cancer	Sinonasal Cancer	Myeloid Leukemia	Oro-/Hypo- Pharyngeal Cancer	Multiple Myeloma	Hodgkin Lymphoma
NRC (2011)[a] *(cont.)*	epidemiologic findings with experimental data and mechanistic data on formaldehyde." (p. 85)		[lymphohematopoietic] cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality." (p. 11)			
NTP (2011)	Causal: Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and … myeloid leukemia among individuals with higher measures of exposure to formaldehyde …, which cannot be explained by chance, bias, or confounding. (p. 195)		"no consistent findings of higher risk among the individuals with the highest exposure levels" (see also NTP 2010).		"Because the evidence for these two types of cancer [myeloma and Hodgkin lymphoma] is mainly limited to the NCI [National Cancer Institute] cohort study, a causal association is not established"	
IARC (2006, Volume 88)	"Overall, the Working Group concluded that the results of the study of industrial workers in the USA, supported by the largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans." (p. 274)	"there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans." (p. 277)	"there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde." (p. 276)	"the overall balance of epidemiological evidence did not support a causal role for formaldehyde in relation to these other cancers." (p. 27)	Data were reviewed but not discussed for these cancers in the summary and evaluation of the human data (Section 5.2, p. 274–277)	

NOTE: [a] The NRC (2011) conclusions are based on integration over the three data streams—human, animal, and mechanistic evidence.

TABLE 5-3 Formaldehyde Cancer Conclusions: Evaluations of Animal Data by EPA, the National Research Council (NRC), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP)

Assessment	Synthesis Judgments for Animal Evidence
EPA (2022a, Draft Assessment)[a]	**Nasopharyngeal Cancer**: "*Robust* … • Tumors of the respiratory tract (predominantly nasal squamous cell carcinomas, SCCs, but including other epithelial and nonepithelial tumors) were consistently observed in mice and in several strains of rats in numerous *high* and *medium* confidence studies, but not in hamsters, generally at formaldehyde levels above 6 mg/m3. • The lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure • The development of these lesions, particularly the SCCs, depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Most notably, the lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level." (pp. 1–338)
	Sinonasal Cancer: "*Moderate* … Same evidence base as for nasopharyngeal carcinoma (NPC) above …. Note: tumors were not reported in the maxillary sinus of exposed animals." (pp. 1–339)
	Oropharyngeal /Hypopharyngeal Cancer: "*Slight*… • While most findings in animals were localized to the nasal cavity, some data suggest that changes in more caudal (e.g., in the trachea) regions, including evidence of dysplasia (a dedicated pre-neoplastic lesion) in one study, can occur with very high formaldehyde exposures and/or different breathing patterns (e.g., oronasal breathing in monkeys). • Changes in the more caudal URT tissues most relevant to OHPC were generally less direct indicators of cancer development, were less severe, or occurred only at very high exposure levels." (pp. 1–340)
	Lymphohematopoietic: "*Indeterminate* for any LHP cancer type … Overall, the available data do not provide evidence supporting the development of LHP cancers in a *high* confidence chronic bioassay of rats and mice, a second *medium* confidence rat bioassay, and two other *low* confidence, long-term exposure studies." (pp. 1–543)
NRC (2014)	"There is sufficient evidence of carcinogenicity in animals based on malignant and benign tumors in multiple species, at multiple sites, by multiple routes of exposure, and to an unusual degree with regard to type of tumor." (p. 18)
IARC (2012, Volume 100F)	"There is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde." (p. 430)
NRC (2011)	"The respiratory tract is considered to be a plausible location of formaldehyde-induced cancers in humans because these cancers occur at the site of first contact and because studies have shown an increased incidence of nasal tumors in rats and mice exposed to formaldehyde …" (p. 9)
NTP (2011)	"There is sufficient evidence for the carcinogenicity of formaldehyde from studies in experimental animals. Formaldehyde caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure."
IARC (2006, Volume 88)	"There is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde." (p. 280)

NOTE: [a] The 2022 Draft Assessment (EPA, 2022a) uses the categories for the synthesis judgments for animal evidence in the 2022 IRIS Handbook (EPA, 2022b), using the terms r*obust* (strong signal of effect with very little uncertainty), *moderate* (signal of effect with some uncertainty), *slight* (signal of effect with large amount of uncertainty), and *indeterminate* (signal cannot be determined for or against an effect).

TABLE 5-4 Formaldehyde Cancer Conclusions by Site: Evaluations of Mechanistic Data by EPA, the National Research Council (NRC), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP)

Assessment	Portal-of-Entry Effects	Systemic Effects
EPA (2022a, Draft Assessment)	"the evidence is sufficient to conclude that a mutagenic MOA [mechanism of action] of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity." (pp. 1–558) "While uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity" (pp. 1–559)	"Taken together, it appears that mechanisms yet to be elucidated that do not involve direct interactions of formaldehyde in the bone marrow need to be considered, and that either the mechanistic pathways stimulated by formaldehyde are different in animals or that the existing animal models tested thus far do not characterize the disease process in humans for these cancers. The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown." (pp. 1–559)
NRC (2014)	"There is experimental evidence that, due to its chemical reactivity, formaldehyde exerts genotoxic and mutagenic effects and cytotoxicity followed by compensatory cell proliferation at the portal of entry in animals and humans exposed to formaldehyde; this provides biologic plausibility of a relationship between formaldehyde exposure and cancer" (p. 15)	"The mechanistic events that were considered by the committee to be relevant to the plausibility of formaldehyde-associated tumors beyond the portal of entry included genotoxicity and mutagenicity, hematologic effects, and effects on gene expression. Overall, in mechanistic studies of experimental animals and exposed humans, the evidence is largely consistent and strong. Both temporal and exposure–response relationships have been demonstrated in studies of humans and animals exposed to formaldehyde. The committee concludes that these findings provide plausible mechanistic pathways supporting a relationship between formaldehyde exposure and cancer, even though the potential mechanisms of how formaldehyde may cause such systemic effects are not fully understood. It would be desirable to have a more complete understanding about how formaldehyde exposure may cause systemic effects, but the lack of known mechanisms should not detract from the findings of an association between formaldehyde exposure and myeloid leukemia in epidemiology studies." (pp. 16–17)
IARC (2012, Volume 100F)	"Mechanistic evidence supporting a causal relation between inhalation of formaldehyde and induction of cancer of the nasopharynx and nasal sinuses is based on the chemical reactivity of formaldehyde in producing DNA–protein crosslinks, and its genotoxicity in vitro and in vivo, including in the nasal cells of exposed humans…" and "Local effects in the nasal passages, genotoxicity, and cell-proliferation rate appear to be the major determinants of nasal carcinogenicity after exposure to formaldehyde." (p. 427)	"Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430)

NRC (2011)	"The committee concludes that two primary modes of action have been observed to contribute to formaldehyde-induced carcinogenicity in nasal tissues: mutagenicity and cytotoxicity with compensatory cell proliferation. There is no doubt that formaldehyde is a DNA-reactive chemical that produces DNA adducts (DNA protein cross-links and DNA-DNA cross-links) that, if not repaired, can lead to mutations and clastogenesis." (p. 45)	"In the case of hematopoietic cancers, particularly leukemia, much less is known about potential modes of action other than mutagenicity, which has been demonstrated in vitro and in a few studies of occupationally exposed humans. Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (p. 45)
NTP (2011)	"Understanding of the mechanisms is more advanced for nasal tumors than for lymphohematopoietic cancer. There is evidence for a genotoxic mode of action for both types of cancer. Formaldehyde is a direct-acting genotoxic compound…." (p. 4, 15th RoC) "Inhalation-exposure studies in experimental animals have shown that airway deposition and cytotoxicity-induced cellular proliferation also are important factors in the carcinogenicity of formaldehyde to nasal cells." (p. 4, 15th RoC)	"Understanding of the mechanisms is more advanced for nasal tumors than for lymphohematopoietic cancer. There is evidence for a genotoxic mode of action for both types of cancer." (p. 4, 15th RoC) "The mechanisms by which formaldehyde causes toxicity at distal sites are unknown" (p. 5, 15th RoC)
IARC (2006, Volume 88)	"The current data indicate that both genotoxicity and cytotoxicity play important roles in the carcinogenesis of formaldehyde in nasal tissues." (p. 279)	"on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." (p. 280)

- For ***sinonasal cancer in humans***, the 2022 Draft Assessment evaluates 20 primary epidemiological studies—7 case-control, 12 cohort study designs, and 1 pooled analysis. The draft explains confidence level determinations for each individual study (Table 1-32). No additional possibly impactful studies for this cancer type were identified through systematic evidence mapping (Appendix F, Table F-8). Overall, the consistency of the observed association was judged on the basis of 17 studies that were deemed *informative* (with various levels of confidence). These studies examined different populations, in different locations, under different exposure settings and used different study designs. Because of the extremely rare occurrence of this type of cancer in humans, a large number of informative studies were classified as having *low* confidence because of the small population size. The overall synthesis judgment for consistency of the findings was that the majority of the studies of different populations, in different locations and exposure settings, and using different study designs reported increased risk of sinonasal cancer associated with formaldehyde exposure that was unlikely to have been confounded by coexposure to wood dust. In addition, EPA implies that the strength of the observed association and temporal and exposure-response relationships was also evident. EPA concluded that the observations of multiple instances of very strong associations in different settings reduce the likelihood that chance, confounding, or other biases can explain the observed associations. In its overall synthesis of the epidemiological evidence, EPA concluded that the available human studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of sinonasal cancer.
- For ***other respiratory tract cancers (oropharyngeal/hypopharyngeal and laryngeal) in humans***, the 2022 Draft Assessment notes that there were fewer epidemiological studies to evaluate, and that it was difficult to discern the exact anatomical locations of the cancers that were evaluated in some studies. For oropharyngeal/hypopharyngeal cancer, EPA evaluated data from nine reports on six distinct study populations—four reports on three cohort studies and five reports on three case-control studies. For laryngeal cancer, the evaluation included 16 *informative* studies—12 cohort studies and 4 case-control studies. The 2022 Draft Assessment concludes that the available epidemiological studies provide only *slight* (for oropharyngeal/hypopharyngeal cancer) or *indeterminate* (for laryngeal cancer) evidence with which to assess the potential for an association between formaldehyde exposure and an increased risk of these cancers because of the challenges with consistency, strength, and temporal and/or exposure-response observations, as well as the potential impact of selection bias, information bias, confounding bias, and chance.

Finding: With respect to cancer hazard identification for respiratory tract cancers in humans exposed to formaldehyde, EPA synthesized the current state of the science in a manner consistent with its state-or-practice methods and presents conclusions based on its expert judgment with the support of the available scientific evidence.

Recommendation 5.1 (Tier 2): While the narrative describing the application of criteria for each site is well done, EPA should enhance clarity by providing explicit statements in section 1.2.5 summarizing synthesis judgments for each criterion (consistency, strength, temporal relationship, exposure-response relationship, etc.).

Recommendation 5.2 (Tier 2): For consistency, EPA should add a summary of the data and evidence synthesis for laryngeal cancer after page 103 of the Assessment Overview.

For studies of respiratory tract cancers in animals, evidence was synthesized for cancer types based on the histopathological classification. The 2022 Draft Assessment presents evidence tables for the experimental animal studies organized by study duration, focusing specifically on chronic exposure (≥1 year) and subchronic exposure (≥3 months) with long-term follow-up (typically assessed after ≥1 year), because of the latency of the expected tumors and their rarity in untreated animals. The challenges faced with evidence integration across studies in animals included species differences in observed effects that were attributed to interspecies differences in airway anatomy; in oral/nasal breathing patterns, including reflex bradypnea; and in other factors (e.g., mucus flow and production, as well as differences in the expression or distribution of enzymes involved in formaldehyde detoxification). Where data were available, the 2022 Draft Assessment also presents tumor incidence plots across the range of concentrations studied.

- For ***squamous cell carcinomas (SSCs) in animals***, the 2022 Draft Assessment evaluates six two-year exposure studies in rats; of these, five showed increases in SCCs that were restricted to the nasal cavity. One two-year study in mice also reported an increased SCC incidence. Nonlinear dose-response relationships were observed in these studies as was strain-to-strain variability among rats. EPA also concluded, based on the synthesis of evidence, that the locations of the induced SCCs were consistent with both the distribution of inhaled formaldehyde and the locations of other formaldehyde-induced nasal pathologies, with SCCs arising from the epithelium lining the airway and not from the underlying glandular epithelium.
- For ***other malignant and nonmalignant neoplasms and dysplasia***, the database is less robust than that for SCCs. Other malignant neoplasms were considered rare but not incidental because they developed only after exposure to the highest formaldehyde concentrations. Other benign tumors of the respiratory tract have been reported following formaldehyde exposure in rats, but not in other species; they have been restricted to the nasal cavity and generally have taken more than 12 months of exposure to develop. Several studies reported increased incidence and severity of dysplasia in long-term formaldehyde inhalation studies in rats and mice (chronic or subchronic exposure, with observation periods of >12 months).
- Overall, the 2022 Draft Assessment concludes that in mice and several strains of rats, but not in hamsters, tumors of the respiratory tract (predominantly SCCs but including other epithelial and nonepithelial tumors) were consistently observed in chronic studies of formaldehyde at concentrations above approximately 6−7 mg/m^3. Precancerous lesions and epithelial dysplasia were also observed, both at the anterior regions of the nasal cavity and sometimes at lower concentrations than those associated with increased tumor formation. The Draft Agreement also concludes that the development of these lesions, particularly SCCs, depended on the duration of observation, and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the duration of formaldehyde exposure.

Finding: With respect to cancer hazard identification for respiratory tract cancers in animals exposed to formaldehyde, EPA synthesized the current state of the science in a manner consistent with its state-of-practice methods and presents conclusions based on its expert judgment with the support of the available scientific evidence.

For consideration of mode of action (MOA) for upper respiratory tract cancers, EPA synthesized the evidence to propose an integrated MOA. The strengths of this portion of the 2022 Draft

Assessment (across the various documents) are the comprehensive evaluation of the available evidence across multiple mechanisms, evaluation of the concordance of temporal and dose-response relationships, and an attempt to integrate the evidence using both MOA and adverse outcome network frameworks. The Draft Assessment acknowledges (Appendix A, p. A-771) that no formal, systematic approach was used to identify and evaluate the literature databases of studies examining mechanistic data relevant to interpreting the potential for formaldehyde to cause upper respiratory tract tumors. The reason given is that because key events are well established, a formal, systematic review approach to the mechanistic evidence may be redundant. The 2022 Draft Assessment evaluates evidence for genotoxicity, cellular proliferation, cytotoxicity and pathology in the nasal airways, and several other mechanisms separately and then provides an integration and summary of the MOA evidence. Key conclusions are that (1) *strong*, consistent evidence from rodent and nonhuman primate models supports the role of both direct (i.e., potentially DNA–protein crosslink or hypermethylated DNA adduct-associated) mutagenicity, as well as indirect genotoxicity, mutagenicity, and regenerative proliferation resulting from respiratory tissue pathology, in rodent upper respiratory tract carcinogenesis; (2) mutagenicity is presumed to be a relevant component of upper respiratory tract carcinogenesis in humans, supported by consistent observations of direct genotoxicity and mutagenicity from human epidemiological studies; and (3) increased nasal epithelial cell proliferation (in rats and nonhuman primates) coincides anatomically with progressive, proliferative lesions in the nasal/buccal epithelium and nasopharynx of chronically exposed humans. Finally, the Draft Assessment notes that mechanistic data provide strong and consistent evidence supporting the contribution of both direct genotoxicity and mutagenicity and cytotoxicity-induced regenerative proliferation as primary mechanistic events. EPA concluded that these mechanisms were highly relevant for informing quantification of nasal cancers in experimental animals following chronic formaldehyde exposure.

> Finding: With respect to evidence on MOA for upper respiratory tract cancers, EPA used its state-of-practice methods to synthesize the evidence.

The 2022 Draft Assessment presents an integrated summary of evidence for upper respiratory tract cancers in both narrative and tabular formats (Table 1-43). Evidence judgments and hazard determinations are presented separately for nasopharyngeal cancer, sinonasal cancer, oropharyngeal/hypopharyngeal cancer, and laryngeal cancer. For each of these cancer types, human evidence, animal evidence, and other inferences were considered separately and then integrated into the overall hazard determination. Mechanistic evidence was integrated throughout each of these lines of evidence to support arguments about biological plausibility. A specific hazard determination (*evidence demonstrates*, *evidence suggests*, or *inadequate evidence*) was made for each of the upper respiratory tract cancers, and potential susceptible subpopulations were also addressed for these cancer types with the classification at the level of *evidence demonstrates*.

> Finding: EPA presents an overall clear and succinct evidence integration summary for effects of formaldehyde inhalation on upper respiratory tract cancers. EPA followed its state of practice for evidence integration at the time the 2022 Draft Assessment was being developed in evaluating studies of cancer outcomes in humans and animals, as well as mechanistic evidence.

> Finding: EPA integrated the mechanistic evidence in considering biological plausibility for the human or animal evidence. However, it separately presents MOA considerations in the "other inferences" section of the evidence integration table (for this endpoint and for other

endpoints throughout the 2022 Draft Assessment). The IRIS Handbook calls out "other critical inferences" as a factor to address in evidence integration (EPA, 2022b, pp. 6-1 and 6-2 in the Assessment Overview; Chapter 6 of the Main Assessment). This concept is applied in the evidence integration sections throughout the Draft Assessment, but the term "other inferences" is not explained. See Chapter 2 of the present report, Recommendation 2.5.

Lymphohematopoietic Cancers

For lymphohematopoietic cancers, the 2022 Draft Assessment focuses on clinical diagnoses of Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia in exposed humans, as well as relevant tumor findings in animals and mechanistic evidence. The evidence was integrated for the overall causality determinations.

For human health effect studies, evidence was synthesized for cancer types based on specific clinical diagnoses that were available in epidemiological studies, as recommended by the NRC (2011). EPA's 2010 Draft Assessment made determinations of causality for lymphohematopoietic cancers in several groupings: "all LHP cancers," "all leukemias," and "myeloid leukemias." The 2011 NRC committee criticized this approach because "it combines many diverse cancers that are not closely related in etiology and cells of origin." The NRC committee recommended that EPA focus on "the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." Accordingly, EPA acknowledged in the section "Overview of Lymphohematopoietic Cancer Biology" that lymphohematopoietic cancers are a heterogeneous group of cancers that encompass a wide variety of leukemias and lymphomas, cancers that are often derived from cells of different origin, can demonstrate unique genetic abnormalities, may arise in different tissues, and may have distinct etiologic underpinnings. While acknowledging the challenges of deducing specific cancer diagnoses from epidemiological studies and differences in terminology among different versions of the International Classification of Diseases (ICD), EPA concluded that four specific types of lymphohematopoietic cancer (myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma) warranted the most attention.

Finding: With respect to cancer hazard identification for lymphohematopoietic cancer in humans exposed to formaldehyde, EPA was responsive to previous recommendations of the NRC (2011, 2014) and focused on the most specific diagnoses of myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma.

- For ***myeloid leukemia in humans***, the 2022 Draft Assessment evaluates data reported in 13 epidemiological publications that were based on 10 different study populations; the majority were cohort study designs. Two publications reanalyzed the evidence detailed in earlier papers by either combining study populations or using a different definition of exposure. Detailed evaluations of confidence in the reported effect estimate of an association from each of these studies are provided in Appendix A, Section A.5.9. In addition, the confidence conclusions are summarized in the evidence table for myeloid leukemia (Table 1-60), and the reported associations for all studies are plotted in Figures 1-37 and 1-38. EPA concluded that consistency of the observed association was supported because the "majority of studies of the 10 populations reported elevated risks of myeloid leukemia (or a specific subtype) associated with exposure to formaldehyde for at least one metric of exposure." EPA assigned confidence levels of *low, medium*, or *high* to each study, with the latter group consisting

of three publications that reported exposure-response trends describing the effect estimates of all association between formaldehyde exposure and risk of myeloid leukemia (Table 1-59). Studies were divided into those that provided population-level exposure assessment (five studies, three of which were classified as having *low* and two as having *medium* confidence), and individual-level exposure assessment (eight studies, four classified as having *low*, one as having *medium*, and three as having *high* confidence). While EPA makes a causal determination for myeloid leukemia overall (acute and chronic), it notes that in studies with separate estimates by subtype, risks were elevated for both acute and chronic myeloid leukemias, with the association for the chronic subtype appearing to be as strong as or stronger than that for acute myeloid leukemia. With respect to the strength of the associations, EPA concludes that overall, studies with higher-quality exposure data, based on individual-level exposure assessment, generally reported higher relative effect estimates. With respect to the temporal relationship of the observed associations, EPA acknowledges that while myeloid leukemia cancer diagnoses were made after the individuals had exposure to formaldehyde, evidence is mixed with respect to the latency period and "time since first exposure." Evaluation of exposure-response relationships is challenging because of the differences in categorizing exposures across studies and cohorts; however, EPA concludes that three *high*-confidence studies demonstrated significant exposure-response trends, even though several additional studies showed no significant relationship. Discussion of why the potential impact of selection bias, information bias, confounding bias, and chance could be excluded in the overall evidence synthesis is also provided. In the overall synthesis of epidemiological evidence, EPA concludes that the available epidemiological studies provide robust evidence of an association consistent with causation between formaldehyde exposure and increased risk of myeloid leukemia.

- For ***lymphatic leukemia in humans***, the 2022 Draft Assessment evaluates nine primary epidemiological studies—two case-control and seven cohort study designs. EPA notes that the diagnosis of lymphatic leukemia in the published studies was largely presented in a way that made it difficult to separate the results into acute and chronic lymphocytic leukemia. The 2022 Draft Assessment explains the confidence level determinations for each individual study in Table 1-61. The overall synthesis judgment for consistency of the findings is that *informative* studies consistently identified null associations—that is, evidence indicative of no association between formaldehyde exposure and the risk of developing or dying from lymphatic leukemia. In addition, EPA concludes that the strength of the null association, lack of temporal concordance, and exposure-response relationships were also evident. EPA concludes that, despite consistent observations of genotoxicity in peripheral blood lymphocytes, exfoliated buccal cells, or nasal mucosal cells in several occupational studies, these data were not sufficient to overturn the judgment on the lack of human evidence for lymphatic leukemia. EPA concludes that the available epidemiological studies provide *indeterminate* evidence with which to assess the carcinogenic potential of an association between formaldehyde exposure and an increased risk of lymphatic leukemia.
- For ***multiple myeloma in humans***, the 2022 Draft Assessment evaluates 14 primary epidemiological studies—five case-control and nine cohort study designs. The 2022 Draft Assessment explains confidence level determinations for each individual study in Table 1-62. The overall synthesis judgment for the consistency of the findings is that there were generally mixed results, with some studies showing nonsignificant

increases in risk and others showing nonsignificant decreases in risk. A number of challenges with exposure assessment and other methodological issues are described in detail for all the studies. In addition, EPA concludes that the strength of the associations was inconsistent, and there was *limited* evidence with which to evaluate temporal relationships or exposure-response relationships, with one study reporting inverse relationships with duration of exposure and time since first exposure. The 2022 Draft Assessment concludes that there were consistent observations of genotoxicity. Overall, EPA concludes that the available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of multiple myeloma, primarily with respect to peak exposure.

- For ***Hodgkin lymphoma in humans***, the 2022 Draft Assessment evaluates 15 primary epidemiological studies—one case-control and 14 cohort study designs; only 12 of these studies were deemed *informative*. The 2022 Draft Assessment explains confidence level determinations for each individual study in Table 1-63. The overall synthesis judgment for consistency of the findings is that the results of the 12 informative studies were not consistent. One possible explanation presented by EPA for their lack of consistency is that the long-term survival rate for Hodgkin lymphoma is far higher than that for other lymphohematopoietic cancers, thus raising a question about the use of cancer mortality as a surrogate for cancer incidence. In addition, EPA concludes that strength of the associations was inconsistent, with effect estimates being highly variable and predominantly less than 1 (unity). Only one study showed a temporal relationship, and EPA cites lack of corroboration of this finding in other studies. Two studies that had the data to evaluate exposure-response relationships showed opposite results. The 2022 Draft Assessment concludes that observations of genotoxicity were consistent. Overall, EPA concludes that the available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of Hodgkin lymphoma.

Finding: With respect to cancer hazard identification for lymphohematopoietic cancers in humans exposed to formaldehyde, EPA used appropriate methods to synthesize the current state of the science and presents conclusions regarding the hazard identification analysis that accord with its framework and criteria, and are based on expert judgment with the support of the available scientific evidence.

Recommendation 5.3 (Tier 2): To add clarity, EPA should, in the captions of figures displaying the findings of epidemiological studies for the different cancers, provide references to the numbers of the tables that describe the confidence in each study (*low*, *medium*, or *high*) and "results" (high vs. medium confidence, as presented in Figure 1-38).

For studies of lymphohematopoietic cancers in animals, EPA concluded that the database for drawing conclusions about causality is limited because most animal studies of formaldehyde did not evaluate tissues beyond the respiratory tract. One chronic-duration inhalation study that reported detailed information on formaldehyde-induced leukemia or lymphoma in rodents (Battelle Columbus Laboratories, 1982) was deemed *indeterminate* because its results remain unpublished. Specifically, in this *high*-confidence chronic study, the incidence of lymphoma in female mice increased from 16 percent in the control group (0 ppm) to 22 percent in the high-dose group (17.6 ppm) (p-value, 0.06); in contrast, the incidence of leukemia in female rats *decreased* from 9 percent in the control to 6 percent in the high-dose group (p-value, 0.006). This study did not examine

lymphohematopoietic tissues at intermediate doses (2.5 and 6.9 mg/m^3). Several additional rat and mouse studies that did examine lymphohematopoietic tissues and did not find statistically significant increases in leukemia or lymphoma were considered to have *medium* and *low* confidence because of methodological and/or reporting deficiencies. EPA deemed the overall database to be *indeterminate* for drawing conclusions regarding the potential for formaldehyde exposure to induce lymphohematopoietic cancers in rodent bioassays.

> Finding: With respect to cancer hazard identification for lymphohematopoietic cancers in animals exposed to formaldehyde, EPA used its state-of-practice methods to synthesize the current state of the science, and presents conclusions regarding the hazard identification analysis based on its expert judgment with the support of the available scientific evidence.

In considering MOA, EPA concluded that no MOA(s) has been established for how formaldehyde inhalation may result in lymphohematopoietic cancers. Instead, evidence was evaluated and synthesized to present plausible mechanisms for lymphohematopoietic cancers through inhalation exposure. This approach is consistent with the conclusions of previous National Academies committees that evaluated the cancer hazard of formaldehyde (Table 5-4). According to the NRC (2011, p. 5), for example, "data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites … a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established. That gap in mechanistic understanding is particularly problematic because the data strongly suggest that formaldehyde is not available systemically in any reactive form. Thus, the committee can only hypothesize that the observed effects result from an unproven mechanism in portal-of-entry tissues." The 2014 NRC committee stated that experimental "findings provide plausible mechanistic pathways supporting a relationship between formaldehyde exposure and cancer, even though the potential mechanisms of how formaldehyde may cause such systemic effects are not fully understood" (NRC, 2014, p. 17.)

EPA reasons in the 2022 Draft Assessment that a network of mechanistic events or pathways is more suitable than a linear MOA to support the biological plausibility for many cancers, including lymphohematopoietic cancers. Specifically, EPA organized the evidence around the following mechanistic events that support the biological plausibility of formaldehyde exposure–induced lymphohematopoietic carcinogenesis: formaldehyde-induced DNA damage in peripheral blood leukocytes; impacts other than genotoxicity on immune cell populations in peripheral blood in humans and inflammation/immune dysfunction; systemic oxidative stress; and other health effects outside of the respiratory system, including developmental and reproductive toxicity (for which hazard classification was that the *evidence indicates* that effects in humans are likely). Each of these plausible mechanistic events is discussed in the general style of a narrative review, and the relevance of each mechanistic event to lymphohematopoietic carcinogenesis is considered in greater detail. Alternative hypotheses and gaps in the current knowledge base are specifically acknowledged. Summary conclusions for each hypothesized mechanistic event are then further summarized in Table 1-66, with explicit statements on human relevance and weight-of-evidence conclusions and considerations for biological plausibility. Overall, EPA concludes that the available evidence supports some events that could contribute to plausible mechanistic pathways relating formaldehyde exposure to lymphohematopoietic carcinogenesis; however, the database was insufficient to support the evaluation or development of any specific MOA. EPA further concludes that while the available mechanistic database has limitations, this does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia in epidemiological studies. This conclusion is identical to that drawn by the NRC (2014).

Finding: With respect to evidence on MOA for lymphohematopoietic cancers, EPA used its state-of-practice methods to synthesize the knowledge. The presentation of conclusions regarding the mechanistic evidence and how it supports hazard identification is appropriate.

The 2022 Draft Assessment presents an integrated summary of evidence for lymphohematopoietic cancers in both narrative and tabular formats (Table 1-67). Evidence judgments and hazard determinations are presented separately for myeloid leukemia, multiple myeloma, Hodgkin lymphoma, and lymphatic leukemia. For each of these cancer types, human evidence, animal evidence, and other inferences are considered separately and then integrated into the overall hazard determination. Mechanistic evidence is integrated throughout each of these lines of evidence to present arguments about biological plausibility. A specific hazard determination (*evidence demonstrates*, *evidence suggests*, or *inadequate evidence*) is made for each of the included lymphohematopoietic cancers, and potential susceptible subpopulations are also addressed for the cancer types with an *evidence demonstrates* determination.

Finding: EPA presents an overall clear and succinct evidence integration summary for effects of formaldehyde inhalation on lymphohematopoietic cancers. EPA followed its state of practice for evidence integration at the time the 2022 Draft Assessment was being developed in evaluating studies of cancer outcomes in humans and animals, as well as mechanistic evidence, where available.

DOSE-RESPONSE ANALYSIS OF CANCER EFFECTS OF FORMALDEHYDE

EPA performed dose-response analysis for nasopharyngeal cancer and myeloid leukemia outcomes. For these cancer outcomes, EPA made a causal determination that the *evidence demonstrates* that inhalation of formaldehyde causally increases risk for these malignancies in humans. The 2022 Draft Assessment does not include a third cancer outcome in this evidence category—sinonasal cancer—because adequate quantitative data for dose-response analysis were lacking.

EPA concluded that the large and diverse body of mechanistic, pharmacokinetic, whole-animal, and human evidence was sufficient to conduct the technically complex dose-response analysis for the nasopharyngeal cancer and myeloid leukemia outcomes. For nasopharyngeal cancer, the 2022 Draft Assessment first analyzes the epidemiological data and estimates a cancer "inhalation unit risk," which is the extra risk (above background) caused by lifetime exposure to an increase of 1 $\mu g/m^3$ unit of formaldehyde.[3] Multiple alternative estimates are also derived from animal bioassay data, and reflect various assumptions about the established and potential mechanisms by which formaldehyde causes nasal cancer, while also addressing pharmacokinetic considerations. Because of a lack of suitable animal data and uncertainties in mechanistic understanding, the unit risk for myeloid leukemia is based only on epidemiological data.

In its review of the 2010 Draft Formaldehyde Assessment, the 2011 NRC committee made a number of recommendations and comments related to methods, assumptions, and other decision points about the cancer dose-response analysis, including the following (NRC, 2011):

- "The draft IRIS assessment does not provide adequate narratives regarding selection of studies and endpoints for derivation of unit risks. The committee strongly recommends that EPA develop, state, and systematically apply a set of selection criteria for studies and cancer endpoints." (p. 145)

[3] Can also be expressed as extra risk per ppm.

- "The committee recommends that EPA … Update the dose-response analysis in the IRIS assessment when findings from the update of the NCI cohort on solid cancers become available." (p. 88)
- "the committee recommends that the CFD [computational fluid dynamic]-based approach also be used to extrapolate to low concentrations, that the results be included in the overall evaluation, and that EPA explain clearly its use of CFD modeling approaches (p. 44)
- "The committee recommends that EPA provide alternative calculations that factor in nonlinearities associated with the cytotoxicity-compensatory cell proliferation mode of action and assess the strengths and weaknesses of each approach." (p. 59)
- "Overall, the committee finds EPA's approach to calculating the unit risks [for systemic cancers] reasonable. However, EPA should validate the Poisson dose-response models for NPC, leukemia, and Hodgkin lymphoma mortality with respect to adequacy of model fit, including goodness of fit in the low-dose range, (log) linearity, and absence of interactions of covariates with formaldehyde exposure. EPA is strongly encouraged to conduct alternative dose-response modeling by using Cox regression or alternative nonlinear function forms." (p. 145)

The present committee considered the recommendations of the 2011 NRC committee, as well as the guidelines presented in EPA's 2022 IRIS Handbook (EPA, 2022b) and 2005 *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a), in evaluating whether appropriate methods were used in developing the 2022 Draft Assessment to synthesize the current state of the science and determine whether the dose-response analysis for the effects of formaldehyde by inhalation with respect to cancer outcomes was supported by the scientific evidence and appropriately conducted.

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 Assessment adequately and transparently evaluates the scientific evidence, and generally documents the dose-response analysis overall in a well-organized and transparent manner. The analyses generally follow the process outlined in the 2022 IRIS Handbook and are consistent with the 2005 *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a, 2022). As documented in Appendix D and in sections on cancer dose-response analyses, the decision points and analyses are also responsive to the recommendations of the 2011 NRC committee.

Finding: The derivation of unit risk is documented in approximately 200 pages in total across the three documents in the 2022 Draft Assessment—the Assessment Overview, Main Assessment, and Appendices—and some redundancies are evident within and across the documents. The sections documenting the derivations based on epidemiological evidence are transparent, and overall are well written and understandable.

INHALATION UNIT RISK FOR NASOPHARYNGEAL CANCER FROM EPIDEMIOLOGICAL DATA

The 2022 Draft Assessment first presents the unit risk estimates derived from epidemiological data, and then presents the analysis based on animal bioassay data and mechanistic, anatomical, and physiological considerations to support the dosimetry using computational fluid dynamic modeling of dosimetry and biologically based dose-response modeling.

Study Selection

The 2022 Draft Assessment uses the Beane Freeman et al. (2013) study in its derivation of unit risk for nasopharyngeal cancer from epidemiological data, stating that it is the only study with sufficient individual exposure data. This study was a follow-up of a large National Cancer Institute (NCI) retrospective cohort made up of workers from 10 U.S. plants in formaldehyde-using industries. Another advantage of this study noted in the assessment is that it included internal comparisons, which minimized the bias associated with a potential healthy-worker effect. In the analysis of the NCI cohort (Beane Freeman et al., 2013), several different exposure metrics were used—peak exposure, average intensity, cumulative exposure, and duration of exposure. This study was published after the 2010 Draft Assessment was released. Other studies that could have been considered for dose-response analysis are generally described as smaller in population size, not having an appropriate internal comparison group, or not reporting adequate exposure metrics for modeling.

Finding: EPA's selection of the Beane Freeman et al. (2013) occupational retrospective mortality study is appropriate and is consistent with the earlier recommendation of the 2011 NRC committee (NRC, 2011, p. 88) that EPA should update the unit risk value when this study became available. While the selection of this study is appropriate, and the major factors for its selection are described, the narrative discussion lacks clarity. The 2011 NRC committee called for EPA to "develop, state, and systematically apply a set of selection criteria for studies and cancer end points" (NRC, 2011, p. 145).

Recommendation 5.4 (Tier 2): While the criteria for selecting the Beane Freeman et al. (2013) study can reasonably be discerned from the 2022 Draft Assessment, EPA should provide clearer statements of the criteria and comparison of studies with such criteria, in tabular format, to improve transparency and clarity. EPA should add to such a table other studies that evaluated the same cancer outcome so it is apparent why the selected study was superior for the purposes of dose-response analysis.

Endpoint Selection

The endpoint selected for dose-response analysis from the Beane Freeman et al. (2013) study was mortality from nasopharyngeal cancer. Although the 2022 Draft Assessment also contains a judgment of a causal link (*evidence demonstrates*) between formaldehyde exposure by inhalation and sinonasal cancer, the latter outcome was not used to conduct a dose-response analysis because the study identifies a total of only five deaths from nose and nasal sinus cancer.

Finding: The selection of nasopharyngeal cancer mortality is appropriate given its causal link to formaldehyde exposure in humans. Nasopharyngeal cancer incidence would be the preferred endpoint over mortality, but could not be modeled because of the study design (mortality cohort). The decision not to develop a unit risk for the sinonasal cancer outcome can be justified on the basis of the small number of cases and the quality of the dose-response relationship in the study.

Dose Metric Selection

Individual exposure assessments were available for each worker in the Beane Freeman et al. (2013) study, enabling the development of various exposure estimates of interest, including peak

short-term exposures, frequency of peak exposures, duration spent in jobs with formaldehyde exposure, and cumulative exposure. EPA selected cumulative exposure as the metric for its characterization of dose-response for deriving unit risk from the Beane Freeman et al. (2013) study. Cumulative exposure was estimated from time in a specific job multiplied by the time-weighted average concentration for that job category.

The 2022 Draft Assessment characterizes frequency of peak exposure as highly uncertain because it was estimated based on assumptions made by the exposure assessors for the study. Although EPA stated that the peak exposure metric produced the strongest exposure-response relationships, it did not use this metric because it is not based on exposure concentration measurements. In addition, EPA expressed uncertainty about how to use peak exposure-based estimates in predicting risks for lifetime exposure to continuous low exposures. Because the average exposure metric did not account for duration and duration does not account for level of exposure, these metrics also were not used.

Finding: The selection of cumulative exposure as the dose metric is adequately justified. The use of cumulative exposure as the dose metric in dose-response modeling is consistent with the 2022 IRIS Handbook (EPA, 2022b, p. 8-4):

> Cumulative exposure (or a dose metric that can be converted to cumulative exposure) is generally the preferred exposure metric for cancer responses; exposure estimates can include a lag period, if warranted.

EPA's language in *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a, p. 3-26) is less definitive with regard to preferential use of the cumulative exposure metric:

> Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is recommended as an appropriate measure of exposure to a carcinogen. … This approach becomes more problematical as the exposures in question become more intense but less frequent, especially when there is evidence that the agent has shown dose-rate effects (EPA, 1986a).

Model Selection and Fit

EPA relied on dose-response modeling performed by Beane Freeman et al. (2013). Poisson regression models for incidence with a log-linear function were applied. Multiple lag periods were modeled to account for the latency period for solid tumors, with a 15-year lag period ultimately being adopted. Stratification was done by calendar year, age, sex, race, and pay category (salary vs. hourly wage). The authors note that the Poisson regression and Cox proportional hazards models yield essentially similar results when age is adjusted for in the cohort. The low-exposure group served as the reference population to address unmeasured confounding associated with nonexposed workers and potential differences in socioeconomic status. The use of low rather than zero exposure as the reference group made little difference in the observed trend for the cumulative exposure dose metric, with the level of statistical significance being quite similar regardless of whether the zero-exposure group was included ($p = 0.07$) or excluded ($p = 0.06$). The effect was more pronounced in the dose-response trend associated with the peak exposure metrics ($p = 0.005$ under exposed person-years and $p = 0.10$ when the zero-exposure group was used as the reference group).

The lead author of the study provided EPA with the regression coefficients reflecting the relative risk per cumulative exposure unit (i.e., per ppm × year) (Beane Freeman et al., 2013, pp.

2–49). The coefficients were nearly identical for the regression with the zero-exposure group included vs. excluded (0.431 vs. 0.439 per ppm × year).

Finding: EPA followed a process consistent with its state-of-practice methods in conducting the dose-response analysis on nasopharyngeal cancers. Log-linear Poisson regression is a standard, widely used, and acceptable approach for modeling large occupational data sets such as that reported in Beane Freeman et al. (2013) (25,610 workers; 998,239 person-years of follow-up). The selected lag period of 15 years was based on expert judgment with supporting evidence; the committee finds this to be appropriate for modeling solid tumors.

Finding: There is uncertainty about the degree to which peak exposure produces the strongest exposure-response relationships. Inclusion of the zero-response group shows a slightly less significant trend for peak exposure ($p = 0.1$ for trend) compared with the use of cumulative exposure as a metric ($p = 0.07$).

Recommendation 5.5 (Tier 2): EPA should acknowledge the uncertainty involved in interpreting the analyses on the degree to which exposure-response relationships are stronger than cumulative exposure for determination of peak exposure and risk.

Point of Departure and Inhalation Unit Risk for Nasopharyngeal Cancer Mortality

A point of departure (POD) is an exposure level that is drawn from the dose-response curve fit to observed data. In cancer risk assessment, it is used as a basis for extrapolation to lower concentrations than those in the study used in its derivation. In this case, the POD is used to derive the slope of the concentration versus cancer response curve. That slope is called the "inhalation unit risk," and is based on the assumption that there is not a threshold concentration below which the cancer risk is zero. The unit risk estimate enables the calculation of "extra risk" from low incremental increases in concentration.

EPA applied the regression coefficients from Beane Freeman et al. (2013) in a life-table program that accounts for competing causes of death to predict extra risk of mortality from nasopharyngeal cancer at different concentrations of formaldehyde. These calculations also used a 15-year lag period. The upper 95 percent confidence bounds on the extra-risk estimates at different concentrations were derived from the reported standard errors on the regression coefficients, and below 0.01 ppm linearly decreased with decreasing dose (Table 2-17, p. 2-50).

EPA used the same approach to calculate the POD, in this case the lower-bound estimate of concentration associated with an extra risk of 0.05 percent. Because background mortality rates for nasopharyngeal tumors are very low, the 2022 Draft Assessment explains that using a higher extra risk would be inappropriate. For example, using an extra risk of 1 percent, typically used for epidemiological data, would result in a relative risk of 53, an upward extrapolation from the observed data, and using 0.1 percent would yield a relative risk of 6.2, on the high end of the observed range in the Beane Freeman et al. (2013) study. At 0.05 percent risk, the relative risk estimate is 3.6, which is in the observed range of the study. The POD associated with the extra-risk level of 0.05 percent is 0.11 ppm.

EPA calculated the unit risk value by dividing the benchmark extra-risk level of 0.05 percent by the POD—that is, the lower-bound estimate of the concentration associated with that extra risk. The unit risk EPA calculated for nasopharyngeal cancer mortality was 3.7×10^{-3} per mg/m^3 (4.5×10^{-3} per ppm).

Finding: In evaluating the nasopharyngeal cancer outcome, EPA's approach of using a life-table procedure to account for competing causes of death in applying the regression coefficient to estimate extra-risk levels is a standard approach for dose-response assessments that are based on epidemiological evidence.

Finding: EPA's choice of an extra-risk value of 0.05 percent for the POD is consistent with its *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a, p. 3-16):

> The POD is an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range without significant extrapolation to lower doses.

Because elevated relative risks in the Beane Freeman et al. (2013) study were associated with significant findings in the range of 2.94 to 11.54, the POD of 0.11 ppm, which is associated with a relative risk of 3.6, can be considered as being at the lower end of the observed range.

Finding: EPA's calculation of the unit risk for mortality is appropriate and consistent with its *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a, p. 3-23).

Finding: Insufficient information is given on the details of the dose-response analysis and the derivation of the unit risk values. For example, the 2022 Draft Assessment states, "An adjustment was also made for the 15-year lag period" (pp. 2–50), without explaining how the adjustment was made. In addition, Appendix B, Table B-18 shows no exposure in infancy and childhood in the life-table example for the derivation of a unit risk for environmental exposures.

Recommendation 5.6 (Tier 2): EPA should state how the adjustment for the 15-year lag was made for nasopharyngeal cancer mortality, and explain the assignment of zero exposure in Table B-18.

Inhalation Unit Risk for Nasopharyngeal Incidence

Because nasopharyngeal cancer has a favorable survival rate (the 2022 Draft Assessment cites 51 percent at five years in the 1990s in the United States), EPA also calculated an incidence-based unit risk. In making this calculation, EPA used the same approach used to derive the mortality extra-risk estimates. However, instead of using the mortality statistics for this cancer, EPA used incidence values from NCI's Surveillance, Epidemiology, and End Results (SEER) program for the period 2000–2010. The same approach was used to calculate the POD of 0.055 ppm at an extra risk of 0.05 percent, which in turn was used to derive the unit risk estimate of 7.4×10^{-3} per mg/m^3 (9.1×10^{-3} per ppm) for formaldehyde-induced nasopharyngeal cancer incidence.

The 2022 Draft Assessment (pp. 2–53) also presents a risk calculation to consider the plausibility of the unit risk for nasopharyngeal incidence. Estimates of formaldehyde-related nasopharyngeal cancer cases in the United States were derived and compared with actual case numbers of this rare cancer. Under the assumption that the U.S. population is exposed to 5 ppb formaldehyde for 75 years, the annual number of incident cases of nasopharyngeal cancer in the United States was estimated to be 180. Using a higher formaldehyde concentration estimate of 20 ppb resulted in an estimate of 730 cases annually. These numbers were compared with the 2,300 actual incident cases per year in the United States—a much greater number.

Finding: EPA's derivation of the unit risk estimate for formaldehyde-associated nasopharyngeal cancer incidence was appropriately done, and the preference for that estimate over the mortality-based unit risk estimate is appropriate and consistent with the 2022 IRIS Handbook (EPA, 2022, p. 8-4) and EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2022b, p. 3-12).

Finding: The prediction of the number of annual incident cases in the United States at upper ends of outdoor (5 ppb) and indoor (20 ppb) formaldehyde exposure levels as a "reality check" on the inhalation unit risk is a useful exercise that would be improved by acknowledging some of the possible environmental and other causative factors of nasopharyngeal cancer in the United States.

Recommendation 5.7 (Tier 2): In Appendix B, Table B-12, increasing the number of significant figures in columns P, H, and L to align with column I would add transparency by making it easier for readers to follow and understand the calculations for nasopharyngeal cancer incidence.

Inhalation Unit Risk for Nasal Cancer from Animal Bioassay Data

Study Selection

EPA also derived inhalation unit risk estimates from two long-term animal studies of formaldehyde in F344 rats (Kerns et al., 1983; Monticello et al., 1996). EPA selected these two studies in part because both reported exposure-dependent incidence of nasal squamous cell carcinoma (SCC). EPA further decided to combine the two studies for dose-response analysis because the combined data had a wider exposure range and larger numbers of animals, providing more robust dose-response information and greater statistical power.

Finding: EPA's selection of studies was appropriate. The studies were identified as having *high* confidence (Section 1.2.5), and each used large numbers of animals per dose group. However, Table 1-37 (p. 1-296) in Section 1.2.5 lays out five *high*-confidence studies with dose-response data. The reason for not selecting the three other high-quality studies is not discussed or referenced in the dose-response section "Animal Nasal Tumor Incidence."

Finding: Combining similarly designed studies is an acceptable approach when data harmonization is feasible. While EPA notes that "the incidences are similar in the two studies," it does not fully discuss the homogeneity or heterogeneity of the two studies and did not adopt statistical approaches to address study heterogeneity. Further, EPA does not clearly state that the data relied upon in the analysis are documented in a memorandum by Elizabeth Gross Bermudez from the Chemical Industry Institute of Toxicology (CIIT) correcting the incidence data and dose levels used in the two studies. Both studies were conducted by CIIT. Kernset al. (1983) report that they used the concentrations 0, 2.0, 5.6, or 14.3 ppm with six hours per day and five days per week exposure for up to 24-months, followed by a nonexposure period of six months and with interim sacrifices at 6, 12, 18, 24, 27, and 30 months. Monticello et al. (1996) report that they used concentrations of 0, 0.7, 2.0, 6.0, 10, or 15 ppm with six hours per day and five days per week exposure for up to 24 months and interim sacrifices at 3, 6, 12, 18, and 24 months. EPA reports concentration levels of 0, 0.7, 2.0, 6.01, 9.93, or 14.96 ppm for the two studies combined, as provided in the Bermudez memorandum and in Table 2-20 of the 2022 Draft Assessment. Listing Bermudez as one of the references

for the animal incidence data in Table 2-20 on p. 2-54 without further explanation is insufficient and confusing.

Recommendation 5.8 (Tier 2): EPA should describe more clearly the procedure and justification for pooling the data from two animal studies into one analysis, and clarify that combined and corrected incidence data are contained in the Bermudez memorandum, which is not readily accessible to the public. The individual animal data for time-to-tumor occurrence used in the model should be provided in an appendix.

Finding: Another advantage of the two CIIT studies is that they provide time-dependent SCC incidence data, and also have companion mechanistic investigations pertaining to the nasal carcinogenicity of formaldehyde. The mechanistic data generated for the CIIT studies include site-specific DNA–protein crosslinks (DPC) as a marker of tissue dose, as well as site-specific changes in cell labeling as a measure of cell division rate.

Cancer Endpoint Selection

EPA selected nasal SCC as the cancer endpoint and used time to tumor as the outcome measure for the dose-response assessment.

Finding: EPA's selection of SCC as the cancer endpoint is appropriate and consistent with its state-of-practice methods.

Dose-Response Modeling

EPA used a computational fluid dynamic (CFD) model for formaldehyde airflow in the nasal passage of rats to characterize regional exposure to formaldehyde (Kimbell et al. 2001a, 2001b; Schroeter et al., 2014). This dosimetry of local exposure of formaldehyde inhalation facilitates biologically based dose-response (BBDR) modeling of SCC incidence. It was also to derive dose surrogates for use in statistical modeling of the dose-response. Because formaldehyde was deemed to be a direct-acting mutagen, EPA also used a physiologically based pharmacokinetic (PBPK) model (Subramaniam et al., 2007) to model DPC as a function of formaldehyde flux. In addition, EPA conducted dose-response modeling of cell proliferation as a precursor outcome of SCC using data from Monticello et al. (1991, 1996).

EPA presents results from several dose-response models for SCC incidence.

- EPA fit the multistage Weibull time-to-tumor model (MSW) to individual animal data from the CIIT animal cancer bioassays. The dose metric was formaldehyde flux derived using the CFD model.
- EPA fit a Weibull model to grouped incidences after adjusting for censoring using Kaplan-Meier survival (Schlosser et al., 2003). EPA presents results for two different dose metrics used by Schlosser et al.: formaldehyde flux and DPC derived from the PBPK modeling. EPA presents the fits using these two dose metrics for the best-fitting Weibull model, which had a nonzero intercept on the dose axis, the so-called "Weibull with threshold" result.
- EPA calibrated a BBDR model with time-to-tumor data. The BBDR model was based on the two-stage clonal expansion (TSCE) model (Moolgavkar et al., 1988), but incorporates DPC as the molecular dose that depended on formaldehyde flux predicted by the

CFD model. DPC tissue concentration was in turn calculated using a PBPK model developed by Conolly et al. (2000). EPA presents results from two different modeling assumptions regarding cell kinetics as a function of exposure.

Finding: EPA's reanalysis largely reproduced the results of Conolly et al. (2003) (Figure 2-4). EPA conducted a thorough uncertainty analysis of the BBDR model, investigating the structure of the model, uncertainties of the model parameters, and model sensitivities to these parameters (Appendix B, Section B.2.2). EPA provides an in-depth discussion of uncertainties from four sources that have potentially larger impact: PBPK model for DPC, use of historical controls, cell replication rates from the labeling data, and model specification for initiated cell kinetics.

Finding: Together, these modeling efforts were highly responsive to the recommendations of the 2011 NRC committee regarding the use of CFD and BBDR models and modeling of time-to-tumor and time-to-death data.

Finding: EPA does not present details of model specification or results of the MSW model and the Weibull incidence model in either the Main Assessment or Appendix B. The form of the Weibull model is not presented. The use of these models came with many restrictions on the parameters that affected the model-fitting results. Regarding the MSW model, it is unclear how EPA treated the lapsed-time parameter t_0—a crucial parameter—although EPA does describe the approach to coding animals with lethal versus incidental tumors. It is also unclear why EPA set the first five coefficients to zero and estimated only the coefficient for the term of fifth power in the multistage polynomial. Although the reader is referred to Appendix B, Section B.2.2 for details, the information on MSW modeling could not be located. The relationships between the administered concentration and the DPC and flux metrics for the rat and the human are not provided. Dose-response fits for the MSW for administered concentration using time-to-tumor data would be informative and useful for comparison given the described uncertainties in the estimates of the dose metrics.

Recommendation 5.9 (Tier 2): To enhance transparency, EPA should provide additional detail on the modeling, including constraints imposed on model parameters, the results of model fitting (goodness-of-fit test), and the approach used to define lag parameters. The relationship between administered dose and the DNA–protein crosslinks and flux dose metrics should also be provided. Given the uncertainties in the dose surrogates, a dose-response analysis and benchmark concentration calculations using administered concentrations should be provided as a point of comparison.

Benchmark Dose Modeling

Using the dose-response models, EPA produced estimates of benchmark concentration (BMC) and benchmark concentration lower bound (BMCL); a summary is presented in Table 2-22. EPA used two versions of the BBDR model—one based on a conservative prediction of formaldehyde flux of inhalation exposure in conjunction with historical control cancer rates of inhalation exposure studies, and the other based on the prediction of a monotonic increase of formaldehyde flux along with the historical control rates used in the first version.

Finding: The estimates of BMC and BMCL at benchmark response (BMR) levels of 0.01, 0.05, and 0.10 are comparable across the MSW and Weibull (with threshold) models and the

BBDR models. EPA also shows (in Table 2-22) that the BMC and BMCL estimates at the BMR = 0.005 level are similar in the two versions of BBDR. Human equivalent concentration (HEC) estimates are also similar. As expected, the Weibull threshold model produced slightly higher estimates. EPA's exercise showed that, assuming the models fit the data well, the model-related uncertainty is limited.

Uncertainty and Variability

EPA discusses extensively uncertainties associated with dose-response analysis and BMC estimation. The discussion includes the use of precursor outcomes (cell proliferation and hyperplasia) for BMC estimation, low-dose extrapolation using BBDR models, model selection, and statistical uncertainties in a BMC estimate within a model. The focus of the discussion is on the use of BBDR for extrapolation, with a list of seven major sources of uncertainty (Table 2-24). EPA concludes that the sources that substantially impacted uncertainty were rat cell labeling data, cell division rates, the assumption that SCC was a fatal tumor, the use of historical controls, and the division and death rates of initiated cells. EPA further concludes that for human extrapolation, the BBDR models suffered two major limitations (Conolly et al., 2004), and did not provide robust measures of human nasal SCC risk at any exposure concentration. Therefore, EPA did not use the BMCL derived from the BBDR models for human risk extrapolation.

Finding: EPA's discussion of the variability and uncertainty in the BBDR models is extensive. The 2022 Draft Assessment correctly states that the statistical uncertainties outside of the data range for the model can be higher. However, the example provided for the MSW model (p. 2-69, line 7-10) is difficult to follow, in part because the full results of the model are not given. The MSW model is quoted identically twice (p. 2-69, line 7-10; p. 2-79, line 7-9) for dose-response estimation and low-dose risk without extrapolation, respectively.

The focus of EPA's discussion is on the use of the BBDR model for extrapolation. EPA's conclusion on the sources of uncertainty with major impact is based largely on the sensitivities of the output of the BBDR models to model inputs related to the associated parameters (e.g., Table 2-25). Despite such a discussion of the uncertainties and variabilities from multiple sources, the unit risk estimates from the BMCs and BMCLs are remarkably similar (Table 2-26) across the models for the animal data.

Recommendation 5.10 (Tier 2): EPA should organize the discussion of uncertainties and variabilities in a manner that is easier to follow, such as by models or by process (models, benchmark concentration estimation, lower dose extrapolation, or extrapolation from animal data to humans).

Recommendation 5.11 (Tier 2): The results from different models and different databases are remarkably similar, supporting each other and suggesting a good degree of robustness. EPA should highlight this robustness to a greater degree while not losing sight of uncertainties within individual studies, endpoints, and models.

Selection of a Unit Risk Estimate for Nasal Cancer

EPA derived inhalation unit risk estimates using the human nasopharyngeal cancer data and animal SCC data. The inhalation unit risk was 7.4×10^{-3} per mg/m^3 based on the nasopharyngeal cancer data and 8.9×10^{-3} to 1.8×10^{-2} per mg/m^3 based on the animal SCC data, and these results

are comparable. Based on EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a), which prefers human data for derivation of risk estimates, EPA designated the inhalation unit risk derived from human nasopharyngeal cancer data as the preferred inhalation unit risk.

Finding: EPA's selection of the inhalation unit risk based on human nasopharyngeal cancer is appropriate and acceptable. The committee concurs with EPA's choice of cumulative exposure as the metric.

Uncertainties and Confidence in the Preferred Unit Risk Estimate for Nasal Cancers

Finding: EPA discusses the uncertainties for the human inhalation unit risk estimate after discussing inhalation unit risk estimates for animal SCC data and the selection of a preferred unit risk estimate. With only 10 cases of nasopharyngeal cancer–specific deaths in the NCI cohort, the use of nasopharyngeal cancer for deriving an inhalation unit risk carries uncertainties, although the monotonic trend (in rate ratio based on the Poisson regression model) somewhat strengthens the dose-response trend ($p = 0.07$). The strength of dose-response between formaldehyde exposure and nasopharyngeal cancer–related deaths can also be affected by other factors, including the confounding of age and misclassification of exposure, which create additional and important uncertainties for discussion.

Recommendation 5.12 (Tier 2): EPA should discuss the extent to which the inhalation unit risk estimates based on animal squamous cell carcinoma data and mechanistic data provide supporting evidence for the inhalation unit risk based on the human nasopharyngeal carcinoma data.

Finding: EPA mischaracterizes the p-value for trend as a p-value for goodness of fit (e.g., Table 2-28; p. 86, lines 8–9; p. 91, lines 13–14).

Recommendation 5.13 (Tier 2): EPA should address technical errors, such as mischaracterization of a trend p-value, with a thorough and technical edit and proofreading.

Inhalation Unit Risk for Myeloid Leukemia from Epidemiological Data

The methods and rationale for derivation of the unit risk estimate for myeloid leukemia are similar to or the same as those for nasopharyngeal tumors discussed earlier. Differences that are particular to myeloid leukemia are emphasized in this section.

Study Selection

As was done for nasopharyngeal cancers, the most recently published primary study of leukemia on the large NCI cohort (Beane Freeman et al., 2009) was chosen as the basis for developing the unit risk for myeloid leukemia. This was the only study with appropriate data for dose-response modeling. The exposure assessment in Hauptmann et al. (2009) was deemed deficient because worker histories were obtained from the next of kin, resulting in lower confidence in such data, and 30 percent of subjects were missing detailed work histories.

Finding: The Beane Freeman et al. (2009) study was appropriately selected, and the rationale for its selection over Hauptmann et al. (2009) is adequate.

Inhalation Unit Risk Value for Myeloid Leukemia

As with the nasopharyngeal cancers, the 2022 Draft Assessment notes that the Poisson regression and Cox proportional hazards models yield essentially the same results when age is well characterized and adjusted for. Also, the regression coefficient estimates from the Poisson regression were provided to EPA by the lead author on the study publication (Table 2-30, footnote "Source").

Utilizing cumulative exposure as the exposure metric in modeling relative risk for myeloid leukemia resulted in a nonsignificant trend ($p = 0.44$) compared with the use of peak exposure ($p = 0.07$). The 2022 Draft Assessment lays out the likelihood of significant underreporting of myeloid leukemia and cites studies supporting the estimate that one-third to one-half of nonspecified leukemias on death certificates could be myeloid leukemias by hospital diagnosis (Percy et al., 1981, 1990). Other/unspecified leukemia amounted to about 30 percent of all leukemia cases in the NCI cohort. To address the issue of likely underreporting of myeloid leukemia, EPA grouped the subcategories of myeloid leukemia and "other/unspecified leukemia." This grouping resulted in a more significant association between these leukemias and cumulative exposure to formaldehyde ($p = 0.1$) compared with myeloid leukemia alone ($p = 0.44$). EPA also considered all leukemias in deriving inhalation unit risk estimates and discusses the limitations of this approach in the Draft Assessment.

EPA used the same approach it used for nasopharyngeal cancer (lifetable, application of regression coefficient, selection of POD, and extra-risk benchmark) to derive inhalation unit risk estimates for myeloid leukemia mortality. Because of uncertainty regarding MOA, EPA used a default linear extrapolation following the 2005 *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a). As with the nasopharyngeal cancer data, incidence-based inhalation unit risk were also derived using the SEER registry data, this time from 2006–2010.

The 2022 Draft Assessment includes three sets of unit risk values for leukemias—myeloid leukemia, all leukemia, and myeloid plus other/unspecified, with the final set identified as the preferred estimates. The uncertainties in the analysis are described, including the nonsignificant increase in risk of myeloid leukemia with increased cumulative exposure and the stronger finding for the other groupings of leukemias. EPA concluded that there is *low* confidence in the inhalation unit risk estimate for myeloid leukemia and did not include it in the overall inhalation unit risk estimate for formaldehyde.

Finding: EPA's use of the same general approach for myeloid leukemia as for nasopharyngeal cancer in deriving unit risk estimate was appropriate. The grouping of myeloid leukemia with other/unspecified leukemia to address possible underreporting of myeloid leukemia was a practical approach, but as recognized in the 2022 Draft Assessment, likely created overcounting of myeloid leukemia since half to two-thirds of the other/unspecified category could be nonmyeloid leukemia. Both under- and overreporting of myeloid leukemia can alter the true shape of the dose-response by impacting the cancer deaths across exposure levels and statistical power in an uncertain fashion.

Finding: EPA states that the p-value of 0.44 for trend is indicative of a poor model fit. This conclusion is erroneous, and this error occurs throughout this section (e.g., p. 2-86, line 8-9; p. 2-91, line 14; Table 2-36, last bullet point). Rather, this p-value is indicative of the lack of statistical significance for the association between myeloid leukemia death risk and cumulative formaldehyde exposure, which results largely from the nonmonotonic relative risk trend

seen in the reported data (0.82 and 1.02 in the second and third exposure categories, respectively; Table 2-29). In contrast, a monotonic trend is observed under the metric of peak exposure ($p = 0.07$; Table 2-29).

Recommendation 5.14 (Tier 2): EPA should discuss the implications and interpretation of nonmonotonic dose-response relationships observed with the cumulative exposure metric (e.g., p. 2-92, lines 2–4).

Uncertainty in the Myeloid Leukemia Inhalation Unit Risk

The 2022 Draft Assessment provides a detailed discussion of the uncertainty associated with the myeloid leukemia inhalation unit risks. The discussion focuses on the statistical significance of the association between myeloid leukemia mortality risk and various exposure metrics due to underreporting of myeloid leukemia. Other important sources of uncertainty include a lack of mechanistic support for myeloid leukemia, uncertainty about the true but unknown shape of the dose-response relationship and its data manifestation, and exposure misclassification. For example, the trend p-values for peak exposure are 0.07 and 0.50 for myeloid leukemia and other/unspecified leukemia, respectively. In contrast, the trend p-values for cumulative exposure are 0.44 and 0.14 for myeloid leukemia and other/unspecified leukemia, respectively.

Finding: The degree of monotonicity of the dose-response in the data dominates the statistical significance of the exposure-response trend. Therefore, combining other/unspecified leukemia with myeloid leukemia does not necessarily reduce the uncertainty due to underreporting of myeloid leukemia.

Finding: EPA estimated inhalation unit risks for all leukemias, myeloid leukemia and other/unspecified leukemia combined, and myeloid leukemia separately, and concluded that these estimates were similar (Tables, 2-34 and 2-35). In part because of the weak dose-response relationship for cumulative exposure and myeloid leukemia data in the NCI cohort, the likely significant underreporting of myeloid leukemia, and the uncertainty in the optimal exposure metric, EPA determined that the inhalation unit risk estimate for myeloid leukemia is of low confidence. The committee concurs with the decision not to carry the myeloid leukemia risk estimate forward into the overall inhalation unit risk estimate for formaldehyde.

Recommendation 5.15 (Tier 2): In the discussion of uncertainties and confidence in the inhalation unit risk for myeloid leukemia, EPA should include the unknown dose rate-response relationship, the choice of statistical model and method, and the lack of understanding of mechanism. The three estimates in Table 2-35 should be presented as alternative, low-confidence inhalation unit risk estimates for myeloid leukemia without selection of a preferred estimate. EPA should not characterize the combining of other/unspecified leukemia with myeloid leukemia as "the best approach."

Human-Based Unit Risk Estimates for Potential Increased Early-Life Susceptibility

Decision to Apply Adjustment for Increased Early-Life Susceptibility

Age-dependent adjustment factors (ADAFs) were used to adjust for potential increased susceptibility resulting from early-life exposure, in accordance with the *Supplemental Guidance for*

Assessing Susceptibility from Early-life Exposure to Carcinogens (EPA, 2005b). The rationale for adjusting for increased early-life susceptibility was that the mutagenic mode of action was established for nasopharyngeal cancers, and the relative risk from formaldehyde exposure is independent of age within the adult age window. For earlier years, relative risk was assumed to be a factor of 10 larger from birth to <2 years and a factor of 3 larger for ages >2 to 16 years. Beyond the 16th birthday, the adult relative risk was assumed.

> Finding: EPA's application of ADAFs is consistent with its *Supplemental Guidance for Assessing Susceptibility from Early-life Exposure to Carcinogens* (EPA, 2005b), which states (p. 36):
>
> ADAFs are only to be used for agents with a mutagenic mode of action for carcinogenesis when chemical-specific data are absent.

While there is uncertainty in the degree to which nonmutagenic processes may also contribute to the carcinogenic activity of formaldehyde inhalation at the point-of-entry tissues, there is sufficient evidence to support the assumption that a mutagenic MOA is involved in the carcinogenesis of formaldehyde in the upper aerodigestive tract in humans. Furthermore, there are no formaldehyde-specific data to inform adjustments for early-life exposure, which further supports use of the default procedure as discussed in the *Supplemental Guidance for Assessing Susceptibility from Early-life Exposure to Carcinogens* (EPA, 2005b). Finally, this approach is concordant with the *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a) which states (p. 3-22):

> If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur.

Approach to Adjustment

An estimate of "adult-only unit risk" was derived by applying the lifetable approach discussed earlier for nasopharyngeal cancers to ages greater than 16 years. This result was scaled by multiplying by 70/54 years to create "adult-based unit risk estimates for nasopharyngeal cancer for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios" (Table 2-38). Calculations were then made using this "adult-based" inhalation unit risk and ADAFs to derive a total lifetime inhalation unit risk estimate assuming exposure from birth to 70 years of age. The resulting estimate is termed a "lifetime unit risk estimate" (p. 2-99). The "adult based" unit risk estimate is identified as the "preferred inhalation unit risk estimate," and the "lifetime unit risk estimate" is termed the "ADAF-adjusted unit risk estimate" (p. 2-102).

> Finding: The use of multiple terms for the same item is confusing, and the "preferred inhalation unit risk" conflicts with the definition of "inhalation unit risk" in EPA's online IRIS glossary:

Inhalation Unit Risk Definition: The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m³ in air.[4]

The "ADAF-adjusted unit risk estimate" meets this definition, while the "preferred" estimate does not. EPA intends the "preferred" estimate to be used in applications for which ADAFs are used to address less-than-lifetime exposures, particularly early in life, or risks when exposure varies with age.

Recommendation 5.16 (Tier 3): Terminology for inhalation unit risk estimates and for potency values used in applying ADAFs should be consistent across the IRIS Program, including with terms in the IRIS glossary.

Recommendation 5.17 (Tier 2): For clarity, EPA should include the lifetable calculations for the adult-only unit risk estimate in Appendix B.

Confidence in the Unit Risk Estimate

EPA assigned the "preferred" unit risk estimate for nasopharyngeal cancer incidence an overall confidence level of *medium*. The 2022 Draft Assessment acknowledges the substantial uncertainty in the dose extrapolation, especially in light of endogenous formation of the chemical and the possible effect on uptake. On the other hand, EPA acknowledges the strength of the large NCI study and the quality of its exposure assessment. A major uncertainty is the inability to include myeloid leukemia in the unit risk estimate because of the quality of the data available for dose-response analysis. The Draft Assessment also describes various sources of uncertainty having to do with the exposure assessment in the NCI study, the selection of the model, and the exposure metric used for the dose-response modeling.

Finding: The sources of uncertainty are well described, and the committee finds the assignment of *medium* confidence appropriate and consistent with EPA's state-of-practice methods. The committee agrees that there is substantial uncertainty regarding extrapolation to lower doses, but notes that the degree of extrapolation is less than typical in environmental health risk assessment because the POD was already at the risk level of 0.05 percent excess risk and well within the range of observation. The committee also agrees that the failure to incorporate in the unit risk estimate cancer activity for cancers other than nasopharyngeal that are causally related to formaldehyde exposure (myeloid leukemia and sinonasal cancer) could raise the possibility of a bias toward underestimation of risk.

Appropriate Exposure Circumstance

This chapter follows the approach described in the "General Assessment Organization" section of the 2022 Draft Assessment of adding the modifier "under appropriate exposure circumstances" to each of the credible hazards identified. It is noted in this orienting section of the document that "the 'appropriate exposure circumstances' alluded to during hazard identification in

[4] Integrated Risk Information System (IRIS) Glossary. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwiH9ZC73p7-AhVKjIkEHdUJC4wQFnoECBEQAQ&url=https%3A%2F%2Fwww.epa.gov%2Firis%2Firis-glossary&usg=AOvVaw29QeD8x7j-7RHqbA05CH2B.

Section 1 are more fully evaluated and defined through dose-response analysis in Section 2 (including, depending on the evidence available, the derivation of toxicity values)."

Finding: The dose-response analysis in Section 2 does not explicitly address the meaning of "appropriate exposure circumstances" in the context of the cancer hazard identifications in Section 1, and in fact nowhere in Section 2 is that term found. Consequently, readers are left uninformed as to how EPA is qualifying its cancer hazard conclusions.

Recommendation (Tier 2): EPA should clearly articulate what is meant by "appropriate exposure circumstances" in Section 2 or abandon the use of the term.

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Appendix A
Committee Member Biographical Sketches

Jonathan M. Samet (*Chair*), is a pulmonary physician and epidemiologist and dean of the Colorado School of Public Health. His research has focused on the health risks posed by the environment, including inhaled pollutants and tobacco. He has served on numerous committees concerned with public health and the environment: the Science Advisory Board of the U.S. Environmental Protection Agency; committees of the National Academies of Sciences, Engineering, and Medicine, including chairing the Biological Effects of Ionizing Radiation VI Committee, the Committee on Incorporating 21st Century Science in Risk-Based Evaluations, the Committee on Research Priorities for Airborne Particulate Matter, the Committee to Review EPA's Draft Integrated Risk Information System Assessment of Formaldehyde, the Committee to Review the IRIS Process, and the Board on Environmental Studies and Toxicology, among others; and the National Cancer Advisory Board. Dr. Samet is a member of the National Academy of Medicine. He received his MD from the University of Rochester, School of Medicine and Dentistry, and his master's degree in epidemiology from the Harvard T. H. Chan School of Public Health.

Aisha S. Dickerson is assistant professor of epidemiology and Bloomberg professor of American health in environmental challenges at the Johns Hopkins Bloomberg School of Public Health. She is an environmental neuroepidemiologist with primary research interests in environmental risk factors for neurodevelopmental and neurodegenerative disorders, including autism spectrum disorder, amyotrophic lateral sclerosis, and dementia. Additionally, she investigates the influence of disparities in autism assessment and service provision, along with environmental justice issues in underserved communities. Dr. Dickerson holds a BS in biology and MSPH in epidemiology from the University of Alabama at Birmingham and PhD in epidemiology from the University of Texas Health Science Center at Houston. She received a year of postdoctoral training at the U.S. Environmental Protection Agency before completing a postdoctoral fellowship at the Harvard T. H. Chan School of Public Health.

Dana C. Dolinoy serves as National Science Foundation international chair of environmental health sciences and professor of environmental health sciences and nutritional sciences at the University of Michigan School of Public Health, and as director of the Michigan Lifestage Environmental Exposures and Disease (M-LEEaD) Center. She leads the Environmental Epigenetics and Nutrition Laboratory, which investigates how nutritional and environmental factors interact with epigenetic gene regulation to shape health and disease. Dr. Dolinoy serves as associate editor of *Environmental Health Perspectives, Environmental Epigenetics, and Toxicological Sciences*, and served as chair of the Gordon Research Conference in Cellular & Molecular Mechanisms of Toxicity. She has been an invited speaker at numerous national and international meetings and authored more than 130 peer-reviewed scientific manuscripts and 10 book chapters. In 2011, Dr. Dolinoy received the Norman Kretchmer Memorial Award from the American Society for Nutrition and the Classic Paper of the Year Award from *Environmental Health Perspectives*. In 2015, she received a National Institutes of Health Director's Transformative Award to develop piRNA epigenetic editing technologies, and in 2021 received the Society of Toxicology Leading Edge in Basic Sciences Award. She has previously served on the National Academies of Sciences, Engineering, and Medicine committee on veterans and Agent Orange. Dr. Dolinoy holds a PhD in genetics and

genomics and integrated toxicology from Duke University, and an MSc in public health from Harvard University

David C. Dorman is professor of toxicology in the Department of Molecular Biomedical Sciences at North Carolina State University. His research interests include neurotoxicology, nasal toxicology, pharmacokinetics, and cognition and olfaction in animals. He is an elected fellow of the Academy of Toxicological Sciences, a fellow of the American Association for the Advancement of Sciences, and a diplomate of the American Board of Veterinary Toxicology and the American Board of Toxicology. Dr. Dorman has chaired or served on multiple National Academies of Sciences, Engineering, and Medicine committees. He completed a combined PhD and veterinary toxicology residency program at the University of Illinois at Urbana-Champaign and holds a DVM from Colorado State University.

Rakesh Ghosh is senior scientist at the University of California, San Francisco, and teaches epidemiology and research methods in the School of Medicine. He has more than 15 years of research experience in examining the effects of environmental pollutants on maternal and newborn health. Dr. Ghosh's contributions include studying the global burden of adverse perinatal outcomes, including neonatal mortality attributable to $PM_{2.5}$ air pollution, and novel evidence about the effect of air pollution, which goes beyond respiratory health and is likely more profound, affecting early childhood growth. He has received several conference awards recognizing his cutting-edge work in this field. Dr. Ghosh has a PhD in environmental epidemiology.

Sabine S. Lange is chief toxicologist at the Texas Commission on Environmental Quality (TCEQ). Her responsibilities include conducting and overseeing health effects risk assessments of air permit applications, ambient air monitoring projects, and hazardous waste sites; development of chemical toxicity factors; and systematic reviews and independent analyses of risk assessments. Dr. Lange's research interests include the toxicology and risk assessment of air pollutants and risk assessment methods used for derivation of toxicity factors. She has served on several peer-review committees for the U.S. Environmental Protection Agency, including as a former member of the chartered Clean Air Scientific Advisory Committee. TCEQ intends to sponsor a separate National Academies consensus study to provide an independent peer review of TCEQ's ethylene oxide cancer risk assessment. Dr. Lange is not involved in the procurement of that separate activity. Dr. Lange received a bachelor's degree in biochemistry from the University of Western Ontario in Canada, and completed a PhD and postdoctoral training in biochemistry and molecular carcinogenesis at the University of Texas MD Anderson Cancer Center. Dr. Lange is a diplomate of the American Board of Toxicology.

Andrew F. Olshan is Barbara S. Hulka Distinguished Professor in the Department of Epidemiology of the Gillings School of Global Public Health at the University of North Carolina (UNC) at Chapel Hill. He served as chair of the department from 2006 to 2018. He is associate director of population sciences, UNC Lineberger Comprehensive Cancer Center. Dr. Olshan's major interests include the epidemiology of cancer and perinatal and pediatric outcomes. His cancer research has focused on genetic and environmental risk factors for childhood cancer, breast cancer, head and neck cancer, and endometrial cancer. He has led multiple cancer studies in North Carolina and nationally and has been principal investigator for multiple studies funded by the National Cancer Institutes, U.S. Environmental Protection Agency, and Centers for Disease Control and Prevention. Dr. Olshan has served on the Institute of Medicine Committees to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. He was vice-chair of the National Research Council's Committee to Review the Draft IRIS Assessment of Formaldehyde. He is editor-in-chief of

Current Epidemiology Reports and past president of the Society for Epidemiologic Research. Dr. Olshan received his doctorate in epidemiology from the University of Washington in Seattle and was a postdoctoral fellow at the University of British Columbia in Canada.

Ivan Rusyn is professor in the Department of Veterinary Physiology and Pharmacology in the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. He is also chair of the Interdisciplinary Faculty of Toxicology at Texas A&M University. His laboratory has an active research portfolio with a focus on the mechanisms of action of environmental toxicants, the genetic determinants of susceptibility to toxicant-induced injury, and the use of new approach methods in regulatory toxicology. His studies on health effects of environmental agents have resulted in more than 300 peer-reviewed publications. Dr. Rusyn is a member of the Research Committee of the Health Effects Institute and was on the Board of Scientific Councilors of the National Institute of Environmental Health Sciences. He also serves as principal investigator of a research consortium funded, in part, by the American Chemistry Council; the funders have no role in directing the research or reviewing publications, and Dr. Rusyn draws no salary from the consortium. He has served on several committees of the National Academies of Sciences, Engineering, and Medicine, including the Board on Environmental Studies and Toxicology, the Committee on Incorporating 21st Century Science into Risk-Based Evaluations, and the Committee on the Design and Evaluation of Safer Chemical Substitutions. Most recently, he chaired the Committee to Review the Report on Long-Term Health Effects on Army Test Subjects and the Workshop Committee to Support Development of EPA's IRIS Toxicological Reviews. Dr. Rusyn received his MD from Ukrainian State Medical University in Kyiv and his PhD in toxicology from the University of North Carolina at Chapel Hill.

Lianne Sheppard is Rohm & Haas Endowed Professor at the University of Washington School of Public Health, and is a member of the departments of Environmental and Occupational Health Sciences, and Biostatistics. Her research interests focus on environmental epidemiology and statistical methods for understanding the health effects of environmental and occupational exposures; they include study design, measurement error, exposure modeling and estimation, and estimation of environmental exposure effects with application to a wide range of health outcomes including cancer, brain health, and cardiovascular disease measures. Dr. Sheppard is a fellow of the American Statistical Association and the 2020 recipient of the International Society for Environmental Epidemiology Research Integrity Award. She is currently chair of the Clean Air Scientific Advisory Committee and a member of the Scientific Advisory Board of the US Environmental Protection Agency. She previously served on the National Research Council Committee on Contaminated Drinking Water at Camp Lejeune. She holds a PhD in biostatistics.

Katya Tsaioun is executive director of the Evidence-Based Toxicology Collaboration at Johns Hopkins Bloomberg School of Public Health, where she leads international efforts to establish evidence-based methodologies and systematic reviews in toxicology. Her research has focused on translation of scientific innovations into technologies enabling improvements in public health. Dr. Tsaioun spent two decades in translational drug discovery research and development in assay development for high-throughput screening and ADME (absorption, distribution, metabolism, and excretion) and toxicology. Based on this experience, she founded a company leading commercialization and application of drug de-risking technologies. Dr. Tsaioun has served on the advisory boards of companies, charities, and review committees at the National Institutes of Health, and serves with private foundations focused on developing therapies for neurodegenerative diseases. She served on committees with the National Academies of Sciences, Engineering, and Medicine in 2018–2020 to review the Integrated Risk Information System and Toxic Substances Control Act

systematic review processes. Dr. Tsaioun earned a PhD in human nutrition science from Tufts University Friedman School of Nutrition Science and Policy, and completed postdoctoral training in neurochemistry at Harvard Medical School.

Joseph Wiemels is professor in the Center for Genetic Epidemiology in the Department of Population and Public Health Sciences and associate director of the Norris Comprehensive Cancer Center at the University of Southern California. He has been a faculty member for more than 21 years, with previous appointments at the University of California, San Francisco. Dr. Wiemels studies the molecular epidemiology of childhood leukemia and brain cancer, concentrating on etiology and prevention and incorporating concepts of genetic susceptibility and interaction with environmental exposures and infections. His research group consists of both laboratory- and computational-based scientists who are focused on the interaction of inherited genetics and environmental factors in causing specific mutational and epigenetic changes, and the specific timing of these events during the development of the child. Dr. Wiemels' doctoral work examined the metabolism and toxicity of benzene and butadiene. Throughout his career, he has worked on establishing mechanistic relationships between environmental agents and cancer risk. He was a Leukemia and Lymphoma Society scholar and is a member of several scientific societies, including the American Association for Cancer Research and the American Society of Hematology. Dr. Wiemels was also a reviewer of the 2011 Formaldehyde Report.

Lauren Zeise is director of the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment. She oversees the department's activities, which include the development of risk assessments, hazard evaluations, toxicity reviews, cumulative impact analyses, frameworks and methods for assessing toxicity and cumulative effects of vulnerability and environmental exposures on communities, and the department's activities in the California Environmental Contaminant Biomonitoring Program. Dr. Zeise was the 2008 recipient of the Society for Risk Analysis' Outstanding Practitioners Award. She has served on advisory boards and committees of the U.S. Environmental Protection Agency, the Office of Technology Assessment, the World Health Organization, and the National Institute of Environmental Health Sciences. Dr. Zeise has served on numerous National Academies of Sciences, Engineering, and Medicine committees, including the Committee to Review Advances to the IRIS Process, the Committee on Incorporating 21st Century Science in Risk-Based Evaluations, and the Committee to Review EPA's Draft Integrated Risk Information System Assessment of Formaldehyde. Dr. Zeise received a PhD from Harvard University.

Yiliang Zhu is professor and chief in the Division of Epidemiology, Biostatistics, and Preventive Medicine of the School of Medicine at the University of New Mexico (UNM). Prior to joining UNM in 2017, he was professor and founding director of the biostatistics PhD program in the Center for Collaborative Research at the University of South Florida College of Public Health. His research focuses on data analytic methods in health risk assessment, including integrative modeling of biological systems, dose-response modeling, benchmark-dose methods, and uncertainty quantification. He also conducts work in biostatistics methods, health service research, as well as directs an ongoing cohort study of the rural health care system and policies in northwestern Loess Plateau China. Dr. Zhu was a Fulbright scholar and studied public policy in China (2012–2013); he was also a science and technology policy fellow of the American Association for the Advancement of Science and the US Environmental Protection Agency (2013–2015). Dr. Zhu has served on a number of National Academies of Sciences, Engineering, and Medicine committees, including the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, Committee to Review the IRIS Process, and Committee to Review Advances Made to the IRIS Process, among others.

Appendix B
Public Session Agendas

Committee to Review EPA's 2022 Draft Formaldehyde Assessment
Meeting 1
Wednesday, October 12, 2022 (all times listed in EST)

9:00 AM–2:00 PM	**Closed Session**
2:00–5:30 PM	**Open Session**
2:00 PM	**Welcome and Introductions** **Kate Z. Guyton**, **PhD**, National Academies Responsible Staff Officer **Jonathan M. Samet, MD,** Committee Chair
2:25 PM	**Presentation on National Academies report *Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version*** **Lisa Bero, PhD,** Professor of Medicine and Public Health, University of Colorado
2:45 PM	**Committee Q&A**
3:00 PM	**Break**
3:15 PM	**EPA Presentation and Committee Q&A** **Andrew Kraft, PhD**, U.S. Environmental Protection Agency (EPA) **Thomas Bateson, ScD**, EPA
5:00 PM	**Opportunity for Public Comment**
5:30 PM	**End of Open Session**

Thursday, October 13, 2022

9:00 AM–3:00 PM	**Closed Session**

Meeting 2
Thursday, December 22, 2022 (all times listed in EST)

2:00–3:00 PM	**Closed Session**
3:00–4:00 PM	**Open Session**
3:00 PM	**Welcome and Introductions** **Kate Z. Guyton**, **PhD**, National Academies Responsible Staff Officer **Jonathan M. Samet, MD,** Committee Chair

3:15 PM	**Opportunity for Public Comment** *(Each commenter must register in advance and will have up to three minutes to comment. Comments will be invited from one speaker per organization, with preference given to those individuals and organizations who have not previously addressed the committee.)*
4:00 PM	**End of Open Session**

Meeting 3

Monday, January 30, 2023 (all times listed in EST)

9:00 AM–2:00 PM	**Closed Session**
2:00–4:20 PM	**Open Session**
2:00 PM	**Welcome and Introductions** **Kate Z. Guyton, PhD**, National Academies Responsible Staff Officer **Jonathan M. Samet, MD,** Committee Chair
2:20 PM	**EPA Presentation and Committee Q&A** **Andrew Kraft, PhD**, EPA **Thomas Bateson, ScD**, EPA
3:20 PM	**Opportunity for Public Comment** *(Each commenter must register in advance and will have up to three minutes to comment. Comments will be invited from one speaker per organization, with preference given to those individuals and organizations who have not previously addressed the committee.)*
4:20 PM	**End of Open Session**
4:20–6:00 PM	**Closed Session**

Tuesday, January 31, 2023

9:00 AM–2:00 PM	**Closed Session**

Speaker Biographies

Thomas Bateson is senior epidemiologist with the U.S. Environmental Protection Agency's (EPA's) Office of Research and Development in the Center for Public Health and Environmental Assessment in Washington, DC. He earned his Master of Public Health in epidemiology and biostatistics from the University of California, Berkeley, and his Doctor of Science in epidemiologic methods from the Harvard T. H. Chan School of Public Health. Before joining EPA in 2006, Dr. Bateson studied the causes of birth defects, children's health and development, the health of military personnel, and the effect of air pollution on the elderly using the case-crossover study design. At EPA, he works together with statisticians and toxicologists from multiple disciplines to identify hazards and to quantify the associated risks. Dr. Bateson has contributed to the EPA Integrated

Risk Information System (IRIS) assessments of environmental agents, such as asbestos, formaldehyde, hexavalent chromium, manganese and PFAS (PFDA, PFHxS, PFNA). He has also contributed to the Office of Chemical Safety and Pollution Protection's Toxic Substances Control Act (TSCA) risk evaluations of chrysotile asbestos and carbon tetrachloride, as well as the Office of Water's evaluations of PFOS and PFOA.

Lisa Bero is professor in the School of Public Health and the School of Medicine (General Internal Medicine) at the University of Colorado CU Anschutz Medical Center. She is also chief scientist at the Center for Bioethics and Humanities at that medical center. In addition, she is affiliated professor at the Charles Perkins Centre and School of Pharmacy in the Faculty of Medicine and Health at the University of Sydney. Dr. Bero is adjunct professor in the Department of Clinical Pharmacy and Institute for Health Policy Studies at the University of California, San Francisco. She is recognized for her methodological studies on bias (including publication/reporting, design, and funding biases) in the fields of clinical medicine (pharmaceuticals), tobacco control, and environmental research, and the use and implications of the evidence for prescribing decisions/policy. She investigates hidden biases in the design, conduct, and publication of research. For more than 20 years, Dr. Bero has been actively involved in the Cochrane Collaboration, a global organization that summarizes the best evidence from research to help make informed choices about health care. She served as a member of the National Academies Board on Health Care Services; Committee to Review the IRIS Process; and Committee on Conflicts of Interest in Medical Research, Education, and Practice. Dr. Bero received a PhD in pharmacology from Duke University.

Andrew D. Kraft is associate director of the Chemical and Pollutant Assessment Division within the Office of Research and Development at the U.S. Environmental Protection Agency (EPA). In this capacity, he oversees the development of Integrated Risk Information System (IRIS) assessments, as well as other technical products supporting Agency decision-making. Since joining EPA in 2011, he has led, coordinated, or contributed to dozens of human health assessments of environmental chemicals and has worked to advance methods for assessment development through collaboration with other EPA programs and regions, other federal and state agencies, and international organizations. Most relevant to the current project, Dr. Kraft has been chemical manager of the IRIS formaldehyde (inhalation) assessment since 2012 and has been a primary author on the IRIS Handbook since its inception. Before joining EPA, he received a PhD from the University of Wisconsin–Madison and did postdoctoral training at the U.S. National Institute of Environmental Health Sciences. Dr. Kraft's graduate and postdoctoral studies were in neurotoxicology, focusing on protective mechanisms against neurodegenerative diseases and environmental insults.

List of Public Commenters

Meeting 1

Richard	Albertini
Paul	Bredwell
Harvey	Checkoway
Rory	Conolly
Pamela	Dalton
James	Enstrom
David	Fischer
Bernard	Gadagbui
John	Graham

Mark	Gruenwald
Stewart	Holm
Kun	Lu
Heather	Lynch
Gary	Marsh
Kenneth	Mundt
Jessica	Ryman-Rasmussen
Thomas	Starr
Chad	Thompson

Meeting 2

Paolo	Boffeta
Kevin	Bromberg
Tony	Cox
Bernard	Gadagbui
Paul	Girard
Gary	Huddleston
Kun	Lu
Sahar	Osman-Sypher
James	Sherman
Bill	Thompson
Lesley	Witter
Clint	Woods

Meeting 3

Preston	Beard
Tokesha	Collins-Wright
Harvey	Clewell
James	Enstrom
Chris	Farmer
Adrian	Krygsman
Kun	Lu
Heather	Lynch
Peggy	Murray
Andy	O'Hare
Leslie	Recio
James	Sherman

Appendix C
Case Study: Hanrahan et al. (1984), Human Sensory Irritation

As noted in Chapter 2 of this report, the committee considers that sufficiently transparent and detailed methods would support replication by us and others. To test whether we could identify and follow the steps described in the 2022 Draft Assessment (EPA, 2022a), we focused on a key study by Hanrahan and colleagues (1984), used by EPA to assess a health outcome (human sensory irritation) and to calculate a candidate reference concentration. We followed EPA's eight-step process (shown in Figure C-1) for identification of studies, outcome evaluation, evidence synthesis and integration, and dose-response study selection. The goal of this case study is to explore whether the 2022 Draft Assessment's methods are adequately described so that they can be utilized by others—a key characteristic of transparent documentation. The case study was not carried out to provide an independent assessment of formaldehyde by the committee.

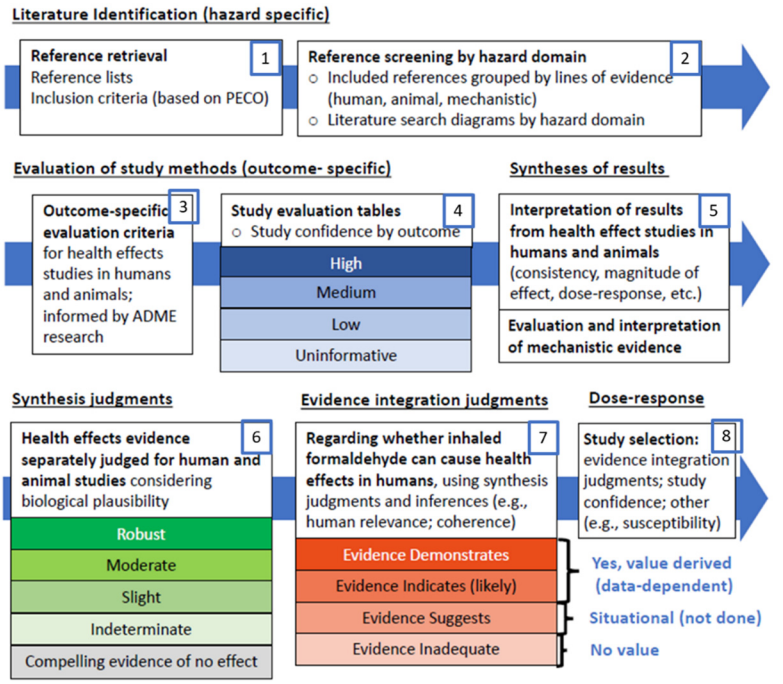

FIGURE C-1 The eight-step process for literature identification, outcome-specific study methods, synthesis of results, synthesis and evidence integration judgments, and dose-response study selection, outlined by the U.S. Environmental Protection Agency (EPA).
NOTES: ADME = absorption, distribution, metabolism, and excretion; PECO = participants, exposure, comparator, and outcome(s).
SOURCE: EPA's 2022 Draft Formaldehyde Assessment.

IDENTIFICATION OF CASE STUDY INFORMATION

The first step in the committee's evaluation was to locate information pertaining to human sensory irritation and the study by Hanrahan and colleagues specifically. The descriptions of EPA approaches used in the 2022 Draft Assessment are located in multiple places, requiring that we collate the methods from three EPA documents. The resulting map of information is shown in Figure C-2.

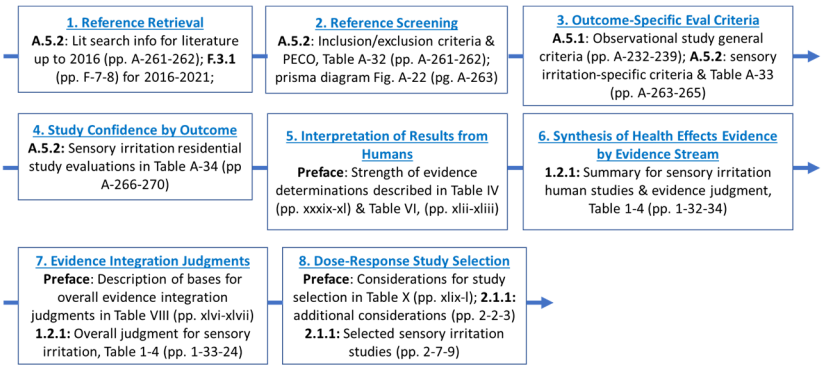

FIGURE C-2 Location of information for each step of EPA's process for the human sensory irritation endpoint.
NOTE: Committee-generated by review of EPA's 2022 Draft Formaldehyde Assessment.

STEPS 1 AND 2: REFERENCE RETRIEVAL AND SCREENING

In Appendix A.5.2, EPA described the literature search strategy for studies published up to 2016, the inclusion and exclusion criteria, the PECO (participants, exposure, comparator, and outcome[s]) statement along with a PRISMA (preferred reporting items for systematic reviews and meta-analyses) diagram documenting the search and article screening. Appendix F.3.1 describes the literature search for studies published from 2016 to 2021 and the evaluation of potentially impactful studies.

Overall, the literature search terms, inclusion and exclusion criteria, and PECO statement are appropriately inclusive of relevant studies for assessing human sensory irritation.

STEP 3: OUTCOME-SPECIFIC EVALUATION CRITERIA

EPA provided outcome evaluation criteria for human observational and animal/human experimental studies in Appendix A.5.1, with sensory irritation–specific criteria in Appendix A.5.2. The information in A.5.2 includes descriptions about particular criteria relevant to the endpoint, as well as a table (Table A-33) that provides information about the exposure and design characteristics of studies, which are assigned quality labels of *high*, *medium, low*, or *not informative*. These descriptions include some of the quality characteristics listed in Appendix A.5.1 and in the text of A.5.2, but not others. For example, none of the criteria in the Selection Bias domain (recruitment, selection into study, participation independent of exposure) are included in Table A-33. In addition, the specific study characteristics are included in some but not all of the quality determination descriptions, such as the use of a validated data collection instrument, which is included in the *high*

and *medium* descriptions, but not those for *low*. The descriptions of these characteristics also sometimes include vague terms, such as "limited exposure assessment" or "less well described," to characterize data collection instruments. This table (A-33) is the first time that sample size is introduced as a study quality characteristic, but without discussion to inform when the sample size would be considered "large," "small," or "may be a limitation."

Table C-1 lists the study quality criteria described by EPA in Appendix A.5.1 and A.5.2.

TABLE C-1 The U.S. Environmental Protection Agency's (EPA's) Study Quality Criteria and Bases for Confidence Ratings for Human Sensory Irritation Studies

Study Quality Criteria	Locations for Criteria in Appendix			Description of Confidence Rating from Table A-33 (approximate matching to appropriate criteria)
	General Criteria Text of A.5.1	Exposure Criteria Text of A.5.1	Sensory Irritation Table A-33	
Selection Bias				
Recruitment, selection into study, participation independent of exposure	X	N/A	X	**NI**: Selection bias away from null
Sufficient reporting detail about subject identification and selection	X	N/A		**NI**: Methods description too sparse for evaluation [a]
Information Bias				
Exposure assessment timing appropriate for outcome observation	X	N/A	X	**High**: Exposure assessment timing appropriate for outcome observation; **Med**: Uncertainty in timing between exposure and outcome assessment
Reporting of distribution and range of exposure	X	X		
Adequate contrast between high and low exposure	X	X		**NI**: Exposure range <0.1 mg/m3
Exposure measurement duration and frequency		X		
Consideration of temp, RH, quality control		X		
For <1 day exposure measurement, details of measurement protocol and influence of sources of exposure should be included		X	X	**Low**: <1 day exposure measure without protocol discussion and quality control
LOD and percent < LOD		X		
Conc. measure captures mean individual exposure			X	**High**: Exposure assessment designed to characterize mean exposures **Med**: More limited exposure assessment
Validated data collection instrument used and described	X	N/A	X	**High**: Validated data collection instrument used and described **Med**: instrument less well described
Outcome ascertainment independent of exposure knowledge	X	N/A	X	**High** and **Med**: Outcome ascertainment independent of exposure knowledge

continued

TABLE C-1 *continued*

Study Quality Criteria	Locations for Criteria in Appendix			Description of Confidence Rating from Table A-33 (approximate matching to appropriate criteria)
	General Criteria Text of A.5.1	Exposure Criteria Text of A.5.1	Sensory Irritation Table A-33	
Timing of outcome assessment with exposure assessment		N/A	X	**High** and **Med**: Symptom assessment concurrent with exposure assessment
Potential for Confounding				
Important confounders addressed in study design or analysis	X	N/A	X	**High**: confounding considered and addressed in design or analysis
Confounding by coexposures addressed	X	N/A	X	**Med**: Confounding considered and addressed in design or analysis, but questions remain about correlation between formaldehyde and coexposures **Low**: High likelihood of confounding preventing differentiation of formaldehyde effect from that of other exposures
Analysis				
Appropriate analytical approach used	X	N/A	X	**High**: Analytic approach for dose-response appropriate for data type **Med**: Analytic approach more limited **Low**: Limited or inappropriate data analysis
Consider alternate explanations for findings	X	N/A		
Quantitative results presented	X	N/A	X	**High**: Quantitative results provided
Other considerations not otherwise evaluated				
Sensitivity (exposure levels, exposure contrast, duration of follow-up, outcome ascertainment)	X	N/A		
Sample size		N/A	X	**High**: Large sample size **Med**: sample size may be a limitation **Low**: small sample size

NOTES: [a] For the not informative category, "methods description too sparse for evaluation" could apply to any of the study evaluation domains.
X denotes the location where the criteria are described in the 2022 Draft Assessment. The final column provides EPA's confidence rating information provided, matched with the corresponding study quality criteria (as determined by the committee, because EPA did not provide the specific domains when describing the characteristics of *high, medium, low*, and *not informative* studies). LOD = limit of detection; NI = not informative; RH = relative humidity.

EPA's evaluation of the Hanrahan study is found in Table A-34 of A.5.2, which provides details for each of the confidence domains. Deficiencies are noted in two domains: Exposure (limited sampling period), and Outcome (no description of self-report questionnaire). The overall confidence in this study is *medium*, and the overall confidence figure shows a central mark in the information bias column only (see Figure C-3).

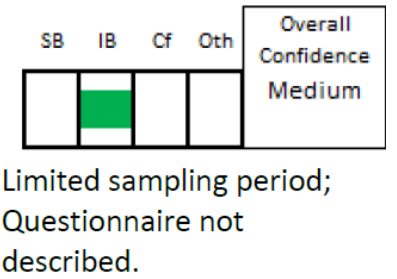

FIGURE C-3 Confidence rating of Hanrahan et al. (1984) as evaluated by the U.S. Environmental Protection Agency.
NOTES: Cf = confounding; IB = Information Bias; Oth = Other; SB = selection bias.
SOURCE: Table A-34 of A.5.2, Appendix A of EPA's 2022 Draft Formaldehyde Assessment.

Table C-2 shows a comparison of the study quality criteria and descriptions provided by EPA for sensory irritation, with the findings reported for Hanrahan et al. (1984) in Table A-34, as well as notes from the committee about how the study quality criteria were applied.

TABLE C-2 Application of the US Environmental Protection Agency's (EPA's) Study Quality Criteria and Confidence Ratings to the Hanrahan et al. (1984) Study

Study Quality Criteria	Description of Confidence Rating from Table A-33	Findings Reported by EPA in Table A-34	EPA Rating and Comments in Table A-34	Committee Notes
Selection Bias			**No Issues Noted in Summary Diagram**	
Recruitment, selection into study, participation independent of exposure	**NI:** selection bias away from null	Randomly selected from list of mobile homes; 31% of respondents from homes with exposure measures returned health questionnaires; participation independent of exposure	Less concern about low response rate because formaldehyde concentrations, age, and gender of participants were comparable to nonrespondents, and participants blinded to formaldehyde concentration	
Sufficient reporting detail about subject identification and selection	**NI:** Methods description too sparse for evaluation	[No information noted]		
Information Bias			**Some Issues Noted in Summary Diagram**	
Exposure assessment timing appropriate for outcome observation	**High**: Exposure assessment timing appropriate for outcome observation; **Med**: uncertainty in timing between exposure and outcome assessment	[No information noted]		Exposure assessed at single time point, symptoms reported for any time since moving into the home; noted as a concern in Section 2.1.1 for Hanrahan dose-response assessment

continued

TABLE C-2 *continued*

Study Quality Criteria	Description of Confidence Rating from Table A-33	Findings Reported by EPA in Table A-34	EPA Rating and Comments in Table A-34	Committee Notes
Reporting of distribution and range of exposure		Median 0.2 mg/m^3, range < 0.12–0.98 mg/m^3		
Adequate contrast between high and low exposure	**NI**: Exposure range < 0.1 mg/m^3	[No information noted]		
Exposure measurement duration and frequency		Average of 1-hr samples from two rooms		
Consideration of temp, RH, quality control		[No information noted]		
For <1 day exposure measurement, details of measurement protocol and influence of sources of exposure should be included	**Low**: <1 day exposure measure without protocol discussion and QC	Average of 1-hr samples from two rooms; exposure sampling protocol referenced	Limited sampling period	<1 day exposure measurement (but protocol was discussed). Classify as medium rather than low? Protocol includes QC but not LOD
LOD and percent < LOD		LOD 0.12 mg/m^3		The study does not report a LOD
Concentration measure captures mean individual exposure	**High**: Exposure assessment designed to characterize mean exposures **Med**: More limited exposure assessment	Average of 1-hr samples from two rooms	Limited sampling period	<1 day exposure measurement, unclear if this is categorized as "more limited"
Validated data collection instrument used and described	**High**: Validated data collection instrument used & described **Med**: instrument less well described	Self-report questionnaire, no description	Questionnaire not described	Medium = less well described; unclear how EPA rates "no description"
Outcome ascertainment independent of exposure knowledge	**High** and **Med**: Outcome ascertainment independent of exposure knowledge	Response blind to formaldehyde measurements		
Timing of outcome assessment with exposure assessment	**High** and **Med**: Symptom assessment concurrent with exposure assessment	[No information noted]		Outcome assessment and exposure assessment done at the same time (although outcome involved recall for entire time in the house)
Potential for Confounding			**No Issues Noted in Summary Diagram**	
Important confounders addressed in study design or analysis	**High**: confounding considered and addressed in design or analysis	Logistic regression model adjusted for age, gender, smoking status		

Confounding by coexposures addressed	**Med**: Confounding considered and addressed in design or analysis, but questions remain about correlation between formaldehyde and coexposures **Low**: High likelihood of confounding preventing differentiation of formaldehyde effect from that of other exposures (Low)	[No information noted]		No information about confounding by coexposures noted, but not noted as a deficiency by EPA
Analysis			**No Issues Noted in Summary Diagram**	
Appropriate analytical approach used	**High**: Analytic approach for dose-response appropriate for data type **Med**: analytic approach more limited **Low**: limited or inappropriate data analysis	Logistic regression		
Consider alternate explanations for findings		[No information noted]		No evidence that this was done (generally not addressed in study quality tables)
Quantitative results presented	**High**: Quantitative results provided	Logistic regression, provided graph of predicted mean prevalence normalized to mean age, and upper and lower 95% confidence interval by concentration from regression model		Only one figure reported regression results, no info about regression coefficients and fit, no other results presented, no reporting of primary results
Other considerations not otherwise evaluated			**No Issues Noted in Summary Diagram**	
Sensitivity (exposure levels, exposure contrast, duration of follow-up, outcome ascertainment)		[No information noted]		
Sample size	**High**: Large sample size **Med**: sample size may be a limitation **Low**: small sample size	N = 61		Assume that a sample size of 61 is large, because EPA did not note a deficiency here

NOTES: Based on Table A-34 of EPA's 2022 Draft Assessment. LOD = limit of detection; NI = not informative; QC = quality control; RH = relative humidity.

The committee's review of the Hanrahan et al. (1984) study generated concerns not captured by EPA's review. These include concerns about the application of criteria relevant to the Information Bias domain:

- The domain includes the criteria "exposure assessment timing appropriate for outcome observation" (A.5.1), and "assessment of symptoms timed concurrent with exposure assessment" (Table A-33, A.5.2), with the latter included in the descriptions of both high and medium quality studies. However, although the exposure measurements and the symptom questionnaire were conducted at the same time, the questionnaire gathered information about symptoms reported for any time since moving into the home. Therefore, the exposure assessment was not concurrent with the symptoms. EPA noted this concern when discussing the Hanrahan et al. study in the dose-response assessment, which states that the confidence in the point of departure derived using the Hanrahan et al. study was medium, "reflecting uncertainty in the temporal relationship of the exposure measurements with respect to the assessment of irritation symptoms." (p. 2-10).
- Table A-33 (A.5.2) describes a medium-quality study as one with the data collection instrument "less well-described." Hanrahan et al. (1984) does not describe the data collection instrument (the survey) at all, which is seemingly inconsistent with a medium quality rating.

For the Analysis domain (summarized in the Other category in the EPA summary figure), one of the criteria is the presentation of quantitative results. The only results data presented in the Hanrahan paper are within a figure showing the regression relationship for one endpoint, with no information about the primary data, the regression coefficients themselves, or model fit. EPA did not call out this deficiency in the Analysis category or in the summary figure.

Inconsistencies are also apparent in how study quality deficiencies are represented in the four-domain summary confidence figure for human sensory irritation studies. For example, descriptions of methods are insufficient for some PECO domains in the six-domain table. These deficiencies are not indicated as colored boxes in the final four-domain summary figure for some studies (e.g., Norsted 1985; Thun, 1982), although they are marked for other studies (e.g., Wantke, 1996b). Also, the overall confidence summaries do not always include descriptions for deficiencies noted in the four-domain figure. For example, for Zhai (2013), a deficiency is noted in the Other category of the figure for analysis of combined respiratory symptoms, with no explanation as to why that category is marked. For the Other category, explanations of deficiencies noted in the four-domain summary figure are often provided below the figure, but not in the corresponding domains (e.g., Analysis, Sample Size) in the table. There is a contrast with the other domains for which any issues described with the summary figure are also explained in the domain-specific column (e.g., for Participation Selection or Exposure) (see, e.g., Dally, 1981; Main and Hogan, 1983).

Overall, there are a number of inconsistencies between the specific evaluation criteria that are presented for the human sensory irritation outcome and how they are applied to the Hanrahan et al. (1984) study, as well as how study limitations are presented for other sensory irritation studies.

STEPS 5 AND 6: SYNTHESIS OF RESULTS AND SYNTHESIS JUDGMENTS

Step 5 of the EPA process involves separately interpreting the evidence from human studies, animal studies, and mechanistic studies. EPA applied a set of considerations and a framework for assessing the strength of evidence in each of the evidence streams, which are described in the Preface of the main document (Tables IV and VI for human evidence).

Step 6 of the process diagram involves applying the synthesis framework from Step 5 to the endpoint and making evidence stream-specific synthesis judgments. The panel used human sensory irritation and animal respiratory pathology as case studies to evaluate EPA's application of their framework.

For human sensory irritation, the information that applied to the synthesis judgments is described in the text of the main document in Section 1.2.1, under the title Integrated Summary of Evidence on Sensory Irritation. EPA determined that the strength of evidence was robust, and they provided information that addressed risk of bias, consistency, biological gradient/dose-response, coherence, mechanism/biological plausibility, and other considerations (from Table VI; the set of studies includes varied populations). The text did not address the strength and precision of the estimates (although this category is not a required criteria to qualify as a robust study, as per Table IV), or the criteria from Table VI that there is "reasonable confidence that chance, bias, confounding, can be ruled out." Although these criteria are not discussed, EPA was clear about the basis of the strength-of-evidence determination overall, and applied it in a way that was consistent with their stated framework.

STEP 7: EVIDENCE INTEGRATION JUDGMENTS

Step 7 in EPA's process diagram comprises evidence integration judgments, which generally equate to the final hazard identification step in the assessment. In the Preface, EPA presented Table VIII, which describes how evidence integration judgments are made, based on synthesis judgments for each evidence stream and considering biological plausibility. This table clearly lays out the types and confidence of evidence that are used to make the judgments of strength of evidence: *evidence demonstrates*, *evidence indicates* (likely), *evidence suggests* (but is insufficient to infer), and *evidence inadequate*. The information provided from Step 6 (synthesis judgments) can be directly applied to the metrics in this table to determine the final evidence judgment. The bases of these judgments appear reasonable and follow from earlier steps in the process.

The committee evaluated the application of these criteria to the sensory irritation endpoint. For sensory irritation, the information about overall evidence integration is described in Table 1-4. This table provides the information that both justifies the synthesis judgment for each evidence stream (for Step 6), as well as presenting information for the Step 7 evidence integration judgment. For human studies (robust), the table summarizes the number of high- and medium-quality studies from each relevant study type (residential, controlled human exposure, longitudinal occupational and anatomy lab). However, the table mistakenly states that there were four high- and medium-confidence residential studies, when there were no high-confidence residential studies (there were four medium-confidence studies). In addition, EPA notes that there were numerous high- and medium-confidence longitudinal (occupational and anatomy lab) studies, but these studies receive limited discussion in the main text. It is unclear why EPA appears to have de-emphasized these studies when evaluating sensory irritation, but then used them as a basis for the *robust* determination when synthesizing the evidence. In addition to the human evidence stream, EPA presented a *robust* evidence judgment for animal evidence (not reviewed in EPA's evaluation, but considered to be a well-documented phenomenon), which provides robust and moderate mechanistic evidence to support biological plausibility of formaldehyde effects on sensory irritation. Overall, EPA's conclusion that Evidence Demonstrates is supported by the evidence and is consistent with the criteria presented in Table VIII.

STEP 8: DOSE-RESPONSE STUDY SELECTION

Step 8 in the EPA process diagram is dose-response study selection. In the Preface, EPA presented considerations for study selection for quantitative dose-response assessment and derivation of toxicity values in Table X. This table provides guidelines for study inclusion in the categories of Overall Confidence Conclusion, Study Confidence, Population, and Exposure Information. Each category includes one or more considerations that EPA considered important for study selection, although EPA did not provide further descriptions of those considerations to aid in interpretation of how they were applied. For example, in the Study Confidence category, EPA did not provide further explanation of what would be considered as reasonably complete reporting of results, or of what study designs are appropriate (aside from long-term animal bioassays). The text of the Preface provided further considerations for study selection in addition to those in Table X, stating that EPA puts particular emphasis on the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels analyzed.

EPA also provided information about study selection in Section 2.1 of the main document (p. 2-1), which states that studies and endpoints that are sufficient for deriving a reference concentration (RfC), including high or medium confidence in the study methodological conduct. It is unclear whether EPA used a determination of a high or medium confidence study in the hazard assessment, in place of conducting an evaluation of the study design considerations listed in Table X from the perspective of the dose-response assessment. Section 2.1 also provides further study selection criteria for human and animal studies. Table C-3 below provides a compilation of the general study selection considerations for dose-response assessment, based on the information from the Preface and Section 2.1.

Additionally, EPA provided endpoint-specific dose-response study selection considerations in Section 2.1.1. For sensory irritation, it stated that studies that conducted the exposure assessment concurrently with the outcome assessment were the most informative for RfC derivation because formaldehyde induces a rapid irritant response.

EPA did not provide a description in Section 2.1.1 or Appendix B as to why they selected the Hanrahan study based on their study selection considerations. Table C-4 compares EPA's study selection criteria and the Hanrahan study, using information about the study that can be found elsewhere in the Draft Assessment, or in the Hanrahan study itself.

For Study Confidence, there are inconsistencies between EPA's criteria of reasonably complete reporting of results and the lack of reporting of results in the paper; and the consideration of an accurate exposure assessment of the 1-hour formaldehyde measurements taken in the Hanrahan et al. (1984) study. In Section 2.1.1, EPA concluded that the Hanrahan exposure assessment "reflect[ed] the usual, relatively constant formaldehyde concentrations in the residences" (p. 2-9), which is not supported by the short duration and the single occasion when measurements were taken at each home.

Another point of concern is how EPA used measurement data from Hanrahan et al. (1984) to draw conclusions about exposure of the study subjects and to derive a point of departure. The only exposure information provided in Hanrahan consists of a measurement range of <0.1–0.8 ppm for the indoor samples, as well as a median of 0.16 ppm and a geometric mean of 0.16–0.17 ppm. Data about outdoor measurements are also provided (mean of 0.04 ppm, standard deviation of 0.03 ppm), but the study does not state that the measurement durations for indoor and outdoor samples were the same (which can impact the limit of detection [LOD]). It seems plausible that 0.1 ppm was the detection limit for the indoor samples (and EPA stated that the LOD for Hanrahan was 0.1 ppm in Table A-34, although the study does not provide an LOD). Using this limited information,

in Section 2.1.1, EPA made estimates about the number of measurements below 100 ppb (44 percent; footnote 33, p. 2-7) and below 50 ppb (36 percent). They then concluded in the text that "a significant proportion of the study population was estimated to be exposed to average formaldehyde concentrations below 0.05 mg/m3" (pp. 2-9 to 2-10). This is not supported by the information in the study where the distribution below 0.1 ppm (0.12 mg/m3) is unknown, because it is likely that 0.1 ppm was the LOD.

SUMMARY AND CONCLUSIONS

This case study was carried out to test the replicability of EPA's approach to carrying out the eight steps of its Integrated Risk Information System (IRIS) Assessment Framework (EPA, 2022b), as applied in the 2022 Draft Formaldehyde Assessment (EPA, 2022a). The committee understands that specific systematic review protocols had not been prepared for this assessment. Instead, through its queries to EPA, the committee established that EPA could provide its methods across the three documents comprising the assessment. The case study shows that the components can be identified, albeit with some difficulty (Figure C-2). The case study adds support to the committee's general concern about the challenge of recreating the review methods of the IRIS Program for this assessment.

The committee walked through the various steps of the assessment in order to evaluate the utility of the documentation identified—not to attempt to "validate" the review outcome for human sensory irritation. While we acknowledge that different groups of expert reviewers may come to different places in a multistep review process, the purpose of this case study was to evaluate the transparency of EPA's review methods. The committee could not replicate the agency's process with complete fidelity, and we identified inconsistencies in EPA's evaluation of the Hanrahan et al. (1984) study versus EPA's stated criteria for study evaluation. However, within the specified approaches for the synthesis and integration steps of the process, the 2022 Draft Assessment reaches justified conclusions within the framework.

TABLE C-3 The U.S. Environmental Protection Agency's (EPA's) General Study Selection Considerations for Quantitative Dose-Response Assessment

Factor	Considerations
Overall Confidence Conclusion	*Evidence demonstrates* or *evidence likely* (if data were amenable); (*evidence suggests* is possible, but not done for this assessment)
Study Confidence	Appropriate study designs (e.g., long-term animal bioassays)
	(Reasonably) Complete results reporting
	No selection bias, information bias, or confounding that substantially alters interpretation of results
	Accuracy of exposure assessment
	Severity of observed effects[a]
	Animal studies: used paraformaldehyde as test article
	Animal studies: longer exposure duration and follow-up
	Animal studies: adequately powered to detect effects at lower levels
Population	Human studies preferred over animals
	Dose-response from most susceptible subgroup, as appropriate (and available)
	Human studies: preference for study groups from general population (e.g., residences, schools)
	Animal studies: preference for animal models that respond most like humans

continued

TABLE C-3 *continued*

Factor	Considerations
Exposure Information	Risk estimates for multiple exposure levels or regression coefficients preferred over LOAEL/NOAEL (provide info about shape of C-R curve and data for BMD modeling)
	Exposure levels analyzed[b]

NOTES: [a] Text does not specify whether more or less severe effects are preferred (in theory the preference should be for less severe effects)
[b] The description "exposure levels analyzed" does not specify if EPA means that multiple exposure levels were assessed, or if levels in a certain concentration range are preferred.
Based on the Preface, Table X, and Section 2.1 of EPA's 2022 Draft Formaldehyde Assessment. BMD = benchmark dose; C-R = concentration-response; LOAEL/NOAEL = lowest observed effect level/no observed effect level.

TABLE C-4 Application of Study Selection Considerations for U.S. Environmental Protection Agency's (EPA's) Dose-Response Assessment to Hanrahan et al. (1984)

Study Selection Considerations for Quantitative Dose-Response Assessment (Draft Assessment Preface, Table X, Section 2.1) (EPA, 2022a)		**Hanrahan et al. (1984), Sensory Irritation**	
Factor	**Considerations**	**Relevant Study/Outcome Characteristics (from hazard assessment)**	**Committee Notes**
Overall Confidence Conclusion	*Evidence demonstrates* or *evidence likely* (if data were amendable); (*evidence suggests* is possible, but not done for this assessment)	*Evidence demonstrates*	
Study Confidence	Appropriate study designs (e.g., long-term animal bioassays)	Formaldehyde concentration measure in homes with survey about symptoms	
	(Reasonably) complete results reporting	Only results are overall percentage indicating prevalence of symptoms and graph of predicted prevalence of burning eyes	Only one figure reported regression results, no info about regression coefficients and fit, no other results presented, no reporting of primary results
	No selection bias, information bias, or confounding that substantially alters interpretation of results	No info on survey used	Some information bias from lack of survey info
	Accuracy of exposure assessment	1-hr exposure measurement	Very short exposure assessment
	Severity of observed effects	Eye irritation ("burning eyes")	
	High- or medium-confidence study	Medium confidence	
	Concurrent exposure and outcome assessment[a]	Concurrent 1-hr measure and survey for symptoms since moving into home	The assessments were concurrent, but the outcome applied to anytime since moving into home

continued

TABLE C-4 *continued*

Study Selection Considerations for Quantitative Dose-Response Assessment (Draft Assessment Preface, Table X, Section 2.1) (EPA, 2022a)		Hanrahan et al. (1984), Sensory Irritation	
Factor	**Considerations**	**Relevant Study/Outcome Characteristics (from hazard assessment)**	**Committee Notes**
Population	Human studies preferred over animals	Human study	
	Dose-response from most susceptible subgroup, as appropriate (and available)	Included adults and teenagers	Sensitive populations not included (on p. 2-9, EPA states that some had chronic disease, but this is not stated in the paper)
	Human studies: preference for study groups from general population (e.g., residences, schools)	Residence study	
Exposure Information	Risk estimates for multiple exposure levels or regression coefficients preferred over LOAEL/NOAEL (provide info about shape of C-R curve and data for BMD modeling)	Estimate of regression from graph of percent Predicted Prevalence x Formaldehyde Concentration	No regression coefficients provided, estimated from graph; exposure levels below 100 ppb were estimated, but not clear if those were actually below LOD of method; no info about model fit
	Exposure levels analyzed	<0.12–0.98 mg/m^3	On pp. 2-9 to 2-10, EPA stated that they estimated a significant portion of the study population to be exposed to <0.05 mg/m^3; this is based on their exposure assumptions (which do not consider the possibility of LOD at 0.12 mg/m^3), not on study info

NOTES: [a] Consideration specific to the sensory irritation outcome (p. 2-7).
BMD = benchmark dose; C-R = concentration response; LOAEL/NOAEL = lowest observed effect level/ no observed effect level; LOD = limitation of detection
SOURCE: EPA's 2022 Draft Formaldehyde Assessment; Hanrahan et al. (1984).

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Appendix D
Point of Departure Analysis Using Two Studies: A Case Study

This Appendix complements analyses performed by the committee and presented in Appendix C. Like Appendix C, this case study focuses on a single health effect, sensory irritation, and the use of the available studies to derive a reference concentration (RfC). In this case study, we followed the methods described in the 2022 Draft Assessment (EPA, 2022) in an attempt to replicate EPA's work. The committee also shows how a point of departure (POD) could be estimated by combining data from two human sensory irritation studies (Hanrahan et al., 1984; Liu et al., 1991). We compared the advantages and disadvantages of EPA's method with the committee's alternative approach.

EPA conducted a search for relevant literature pertaining to sensory irritation for the 2022 Draft Assessment. After evaluation of study quality, the agency characterized each study as either high, medium, low confidence, or not informative. Both studies (Hanrahan et al., 1984; Liu et al., 1991) discussed in this case study were deemed by EPA as having medium confidence. Studies deemed as high or medium confidence were used to estimate PODs and were subsequently used to derive candidate reference concentrations (cRfCs). EPA selected the study by Hanrahan et al. (1984) to estimate the POD for sensory irritation.

With regard to the selection of the Hanrahan et al. (1984) study for the dose-response assessment, the committee recognizes that the IRIS Program turns to the older literature because of the exposure range and the potential to fit a model to estimate the dose-response relationship. This study was reported four decades ago as a two-page publication that does not meet the current norm for documentation and data access. Consequently, the agency takes work-around steps, including digitizing model estimates from a published figure that provides results of a logistic regression analysis. The committee finds that the full scope of uncertainty associated with the Hanrahan et al. dose-response relationship is not adequately acknowledged in the 2022 Draft Assessment. In this case study, the committee shows that consideration of the Liu et al. study, which also meets the criteria for selection, leads to a similar estimate. As recommended previously (NRC, 2014), consideration of estimates based on multiple studies would reduce uncertainty.

DESCRIPTION OF THE METHODS

Step 1: Replication of EPA Methods

Hanrahan et al. (1984) used logistic regression analysis to estimate potential symptom risk ratio dependency upon respondents' age, smoking status, gender, and the formaldehyde concentration measured in the home. EPA used data from Figure 1 in the Hanrahan et al. (1984) study to estimate the prevalence odds for corresponding formaldehyde concentrations. A third-order polynomial function was used to obtain the best-fitting curve (see Equation 1). An intercept of 0.03 was inputted into the model to represent a 3% background prevalence of sensory irritation. The third-order polynomial function was used to estimate formaldehyde concentration (exposure) that would increase the background prevalence by 10%. The corresponding prevalence odds that would generate a 10% risk difference was estimated to be 0.145. Equating the prevalence odds of 0.145

in Equation 1, where x represents formaldehyde exposure, EPA obtained a benchmark concentration (BMC_{10}) of 0.153 ppm (= 0.188 mg/m^3 at 25 °C).

$$log\ odds\ = 0.145 = 6.1949 \times x^3 + 3.7689 \times x^2 + 0.0309 \times x + 0.03 \cdots\cdots\cdots Equation\ 1$$

Step 2: Generation of the Exposure Distribution for Liu et al. (1991) from the Sexton et al. (1986)

Figure 1 in Liu et al. (1991) reports the percentages of respondents with burning eyes for three time-weighted exposure categories, by season. As these time-weighted exposure categories cannot be used to apply the same methods that EPA used for the Hanrahan et al. (1984) study (unweighted exposures), the committee used the exposure distribution presented in Figure 3 in Sexton et al. (1986). Figure 3 in Sexton et al. (1986) reports exposure for the same group of respondents as in the Liu et al. (1991) study. WebPlotDigitizer (Rohatgi, 2022) was used to generate the metadata from the histograms presented in Figure 3 from Sexton et al. (1986). The original histograms alongside the recreated graphs are shown in Figure D-2.

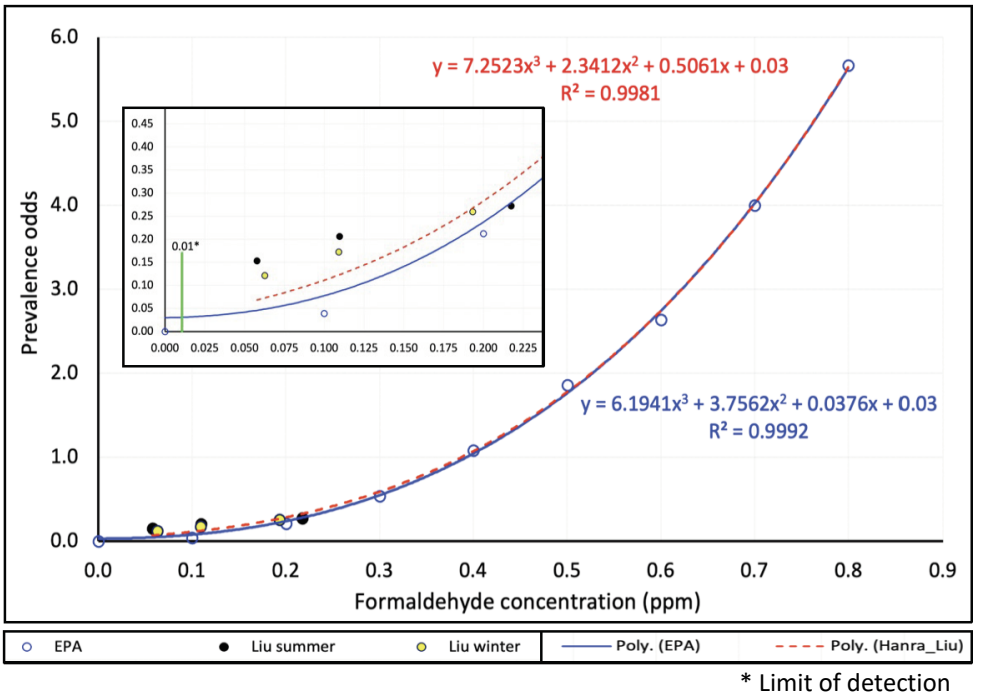

FIGURE D-1 Plots of prevalence odds by formaldehyde concentration using EPA's choice (Hanrahan study, blue solid line) and using both Hanrahan and Liu studies (red broken line).
SOURCES: Hanrahan et al., 1984; Liu et al., 1991.

From the recreated plots, we assigned the proportion of the total respondents in Liu et al. (1991) to the respective exposure bins (Figure D-1, left panels). We estimated population weighted exposure for each bin, separately for summer and winter. The recreated residential indoor formaldehyde concentration distribution, shown in Table D-1, is supported by published data from Table 1 in Liu et al. (1991).

TABLE D-1 Comparison of the Exposure Categories Recreated from the Graph with Published Data from Liu et al. (1991)

Indoor Concentrations	Data from the Recreated Histograms (%)	Published Data from Liu et al. (%)
Summer		
<0.05 ppm	30.1	30.8
0.05–0.1 ppm	38.9	39.7
>0.1 ppm	31.0	29.5
Winter		
<0.05 ppm	20.5	20.4
0.05–0.1 ppm	48.0	49.6
>0.1 ppm	31.5	30.0

SOURCE: Based on data from Liu et al., 1991.

The numbers of mobile homes included in the study were 663 and 523, and the numbers of participants in the 20–64 age group were 739 and 587, in summer and winter, respectively. The committee used the 20–64 age group because the prevalence of eye irritation in Liu et al. was presented for this age group (see Figure 1 in Liu et al., 1991).

Hanrahan et al. (1984) presents unweighted exposure estimates. For Liu et al. (1991), the committee used weekly average indoor concentrations. To do that, we assumed that the distribution of the weekly average indoor formaldehyde concentrations in the mobile homes approximates the distribution of the time-weighted individual exposures in the Liu et al. (1991) study. This assumption is partially supported by an observation made by Liu et al. (1991), "For a person who spends 60% of the time inside his or her home, a weekly average HCHO [formaldehyde] exposure of 7 ppm-hr can be translated into a weekly average HCHO concentration of 0.07 ppm" (p.94). EPA made a similar assumption while comparing the benchmark concentration lower bound ($BMCL_{10}$) obtained from the Hanrahan et al. (1984) study with that of the Liu et al. (1991) study (page 2-8, lines 14–17, main document).

Step 3: Modeling the Polynomial Function Using Data from Liu et al. (1991) and Hanrahan et al. (1984)

The committee used three data points for the prevalence of sensory irritation in summer (black circle) and three data points for winter (yellow circle), as shown in Figure D-1. The percentages were obtained from Figure 1 in Liu et al. (1991) and plotted against the unweighted indoor concentration exposure scale to make them consistent across the two studies. As the indoor concentrations within each category are within a relatively narrow range, we used the midpoint (population-weighted arithmetic mean) of the category to plot the prevalence from Liu et al. (1991).

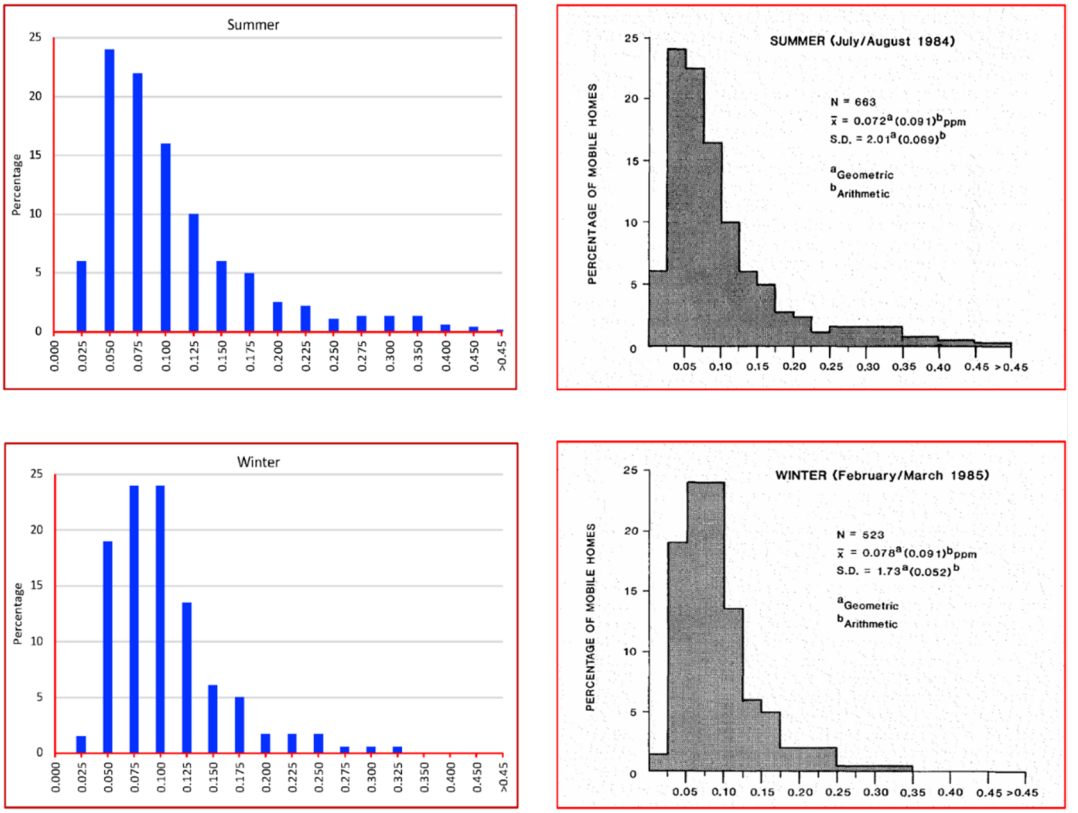

FIGURE D-2 Exposure distributions presented in Sexton et al. (1986) recreated for use in the point of departure analysis.
SOURCE: Based on data from Sexton et al., 1986.

Next we fit a similar third-order polynomial function using a fixed intercept of 0.03 to represent a 3% background risk. The curve representing the polynomial plot is shown by the broken red line in Figure D-1. The mathematical function is shown in Equation 2 below, where x represents formaldehyde concentration.

$$log\ odds\ = 0.145 = 7.2544 \times x^3 + 2.3384 \times x^2 + 0.507 \times x + 0.03 \cdots\cdots\cdots Equation\ 2$$

The BMC_{10} value obtained from the new function developed using both Hanrahan et al. (1984) and Liu et al. (1991) is 0.1256 ppm (= 0.1542 mg/m^3 at 25 °C), as shown in Table 2. Continuing to replicate EPA's methods, we estimated the BMC_{10} values by varying the background prevalence of sensory irritation to 2%, 1%, and 0% (see Table D-2).

TABLE D-2 Comparison of BMC_{10} Values Using Different Background Prevalences Generated Using EPA's Methods, Hanrahan et al. (1984), and Liu et al. (1991)

Background Prevalence	BMC_{10} (EPA; Hanrahan only), ppm (mg/m^3)	BMC_{10} (Hanrahan + Liu), ppm (mg/m^3)	Difference, ppm (mg/m^3)
3%	0.1525 (0.1871)	0.1256 (0.1542)	0.0269 (0.0329)
2%	0.1531 (0.1879)	0.1261 (0.1548)	0.0270 (0.0331)
1%	0.1538 (0.1887)	0.1266 (0.1553)	0.0272 (0.0334)
0%	0.1544 (0.1895)	0.1270 (0.1560)	0.0274 (0.0335)

NOTE: To convert ppm to mg/m^3 we used values recommended by EPA. Molecular mass = 30.03 g/mol, molar volume = 24.45 L, and temperature = 25 °C. BMC = benchmark concentration; EPA = US Environmental Protection Agency.
SOURCES: EPA 2022 Draft Formaldehyde Assessment; Hanrahan et al., 1984; Liu et al., 1991.

Findings: The BMC_{10} values estimated by EPA and those obtained by combining data from both studies are presented in Table D-2 and Figure D-1. Regardless of the background prevalence, the BMC_{10} values were consistently lower when data from both Hanrahan et al. (1984) and Liu et al. (1991) studies were used, compared with the values estimated using only the Hanrahan et al. (1984) study. The results also demonstrate that background prevalence does not substantially affect the BMC_{10} value.

COMPLEMENTARY CHARACTERISTICS OF HANRAHAN ET AL. (1984) AND LIU ET AL. (1991)

The two studies, Hanrahan et al. (1984) and Liu et al. (1991), share some key characteristics, which when considered together are likely to complement one another and strengthen the POD analysis:

- Indoor concentrations in Hanrahan et al. (1984) were estimated as the average of two samples (kitchen/living room and bedroom), with a range between <0.1 ppm and 0.8 ppm; the median was 0.16 ppm. About half of the indoor concentrations in Hanrahan et al. (1984) were between 0.1 and 0.16 ppm. Liu et al. (1991) measured indoor concentration over 7 days in the kitchen and bedroom. The values range between 0.01 (limitation of detection [LOD]) and 0.46 ppm with a geometric mean of 0.072 ppm for summer and between 0.17 and 0.314 ppm, with a geometric mean of 0.078 ppm, for winter.
- Although there is some overlap of concentrations between the two studies, Liu et al. (1991) indoor concentrations for two-thirds (68%) of the respondents were below 0.1 ppm, which is an approximate starting point of indoor concentrations in Hanrahan et al. (1984). The Hanrahan et al. (1984) study covers a wider range of exposure at the higher end (0.8 ppm), but data may be sparse at higher concentrations, given the median of 0.16 ppm and a total sample of 61 respondents.
- The Liu et al. (1991) study collected hours spent at home per day for the period of air sample collection, which allowed estimation of time-weighted exposure. However, these data cannot be combined with the Hanrahan et al. (1984) study data.
- The relevant sample in Liu et al. (1991) was about 10 times more than that in Hanrahan et al. (1984). More importantly, the prevalence of sensory irritation in Liu et al. (1991) covered an age group of 20–64 years. In comparison, Hanrahan et al. (1984) included teenagers and adults, but the prediction model that was used to derive the BMC is

centered on the mean age of 48 years. In other words, although the model was developed using other ages, the predicted prevalence is for a population with a mean age of 48 years, somewhat limiting the generalizability.

LIMITATIONS

An important limitation of this case study is the unavailability of data, which led the committee to make an assumption about the exposure distribution in the Liu et al. (1991) study. Our finding of a lower BMC_{10} value when data points from both studies are used may not hold if the distribution of (unweighted) indoor concentrations differs markedly from the distribution of person–time exposure in Liu et al. (1991). Other limitations include the following:

- There is potential for selection bias in both studies.
- It is unclear whether Figure 1 in Liu et al. (1991) is based on predicted values from an adjusted model. In contrast, Hanrahan et al. (1984) estimates are adjusted for age and may also be adjusted for smoking and gender.
- In Hanrahan et al. (1984), mean (geometric) exposure for the respondents was reported to be 0.16 ppm (0.20 mg/m^3), but 0.17 ppm (0.22 mg/m^3) for nonrespondents (i.e., respondents were underexposed by 0.02 mg/m^3).

Overall, the committee was able to replicate EPA's methods. BMC_{10} values can be obtained by analyzing data from complementary studies that share some key characteristics.

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Appendix E
Examples of Issues Identified by the Committee

This appendix details some examples of the issues that the committee identified with regard to the transparency and consistency of presentation in EPA's 2022 Draft Assessment. While not exhaustive, they are provided as illustrative of the Tier 2 and 3 recommendations from the committee and as a guide to EPA's revision. References are provided in the main chapters of the report (Chapters 2–5).

The issues are organized according to the steps of EPA's review process (see Figure 1-3): literature identification, study evaluation criteria, synthesis and judgments including any mode of action considerations, overall hazard conclusions, and dose-response evaluation. A final section details some general issues identified by the committee.

LITERATURE IDENTIFICATION

Figure 2-3 needs to be modified to more accurately show representative ranges of outdoor and indoor formaldehyde concentrations levels.

For respiratory pathology, it is unclear how search terms were used (e.g., controlled vocabulary [MeSH] and keyword terms).

For sensory irritation, it is unclear if other MeSH terms like eye, ear, nose, or skin were used in the search because they were not reported in Table A-31. The number of studies (38 observational and 20 controlled trials) included in the 2022 Draft Assessment, as presented in Figure A-22, does not match the number of studies presented in Tables A-34 (13 residential studies), A-35 (1 school study), and A-36 (21 controlled trials). Neither of the numbers match with Tables 1-1 (14 controlled trials) and 1-2 (6 residential studies) in the Main Assessment.

Regarding the nervous system, Figure A-35 of the Supplemental Information indicates that 40 human studies were considered, but only 12 are described in the Main Assessment in (Tables 1-44 and 1-45), and 15 were included in the Appendices (Tables A-84 and A-85). The narrative indicates that studies that were evaluated as *not informative* were excluded from these tables; however, both the Kilburn (2000) and Schenker et al. (1982) studies are described despite their overall confidence evaluation of *not informative*. Thus, it is not clear why these studies were included in the table. Clear reasoning for exclusion from tables need to be provided or the literature described in Tables A-84 and A-85 need to be updated to be consistent with the information provided at the end of Figure A-35.

Table A-84 incorrectly describes the sample for the Bellavia et al. (2021) paper as "cancer cases"; however, they were amyotrophic lateral sclerosis (ALS) studies from registry data. The job exposure matrices (JEMs) for this study was developed for a previous cancer study; ALS cases were identified through Danish medical records without consideration of cancer status. The details in Table A-84 need to be reviewed for accuracy, and minor typographical errors need to be addressed.

STUDY EVALUATION CRITERIA

For sensory irritation, EPA needs to clarify how concurrent assessment ensures that exposure preceded health effects for studies in which the outcomes are considered to be acute effects.

On page A-267 column 2, EPA compared the reporting of asthma prevalence in Liu et al. (1991) (~4%) to the national prevalence of asthma at that time and concluded there was "minimal concern for selection bias" in that study. The committee has some concern that this conclusion may not be fully supported. For example, there are several sets of selection factors between the general US population and the study population that need to be considered:

- Total eligible sample—eligible sample who finally participated in the study (represented as S1) and eligible sample who were invited but did not participate (S2). S1 + S2 = total eligible random sample.
- Target accessible population (S3)—the larger universe of mobile homes in California from which the random sample was drawn.
- Target population (S3)—all mobile homes in the entire country.
- General population in the country (S4).

At best, the comparison that EPA described in page A-267 for the Liu et al. (1991) study makes a case for the generalizability (external validity) of the findings, if it is assumed that the Liu study sample is representative of the US general population. It does not make a case against selection bias. One argument against selection bias would be to demonstrate that those who participated (S1) have comparable characteristics with those who were invited but did not participate (S2). It is also not known how the randomly selected sample compares with the target to the accessible population. If it is not a true random sample, there could be additional potential for selection bias.

For pulmonary function, while the study evaluation criteria provided in Table A-43 appear to be appropriate, they do not overlap with the methodologic issues mentioned in the text.

EPA's approach appears to contradict the expert panel's advice for asthma. Several studies in infants and young children (<3 years) are examined (p. 1-17 and Table 1-20), where the EPA considers diagnoses in young children to likely be exacerbations of respiratory tract infections rather than representing a true "asthma" phenotype.

Potential updates are needed for some studies across the noncancer outcomes considered. For instance:

- Annesi-Maesano (2012) is rated high confidence, despite the vague description of the outcome in Table 1-12. EPA needs to indicate whether this study used an appropriate questionnaire, which would support the high confidence rating.
- Two high-confidence studies (Ozen, 2002, and Ozen, 2005) could be reassessed based on small sample size (N < 10) for reassignment to medium confidence. One medium-confidence study (Sapmaz, 2018) could be reevaluated for consideration as high confidence because the test article box was flagged gray, when it likely ought to be clear. However, the potential reassignment of these three studies would not affect synthesis judgements and the next assessment steps, since all medium and high studies were considered in the next steps.
- The study by Smedje and Norback (2001) is rated as low confidence in Table 1-12, page 1-91, contradictory to the text on pages 1-81 and 1-83, which states it is medium. This discrepancy needs to be rectified. The low confidence rating is justified by the large proportion of exposures below the limit of detection, and possible information bias and confounding; however, the "alternative evaluation" of medium confidence features strongly in recommendations and the confidence judgment needs to be consistent throughout the document to avoid confusion. The alternative evaluation (i.e., medium

confidence) must be adopted throughout the document for consistency, and its being a prospective study needs to be a criterion in the initial evaluation, not in its alternative reevaluation. It would be helpful to check all the reference table confidence statements with their citations in the text of the documents. Additionally, the tabulated data in the main document need to be checked for consistency with the longer descriptions located in Appendix A.5.4 regarding confidence judgments.

- Pinkerton et al. (2013) was rated with high confidence, with a comment of "small number of cases" in reference to eight ALS deaths. However, other studies with a small number of cases were rated as medium.
- Kilburn (2000) and Schenker et al. (1982) were assessed as not informative with comments about limited or no exposure measures. However, it is important to note that two of the included manuscripts used some version of the same set of Danish registry data (Bellavia et al., 2020; Seals et al., 2017), both used JEMs derived from the Swedish JEM used in the Peters et al. (2017) manuscript as part of the Nordic Occupation Cancer Study, and each of these JEMs estimate exposure based on previous studies of biological samples, air and dust monitoring, and expert opinion, and are not direct exposure measures. Furthermore, the occupational codes used to determine exposures are not based on job title, but only on tax-recorded industry codes. Therefore, exposure assessment provided in these studies is not significantly better than that provided in the studies ranked with low confidence.
- In Table 1-2, where the entry for the Main and Hogan (1983) study shows two sources of biases with one box fully colored. The classification scheme in Figure II would suggest this study is of medium confidence, but a fully colored box likely means something more, which needs to be explained.

EVIDENCE SYNTHESIS AND JUDGMENTS

Regarding pulmonary function, Table 1-11 indicates there are multiple additional studies included in the evidence judgment for long-term effects, although none of these are referenced. The evidence cited in the table and narrative need to be revised to provide more informative statements. For instance, "concentration-related associations" would preferably be rephrased as "concentration-related decrements in lung function."

Regarding Figure 1-5:

- EPA needs to order the studies within industry by formaldehyde exposure levels, or the exposure difference between groups.
- EPA needs to improve the labeling of the figure to provide clarity, such as by indicating that the numbers before the plotted results refer to sample sizes.
- The text refers to Figure 1-5 summarizing ten studies, while the figure caption notes there are eight.
- Clarity would be improved by ensuring that the comparison being reported (i.e., preshift pulmonary function differences in prevalence studies) is clearly stated in the caption and accompanying text.
- Reference information is needed for the study discussed on page 1-45, lines 11–15, and the study referred to as "this study" on line 15.

The pulmonary function section would benefit from a summary table that refers to all summarized studies and provides an organized distillation of the points made in the text.

Tables need to be formatted clearly to correspond to the information highlighted in the synthesis discussion (e.g., for pulmonary function, which occupational studies had employees that worked at least 5 or at least 10 years—see the Assessment Overview, p. 52, line 33; or indicate the main conclusions EPA reached for each group of studies).

EPA needs to reconcile information provided in the text and in the tables for animal studies of male reproductive toxicity.

EPA needs to document whether the evidence integration summary tables in the Main Assessment and Assessment Overview are identical.

DOSE-RESPONSE EVALUATION

Regarding sensory irritation, in Tables 1-1 and 1-2, several studies have been identified as high or medium confidence, but only six were included in the sensory irritation dose-response analysis (Table 2-1). It is unclear why only these six studies were chosen.

Regarding reproductive and developmental toxicity, EPA needs to double check the publication year for references in Tables 30 and 31. The testes endpoint is likely incorrectly cited, linking to Ozen (2005) when it ought to be Ozen (2002). For animal male reproductive toxicity studies, Ozen (2002) was appropriately considered to be the stronger of the two studies and was therefore used to derive the RfC.

Regarding the RfC derivation, specific examples of issues concerning consistency, accuracy, and lack of transparency include the following:

- EPA followed its guidelines (BMD; RfC) to conduct dose-response modeling for selected studies/endpoints when the data supported such reanalyses. In many cases where raw data were not available, EPA extracted secondary data from reported results. For example, EPA extracted eight distinct model-predicted means, one for each exposure concentration, from the Hanrahan et al. (1984) by reading a plot (Figure 1), and then refitted a logistic regression model with a polynomial of order 3. The resulting logistic regression model has artificially narrow standard errors for the model parameters compared with those fitted to the raw data because the model-predicted means failed to reflect the true data variation. As a result, the model-based BMDL (0.09 mg/m^3, Table 2-2) is biased. Therefore, the use of the cRfC derived from Hanrahan et al. (1984) as the osRfC for sensory irritation needs additional justification.
- In deriving a POD based on the human studies of Kulle et al. (1987) and Andersen and Molhave (1983), EPA correctly recognized that the same group of volunteers were exposed to multiple concentrations, and the responses from individual volunteers were correlated across different exposure concentrations. EPA's benchmark dose (BMD) modeling failed to account for such data dependence, and thus likely underestimated the variation of the BMC. EPA subsequently divided the benchmark concentration (BMC) by a factor of 2 to replace the model-based benchmark concentration lower bound (Table 2-2). However, it is uncertain whether a factor of 2 is greater than the true ratio of BMC/BMCL (i.e., whether it is sufficiently large to account for the data dependence). This practice appears inconsistent with EPA's own guidelines and EPA did not provide a justification.
- Kulle et al. (1987) measured eye irritation using a four-point Likert scale for none, mild, moderate, and severe, and reported the mean score difference (standard error) between 180 minutes postexposure and baseline. EPA's dose-response modeling of Kulle et al. (1987) and Andersen and Molhave (1983) was, however, for the fraction of affected

(i.e., prevalence of eye irritation). EPA did not provide information in the Main Assessment or Appendices on the conversion of the Likert-scale in Kulle et al. (1987) to the dichotomous variable used to estimate prevalence.

- EPA used either a group median (e.g., current asthma, Krzyzanowski et al. [1990]) or a group mean (e.g., atopic eczema, Matsunaga et al. [2008]) as an estimate of lowest observed effect level / no observed effect level (LOAEL/NOAEL) when a range of exposure concentrations was reported within the group. EPA also seemed to have used either an arithmetic mean or a geometric mean to estimate a LOAEL/NOAEL. Dannemiller et al. (2013) reported the geometric mean of 54.0 and 34.4 ppb in the "very poor control" group and "all others" group, respectively. EPA seemed to have designated 34.4 ppb as the NOAEL (0.042 mg/m^3, Table 2-4). (Note that the reference in the last row of Table 2-4 ought to be Dannemiller et al. [2013]). The study of Dannemiller et al. (2013) was dropped from the discussion for cRfC derivation thereafter. EPA did not give reasons for excluding this study. The text starting from page 2-16, line 19, appears corrupted.
- For pulmonary function, EPA relied on the linear mixed-effects model results reported by Krzyzanowski and colleagues (1990). The original regression model incorporated whether or not the children had asthma and whether or not the exposure measurements were taken in the morning. EPA's derivation of the BMCL was based on children without asthma exposed at times other than the morning. This approach was inconsistent with EPA's state-of-the-practice methods (i.e., using more vulnerable subpopulations for risk estimation). To its credit, however, EPA conducted a sensitivity analysis for children with asthma and morning exposures. The sensitivity analysis, however, was based on BMC, but would more appropriately be based on BMCL. The derivation of a BMCL for children with asthma can be achieved by first determining the standard errors of the combination of regression coefficients associated with the terms of formaldehyde concentration and concentration squared. Note that children with asthma had their own baseline prospective epidemiological risk factor (PERF) (348.09) and the corresponding 10 percent decrease of 34.8. The intercept in equation B-9 is incorrect.
- EPA reanalyzed the animal data of Kerns et al. (1983) (Level I of sagittal cross-section I only) and of Woutersen et al. (1989) (anterior, Levels I and II). EPA did not disclose whether it obtained raw data or extracted secondary data from the original report. Multiple models were fit to the datasets, and the one with the smallest Akaike information criterion (AIC) was chosen. Note that AIC is a relative criterion for comparison across models. Alone, AIC does not tell how well a model fits the data. EPA did not report goodness-of-fit tests, a practice inconsistent with the reanalysis of other studies in the Assessment.
- In the reanalysis of the data from Ozen et al. (2005), EPA stated that (p. B-23, lines 6–8): "If the BMDL estimates were 'sufficiently close,' that is, differed by at most xx-fold, the model selected was the one that yielded the lowest AIC value. If the BMDL estimates were not sufficiently close, the lowest BMDL was selected as the POD." This criterion is vague and does not enhance transparency.
- The various model-based tests for the Ozen et al. (2005) study were labeled as "test 1," "test 2," etc. (Table B-17, p. B-29) without explanation.
- In conducting BMD modeling of Ozen et al. (2002) and Ozen et al. (2005), which had three and four distinct concentration levels (including the control), respectively, EPA fit models with three or four parameters, resulting in parameter saturation in the model or failure in model fitting.

- The osRfC for respiratory pathology was based on Woutersen et al. (1989). Kerns et al. (1983) was incorrectly cited in Table 2-11.
- Figure 2-2 displays variability and uncertainty across all osRfCs along three dimensions: confidence, uncertainty, and risk size. The committee found this graphic display to be an effective visual aid. The size of the plot symbol for each osRfC was determined by three factors: the level of the confidence in the study(ies) and health hazard identification; risk estimate(s) (EPA gives slightly greater weight to the risk estimate than other factors); and completeness of evidence database for each health outcome. However, EPA was not explicit about how these factors were weighted.
- Figure 2-3 is also interesting and informative. It graphically displays the uncertainties within a cRfC as well as variations and uncertainties between cRfCs.
- EPA presented a detailed discussion of uncertainties and variabilities, and noted that the osRfCs for asthma, pulmonary function, allergies, and sensory irritation were 0.006, 0.007, 0.008, and 0.009 mg/m^3, respectively, reflecting the impact of formaldehyde on the respiratory system. EPA proposed the overall RfC of 0.007 mg/m^3, but was not explicit about how it was chosen.

GENERAL ISSUES

In some cases, Tables and Figures included in the Appendices are not cited in other documents (e.g., Figures A-24 to A-26).

As an example of inconsistencies that EPA needs to address, Figure A-36 shows 20 human studies and 35 animal studies for inclusion. Table A-93, which summarizes the animal data for developmental and reproductive toxicity and animal studies, contains 29 rows, with one row containing two studies (Vosoughi et al., 2012, 2013), resulting in 30 total animal studies (not 35 as stated in Figure A-36).

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Environmental Health Criteria 89

Formaldehyde

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World Health Organization

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 89

FORMALDEHYDE

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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ENVIRONMENTAL HEALTH CRITERIA FOR FORMALDEHYDE

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR FORMALDEHYDE

Members

Professor O. Axelson, Department of Occupational Medicine, University Hospital, Linköping, Sweden
Dr Birgitta Berglund, Department of Psychology, University of Stockholm, Stockholm, Sweden
Professor D. Calamari, Institute of Agricultural Entomology, Faculty of Agriculture, Milan, Italy (*Vice-Chairman*)
Dr Ildiko Farkas, National Institute of Hygiene, Budapest, Hungary
Dr V.J. Feron, TNO-CIVO Toxicology and Nutrition Institute, AJ Zeist, Netherlands
Dr O.J. Grundler, BASF AG, Ludwigshafen, Federal Republic of Germany
Professor J.M. Harrington, Institute of Occupational Health, University of Birmingham, Birmingham, United Kingdom

Dr H.D. Heck, Chemical Industry Institute of Toxicology, Research Triangle Park, USA
Dr R.F. Hertel, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany (*Rapporteur*)
Professor F. Klaschka, Department of Dermatology, Clinic and Polyclinic in the Steglitz Clinic of the Free University of Berlin, Berlin (West)
Dr Y. Kurokawa, Division of Toxicology, National Institute of Hygienic Sciences, Tokyo, Japan
Dr Mathuros Ruchirawat, Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand
Dr A. Schaich Freis, Danish National Institute of Occupational Health, Copenhagen, Denmark
Dr A. Shaker, Environmental and Occupational Health Center, Ministry of Health, Cairo, Egypt
Dr J.A.J. Stolwijk, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, USA (*Chairman*)
Dr U. Thielebeule, Bezirks Hygiene Inspection, Rostock, German Democratic Republic

Observers

Dr J.C. Aubrun, (representing the European Council of Chemical Manufacturers) Courbevoie, France
Dr A. Basler, Federal Health Office, Berlin (West)
Dr J.-C. Berger, Health and Safety Directorate, Commission of the European Communities, Luxembourg
Dr M.A. Cooke, University of Aston, Birmingham, United Kingdom
Mr W.R. Gaffey (representing Formaldehyde Institute), Department of Medicine and Environmental Health, Monsanto Company, St. Louis, USA
Dr P. Messerer, BASF AG, Occupational Medicine and Health Protection, Ludwigshafen, Federal Republic of Germany
Dr M.G. Penman (representing the European Chemical Industry Ecology and Toxicology Centre), ICI, Central Toxicology Laboratory, Macclesfield, United Kingdom
Dr N. Petri, BASF AG, Ludwigshafen, Federal Republic of Germany
Mr V. Quarg, Federal Ministry for Environment, Nature Conservation and Nuclear Safety, Bonn, Federal Republic of Germany

Dr A.G. Smith (representing the European Chemical Industry Ecology and Toxicology Centre), Ciba Geigy (UK), Macclesfield, United Kingdom
Dr K. Ulm, Institute for Medical Statistics and Epidemiology of the Technical University of Munich, Munich, Federal Republic of Germany
Dr G. Vollmer, Federal Ministry for Environment, Nature Conservation and Nuclear Safety, Bonn, Federal Republic of Germany

Secretariat

Dr D. Kello, Environmental Health Division, World Health Organization, Regional Office for Europe, Copenhagen, Denmark
Dr E. Smith, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
Dr Linda Shuker, Division on Environmental Carcinogenesis, International Agency for Research on Cancer, Lyons, France

NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in

subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 7988400 - 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR FORMALDEHYDE

A WHO Task Group on Environmental Health Criteria for Formaldehyde met at the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany, from 9 to 13 November, 1987. Professor U. Mohr opened the meeting and welcomed the members on behalf of the host Institute, and Dr G. Vollmer spoke on behalf of the Federal Government, which sponsored the meeting. Dr D. Kello, opened the meeting on behalf of the Director-General, World Health Organization and Dr E. Smith addressed the meeting on behalf of the three cooperating organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and the environment of exposure to formaldehyde.

The drafts of this document were prepared by DR R.F. HERTEL and DR G. ROSNER of the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany. Available international and national reviews of formaldehyde were consulted during the preparation of the criteria document and are listed in the Appendix. Dr E. Smith of the IPCS Central Unit was responsible for the overall scientific contents of the document and Mrs M.O. Head of Oxford for the editing.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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1. SUMMARY AND CONCLUSIONS

1.1 Physical and Chemical Properties, and Analytical Methods

Formaldehyde is a flammable, colourless and readily polymerized gas at ambient temperatures. The most common commercially available form is a 30-50% aqueous solution. Formaldehyde is readily soluble in water, alcohols, and other polar solvents, but has a low degree of solubility in non-polar fluids.

Methanol or other substances are usually added to the solutions as stabilizers to reduce intrinsic polymerization.

Formaldehyde decomposes at 150 °C into methanol and carbon monoxide; in general it is highly reactive with other chemicals. In sunlight, it is readily photo-oxidized to carbon dioxide. It has a very low *n* -octanol/water partition coefficient as well as a low soil-absorption coefficient. The Henry constant is relatively high at 0.02 Pa x m^3/mol.

Chemical analysis for formaldehyde involves direct extraction from solid and liquid samples while absorption and/or concentration by active (filtration) or passive (diffusion) sampling is necessary for air samples. A variety of absorbants is available. The most widely used methods of analysis are based on photometric determination. Low concentrations in air can be detected, after appropriate absorption, by means of high performance liquid chromatography.

1.2 Sources of Human and Environmental Exposure

Formaldehyde is present in the environment as a result of natural processes and from man-made sources. It is formed in large quantities in the troposphere by the oxidation of hydrocarbons. Minor natural sources include the decomposition of plant residues and the transformation of various chemicals emitted by foliage.

Formaldehyde is produced industrially in large quantities and used in many applications. Two other important man-made sources are automotive exhaust from engines without catalytic converters, and residues, emissions, or wastes produced during the manufacture of formaldehyde or by materials derived from, or treated with it.

It has been calculated that the average rate of global production from methane in the troposphere is of the order of 4 x 10^{11} kg/year, while the total industrial production in recent years has been about 3.5 x 10^9 kg/year; the emission from automotive engines has not been quantifiable on a global basis.

Formaldehyde has a variety of uses in many industries, it has medical applications as a sterilant and is used as a preservative in consumer products, such as food, cosmetics, and household cleaning agents.

One of the most common uses is in urea-formaldehyde and melamine-formaldehyde resins. Urea-formaldehyde foam is used to insulate buildings (UFFI); it can continue to emit formaldehyde after installation or constituting a source of persistent emission. Phenolic plastics and polyacetal plastics are also important fields of application, but are not expected to release formaldehyde.

There are several indoor environmental sources that can result in human exposure including cigarettes and tobacco products, furniture containing formaldehyde-based resins, building materials containing urea-formaldehyde resins, adhesives containing formaldehyde used for plastic surfaces and parquet, carpets, paints, disinfectants, gas cookers, and open fireplaces.

Indoor areas of special importance are hospitals and scientific facilities where formaldehyde is used as a sterilizing and preserving agent, and living spaces, such as schools, kindergartens, and mobile homes or apartments where there may be uncontrolled emissions of formaldehyde from tobacco smoking, building materials, and furniture.

1.3 Environmental Transport, Distribution, and Transformation

Air is the most relevant compartment in the formaldehyde cycle, most of the production and/or emissions, and degradation processes occurring in the atmosphere.

Photolysis and reaction with hydroxyl radicals rapidly remove formaldehyde from the atmosphere. The calculated half-life of each process is a matter of hours, according to environmental conditions. Transport of formaldehyde over distances is probably not of great importance, nevertheless some organic compounds (air pollutants or natural) from which formaldehyde can be derived are more stable and can contribute to the formation of formaldehyde over considerable distances. The compound can be dissolved in the atmosphere in cloud and rainwater and can be adsorbed as an atmospheric aerosol.

The value of the Henry constant suggests that formaldehyde in aqueous solution is less volatile than water and that volatilization from an aquatic environment is not expected under normal environmental conditions. The high water solubility and the low *n* -octanol/water partition coefficient suggest that adsorption on suspended solids and partition in sediments is not significant. In water, formaldehyde is rapidly (days) biodegraded by several species of microorganisms, provided the concentration is not too high. Formaldehyde is also readily biodegradable in the soil. Because the soil adsorption coefficient is very low, leaching occurs easily and mobility in soil is very high.

As it has a low *n* -octanol-water partition coefficient (log P_{ow}), formaldehyde is not be expected to bioaccumulate in aquatic organisms. Furthermore, aquatic organisms are able to metabolize and transform it through various metabolic pathways.

1.4 Environmental Levels and Human Exposure

Air concentrations of formaldehyde, near the ground in coastal, mountain, or oceanic areas, ranged from 0.05 to 14.7 µg/m^3, and the majority of concentrations were within the range 0.1-2.7 µg/m^3. In the presence of man-made inputs, but away from any industrial plants, mean values ranged from 7 to 12 µg/m^3 with a few peaks up to 60-90 µg/m^3. Data from different parts of the world were in good agreement.

Rain water contains 110-174 µg/litre with peaks as high as 310-1380 µg/litre.

Emissions of formaldehyde from industrial processes vary widely according to the types of industry. A considerable amount of formaldehyde comes from the exhaust emissions of motor vehicles, but this varies greatly according to country and the grade of fuel.

There is some natural formaldehyde in raw food, levels ranging from 1 mg/kg up to 90 mg/kg, and accidental contamination of food may occur through fumigation, the use of formaldehyde as a preservative, or through cooking.

Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of indoor formaldehyde.

Indoor air levels (non-workplace), measured in various countries, depended on several factors, but mainly on the age of the building and the building materials, the type of construction, and the ventilation. They varied widely with different situations, but most ranged from a minimum of 10 µg/m^3 up to a maximum of 4000 µg/m^3. In some cases, low values were found in rooms with substantial sources of formaldehyde

emission. Disinfection of areas of hospitals produced the highest levels, up to 20 000 µg/m^3, but the personnel carrying out disinfection wear protective equipment and the areas are not occupied until formaldehyde levels have fallen to 1.2 mg/m^3 (1 ppm) and below. Levels in rooms in which there is tobacco smoking can exceed 100 µg/m^3.

The contributions of various atmospheric environments to the average human daily intake has been calculated to be 0.02 mg/day for outdoor air, 0.5-2 mg/day for indoor conventional buildings, < 1-10 mg/day for buildings with sources of formaldehyde, 0.2-0.8 mg/day for work places without occupational use of formaldehyde, 4 mg/day for work places using formaldehyde, and 0-1 mg/day for environmental tobacco smoke. Smoking 20 cigarettes per day corresponds to an intake of 1 mg/day through inhalation.

The formaldehyde concentration in drinking-water is generally about 0.1 mg/litre resulting in a mean daily intake of 0.2 mg/day. The quantity of formaldehyde ingested in food depends on the composition of the meal and, for an average adult, may range from 1.5 to 14 mg/day.

1.5 Kinetics and Metabolism

Formaldehyde is readily absorbed in the respiratory and gastrointestinal tracts. Dermal absorption of formaldehyde appears to be very slight. Increases in blood concentrations of formaldehyde were not detected in rats or human beings exposed to formaldehyde through inhalation, because of rapid metabolism.

The metabolites of formaldehyde are incorporated into macromolecules via one-carbon pathways or are eliminated in the expired air (CO_2) and urine. Formaldehyde that escapes metabolism can react with macromolecules at the site of entry. DNA-protein cross-links have been detected in tissues exposed directly to formaldehyde, but not in tissues remote from the absorption site.

1.6 Effects on Organisms in the Environment

Formaldehyde is used as a disinfectant to kill viruses, bacteria, fungi, and parasites, but it is only effective at relatively high concentrations.

Algae, protozoa, and other unicellular organisms are relatively sensitive to formaldehyde with acute lethal concentrations ranging from 0.3 to 22 mg/litre. Aquatic invertebrates showed a wide range of responses; some crustaceans are the most sensitive with median effective concentration (EC_{50}) values ranging from 0.4 to 20 mg/litre. In 96-h tests on several fish species, the LC_{50} of formaldehyde for adults ranged from a minimum of about 10 mg/litre to a maximum of several hundred mg/litre; most species showed LC_{50} values in the range of 50-100 mg/litre. The responses of various species of amphibians are similar to those of fish with median acute lethal concentrations (LC_{50}) ranging from 10 to 20 mg/litre for a 72-h exposure.

No data are available on long-term aquatic studies.

Eggs and larvae of some cattle parasites were killed by formaldehyde solution (1-5%) and some nematodes by a 37% solution, whereas other nematodes were unaffected. In ruminant mammals, formaldehyde protects dietary protein from microbial proteolysis in the rumen and increases the efficiency of utilization of amino acids.

Few data are available on the effects of formaldehyde on plants. However, from the agricultural use of urea-formaldehyde fertilizers, it appears that, at recommended concentrations, formaldehyde does not

alter nitrogen and carbohydrate metabolism in plants, but that high doses have negative effects on soil metabolism. Formaldehyde impairs pollen germination.

1.7 Effects on Experimental Animals

Acute inhalation exposure of rats and mice to formaldehyde at very high concentrations (120 mg/m^3) produced salivation, dyspnoea, vomiting, spasms, and death. At a concentration of 1.2 mg/m^3, eye irritation, decreased respiratory rate, increased airway resistance, and decreased compliance appeared. Mice were more sensitive than rats.

Short-term, repeated exposures (7-25 mg/m^3) of rats produced histological changes in the nasal epithelium, such as cell degeneration, inflammation, necrosis, squamous metaplasia, and increased cell proliferation.

There is growing evidence that it is concentration rather than dose that determines the cytotoxic effects of formaldehyde on the nasal mucosa of rats; concentrations below 1 mg/m^3 do not lead to cell damage and hyperplasia.

Dose-related lesions observed in long-term, repeated inhalation exposure (2.4, 6.7, or 17.2 mg/m^3) were dysplasia and squamous metaplasia of the respiratory and olfactory epithelia, which regressed to some extent after cessation of exposure.

Formaldehyde produced nasal squamous cell carcinomas in rats exposed to high concentrations (17.2 mg/m^3), which also caused severe tissue damage. The concentration - response curve was extremely non-linear with a disproportionate increase in tumour incidence at higher concentrations. A low, but not statistically significant, incidence of nasal tumours occurred at 6.7 mg/m^3. No tumours were found at other sites. Mice developed squamous cell carcinomas of the nasal cavity with long-term exposure to 17.2 mg/m^3, but this finding was not statistically significant. No tumours were found at other sites. No tumours were found in hamsters.

Long-term oral administration of formaldehyde (0.02-5% in the drinking-water) to rats was found to induce papillomas in the forestomach.

Several skin initiation/promotion studies with formaldehyde did not produce evidence of skin carcinogenicity in mice; the results with respect to promotion were either negative or inconclusive.

1.8 Effects on Man

Formaldehyde has a pungent odour detectable at low concentrations, and its vapour and solutions are known skin and eye irritants in human beings. The common effects of formaldehyde exposure are various symptoms caused by irritation of the mucosa in the eyes and upper airways. In the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population and between hyperreactive and sensitized people.

There are a few case reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a sensitization effect (neither Type I nor Type IV) and the symptoms were considered to be due to irritation. Skin sensitization is induced only by direct skin contact with formaldehyde solutions in concentrations higher than 20 g/litre (2%). The lowest patch test challenge concentration in an

aqueous solution reported to produce a reaction in sensitized persons was 0.05% formaldehyde.

The available human evidence indicates that formaldehyde does not have a high carcinogenic potential. While some studies have indicated an excess of cancer in exposed individuals or populations, only nasal or nasopharyngeal tumours are likely to be causally related to formaldehyde exposure.

Formaldehyde does not have any adverse effects on reproduction and is not teratogenic.

Formaldehyde *in vitro* interferes with DNA repair in human cells, but there are no data relating to mutagenic outcomes.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula: CH_2O [HCHO]

Chemical structure:

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H
|
C = O
|
H
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CAS registry number: 50-00-0

RTECS registry number: LP 8925000

UN number: 1198, 2209, 2213

EC numbers: 605-001-01 (solution 5% to < 25%)
605-001-02 (solution 1% to < 5%)
605-001-005 (solution $\geq$ 25%)

IUPAC name: Methanal

Common synonyms: formaldehyde, methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane

Common names for solutions of formaldehyde: Formalin, Formol

Formaldehyde is a colourless gas at normal temperature and pressure, with a relative molecular mass of 30.03.

The most common commercially available form is a 30-50% aqueous solution. Methanol or other substances are usually added to the solution as stabilizers to reduce intrinsic polymerization. The concentration of methanol can be up to 15%. The concentration of other stabilizers is of the order of several 100 mg/litre. Concentrated liquid formaldehyde-water systems containing up to 95% formaldehyde are obtainable, but the temperature necessary to maintain solution and prevent separation of polymer increases from around room temperature to 120 °C as the solution concentration increases.

In solid form, formaldehyde is marketed as trioxane $(CH_2O)_3$, and its polymer, paraformaldehyde, with 8-100 units of formaldehyde. Paraformaldehyde has become technologically important.

2.2 Physical and Chemical Properties

Formaldehyde is a flammable, colourless, reactive, and readily polymerized gas at normal temperature. The heat of combustion for formaldehyde gas is 4.47 Kcal per gram. It forms explosive mixtures with air and oxygen at atmospheric pressure. Flammability is reported to range from 12.5 to 80 volume %, a 65-70% formaldehyde-air mixture being the most readily flammable.

Formaldehyde is present in aqueous solutions as a hydrate and tends to polymerize. At room temperature and a formaldehyde content of 30% and more, the polymers precipitate and render the solution turbid.

Formaldehyde decomposes into methanol and carbon monoxide at temperatures above 150 °C, although uncatalysed decomposition is slow below 300 °C.

Under atmospheric conditions, formaldehyde is readily photo-oxidized in sunlight to carbon dioxide. It reacts relatively quickly with trace substances and pollutants in the air so that its half-life in urban air, under the influence of sunlight, is short. In the absence of nitrogen dioxide, the half-life of formaldehyde is approximately 50 min during the daytime; in the presence of nitrogen dioxide, this drops to about 35 min (Bufalini et al., 1972).

Some physical and chemical properties of formaldehyde are presented in Table 1.

Table 1. Physical and chemical properties of formaldehyde[a]

Relative molecular mass	30.03
Relative gas density (air = 1)	1.04
Melting point (°C)	-118[b]
Boiling point (°C)	-19.2[b]
Explosivity range in air (vol %)	7-73
(g/m^3)	87-910
n-octanol/water partition coefficient) (log P_{ow})	-1
Specific reaction rate (k) with OH radical (k OH)	15.10-18 m^3/mol x s
Distribution water/air: Henry constant (H)	0.02 Pa. m^3/mol
Vapour pressure	101.3 kPa at -19 °C 52.6 kPa at -33 °C

[a] Modified from: BGA (1985).
[b] From: Diem & Hilt (1976) and IARC (1982).
From: Neumüller (1981) and Windholz (1983).

2.3 Conversion Factors

1 ppm formaldehyde = 1.2 mg/m^3 at 25 °C, 1066 mbar
1 mg formaldehyde/m^3 = 0.83 ppm

A number of other conversion factors have been cited but, for this draft, 0.83 has been used.

2.4 Analytical Methods

The most widely used methods for the determination of formaldehyde are based on photometric measurements. Methods for the sampling and determination are summarized in Table 2. The type of sampling depends on the medium in which the formaldehyde is to be determined.

Direct and indirect methods can be used for sampling formaldehyde in air. Indirect sampling (by means of a grab sample) is used when formaldehyde is present in extremely low concentrations or where sampling sites are removed from analytical laboratories. However, lack of preconcentration means that a very sensitive analytical technique is needed and there may also be absorption on the wall of the collecting container. Alternatively, the sample may be preconcentrated by passing air (active sampling) through an absorbing liquid. The collection efficiency of some liquids is reported in NRC (1981):

Water	80-85% (85% with ice bath)
1% aqueous bisulfite	94-100% (with ice bath)
3-methyl-2-benzothiazolene hydrazine (MBTH)	84-92%
Chromotropic acid in concentrated sulfuric acid	99%
Concentrated sulfuric acid	99%

Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). Aqueous or 50% 1-propanol solutions are used for formaldehyde sampling. For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolonehydrazone (MBTH), chromotropic acid, or 2,4-dinitrophenylhydrazine (DNPH) are generally used as the absorbing solution (Stern, 1976). For passive sampling, sodium bisulfite (Kennedy & Hull, 1986), triethanolamine (Prescher & Schönbude, 1983), and DNPH (Geisling et al., 1982) are used and sorbents such as silica gel, aluminium oxide, and activated carbon, sometimes specially pretreated, may be useful for taking samples at the work place (DFG, 1982).

Table 2. Sampling and analytical methods for formaldehyde[a]

Method	Sampling	Analysis	Sensitivity mg/litre (ppm)	
			15-min	long-term
Chromotropic acid: NIOSH 3500	midget impinger	spectrophotometry	0.19 (0.16)	0.05 (0.04) (1 h)
Paraosaniline (original)	midget impinger	spectrophotometry	0.02 (0.02)	0.0006 (0.0 (8 h)
Paraosaniline (modified)	midget impinger	spectrophotometry	0.05 (0.045)	0.0012 (0.0 (8 h)
Paraosaniline (TGM-555)	continuous	colorimetric	0.06 (0.05)	NA
MBTH	absorber	spectrophotometry	0.12 (0.10)	0.0036 (0.0 (8 h)

Acetylacetone spectrophotometric	midget impinger	spectrophotometry	0.12 (0.10)	---
Acetylacetone fluorimetric	midget impinger	fluorimetry	0.05 (0.04)	---
2.4-DNPH aqueous ethanol	midget impinger	HPLC	0.00007 (0.00006)	0.000018 (0 (1 h)
2.4-DNPH coated adsorbent	adsorbent tube	HPLC	1.58 (1.32)	0.12 (0.10) (3 h)
NIOSH 3501	midget impinger	polarography	1.94 (1.62)	0.32 (0.27) (1.5 h)
OSHA acidic hydrazine	midget impinger	polarography	0.12 (0.10)	0.012 (0.01 (2.5 h)

Table 2 (contd).

Method	Sampling	Analysis	Sensitivity mg/litre (ppm)	
			15-min	long-term
NIOSH 2502	reactive adsorbent	gas chromatography	9.38 (7.82)	0.6 (0.5) (4 h)
MIRAN	continuous	infrared	0.5 (0.4)	NA
Draeger	reactive adsorbent	visual	0.6 (0.5)	NA
Passive monitor 3M	reactive adsorbent	spectrophotometry (CA)	3.84 (3.2)	0.12 (0.1) (8 h)
DuPont	reactive adsorbent	spectrophotometry (CA)	9.6 (8)	0.3 (0.25) (8 h)
Air Quality Research	reactive adsorbent	spectrophotometry (CA)	8.04 (6.7)	0.25 (0.21) (8 h)
Envirotech	moist adsorbent	spectrophotometry (PUR)	0.86 (0.72)	0.07 (0.06) (8 h)

[a] Modified from: Consensus Workshop on Formaldehyde (1984).

In 1981, the US National Institute of Occupational Safety and Health (NIOSH) developed a solid-sorbent sampling method in which samples collected can be stored for at least 14 days, at room temperature, before analysis, without loss of the analyte (Blade, 1983).

A method for the specific and sensitive determination of formaldehyde and other aldehydes and ketones in air has been described by Binding et al. (1986). The specificity is based on subsequent high performance liquid chromatographic separation. In air samples of 5 litres, the detection limit is 0.05 ml/m^3. The method is suitable for determining 5-min short-term values, as well as for continuous sampling over a whole work shift.

A sensitive method for the determination of formaldehyde is based on the Hantzsch reaction between acetylacetone (2,4-pentanedione) ammonia and formaldehyde to form 3,5-diacetyl-1,4-dihydrolutidine. Formaldehyde concentration can be determined colorimetrically (Nash, 1953) or, more sensitively, by fluorimetry (Belman, 1963). The method is subject to interference by oxides of nitrogen, sulfur dioxide and ozone but is less subject to interference by phenol than the chromotropic acid method.

Photometric assay, using the sulfite-pararosaniline or the chromotropic acid method, is usually applied to determine formaldehyde in air. Automated analytical equipment has been developed.

Suitable analytical methods for monitoring air in the work-place environment have been developed and recommended by the German Research Society, DFG (1982) and by NIOSH (1984).

Menzel et al. (1981) described a special continuously-operating measuring device, developed for determining formaldehyde in particle boards for classification purposes; equipment for continuous measurements using the pararosaniline method is available (Lyles et al., 1965).

A simple colour reaction for the identification of urea formaldehyde resins and diisocyanates, carried out on the surface of wood-based panels, has been described by Schriever (1981). This is based on the reaction with *p* -dimethyl-aminocinnamaldehyde (DACA), resulting in a red colour for both the resins and diisocyanates. The reaction of purpald with formaldehyde is used to distinguish between urea formaldehyde resins and diisocyanates and it is possible to identify diisocyanates when mixed with urea formaldehyde resins.

Water sampling may be by means of grab samples. Where water or individual effluents are not homogeneous several subsamples may be collected at different times from different sampling locations and combined for analysis. If sample storage is necessary it should be frozen or at least kept at 4 °C to prevent biological or chemical degradation of formaldehyde. An organic solvent is used for extraction of formaldehyde prior to analysis.

Concentrations of formaldehyde in the air in the range of 0.05-40 mg/m^3 can be determined by the use of gas-detector tubes which contain a colour reagent (Leichnitz, 1985). They cannot be relied upon in the presence of other substances, e.g., tobacco smoke or below a concentration of 0.05 mg/m^3.

Formaldehyde can be extracted from foods using a solvent, such as isopetane, or by steam distillation and extraction with ether. Before extraction foodstuffs may be pulverized or homogenized.

The Association of Official Analytical Chemists (AOAC, 1984) recommends the Helmer-Fulton Test (registration No. 20.081) for the determination of formaldehyde in food and a spectrophotometric method (Nash's reagent B; registry no. 31203) for the determination of formaldehyde in maple syrup.

3. SOURCES IN THE ENVIRONMENT

3.1 Natural Occurrence

Formaldehyde is naturally formed in the troposphere during the oxidation of hydrocarbons. These react with OH radicals and ozone to form formaldehyde and/or other aldehydes as intermediates in a series

of reactions that ultimately lead to the formation of carbon monoxide and dioxide, hydrogen, and water (Zimmermann et al., 1978; Calvert, 1980).

Of the hydrocarbons found in the troposphere, methane occurs in the highest concentration (1.18 mg/m^3) in the northern hemisphere. Thus, it provides the single most important source of formaldehyde (Lowe et al., 1981).

Terpenes and isoprene, emitted by foliage, react with the OH radicals, forming formaldehyde as an intermediate product (Zimmermann et al., 1978). Because of their short life-times, this potentially important source of formaldehyde is only important in the vicinity of vegetation (Lowe et al., 1981). The processes of formaldehyde formation and degradation are discussed in section 4.

Formaldehyde is one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil (Berestetskii et al., 1981).

3.2. Man-Made Sources

The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters (Berglund et al., 1984; Guicherit & Schulting, 1985).

3.2.1 Production levels and processes

Table 3. World production figures for formaldehyde

Year	Area	Quantity (million kg)
1978	USA, 16 companies	1073
1978	Canada, 4 companies	88
1979	USA, 16 companies	1003
1983	USA	905
1983	Germany, Federal Republic of, 11 companies	534
1983	Japan, 24 companies	403
1983	Major producing countries total	3200
1984	Major producing countries total	5780
1985	USA, 13 companies	941

3.2.1.1 World production figures

The total production figures for formaldehyde are calculated on a 100% formaldehyde basis, though a variety of concentrations and forms are produced. In 1984, the overall production capacity of major industrial countries was approximately 5780 million kg/year (European Economic Community 1700 kg/year, other Western European countries 530, USA 1440, Japan 640, other Asian countries and Australia 1240, Latin America 230). Formaldehyde is also produced in Africa and the USSR. No production figures for formaldehyde are available for eastern industrialized countries (Izmerov, 1982). Table 3 shows actual production figures for some western industrialized countries.

3.2.1.2 Manufacturing processes

Formaldehyde is produced by oxidizing methanol using two different procedures: (a) oxidation with silver crystals or silver

nets at 600-720 °C; and (b) oxidation with iron molybdenum oxides at 270-380 °C. Formaldehyde can be produced as a by-product of hydrocarbon oxidation processes (Walker, 1975), but this method is not used commercially.

Formaldehyde is an inexpensive starting material for a number of chemical reactions, and a large number of products are made using formaldehyde as a base. Thus, it is important in the chemical industry.

3.2.2 Uses

Products manufactured using formaldehyde as an intermediate product are listed in Table 4.

In animal nutrition, formaldehyde is used to protect dietary protein in ruminants (section 7.3). In the USA, formaldehyde is used as a food additive to improve the handling characteristics of animal fat and oilseed cattle food mixtures by producing a dry free-flowing product (US FDA, 1980). Urea formaldehyde fertilizer is used in farming as a source of nitrogen to improve the biological activity of the soil (section 7.1).

3.2.2.1 Aminoplastics (urea formaldehyde resins and melamine formaldehyde resins)

Reaction of formaldehyde with urea or melamine yields urea formaldehyde (UF) or melamine formaldehyde (MF) (condensation process). These synthetic resins are then delivered in solution or powder form at various concentrations for further processing.

Table 4. Products produced with formaldehyde as a compound[a]

Intermediate product	Product
urea formaldehyde resins	particleboard, fibreboard, plywood, paper treatment, textile treatment, moulding compounds, surface coatings, foam
phenolic resins	plywood adhesives, insulation, foundry binders
melamine resins	surface coatings, moulding compounds, laminates, wood adhesives
hexamethylenetetramine	phenolic thermosetting, resin curing agents, explosives
trimethylolpropane	urethanes, lubricants, alkyd resins, multifunctional acrylates
1,4-butanediol	tetrahydrofuran, butyrolactone, polybutylene terephthalate
polyacetal resins	auto applications, plumbing components
pentaerythritol	alkyd resins, synthetic lubricants, tall oil esters, foundry resins, explosives
urea formaldehyde concentrates	controlled release fertilizers

[a] From: Archibald (1982).

In the Federal Republic of Germany, about 70% of the total amount of aminoplastics produced, i.e., 170 000 tonnes of formaldehyde per annum, is used as glue in the manufacture of particle boards. These boards are mostly manufactured from urea formaldehyde resins, the water resistance of which is less than that of other resins, but is sufficient for use in enclosed areas. About 10% of the aminoplastic glues used are melamine-urea-formaldehyde resins, i.e., products where melamine and urea are co-condensed with formaldehyde. Melamine resins are more damp-proof than urea resins, but they are also more expensive.

Formaldehyde can be released from such wood products over a long period, even years, at a continuously declining rate. This occurs especially if the particle board material has become wet due to careless handling, e.g., in construction work. The emission is composed of the excess of formaldehyde used during actual production of the wood products and that produced by hydrolytic cleavage of unreacted methylol groups in the resins. Melamine formaldehyde resins are generally more stable and the amounts of formaldehyde emitted from them are much lower (Deppe, 1982).

Aminoplastics are also used as glue for plywood and in the manufacture of furniture. Paper saturated with aminoplastics and with a high melamine-formaldehyde-resin content is used to coat surfaces of particle boards. Aminoplastics are used to increase the wet strength of certain products in the paper industry.

Urea formaldehyde resins are used as urea formaldehyde foam insulation (UFFI), or as reinforcing foams in the insulation of buildings and in mining, where hollow areas are filled with foam. UFFI is produced by the aeration of a mixture of urea formaldehyde resin and an aqueous surfactant solution containing a phosphoric acid curing catalyst (Meek et al., 1985). This type of foam can emit formaldehyde, even after completion of work, depending on factors such as process and installation, age of building materials, temperature, and humidity.

Condensed aminoplastics of very low relative molecular mass serve as textile treatments to make cotton and fabrics containing synthetic fibres creaseproof and permanently pressed. In the USA, it is estimated (CPSC, 1979) that approximately 85% of all fabrics used in the clothing industry have been treated in this way. Extremely stable aminoplastics are used in order to ensure that they will not degrade during the lifetime of the articles. Formaldehyde concentrations ranging from 1 to 3000 mg/kg were found in such fabrics in the early years of this type of use (Schorr et al., 1974). However, residues of free formaldehyde from the manufacturing process can largely be removed by heat treatment with washing during the textile finishing process. In the last 10 years, the processing of finishing agents in the textile industry has improved and textiles treated with formaldehyde-containing finishing agents contain very little free formaldehyde and cannot cause allergic contact dermatitis (Bille, 1981).

Compounds similar to those used in finishing textiles are used in the tanning of leather. Another field of application is for aminoplastics mixed with rock or wood dust, fibres, or synthetic pulp in hard materials manufactured by hot moulding. They are used in electrical engineering, e.g., in light switches, sockets, and in parts of electrical motors; in mechanical engineering; in the motor-vehicle industry; and for household articles, e.g., camping dishes, parts of electrical household appliances, lamps, and plumbing components.

Aminoplastics are used in the paint industry as carriers in

binders for special types of lacquer and paint, e.g., for cars. In agriculture, they are used as preservatives. They are also used in carpet-cleaning agents in the form of foam resin.

The fields of application of aminoplastics in the Federal Republic of Germany are given in Tables 5 and 6.

3.2.2.2 Phenolic plastics (phenol formaldehyde resins)

Phenolic plastics are synthetic resins in which formaldehyde is condensed with phenols. Phenol, resorcinol, and cresols are among the phenolic components. Owing to the stable binding of phenol and formaldehyde, formaldehyde should not be emitted from the final products made of phenolic plastics, as long as there is no free formaldehyde present.

As in the case of aminoplastics, the wood-working industry is a major consumer.

Table 5. Uses of melamine formaldehyde resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Adhesive resins for timber products, especially particle boards (adhesives)	30	12 000
Resin varnishes	36	14 500
Hardenable moulding material for plastic products	10	4 000
Raw materials for paints	8	3 000
Paper and textile finishing	5	2 000
Other	11	4 500

[a] From: BASF (1984).

Other major areas of application are the production of hard materials, similar to those produced from aminoplastics, as a moulding material, and as a binder in enamel, paints, and lacquers.

Phenolic plastics are used as binders in the production of insulating materials from rock wool or glass fibres, in brake linings, abrasive materials, and moulded laminated plastics. They also serve as binding agents for moulding sand in foundries. Fields of application of phenolic plastics in the Federal Republic of Germany are listed in Table 7.

Emissions of formaldehyde are produced when processing phenolic plastics at high temperatures. Phenol and formaldehyde emissions during moulding led to complaints in previous decades about annoying smells. Now, resins have been improved to meet work-place environment standards and emissions should not cause annoyance.

3.2.2.3 Polyoxymethylene (polyacetal plastics)

Polyoxymethylenes (POM) are another type of plastics produced by

polymerizing formaldehyde. Like the final products from phenolic plastics, articles made of polyoxymethylene are not expected to emit formaldehyde.

Polyoxymethylenes are harder, tougher, and longer-lasting than other plastics and are used in many areas of application in which metallic materials were previously used. They are used in producing motor-

vehicle and machine parts that are subjected to mechanical or thermal stress, parts for precision and communication engineering, parts for household appliances, and plumbing fixtures.

Table 6. Uses of urea formaldehyde resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Adhesive resins for timber products, especially particle boards (adhesives)	80	160 000
Paper finishing	4	8 000
Hardenable moulding material for plastic products	4	8 000
Textile finishing	3	6 000
Resin varnishes for impregnating, e.g., moulded, laminated plastics	2	4 000
Foam resins	2	4 000
for: building insulation	0.2	
mining	1.0	
amelioration	0.4	
carpet-cleaning products	0.3	
other purposes	0.1	
Raw materials for paints	2	4 000
Binding agents for fibre mats, etc.	1	2 000
Foundry resins	1	2 000
Other	1	2 000

[a] From: BASF (1984).

3.2.2.4 Processing formaldehyde to other compounds

Formaldehyde is an important raw material in the industrial synthesis of a number of organic compounds.

In the Federal Republic of Germany during 1981-82, the chemical industry processed 34% of all formaldehyde products to the following derivative substances (BASF, 1984):

- 1,4 butane diol 10%
- pentaerythritol 6%

- methylenediphenyldiisocyanate 5%
- trimethylolpropane and neopentylglycol 4%
- hexamethylenetetramine 2%
- chelating agents (NTA, EDTA) 2%
- miscellaneous (e.g., dyes, dispersion, pesticides, perfumes, vitamins) 5%

Table 7. Uses of phenolic plastic resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Hardenable moulding material for plastic products	23	9000
Adhesive resins for timber products, especially particle boards (adhesives)	20	8000
Binding agents for rock wool, glass wool, etc.	17	7000
Raw materials for paints	14	5500
Foundry resins	7	3000
Resin varnishes for impregnating, e.g., moulded, laminated plastics	4	1500
Abradant binders, e.g., for sandpaper	3	1000
Binding agents for friction surfaces, e.g., brake linings	3	1000
Rubber chemicals	2	1000
Other	7	3000

[a] From: BASF (1984).

3.2.2.5 Medical and other uses

The use of formaldehyde in medical and other fields is relatively small (1.5% of the total production) compared with its use in the manufacture of synthetic resins and chemical compounds. However, its use in these areas is of great significance for human beings, since it occurs either as free formaldehyde and can therefore be easily liberated and affect people (e.g., when used as a disinfectant) or it may reach many people via various consumer goods, such as preservatives and cosmetics. The use of formaldehyde for the preservation of organic material is of historical importance.

Examples of fields of application are listed in Table 8.

Table 8. Use of products containing formaldehyde in medicinal and other technical areas[a]

Area	Use

Detergents and cleaning agents industry	Preservative in soaps, detergents, cleaning agents
Cosmetics industry	Preservative in soaps, deodorants, shampoos, etc; additive in nail hardeners and products for oral hygiene
Sugar industry	Infection inhibitor in producing juices
Medicine	Disinfection, sterilization, preservation of preparations
Petroleum industry	Biocide in oil well-drilling fluids; auxiliary agent in refining
Agriculture	Preservation of grain, seed dressing, soil disinfection, rot protection of feed, nitrogen fertilizer in soils, protection of dietary protein in ruminants (animal nutrition)
Rubber industry	Biocide for latex; adhesive additive; anti-oxidizer additive also for synthetic rubber
Metal industry	Anti-corrosive agent; vehicle in vapour depositing and electroplating processes
Leather industry	Additive to tanning agents
Food industry	Preservation of dried foods; disinfection of containers; preservation of fish and certain oils and fats; modifying starch for cold swelling
Wood industry	Preservative
Photographic industry	Developing accelerator; hardener for gelatin layers

[a] Modified from: BASF (1984).

(a) Disinfectants and sterilizing agents

At present, formaldehyde is the disinfectant with the broadest efficiency; its virucidal property makes it indispensable for disinfection in the clinical field. It is an important active substance in disinfectants that kill and inactivate microorganisms and are used in the prevention and control of communicable diseases and hospital infections

(BGA, 1982). Agents containing formaldehyde are marketed as concentrated solutions and must be diluted appropriately by the user. These concentrates usually contain 6-10% formaldehyde, occasionally up to 30%. The formaldehyde contents of the diluted mixtures lie between 0.3 and 0.5% and, in exceptional cases, 0.9%. Application of the solutions is supposed to kill pathogenic organisms on the surfaces of objects. The ensuing effect is proportional to the concentration of formaldehyde, length of application, and temperature (Spicher & Peters, 1981). The objects to be disinfected are either placed in the formaldehyde solution (e.g., disinfecting linen in washing machines) or wiped and/or sprayed with the solutions. When disinfecting a room, a formaldehyde solution is either vaporized or atomized. Disinfecting in a formaldehyde chamber and gas sterilization both work on a similar principle, that is a mixture of formaldehyde and water vapour is pumped into a special air-tight chamber in which the objects to be disinfected or sterilized have been placed. This method is also used to disinfect

incubators for premature babies and haemodialysis equipment.

(b) Medicines

Pharmaceutical products containing formaldehyde are rarely used for disinfecting the skin and mucous membranes, but formaldehyde is added to pharmaceutical products as a preservative.

Root canal filling sealants containing paraformaldehyde are used in dental surgery.

(c) Cosmetics

Formaldehyde is used as a preservative in cosmetics and in nail-hardening agents. Traces can be found in cosmetics resulting from the disinfecting of apparatus used in their manufacture. Furthermore, products containing formaldehyde are used for other purposes, e.g., anti-perspirants and skin-hardening agents. The formaldehyde content of some cosmetics has been reported to be up to 0.6% and is as high as 4.5% in nail hardeners (Marzulli & Maibach, 1973; Consensus Workshop on Formaldehyde, 1984). Concentrations in dry-skin lotion, creme rinse, and bubble bath oil are in the range of 0.4-0.6%. Present regulatory values are given in section 11.

Formaldehyde is considered technically superior to a number of other preservatives, especially in products with a high water content, e.g., shampoos. As a preservative, formaldehyde also assures that the product is germ-free, prevents microbial contamination during production and packaging, multiplication of residual organisms during storage, and re-contamination during use.

(d) Consumer goods and other products

The use of formaldehyde in consumer goods is intended to protect the products from spoilage by microbial contamination.

It is used as a preservative in household cleaning agents, dish-washing liquids, fabric softeners, shoe-care agents, car shampoos and waxes, carpet cleaning agents, etc. As a rule, the formaldehyde concentration is less than 1%. Disinfecting cleaning agents contain higher concentrations (up to 7.5%) and are diluted before use.

Flooring adhesives contain formaldehyde. It is added to paper, leather, dyes, wood preservatives, sealing agents for parquet floors, as a preservative with fungicidal and bactericidal properties (see also Table 4).

Formaldehyde is a component of reactive resins (urea formaldehyde resins, melamine formaldehyde resins, phenol formaldehyde resins, benzoguanomine formaldehyde, and polymers on a methyloacylamide and/or methylomethacrylamide basis), which control the hardening properties of lacquers and varnishes and are essential for the surface properties of the treated products. The resins used for these purposes contain free formaldehyde at concentrations of up to 3%, this means up to 0.3% in ready-to-use varnishes (BASF, 1983). This free formaldehyde is emitted during application. Thermal degradation of resins during the baking of paints may cause additional emissions of formaldehyde.

3.2.3 Sources of indoor environmental exposure

The major man-made sources affecting human beings are in the indoor environment. Primary sources include cigarette smoke, particle board and plywood, furniture and fabrics, gases given off by heating systems,

and cooking.

Thus, the indoor levels of formaldehyde differ clearly from the concentrations in the outdoor air. Indoor concentrations are influenced by temperature, humidity, ventilation rate, age of the building, product usage, presence of combustion sources, and the smoking habits of occupants. When considering the indoor presence of formaldehyde, it is necessary to differentiate between:

- Hospitals or other scientific facilities, where formaldehyde has to be used as a disinfectant or preservative; and
- All other indoor areas, especially living spaces, schools, kindergartens, and mobile homes where there may be uncontrolled emissions of formaldehyde from sources such as smoking, building materials, and furniture. This sector presents the specific problems in indoor areas.

Possible sources of indoor formaldehyde emissions are:

- cigarettes and other tobacco products;
- particle boards;
- furniture; urea formaldehyde foam insulation (UFFI);
- gas cookers;
- open fireplaces;
- other building materials made with adhesives containing formaldehyde, such as plastic surfaces and certain parquet varnishes;
- carpeting, drapes, and curtains;
- paints, coatings, and wood preservatives; and
- disinfectants and sterilizing agents.

Other products containing formaldehyde do not noticeably contribute to indoor exposure because of their stable formaldehyde binding, e.g., plastic articles made by moulding, or because of their low rate of emission, e.g., cosmetics. Data are summarized in Tables 15 and 16 (section 5.2).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport and Distribution

The degradation of methane is a major source of the natural background concentration of formaldehyde in the atmosphere. Since methane is widely distributed naturally and has a half-life of several years, formaldehyde is formed on a global scale.

Fig. 1 provides a survey of processes that may contribute to formaldehyde concentrations in ambient air.

Formaldehyde is a highly reactive compound with a half-life in the atmosphere of about 1-3 h in the sunlit troposphere at 30° N at mid-day (Bufalini et al., 1972; Lowe & Schmidt, 1983). Therefore, transportation of formaldehyde over distances is probably not of great importance.

The organic compounds from which formaldehyde is derived are usually much more stable. Thus, emissions of organic air pollutants can contribute to the formation of formaldehyde over considerable distances.

Various photochemical models have also been used to predict formaldehyde distribution in the troposphere, but the computed values are difficult to compare, because of the different assumptions used to generate the models.

Lowe et al. (1981) estimated a chemical life-time for formaldehyde using the following reactions for formaldehyde formation (Levy, 1971):

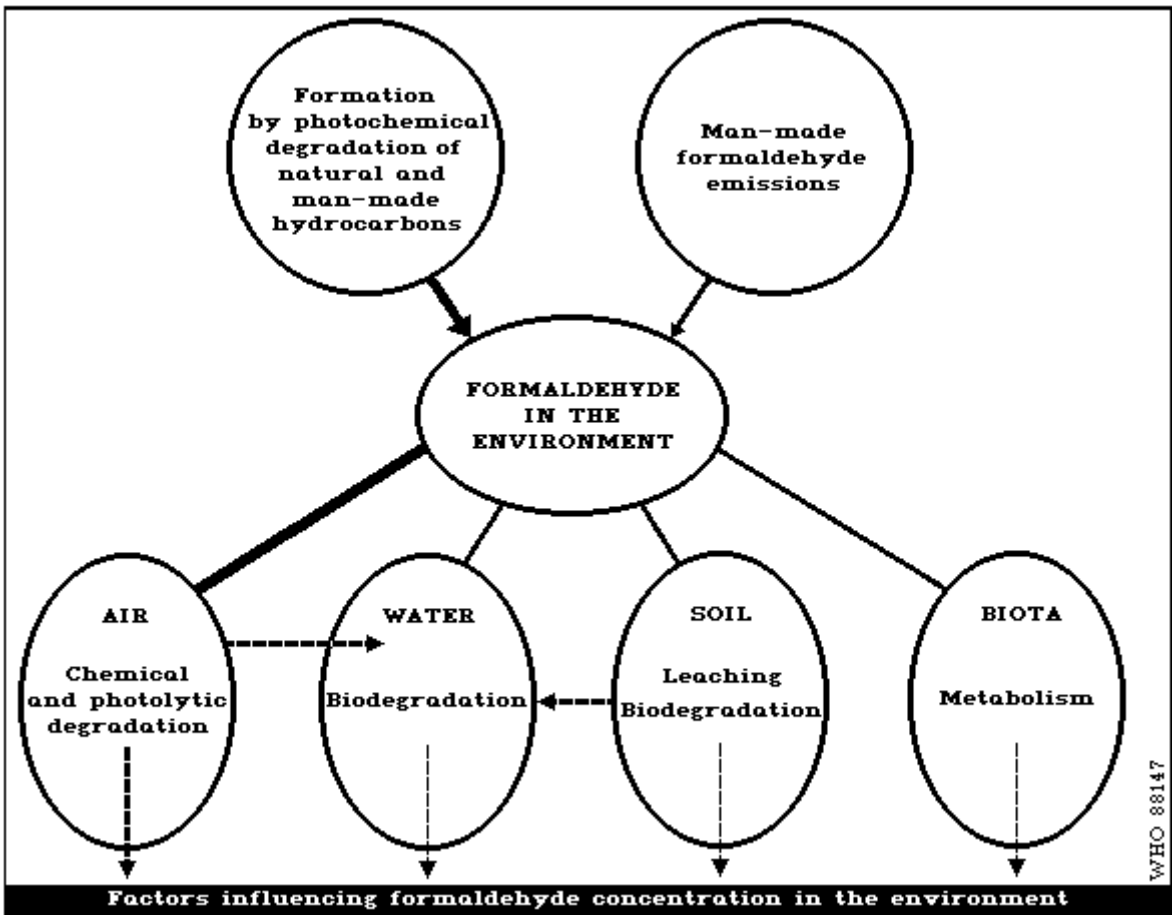
$$CH_4 + OH \rightarrow CH_3 + H_2O \quad (1)$$
$$CH_3 + O_2 + M \rightarrow CH_3O_2 + M \quad (2)$$
$$CH_3O_2 + NO \rightarrow NO_2 + CH_3O \quad (3)$$
$$CH_3O + O_2 \rightarrow HCHO + HO_2 \quad (4)$$

Wofsy et al. (1972) considered that reaction (3) was unlikely and suggested that methyl hydroperoxide (CH_3OOH) could be an intermediate in the reaction series producing formaldehyde.

$$CH_3O_2 + HO_2 \rightarrow CH_3OOH + O_2 \quad (5)$$
$$CH_3OOH + h\nu \rightarrow CH_3O + OH \quad (6)$$
$$CH_3O + O_2 \rightarrow HCHO + HO_2 \quad (7)$$

For the purposes of estimating a chemical life-time for formaldehyde in the troposphere, reactions (1)-(4) are assumed, with reaction (1) as the rate-limiting step. Hence, the rate of formaldehyde production (P) from methane can be written as:

$$P = K_1 [OH] \times [CH_4] \quad (8)$$



Factors influencing formaldehyde concentration in the environment

Using $K_1 = 2.4 \times 10^{-12} e^{-1710/T}$ (Lowe et al., 1981), OH profiles for latitude 45 °N (Logan, 1980), and a mean tropospheric methane mixing ratio of 1.18 mg/m^3, equation (5) can be numerically integrated over a 10-km high troposphere to yield an average column formaldehyde production rate, due to methane oxidation, of 9×10^{-5} g/cm^2 per year.

Similar results are obtained using a mean tropospheric OH concentration of 6.5×10^5 molecules/cm^3 (Volz et al., 1981) with a mean

methane mixing ratio of 1.18 mg/m^3 giving a column formaldehyde production in a 10-km high troposphere of 8 x 10^{-5}g/cm^2 per year. This is equivalent to an average world production rate of formaldehyde from methane of 4 x 10^{11} kg/year, which greatly exceeds the total industrial formaldehyde production rate (6 x 10^9 kg/year).

Various processes contribute to the removal of formaldehyde from tropospheric air. The action of solar ultraviolet radiation on formaldehyde results in its photolysis via two channels (Moortgat et al., 1978; Calvert, 1980).

$$HCHO + h\nu \rightarrow H_2 + CO \quad (9)$$
$$HCHO + h\nu \rightarrow H + HCO \quad (10)$$

Formaldehyde is also removed from the troposphere by reaction with the OH radical (Stief et al., 1980).

$$HCHO + OH \rightarrow HCO + H_2O \quad (11)$$
$$HCO + O2 \rightarrow HO_2 + CO \quad (12)$$

Through the reaction series (1)-(4) and reactions (9)-(12), CO and H_2 are produced in the atmosphere via formaldehyde as an intermediate product. The destruction of one methane molecule leads to the production of approximately one formaldehyde molecule and ultimately to the production of a CO molecule. The series of reactions also results in a net production of HO_2 radicals, resulting in an overall increase in the chemical reactivity of the atmosphere.

From equations (9), (10), and (11), it follows that the chemical destruction of formaldehyde (D) is given by:

$$D = [HCHO][K_{11}[OH] + J_9 + J_{10}] = \frac{[HCHO]}{tau} \quad (13)$$

where K_{11} is the rate constant of equation (11), J_9 and J_{10} are the photodissociation coefficients for equations (9) and (10) and tau $[s]^{-1}$ is the chemical life-time of formaldehyde in the lower troposphere.

Substituting J_9+J_{10} = 4.5 x 10^{-5} s^{-1} (mean estimated from Calvert, 1980), K_{11} = 1.05 x 10^{-11} (Stief et al., 1979), and [OH] = 5 x 10^6 molecules/cm^3 (Logan et al., 1981) into equation (13) yields an average chemical life-time for formaldehyde in the lower troposphere during daylight, of 3 h. Under atmospheric conditions in the presence of nitrogen dioxide (NO_2), the half-life of formaldehyde was found to be 35 min (Bufalini et al., 1972).

At ground level in the atmosphere, reaction with the OH radical is the dominant removal process for formaldehyde. However, in the first few kilometres of the troposphere, the importance of the OH radical as a removal process decreases with altitude and the photodissociation coefficients J_9 and J_{10} increase in importance.

Formaldehyde is also removed from the troposphere by rainout (gaseous constituents of the atmosphere are absorbed during the formation of cloud droplets), washout (falling raindrops scavenge gases, particles, and aerosols from the atmosphere), and by deposition at the surface. However, these processes are only of minor importance in the free troposphere. For example, from formaldehyde measurements made in rainwater collected at an equatorial site in the Pacific, Zafiriou et al. (1980) estimated that rainout was responsible for removing only 1% of the formaldehyde produced in the atmosphere by the oxidation of methane. In addition, Warneck et al. (1978) showed that washout, as a removal process for gaseous formaldehyde in the troposphere, is import-

ant only in polluted regions and may be ignored in unpolluted air.

Dry deposition at the surface is usually defined by a deposition velocity, (v_o (cm/second)), and the flux (f_o) to the surface may be estimated by:

$$f_o = v_o \times [HCHO]_o \qquad (14)$$

where $[HCHO]_o$ is the mean formaldehyde concentration above the surface.

The deposition velocity depends on the surface. For example, from measurements made at an equatorial Pacific atoll, Zafiriou et al. (1980), deduced a value for v_o of 0.4 cm/second at the ocean surface.

The mean formaldehyde mixing ratio, $[HCHO]_o$, measured during an oceanographic expedition in the north and south Atlantic, was 0.29×10^{-3} mg/m^3, corresponding to a concentration of 5.9×10^9 molecules/cm^3 (Lowe et al., 1981). With a deposition velocity of 0.4 cm/second, equation (14) suggests a loss due to deposition at the ocean surface of 2.4×10^9 molecules/cm^2 per second or about 4% of the column formaldehyde production from methane oxidation calculated above. Although v_o for formaldehyde is expected to vary with wind velocity, it is unlikely to exceed 1 cm/second. Hence, loss of formaldehyde from the troposphere due to deposition will only be important near the surface itself.

More recently, consideration has been given to the possibility of how much formaldehyde indirectly contributes to the overacidification of precipitation (Richards et al., 1983). Formaldehyde reacts with sulfur dioxide (SO_2) and gives off relatively concentrated hydroxymethanesulfonic acid, whereby SO_2 may contribute to the acid content of precipitation without preceding oxidation to sulfuric acid, which is a relatively slow process. More in-depth investigations have to be carried out, in order to ascertain to what extent this process is important for acid formation.

4.2 Transformation

4.2.1 Special products of degradation under specific conditions

Highly carcinogenic bis(chloromethyl)ether can be produced by a condensation reaction between formaldehyde and hydrogen chloride (Thiess et al., 1973; Nelson, 1977; Albert et al., 1982; Sellakumar et al., 1985). The maximum equilibrium concentration of bis(chloromethyl)ether generated from atmospheric formaldehyde and hydrogen chloride was estimated to reach 4×10^{-16} ppb; it was concluded that this represented little impact on human health (NRC, 1981). According to Keefer & Roller (1973), formaldehyde is able to catalyze nitrosation of a series of secondary amines to carcinogenic nitrosamines or *N*-nitroso-compounds.

4.2.2 Microbial degradation

Formaldehyde released into the aquatic environment appears to undergo relatively rapid biodegradation. Kamata (1966) examined the biodegradation of formaldehyde in natural water obtained from a stagnant lake in Japan. Under aerobic conditions, known quantities of added

formaldehyde were decomposed in ca. 30 h at 20 °C, anaerobic decomposition required ca. 48 h. No decomposition was noted in sterilized water.

Various activated sludges and microorganisms isolated from activated sludges have been shown to be very efficient in degrading formaldehyde in aqueous effluents, providing the formaldehyde concentration does not exceed 100 mg/litre (Verschueren, 1983). Essentially complete degradation is achieved in 48-72 h, if the proper temperature and nutrient conditions are maintained (Kitchens et al., 1976). Grabinska-Loniewska (1974) isolated 44 bacteria strains from an industrial activated sludge and found that formaldehyde was used as a sole carbon source by various Pseudomonas strains but not by strains of *Achromobacter*, *Flavobacterium*, *Mycobacterium*, or *Xanthomonas*. Several studies have revealed significant degradation of formaldehyde by mixed cultures obtained from sludges and settled sewage (Heukelekian & Rand, 1955; Hatfield, 1957; Sakagami & Yokoyama, 1980; Speece, 1983; Behrens & Hannes, 1984), while in other studies, little or no degradation has been found (Placak & Ruchhoft, 1947; Gerhold & Malaney, 1966; Belly & Goodhue, 1976; Kalmykova & Rogovskaya, 1978; Chou et al., 1979).

A number of pure culture studies have shown that formaldehyde is biologically degradable. Cell extracts of *Pseudomonas methanica* and *Methylosinus trichosporium* (Patel et al., 1979) and cell-free extracts of yeast strains of the Candida sp. are able to oxidize formaldehyde (Fujii & Tonomura, 1972, 1974, 1975; Sahm, 1975; Pilat & Prokop, 1976). Cell extracts of *Pseudomonas oleovorans* (Sokolov & Trotsenko, 1977), *Pseudomonas putida* Cl (Hohnloser et al., 1980), *Hansenula polymorpha* (Van Dijken et al., 1975), *Methylococcus capsulatus* (Patel & Hoare, 1971), *Methanobacterium thermoautotrophicum*, *M. voltae* and *M. jannaschii* (Escalante-Semerena & Wolfe, 1984) and *Alcaligenes faecalis* (Marion & Malaney, 1963) can also oxidize formaldehyde.

Yamamoto et al. (1978) isolated 65 strains of methanol-utilizing bacteria from seawater, sand, mud, and weeds of marine origin and found that all were able to use formaldehyde as a sole carbon source for growth. In contrast, Kimura et al. (1977) found that 336 strains of bacteria, isolated from coastal seawater and mud, could not use formaldehyde as a sole carbon source for growth.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

5.1.1 Air

Measurements in maritime air yielded average formaldehyde concentrations of < 1-14 µg/m^3 (Table 9).

Table 9. Measurements of aldehyde mixing ratios in the air near the ground[a]

Location	RCHO	HCHO	Number of measurements	Reference
	(µg/m^3)			
Baltic sea coast	-	0.7-2.7	5	Hadamczik (1947)
Panama	1.2-4.8	-	?	Lodge & Pate (1966)
Antarctica	<0.6-12	-	?	Breeding et al. (1973)
Panama	<0.3-3.7	-	?	Breeding et al. (1973)
Amazon Basin	1.2-7.4	-	?	Breeding et al. (1973)

Irish west coast	-	0.1-0.5	5	Platt et al. (1979)
Eastern Indian Ocean	-	< 1-14	63	Fushimi & Miyake (1980)
Central Pacific	-	0.1-0.8	7	Zafiriou et al. (1980)
South Africa	-	0.3-1.0	5	Neitzert & Seiler (1981)
Irish west coast	-	0.1-0.6	36	Lowe et al. (1981)
Bürserberg, Austria	-	0.05-2.3	55	Seiler (1982)

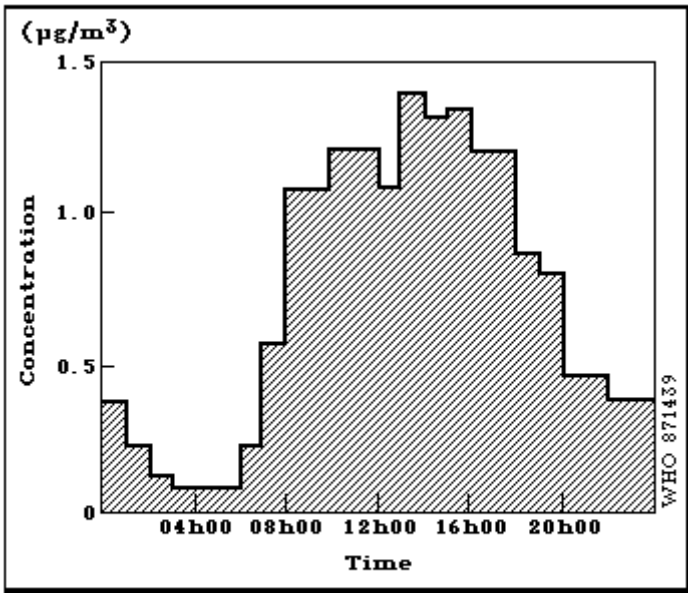
[a] Modified from: Lowe et al. (1981).

Higher values were generally obtained in the equatorial zone and the Pacific (Fushimi & Miyake, 1980; Guderian, 1981; Seiler, 1982). Measurements of the Nuclear Research Centre (Jülich, Federal Republic of Germany), carried out with different measurement procedures in the North and South Atlantic, yielded values of 0.1 µg/m^3 and less (Lowe et al., 1981). In the vicinity of the Pacific islands, values of up to 14 µg/m^3 were reported (Fushimi & Miyake, 1980). However, it should be borne in mind that considerable technical difficulties are involved in measuring such low concentrations, with ensuing uncertainties.

The values measured in continental air are higher (0-16 µg/m^3). Measurements in Bürserberg, Austria, at 1250 m above sea level (Seiler, 1982), showed a mean value of 0.6 µg/m^3 with a variation range of 0.05-2.3 µg/m^3.

Measurements made by the Federal Environmental Agency at Deuselbach, Hunsrück, Federal Republic of Germany, have proved to be representative for the air in the rural areas of Central Europe (Seiler, 1982). The mean value was about 1.5 µg/m^3, ranging from 0.1 to 4.5 µg/m^3 (Seiler, 1982). The lowest values were measured when there was a rapid inflow of maritime air over extended periods. The elevated values were probably due to man-made organic compounds that had been transported long distances. Values of 6 µg/m^3 generally appear together with increased concentrations of carbon monoxide and sulfur dioxide, indicating man-made air pollution. Man-made emissions dominate in the highly industrialized areas of Central Europe (Ehhalt, 1974).

Pronounced diurnal concentrations of formaldehyde are recognizable. A typical example is given in Fig. 2. The resulting values are higher in summer than in winter. They vary from season to season because of the variation in intensity of the ultraviolet radiation.



Diurnal formaldehyde concentrations in Bürserberg/Tschengla, Austria in the month of July - clean air area. From: Seiler (1982).

5.1.1.1 Air in the vicinity of industrial sources and in urban communities

Estimated formaldehyde concentrations in emissions from various sources are summarized in Table 10.

Table 10. Estimated formaldehyde concentrations in emissions from various sources[a]

Emission source	Formaldehyde level
Natural gas combustion	
Home appliances and industrial equipment	2400-58 800 µg/m^3
Power plants	15 000 µg/m^3
Industrial plants	30 000 µg/m^3
Fuel-oil combustion	0-1.2 kg/barrel oil
Coal combustion	
Bituminous	< 0.005-1 g/kg coal
Anthracite	0.5 g/kg coal
Power plant, industrial and commercial combustion	
Incinerators	
Municipal	0.3-0.4 g/kg refuse
Small domestic	0.03-64 g/kg refuse
Backyard	11.6 g/kg (max) refuse
Oil refineries	
Catalytic cracking units	4.27 kg/barrel oil
Thermofor units	2.7 kg/barrel oil
Mobile sources	
Automobiles	0.2-1.6 g/litre fuel

Diesel engines	0.6-1.3 g/litre fuel
Aircraft	approximately 0.3-0.5 g/litre fuel

[a] From: Kitchens et al. (1976).

Motor vehicle exhaust from automobiles not equipped with catalyzers is the major source of formaldehyde in ambient outdoor air (Kitchens et al., 1976).

Only a few highly industrialized areas, which are also areas with heavy traffic, have been covered completely by measurements of the formaldehyde burden. In one such area in the Federal Republic of Germany (Ludwigshafen-Frankenthal), annual mean values of 7-12 µg formaldehyde/m^3 were measured during 1979-84. The annual mean value was the arithmetic average of all half-hour values measured within a year (long-term value). Peak concentrations in certain subareas, one square km in size, ranged from 16 to 69 mg/m^3. These were based on the 95-percentile, i.e., 5% of the measured values were allowed to be in excess of the prescribed parameters for concentrations in ambient air (MSGU RP, 1984). The majority of subareas showed 95-percentile values of about 25 µg/m^3.

A mean value of 7 µg/m^3 was determined in 1971-73 for the 43 measurement points in the Lower Main District, Federal Republic of Germany, which is a radial measuring network with downtown Frankfurt/Main (Federal Republic of Germany) as its centre. This was based on 1-h measurements (n = 862). The 95% value of the cumulative frequency distribution was 18 µg/m^3, and the 4 highest single values were 69, 65, 59, and 52 µg/m^3 (Lahmann, 1977).

In another area at Mainz-Budenheim (Federal Republic of Germany), continuous exposure to 8-20 µg/m^3 was measured, with short-term values of 23-99 µg/m^3. Analysis of the causes of these high levels showed that they were not only caused by industrial emissions. Individual measurements showed a correlation with carbon monoxide levels and were not season-dependent. Hence, it can be assumed that motor vehicles not equipped with catalyzers are responsible, to a considerable extent, for the concentrations in ambient air (section 5.1.1.2). Usually, concentrations in ambient air are below 1 µg/m^3. Data on concentrations of formaldehyde in ambient air are presented in Table 11.

Formaldehyde concentrations in ambient air in areas with a high level of air pollution, away from the vicinity of industrial plants, are presented in Table 12.

Ambient air concentrations of formaldehyde, measured in Los Angeles, California, during the autumn in 1961 and 1966, were 0.006-0.197 mg/m^3 (Kitchens et al., 1976) and a daily average of 0.06-0.148 mg/m^3 (Patterson et al., 1976), respectively. Concentrations of formaldehyde in the Los Angeles area ranged from 0.003 to 0.167 mg/m^3 in 1969 (Kitchens et al., 1976). More recent air measurements taken during 1979 in Los Angeles indicated levels of less than 18.5 µg formaldehyde/m^3 (Versar Inc., 1980).

The results of continuous analyses of formaldehyde concentrations in ambient air at the National Autoexhaust Monitoring Station at Kasumigaseki in Tokyo were studied by Matsumura et al. (1979). The hourly, daily, monthly, and yearly average concentrations were 1-88, 1-34, 3.7-23, and 5.5-12.6 µg/m^3 (1-73, 1-28.4, 3.1-19.1, and 4.6-10.5 ppb), respectively, with a 9-year average value of 8.5 µg/m^3

(7.1 ppb). Daily average concentrations showed logarithmic normal distribution. Ratios of the daily to hourly average concentrations were about 1 to 2. The daily maximum value was observed at around noon and the yearly maximum was found during June and August.

Richards et al. (1983) collected cloud water samples in the Los Angeles Basin during 5 aircraft flights (altitude not reported) and found a median of 2 mg formaldehyde/litre (68 µmol/litre) (range, 11-142 µmol/litre).

Measurements taken in 4 cities in New Jersey showed median daily concentrations in the range of 4.67-8.12 µg/m^3 (Cleveland et al., 1977).

A study in Switzerland showed formaldehyde concentrations of 11.4-12.3 µg/m^3 in street air (Wanner et al., 1977). Maritime air in the northern part of the Federal Republic of Germany has been reported to contain formaldehyde at levels of 0.12-8 µg/m^3 (Platt et al., 1979).

Tanner & Meng (1984) observed strong seasonal variations in the levels of formaldehyde, maximum levels being observed in the summer. The formaldehyde samples were collected at an unidentified northeast coastal site in the USA, using an impinger containing acetonitrile and DNPH; they were analysed using high-pressure liquid chromatography. The concentrations ranged from 1 to 58 µg/m^3 (0.9 to 48 ppbv) with an overall mean of 9 µg/m^3 (7.5 ppbv). The monthly average ambient levels were:

			equivalent to:
July/August:	1982:	15.8 ppbv, 16 samples	16 µg/m^3
October/November:	1982:	4.4 ppbv, 24 samples	4 µg/m^3
March:	1983:	3.8 ppbv, 59 samples	4 µg/m^3
April:	1983:	11.2 ppbv, 11 samples; and	11 µg/m^3
May:	1983:	12.2 ppbv, 25 samples	12 µg/m^3

Table 11. Levels of formaldehyde in ambient air[a]

Country	Sampling area	% of samples	Analytical method	Source	HCHO[b] (µg/m^3)	Co
Federal Republic of Germany	Eifel Region (51°N, 6°E)	-	2,4 dinitrophe-nylhydrazine	easterly winds from indus-trial area; westerly maritime winds	5.0-6.1 0.37 0.12	Wi la ab la 5-
Federal Republic of Germany	Mainz-outskirts of city; Deuselbach-rural	8 54	glass fibre filters	automobiles some auto-mobile industry	0.063 0.037-0.39	fo ae
France	Paris roadside		2,4-dinitrophe-nylhydrazine	automobiles	41-120	to
Ireland	Mace Head and Loop Head located on shoreline	28	glass fibre filters	maritime air	0.049-0.082	fo ae

Italy	Northern - near Swiss border	15	2,4-dinitrophe-nylhydrazine		7.06
Nether-lands	Terschelling Island - small population; Delft - small city; Rotterdam - heavily industrialized	350 at each site	chromatropic acid method		7.4

Table 11 (contd).

Country	Sampling area	% of samples	Analytical method	Source	HCHO[b] ($\mu g/m^3$)	Com
USA	Rural Illinois and Missouri; 3 samples 1 m above ground, 1 sample 20-15 m above tree tops	30	3-methyl-2-benzothiazolone hydrazone	-	<1.2-5.0	tot al
USA	Los Angeles-downtown	31	30 or 60 litres of air at 1 litre per min through 20 ml of 0.1% chromotropic acid in conc. H_2SO_4	-	49.1 55.3	Ju 19 Se
USA	Riverside, California	32	Fournier-transform infrared system		< 5-12	
USA	Lennox, Calif., roof top Azusa, Calif., roof top	36 36	Microimpinger method with 2,4-dinitro-phenylhydra-zine	industrial emissions photo-chemical pollutants	0.6-48.6 0.9-43	le 07 du lu
	Los Angeles Area	20			4.5-70.1	be 16 po
USA	Bayonne, Camden, Elizabeth and Newark, New Jersey	hourly samples between May 1 and Sept. 30, 1974	dichlorosulfit-omercurate complex and acid bleached pararo-saniline hydro-chloride	automobiles	17.2-20.0 4.7-8.1	ra le si ra le 4

[a] Modified from: Meek et al. (1985).
[b] Unless other specified, mean or ranges.

Table 12. Measurements of formaldehyde in ambient air in areas remote from industrial emission sources[a]

Location	Period	Mean value or range	Maximum value	Remarks

		(ug/m^3)	(ug/m^3)	
Federal Republic of Germany				
Berlin	1973-74	0.6	18	118-h mean
		2.1	32	119-h mean
Berlin - Airport		2.2	29	72-h mean
Berlin - Steglitz	1966-67		39	243-h mean
Berlin - Tempelhof	1973-74	0.5	12	71-h mean
Frankfurt - Airport	1983	9-11	23	half-hour mean
Frankfurt - City	1983	7-13	9-25	
Köln - Neumarkt	December 1975	2.3	8.5	95-percentile
	June 1978	8.2	18.3	95-percentile
	June 1978		23.1	rush-hour traffi
Mainz - University	1979	4.4	7.5	65 measurements
Mainz - Finthen	1979-80	1.6	3.8	33 measurements
Switzerland				
Street air	1976	11.4-12.3	-	
USA				
California	1960-80	8-70	160	
Los Angeles, California	1961-66	6-197	-	
Northeastern coastal site	1982-83	1-48	-	

[a] From: BGA (1985).

5.1.1.2 Emissions from industrial plants

(a) Chemical industry

The following emission factors per metric tonne of formaldehyde produced by formaldehyde-manufacturing plants in the Federal Republic of Germany are given on a 100% basis (section 3.2.1.1).

Silver catalyst process with afterburning of flue gas in power plant and gas displacement devices: 0.003-0.008 kg/metric tonne formaldehyde produced; silver catalyst process with flaring of off-gas, without gas displacement devices: 0.05-0.2 kg/metric tonne produced; metal-oxide catalyst process without afterburning: approximately 0.5 kg/metric tonne produced; metal-oxide catalyst process with afterburning but without gas displacement devices: 0.08-0.2 kg/metric tonne produced.

(b) Wood-processing industry

Several studies are available that deal with formaldehyde emissions at particle board factories in the Federal Republic of Germany (WKI, 1978; Marutzky et al., 1980; Schaaf, 1982).

In 1980, the emissions in the exhaust air of several plants reached a mean value of 40 mg formaldehyde/m^3 off-gases. No measures had been taken at any of the plants to clean the off-gases. Pilot studies at a particle board factory showed that a concentration (pure gas) of less than 20 mg/m^3 could be obtained using bioabsorption equipment. Meanwhile, the emittable formaldehyde content of the resins used was further reduced, resulting in even lower formaldehyde concentrations in the off-gases (BGA, 1985).

5.1.1.3 Emissions from furnaces

Incomplete combustion in furnaces is also a cause of formaldehyde emission (Schmidt & Götz, 1977). Various types of furnaces differ considerably in their emission of formaldehyde, depending on the rate of combustion.

Investigations on a small solid-fuel boiler running on wood (Schriever et al., 1983) showed that there was a formaldehyde concentration of more than 1000 mg/m^3 in the gaseous emission during the first phase of combustion, i.e., that of degasification. During the subsequent burning-out phase, the emissions of formaldehyde were about 50-100 mg/m^3.

Lipari et al. (1984) measured formaldehyde emissions in the exhaust gases of a free-standing wood-burning fireplace in the laboratory. When burning green ash (quartered logs), values of 708 mg/kg wood were found; the formaldehyde content of the exhaust gases, when burning red oak, ranged from 89 mg/kg (quartered logs) to 326 mg/kg (split wood). It is likely that wood burning in the home is a major source of primary aldehydes during the winter.

In the Federal Republic of Germany, it is estimated that about 2.8 million tonnes of firewood off-gas are consumed in small heating systems for heating buildings. On the basis of an average formaldehyde concentration of 100 mg/m^3 firewood, an overall annual emission of approximately 1000 tonnes of formaldehyde has been calculated.

5.1.1.4 Emissions from motor vehicles

Formaldehyde is also emitted as a product of incomplete combustion by internal combustion engines. The amounts emitted depend greatly on the operating conditions. Very high values are reached in emissions from a cold engine. Kitchens et al. (1976) reported a formaldehyde emission of 700 mg/litre gasoline or diesel fuel. Given an assumed average value for gasoline consumption of 23 million tonnes and for diesel fuel consumption of 13 million tonnes in the Federal Republic of Germany, the total formaldehyde emission would be 35 000 tonnes per year. Hence, motor vehicles are by far the most important source of formaldehyde emission. The use of exhaust catalytic converters reduces the emissions to less than one-tenth. Emission factors of between 1.8 and 2.4 mg/km have been reported for the USA (VDA, 1983).

Four-stroke engines, running on alcohol, emit more aldehydes than similar engines fuelled with petrol. The formaldehyde concentration in the exhaust fumes can be reduced by a factor of 10 by installing exhaust catalytic converters in vehicles powered with methanol, but the concentration is still higher than that of vehicles with petrol-burning engines. Emission factors of about 250-300 mg/km have been given for vehicles with methanol-burning engines without an exhaust catalyser (Menrad & König, 1982). The odour of such amounts of formaldehyde is perceptible near the vehicle. Diesel engines also emit formaldehyde; diesel oil produces 1-2 g aldehydes/litre of which 50-70% is formaldehyde (Guicherit & Schulting, 1985).

5.1.2 Water

In the atmosphere, formaldehyde is absorbed during the formation of cloud droplets ("rainout") or scavenged by falling raindrops ("washout"). Some concentrations in rainwater and aerosols are given in Table 13. When the rainfall continued for a long period, remaining concentrations in the air of 0.05 µg/m^3 (detection limit: 0.03 µg/m^3) were found by Seiler (1982). Concentrations in rainwater at a remote site in the central equatorial Pacific averaged 8 ± 2 µg/kg (Zafiriou et al., 1980). Kitchens et al. (1976) reported

concentrations of 0.31-1.38 mg/litre.

Table 13. Formaldehyde concentrations in rainwater and aerosol[a]

Location (year)	Rainwater concentration (mg/litre)	Aerosol concentration (ng/m^3)
Mainz, Federal Republic of Germany (1974-77)	0.174 ± 0.085	-
Deuselbach, Federal Republic of (1974-76)	0.141 ± 0.048	40.9 ± 26.0
Ireland (1975, 1977)	0.142 ± 0.059	5.36 ± 2.4
Ireland[b] (1977)	0.111 ± 0.059	-

[a] From: Klippel & Warneck (1978).
[b] Very clean air.

Fish-culture activities are also a source of formaldehyde in the aquatic environment. Formalin is one of the most widely and frequently used chemicals for treating fish with fungal or ectoparasitic infections. After use, formaldehyde solutions are often discharged into the hatchery effluent (NRC, 1981).

5.1.3 Soil

Formaldehyde is formed in the early stages of plant residue decomposition in soil (Berestetskii et al., 1981). It is degraded by certain bacteria in the soil, and therefore bioaccumulation does not occur. Completely polymerized urea-formaldehyde resins persist in the environment and do not emit formaldehyde. Partially polymerized condensation products of low relative molecular mass degrade gradually, thus releasing formaldehyde vapour that can be broken down by soil microflora (Kitchens et al., 1976; Hsiao & Villaume, 1978).

5.1.4 Food

There is some natural formaldehyde in raw food. Formaldehyde concentrations in various food are given in Table 14.

Table 14. Formaldehyde content of foodstuffs

Food	Formaldehyde content (mg/kg)	Reference
Fruits and vegetables		
pear	60[a] (38.7)[b]	Möhler & Denbsky (1970)
apple	17.3 (22.3)	Tsuchiya et al. (1975)
cabbage	4.7 (5.3)	Tsuchiya et al. (1975)
carrot	6.7 (10)	Tsuchiya et al. (1975)
green onion	13.3 (26.3)	Tsuchiya et al. (1975)
spinach	3.3 (7.3)	Tsuchiya et al. (1975)
tomato	5.7 (7.3)	Tsuchiya et al. (1975)
white radish	3.7 (4.4)	Tsuchiya et al. (1975)

Meat		
pig	20	Florence & Milner (1981)
sheep	8	Mills et al. (1972)
poultry	5.7	Möhler & Denbsky (1970)
Milk and milk products		
goat's milk	1	Mills et al. (1972)
cow's milk	up to 3.3	Möhler & Denbsky (1970)
cheese	up to 3.3	Möhler & Denbsky (1970)
Fish		
freshwater (fumigated)	8.8	Möhler & Denbsky (1970)
sea (fumigated)	20	Möhler & Denbsky (1970)
cod (frozen)	20	Rehbein (1986)
shrimp (live)	1	Radford & Dalsis (1982)
crustacea (Mediterannean)	1-60	Cantoni et al. (1977)
crustacea (ocean)	3-98	Cantoni et al. (1977)

[a] Analysis by chromotropic acid.
[b] Analysis using Schiff's reagent.

Accidental contamination can occur through fumigation (e.g., in grain) or by using formaldehyde-containing food additives.

Hexamethylenetetramine has been reported to decompose gradually to formaldehyde under acidic conditions or in the presence of proteins (Hutschenreuter, 1956; WHO, 1974a). Its use is not recommended when there is a possibility that nitrate might also be present in food, because of the risk of nitrosamine formation (WHO, 1974b).

Formaldehyde can be introduced into food through cooking and especially through smoking of food, from utensils, and as a combustion product; it can be eluted from formaldehyde-resin plastic dishes with water, acetic acid, and ethanol in amounts directly proportional to the temperature (Table 15, 16).

Release of formaldehyde may increase with the repeated use of melamine resin tableware (Table 16). The molar concentration ratio of formaldehyde to melamine (y), in 4% acetic acid maintained at 95 °C for 30 min in melamine cups, decreases biexponentially between the first and fifth treatments according to the following formula: $\ln y = -1.0755 \ln x + 2.2462$, where x = the number of times that the heat treatment is repeated. After the sixth treatment, the value of y is reported to remain constant (Inoue et al., 1987).

Daily intake of formaldehyde through food is difficult to evaluate, but a rough estimate from available data is in the range of 1.5-14 mg/day for an average adult, most of it in a bound and unavailable form.

5.2 Indoor Air Levels

Indoor air levels of formaldehyde in various countries were presented during the International Conference on Indoor Air Quality in Stockholm (Berglund et al., 1984).

A survey of indoor air quality under warm weather conditions, in a variety of residences in Houston, Texas, USA, not selected in response to occupant complaints, revealed a distribution of indoor formaldehyde concentrations ranging from < 0.01 to 0.35 mg/m^3, with an arithmetic

mean of 0.08 mg/m^3 (Stock & Mendez, 1985). Levels in approximately 15% of the monitored residences exceeded 0.12 mg/m^3. Formaldehyde levels depended on the age and structural type of the dwelling. These factors were not independent and reflected the influence of more fundamental variables, i.e., the rate of exchange of indoor and outdoor air and the overall emission potential of indoor materials. The results of this survey suggested that considerable population exposure to excess (>0.12 mg/m^3) formaldehyde concentrations might have occurred in the residential environment, indicating the need for improved control strategies.

Hawthorne et al. (1984) measured formaldehyde levels in 40 East-Tennessee homes. Levels in older houses averaged 0.048 mg/m^3 while those in houses less than 5 years old averaged 0.096 mg/m^3.

The effects of foliage plants on the removal of formaldehyde from indoor air in energy-efficient homes is discussed in section 7.3.

Measurements made in living areas, schools, hospitals, and other buildings are listed in Table 17 to 19.

Table 15. Migration of formaldehyde from melamine and urea-resin tableware (mg/ different solvents. Detection limit 0.4 mg/litre[a].

Resin	Temperature	Water		4% Acetic acid		15% Ethanol		3
		30 min[b]	30 min[c]	30 min[b]	30 min[c]	30 min[b]	30 min[c]	30 min
Melamine resin	25 °C	n.d.[d]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d
	60 °C	n.d.	n.d.	0.5	n.d.	0.4	n.d.	n.
	70 °C	n.d.	n.d.					
	80 °C	0.5	1.4	0.6	3.0	0.5	1.6	0.
	90 °C	2.2	2.6					
	100 °C	2.6	5.2	0.8	8.9	0.5	4.6	0.
Urea resin	25 °C	0.4	0.4	0.4	0.5	0.5	0.5	0.
	60 °C	2.9	4.3	3.1	8.3	3.1	3.8	2.
	70 °C	5.0	13.0					
	80 °C	9.1	23.4	9.6	126.0	7.4	30.0	8.
	90 °C	13.0	39.2					
	100 °C	18.0	48.2	27.6	648.0	19.0	54.0	18.

[a] From: Homma (1980).
[b] Standing at room temperature.
[c] Maintained at a definite temperature.
[d] Not detected.

Table 16. Migration from melamine cups with 4% acetic acid concentration in the migration solution[a]

Conditions	Melamine mg/litre	Formaldehyde mg/litre
60 °C, 30 min	0.5 ± 0.6	nd[b]
Microwave oven 1.5 min (90 °C) and stood at room temperature for 30 min (60 °C)	1.7 ± 1.2	(1.1 ± 0.4)
95 °C, 30 min repetition 1	9.5 ± 3.1	(4.1 ± 0.8)

	2	28.1 ± 6.0 (12.0 ± 2.6)
	3	37.7 ± 10.3 (17.3 ± 3.4)
	5	46.4 ± 13.9 (19.4 ± 2.8)
	7	50.4 ± 3.6 (22.2 ± 2.2)

[a] From: Ishiwata et al. (1986).
[b] Not detected.

Tobacco smoke contains an average of 48 mg formaldehyde/m^3 and is an important source of formaldehyde in indoor air. Two cigarettes smoked in a 30 m^3 room increased the formaldehyde level to more than 0.1 mg/m^3 (Jermini et al., 1976). Formaldehyde from tobacco smoke is absorbed by furniture, carpets, and curtains, and only slowly desorbed if the formaldehyde concentration in the indoor air decreases. Particle boards and, to a lesser extent, urea-formaldehyde-foam insulation (UFFI) were also listed as causes of increased indoor exposure. Disinfectant products may cause high exposure. These sources of emission are described in Table 17, 18, and 19.

Formaldehyde concentrations in 49 Dutch houses and 3 old peoples' homes where no UF-foam or particle board had been used were analysed by Cornet (1982). The houses were of different construction types and periods, in which it could be established that no particle board as construction material nor UF-foam had been used. However, several of these houses had particle board furniture. Overall, construction types and conditions of use were typical for Dutch circumstances. Average formaldehyde concentrations were 65 µg/m^3, ranging mainly from 30 to 100 µg/m^3. Ventilation rates ranged usually from 0.3-1.5 air changes per hour in living rooms and 0.2-1.2 in bedrooms. During the measurements no smoking took place.

No clear correlations could be established between the amount of particle board present in furnishings, ventilation rates, and formaldehyde concentrations.

5.2.1 Indoor exposure from particle boards

Nuisance from bad smells led to complaints by students and teachers in several new schools in Köln, Federal Republic of Germany, in 1975 and 1976. Formaldehyde concentrations of up to 1.2 mg/m^3 were measured with the windows closed (Deimel, 1978). A combination of ceilings and furniture made of particle boards and insufficient ventilation was the cause of these high indoor concentrations (Anderson et al., 1975). There have been complaints from schools, kindergartens, private homes, and, especially in the USA, mobile homes. Formaldehyde concentrations of more than 0.12 mg/m^3 and sometimes more than 1.2 mg/m^3 were measured.

During the 1970s, increased use of UF-bonded particle board as a construction material in The Netherlands resulted in many consumer complaints, attributed to formaldehyde. In 1978, a level of 120 µg/m^3 was officially recommended as an acceptable upper limit. In the years 1978-81, measurements of indoor formaldehyde concentrations were carried out, guided by consumer complaints. In 1981, a summary of 950 measurements was presented to the Dutch Parliament (Dutch State Secretary of Health and Environment, 1981). In 435 cases, formaldehyde concentrations exceeded 120 µg/m^3, whereas in 515 cases, notwithstanding complaints, levels were below 120 µg/m^3. Since 1981, many hundreds of measurements of formaldehyde levels in houses, schools, hospitals etc. have been carried out, guided also by consumer complaints. But the overall picture has remained the same,

except for extremes; values exceeding 200-250 µg/m^3 have seldom been reported since the introduction of the new standard. However, occasionally, higher concentrations of up to 400 µg/m^3 have arisen as a result of the use of particle board or trimmings of bad quality in furniture.

Table 17. Formaldehyde levels in homes[a]

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)[b]	Co
Canada (1981)	378	-	-			0.042 (2.6% > 0.123)	ho UFF
	1897	-	-			0.066 (10.4% > 1.23)	ho
Canada (1981)	6	67 (8-100) years		21.5 (21-23)	61% (59-65)	0.014 (<0.012-0.027)	ho UFF
	43	52 (3-140) years		20.4 (15-25)	62% (54-71)	0.066 (<0.012-0.246)	ho
Canada (1983)	46	-	-	-	23-48% 39%	0.11 (0.04-0.30) > 0.123	lo ho
Denmark (1973)	25[c]	15.3 months	23[d]	22.8	7.1	0.62	
	25[g]	15.3 months	23[d]	23	7	0.64	cor st co
Denmark (1976)	7[f]	-	-	26	9.7	0.64	
	7[g]	-	-	23	7	0.30	cor st di
Finland	432	-		-	-	0.20 0.11 0.33	av 25 75

Table 17 (contd).

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)b	Co
Germany, Federal	1					0.069	mi an

Republic of (1974)	1				0.10	ro bo
	1	furniture 1-1.5 years old	60		0.039	mi ro cu
	1		60		0.050	ne
	1	new house	11		0.16	ki cu
	1	new house	54		0.10	li
	1	new house			0.084	ki
	1	new house			0.075	li
	1	old house	35		0.242	li (7 cu
Germany, Federal Republic of	984			57.3% 22.3% 22.3% 11.4% 3% 6%	< 0.05 < 0.05 0.05-0.07 0.071-0.096 0.097-0.12 > 0.12	
Italy (1983-84)	15				0.029 (0.008-0.052)	ap ho

Table 17 (contd).

Japan					up to 0.041 0.113	li pr ho
Switzerland (1981-82)	8	< 6 months to 1 year			0.33 0.14	jus oc
The Netherlands (1980)	15				0.27	be co me
	8				0.29 0.10	be 6 tr
The Netherlands (1977-1980[b])	5		21	56%	0.17	li be tre
			21	60%	0.09	af

	5		20	54%	0.32	be tr
			21	60%	0.20	af
	36				0.34	av me
USA (1982)	40	0-30 years			0.076 ± 0.095	59
	18	0-5 years			0.103 ± 0.112	me
	11	5-15 years			0.052 ± 0.052	
	11	>15 years			0.039 ± 0.052	
	18	0-5 years			0.107 ± 0.114	sp
					0.136 ± 0.125	su
					0.058 ± 0.068	au

Table 17 (contd).

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)b	Co
USA (1982) contd.							
	11	5-15 years				0.053 ± 0.049	sp
						0.060 ± 0.059	su
						0.042 ± 0.043	au
	11	>15 years				0.044 ± 0.063	spr
						0.036 ± 0.046	su
						0.032 ± 0.028	au
USA (1981)	41					0.04 (0.012-0.098)	ho UF
	636					0.15 (0.012-4.2)	ho
USA	244						UF
						>1.23	2.8
						0.61-1.22	1.
						0.12-0.60	24
						<0.12	71.
							no ap
	59					>1.23	1.8
						0.61-1.22	1.
						0.12-0.60	36
						<0.12	60.
USA (1978-79)	13	building material 3-92 months (5.2 months median)				0.12 (median)	

Table 17 (contd).

USA (1979)	1			0.098 (0.04-0.15)	en ef ho HC
	1			0.081 ±0.007	un fu
				0.225 ±0.016	un fu
				0.263 ± 0.026	oc da
				0.141 ± 0.044	oc ni
USA (1980/81)	9	2 years	445 (total)	0.044 ± 0.022	ai co (h ga
				0.033 ± 0.020	me la
	1	6 years	441 (total)	0.017	"l ti
USA (1983)	20	<6 years		0.076	ene ef ne
	16			0.037	lo mo

[a] Modified from: Meek et al. (1985). Where blanks appear, relevant information
[b] Means, ranges or standard deviations, unless otherwise specified.
[c] Ventilation = 0.8 air changes/h.
[d] Loading (ratio of unit area of formaldehyde source to room volume) = 1.2 m2/m^3.
[e] Standard conditions were: 23 °C, 7 g H_2O/kg air, 1 air change/h.
[f] Ventilation = 0.32 air change/h.
[g] Ventilation = 1 air change/h.
[h] House had a gas stove and 3 occupants, no cigarette smokers.

Table 18. Formaldehyde levels in mobile homes[a]

Country	No. of mobile homes studied	Age of homes	HCHO (mg/m^3)	Comments
Germany, Federal Republic of		1 year	5.26	trailer
		1 year	1.06	trailer opened up for 1 h
		3 years	0.06	trailer shut for 1 day
	3	1 year	0.11	trailer
	3	2 years	0.05	trailer
USA	110	< 2 years	0.95	complaint homes, Washing
	38	< 2 years	0.89	complaint homes, Wiscons
	66	< 2 years	1.04	complaint homes, Minneso

		< 2 years	0.66	random sample, Wisconsin
	77	2-10 years	0.58	complaint homes, Washing
	9	2-7 years	0.56	complaint homes, Wiscons
	43	2-10 years	0.34	complaint homes, Minneso
USA	65	0.2-12 years median 1.3 years	0.59 (median)	complaint homes, Wiscons
USA	430		> 1.23	4 % of sample
			0.61-1.22	18% of sample
			0.12-0.60	64% of sample
			< 0.12	14% of sample
USA	431		0.47 (0.012-3.60)	
USA	65		0.20 (median)	65 out of 208; random sample of mobile homes in Wisconsin

[a] From: Meek et al. (1985).

Table 19. Formaldehyde levels in public buildings[a]

Country	No. of build-ings	Average age of buildings	Loading, (m^2/m^3)b	Air temp. (°C)	Ventila-tion (air changes/h)	HCHO (mg/m^3)[c]	Comments
Denmark	7	6 months	-	-	0.5	0.45	mobile day centre
Germany, Federal Republic of	3	-	-	-	-	0.469	schools co some UF bu material
	441						dwellings, hospitals, workshops,
	-	-	-	-	-	0.014-0.31 mean 0.06	dwellings gas cookin
	-	-	-	-	-	0.064-0.2 mean 0.06	dwellings gas cookin
	-	-	-	-	-	0.01-0.13 mean 0.05	offices, s
	-	-	-	-	-	0.02-0.1 mean 0.05	offices, n
	-	-	-	-	-	0.026-0.22 mean 0.12	joiner's w
	-	-	-	-	-	0.012-0.1 mean 0.05	hospital r

Table 19 (contd).

Country	No. of buildings	Average age of buildings	Loading, (m^2/m^3)[b]	Air temp. (°C)	Ventilation (air changes/h)	HCHO (mg/m^3)[c]	Comments
Japan	-	-	-	-	-	0.048	department
						up to 0.046	grocer's s
						0.035	offices
						0.003	cinema
Switzerland	11	< 6 months	-	-	-	0.410	office: mea ment taken recent occ
		1 year	-	-	-	0.160	and after
	16	< 6 months				0.60	school: mea taken afte occupancy
		1 year				0.23	after agei
The Netherlands	10	-	-	-	-	0.758	average of measuremen schools
	13	-	-	-	-	0.245	average of measuremen commercial blishments
	1	-	-	-	-	2.30	highest va UFFI build
Yugoslavia	24	-	-	26	-	1.083	offices
	2	-	-	30	-	2.60	stores
	3	-	-	18	-	0.15	furniture

Table 19 (contd).

Yugoslavia	6	1-3 years	-	-	-	0.143	offices
	6	11-43 years				0.087	offices
	7	1-10 years				0.141	kindergart
	3	11-50 years				0.109	kindergart
	8	4-23 years				0.043	schools
	2	90-100 years				0.023	schools
USA	1	4 years	-	-	-	0.025-0.037	office rec renovated UF materia
	2	4 years	-	-	-	0.36-1.22	office rec renovated particle b
	1	-	-	-	-	0.14-0.45	particle b shelving
	1	-	-	-	-	0.11-0.14	particle b furniture plywood fl

[a] Modified from: Meek et al. (1985). Where blanks appear, relevant information

[b] Ratio of unit area of formaldehyde source to room volume.
[c] Means or ranges, unless otherwise specified.

5.2.2 Indoor air pollution from urea-formaldehyde foam insulation (UFFI)

Foam made from specific aminoplastic resins is used for the thermal insulation of spaces in walls or other elements of construction. In this process, an acidic surfactant solution is foamed by compressed air and continuously mixed with aqueous UF resin. Formaldehyde is emitted during and after completion of the hardening process. The resulting indoor exposure depends, among other factors, on the age of the building, type of resin, the application and the care taken, the amount of excess formaldehyde, the amount and rate of emission, the prevailing temperature, humidity, and rates of ventilation.

Most of the studies performed on UFFI and mobile homes have been carried out in Canada and the USA (Table 18), but they are currently of less importance.

Studies by Everett (1983) showed that there is some increase in formaldehyde levels in dwellings, directly after foaming, but that this decays over a period of a few weeks. Everett (1983) noted that, though there were isolated high values up to 1.2 mg/m^3, 70% of the results after foaming were below 0.1 mg/m^3.

Girman et al. (1983), conducting the 40-home East Tennessee study, obtained formaldehyde measurements that led to the following major conclusions:

The average formaldehyde levels exceeded 0.12 mg/m^3 (0.1 ppm) in 25% of the homes;

Formaldehyde levels were positively related to temperature levels in homes. In houses with UFFI, a temperature-dependent relationship with measured formaldehyde levels frequently existed;

Formaldehyde levels generally decreased with increasing age of the house. This is consistent with decreased emission from materials due to aging;

Formaldehyde levels were found to fluctuate significantly both during the day and seasonally.

5.2.3 Indoor air pollution from phenol-formaldehyde plastics

Popivanova & Beraha (1984) carried out a study on phenol-formaldehyde penoplast in order to establish the amount and dynamics of formaldehyde migration into the indoor air in relation to three major factors, i.e., age of the material, air temperature, and air exchange rate. Age of the material was found to be the most important factor influencing formaldehyde migration, followed by temperature elevation. The rate of air exchange was inversely related to formaldehyde migration level. A mathematical model of these processes has been developed and a regression equation proposed. A review of factors influencing formaldehyde migration from formaldehyde resins was published by Popivanova (1985).

5.2.4 Exposure to indoor air containing cigarette smoke

As with all other incomplete combustion processes, formaldehyde is emitted in the smoke from cigarettes. About 1.5 mg of formaldehyde was found in the total smoke from one cigarette, which was distributed between the main and side stream in the ratio of 1:50, i.e., 30 µg in

the main stream (= inhaled smoke) and 1526 µg in the side stream (Jermini et al., 1976; Klus & Kuhn, 1982). Other investigators measured up to 73 µg of formaldehyde per cigarette in the main stream (Newsome et al., 1965; Mansfield et al., 1977). Concentrations of 60-130 mg/m^3 were measured in mainstream smoke. For an individual smoking 20 cigarettes per day, this would lead to an exposure of 1 mg/day (Weber-Tschopp et al., 1977). Exposure to sidestream smoke (or environmental tobacco smoke) can be estimated from chamber measurements. Thus, in a 50-m^3 chamber with one air exchange per hour, 6 cigarettes smoked in 15 min yield over 0.12 mg/m^3 (WKI, 1982). Weber-Tschopp et al. (1976) measured the yield of 5-10 cigarettes in a 30-m^3 chamber with 0.2-0.3 air exchanges per hour as 0.21-0.35 mg/m^3, which would be about 0.05-0.07 mg/m^3 at one air exchange per hour. This concentration is in the same range as that likely to be found in the rooms of most conventional buildings where there is no smoking (section 5.2). Levels of formaldehyde emitted from combustion sources other than cigarette smoke are presented in Table 20.

Table 20. Formaldehyde levels from combustion[a]

Source	Comments	Emission rate (g fuel/min)	Air ch per h
Gas stove in test kitchen, 27 m^3	ventilation conditions:		
	no stove vent or hood		0.25
	hood vent (without fan) above stove		1.0
	hood vent, fan at low speed (1.4 m^3/min)		2.5
	hood vent, fan at high speed (4 m^3/min)		7.0
	outdoor concentration during test		
Undiluted exhaust gases:			
Household natural gas appliances Cooking range (oven) Floor furnace			
Kerosine heaters:	27 m^3 environmental chamber, temp. < 26 °C		0.4
radiant (new)	fired in chamber	3.13	5.1
	10-min warm-up outside chamber	3.16	4.0
radiant (1 year old)	10-min warm-up outside	2.54	0.67
convection (new)	fired in chamber	3.03	0.36
	10-min warm-up outside chamber	3.0	1.3
convection (5 years old)	fired in chamber	2.1	6.7
	10-min warm-up outside chamber	2.2	5.6

Table 20 (contd).

Radiant heater	21 m^3 room, closed door,	3.6	0.5
Radiant heater		3.6	
Convection heater		2.7	
Cigarette smoke	30 m^3 climate chamber,		0.3
	1 cigarette (1 min)		
	3 cigarettes (2 min)		
	5 cigarettes (3 1/2 min)		
	10 cigarettes (7 min)		
	15 cigarettes (10 1/2 min)		
Cigarette smoke	45.8 m^3 room, 5 subjects,		
	20 cigarettes smoked over 30 min:		
	original background level		
	level after 30 min		
Cigarette smoke	undiluted smoke		

[a] From: Dept National Health Welfare Canada (1985).
[b] mg/h.

5.3 General Population Exposure

The possible routes of exposure to formaldehyde are inhalation, ingestion, dermal absorption, and, rarely, blood exchange, as in dialysis.

5.3.1 Air

The daily inhalation exposure for an average adult can be estimated by assuming a respiratory volume of 20 m^3/day, given the exposures mentioned above, and making different assumptions about the duration of exposure periods (Table 21). Average time estimates lead to the conclusion that people spend 60-70% of their time in the home, 25% at work, and 10% outdoors. If it is assumed that normal work exposures are similar to home exposures, the daily exposure resulting from breathing is about 1 mg/day, with a few exposures of > 2 mg/day, and a maximum of 5 mg/day; this compares favourably with the estimated range of 0.3-2.1 mg/day, based on the work of Kalinic et al. (1984), with estimated weighted average exposures of 0.02-0.14 mg/m^3.

Matsumura et al. (1985) determined the levels of exposure to formaldehyde of housewives by using personal air sampling apparatus (Sampler: silica gel impregnated with triethanolamine, Hydrazine-method). The highest exposure level was 0.311 mg/m^3 (0.259 ppm) (3.73 mg/day), while the lowest was 0.011 mg/m^3 (0.009 ppm) (0.13 mg/day). The usual exposure range was 0.018-0.030 mg/m^3 (0.015-0.025 ppm) (0.22-0.36 mg/m^3). The highest exposure level was that of a housewife living in a newly constructed house, where irritation of the eyes and throat, lachrymation, and cough were observed in the family.

Chemical toilet fluids, used in caravans, on camping sites, in aeroplanes, and in boats often include formaldehyde. In an experiment, a 10% formaldehyde solution (normally found on the market) was applied in a 2 m^3 toilet room (Reus, 1981a). The toilet bowl was filled with 1 1/2 litres of water and 110 ml of the disinfectant, giving a solution of 0.75% formaldehyde. The ventilation rate was not determined, but

estimated to be 3-5 air changes per hour, temperature 20-22 °C. Air concentrations of formaldehyde, which rose to 150-350 µg/m^3 during the filling of the toilet, gradually decreased within 1 h to 60-90 µg/m^3 and then remained constant. Closing the lid caused a further decrease to < 20 µg/m^3.

5.3.1.1 Smoking

Concentrations of 60-130 mg/m^3, measured in mainstream smoke, would lead to an average daily intake of 1 mg formaldehyde per day (daily consumption: 20 cigarettes; WHO, 1987).

Formaldehyde produced by cigarettes can also mean considerable exposure for the non-smoker through passive smoking, the more so since it has been reported that the effects of gaseous formaldehyde are potentiated by smoke particles and aerosols (Rylander, 1974; Weber-Tschopp et al., 1977; WHO, 1987).

Table 21. Contribution of various atmospheric environments to average exposure[a]

Source	Average exposure (mg/day)
Air	
Ambient air (10% of the time)	0.02
Indoor air	
Home (65% of the time)	
- Conventional	0.5-2
- Prefabricated (particle board)	1-10
Work-place air (25% of the time)	
- Without occupational exposure[b]	0.2-0.8
- Exposed occupationally to 1 mg/m^3	5
- Environmental tobacco smoke	0.1-1.0
Smoking	
20 cigarettes/day	1.0

[a] From: WHO (1987).

[b] Assuming the normal formaldehyde concentration in conventional buildings.

5.3.2 Drinking-water

Concentrations in drinking-water are normally less than 0.1 mg/litre, which means that, except for accidental ingestion of formaldehyde-contaminated water, intake is negligible (below 0.2 mg/day; WHO, 1987).

5.3.3 Food

The daily formaldehyde intake depends on the composition of the meal and may range between 1.5 and 14 mg for an average adult (see Table 14, section 5.1.4).

In a residue study of the Food Inspection Service in The Netherlands, it was found that 53% of 162 samples of soft drinks, alcoholic beverages, sugar-containing foodstuffs, such as marmalade, and meat and meat products contained formaldehyde at levels exceeding

1 mg/kg. Up to 20% of samples contained levels exceeding 2 mg/kg; levels in 15 samples of meat and meat products even exceeded 10 mg/kg, with some reaching about 20 mg/kg. The source of the formaldehyde could not be established for any of the cases (Nijboer, 1984). In an additional study, the formaldehyde contents of meat and meat products were analysed (Nijboer, 1985) and, in 62 out of 86 samples, were found to exceed a level of 1 mg formaldehyde/kg. Levels in 50% of samples were between 1 and 2 mg/kg and 22% exceeded 2 mg/kg with some levels as high as 14-20 mg/kg. Again, no source for the formaldehyde residue could be established.

5.3.4 Other routes of exposure

Dermal exposure and absorption occur through contact with cosmetics, household products, disinfectants, textiles (especially of artificial origin) and orthopaedic casts. Most of these exposures are likely to remain localized (though gaseous formaldehyde will be available for inhalation). The estimates of the systemic absorption of formaldehyde through the entire epidermal layer and across the circulatory layer, are negligible (Jeffcoat, 1984; Robbins et al., 1984; Bartnik et al., 1985). Contact with liquid barriers, as in the eyes does not appear to lead to absorption. There have been case reports of newborn infants being exposed to formaldehyde-containing disinfectants in incubators.

In certain rare events, formaldehyde in aqueous solution enters the blood stream directly. These events are most likely to occur during dialysis or in circulation-assisted surgery in which the dialysis machine and tubes that have been disinfected with formaldehyde, still contain the compound because of adsorption or back wash, and it is then introduced into the patient's bloodstream (Beall, 1985).

5.4 Occupational Exposure

In the work-place, exposure may be caused by either producing or handling formaldehyde or products containing formaldehyde. Concentrations of formaldehyde in occupational settings in the USA were reported by the Consensus Workshop on Formaldehyde (1984) (Table 22, see also section 9.2).

Airborne formaldehyde concentrations in 7 funeral homes in 1980 in the USA ranged from 0.12 to 0.42 mg/m^3 during the embalming of non-autopsied bodies and from 0.6 to 1.4 mg/m^3 during the embalming of autopsied bodies (Williams et al., 1984). In a study on formaldehyde exposure in an embalming room, levels of up to 4.8 mg/m^3 were found when the exhaust ventilation system was not functioning (Anon., 1980a,b).

Formaldehyde concentrations were determined in Dutch pathological laboratories, under practical conditions, where a 4-6% solution of formaldehyde in water was used. No detailed information on ventilation is available, but a special ventilation system was applied at the dissection table, where concentrations amounted to 75 µg/m^3. A concentration of 195 µg/m^3 was found in the cleaning section of the laboratory (Reus, 1981).

Table 22. Formaldehyde monitoring data in occupational settings[a]

Industry	Job or work	Exposure levels mg/m^3 (ppm)	Area or personal	Number o observa

	area	range	mean	median	monitoring	tions
Formaldehyde production	production operator	-	1.68 (1.4)	-	personal	-
	laboratory technician	-	1.57 (1.31)	-	personal	-
Resin and plastic materials production	production operator	-	1.67 (1.39)	-	personal	-
	resin plant	0.06-0.44 (0.05-0.37)	0.29 (0.24)	-	area	8
	resin plant	0.11-0.20 (0.09-0.17)	0.16 (0.13)	-	area	2
	UF resin production (2 plants)	0.14-0.66 (0.12-0.55)	-	-	area	-
		0.22-6.48 (0.18-5.4)	-	-	area	-
		0.24-0.89 (0.2-0.74)	-	-	area	-
		0.72-0.41 (0.6-0.34)	-	-	area	-
	UF resin production	0.14-6.48 (0.12-5.4)	1.08 (0.90)	-	personal	18
		0.24-0.89 (0.20-0.74)	0.47 (0.39)	-	personal	5
		0.72-0.41 (0.06-0.34)	0.23 (0.19)	-	personal	5

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitoring	Number of observations
Textile finishing	textile warehouse	0.05-0.88 (0.04-0.73)	0.37 (0.31)	-	area, personal	11
		0.10-0.61 (0.08-0.51)	0.30 (0.25)	-	area, personal	11
	textile facilities	< 0.12-1.56 (< 0.1-1.3)	-	0.96 (0.8)	area, personal	28
		< 0.12-1.68 (< 0.1-1.4)	-	0.84 (0.7)	area, personal	15
	textile manufacture	0.13-1.60 (0.11-1.33)	0.83 (0.69)	0.77 (0.64)	personal	6
		0.18-1.44 (0.15-1.2)	0.64 (0.53)	0.54 (0.54)	area	13
Clothing production	permanent press	0.18-0.46 (0.15-0.38)	0.37 (0.31)	-	area	9
		0-3.24	0.89	-	area	32

		(0-2.7)	(0.74)			
	warehouse	0.13-0.68	0.47	0.44	personal	13
		(0.11-0.57)	(0.39)	(0.37)		
		0.05-0.23	0.14	0.18	area	9
		(0.04-0.19)	(0.12)	(0.15)		
	sewing machine operators	0.61-1.09	0.86	0.85	personal	16
		(0.51-0.91)	(0.72)	(0.71)		
		0.36-2.16	1.44	1.44	personal	41
		(0.3-1.8)	(1.2)	(1.2)		
	clothing pressers	0.006-1.14	0.08	0.065	personal	40
		(0.005-0.95)	(0.07)	(0.054)		

Table 22 (contd).

Plywood particle-board production	all workers	-	1.2-3.0 (1-2.5)	-	area	-
Wood furniture manufacture	particle board	0.01-0.3	0.14	-	area	11
		(0.008-0.25)	(0.12)			
	veneering	1.08-7.68	3.30	-	area	-
		(0.9-6.4)	(2.75)			
		0.24-0.66	0.48	-	area	9
		(0.2-0.55)	(0.40)			
		0.24-3.0	0.84	-	area	13
		(0.2-2.5)	(0.70)			
Plastic moulding	injection mold	0.01-0.12	0.044	-	personal	9
		(0.01-0.1)	(0.037)			
	area samples	0.01-0.64	0.24	-	area	8
		(0.01-0.53)	(0.20)			
	operators	< 2.4	< 2.4	< 2.4	personal	28
		(< 2)	(< 2)	(< 2)		
	near grinder hopper	2.4-4.8	3.6	3.6	area	3
		(2-4)	(3)	(3)		
	sand mould production	0.12-0.84	0.37	0.24	personal	28
		(0.1-0.7)	(0.31)	(0.2)		
		ND-1.32	0.20	0.12	area	29
		(ND-1.1)	(0.17)	(0.1)		
Paper and paper-board manufacture	paper treatment resin) impregnated	0.05-0.19	0.10	-	personal	15
		(0.04-0.16)	(0.08)			
		0.04-0.08	0.07	-	area	7
		(0.03-0.07)	(0.06)			
		0.01-0.28	0.06	-	personal	30
		(0.01-0.23)	(0.05)			

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number o observa tions

					ing	
Paper and paper-board manufacture (contd).		0.02-0.34 (0.02-0.28)	0.06 (0.05)	-	personal	10
	treated paper products	0.17-1.19 (0.14-0.99)	-	0.70 (0.59)	area	64
		0.17-1.08 (0.14-0.90)	-	0.41 (0.34)	personal	37
	coating preparation	< 0.01-3.6 (< 0.01-3)	1.2 (1.0)	0.01 (0.01)	area	7
		0.96-0.50 (0.8-0.42)	0.61 (0.51)	0.50 (0.42)	area	4
Foundries (steel, iron, and non-ferrous)	bronze foundry, core machine operators	0.29-0.96 (0.24-0.80)	0.64 (0.53)	0.66 (0.55)	personal	4
		0.14-0.83 (0.12-0.69)	0.47 (0.39)	0.47 (0.39)	area	11
	iron foundry, core machine operators	< 0.02-22.0 (0.02-18.3)	-	0.52 (0.43)	personal	14
		0.08-0.40 (0.07-0.33)	0.19 (0.16)	-	personal	3
	moulding	0.04-0.16 (0.03-0.13)	0.11 (0.09)	-	personal	6
		0.08-0.94 (0.07-0.78)	0.25 (0.21)	-	area	6
Rubber hose production	-	ND-0.05 (ND-0.04)	0.05 (0.04)	-	personal	10

Table 22 (contd).

Asphalt shingle production	producers	0.04-0.08 (0.03-0.07)	0.06 (0.05)	0.06 (0.05)	area	2
Fibreglass insulation	installers	0.008-0.04 (0.007-0.033)	0.028 (0.023) (TWA)[c]	0.023 (0.019)	personal	13
Urea-formaldehyde foam insulation dealing and installation	suburban shopping centre insulated with UF foam	0.08-2.4 (0.07-2)	-	-	-	-
		0.96-1.92 (0.8-1.6)	1.26 (1.05)	-	area	36
		0.36-3.72 (0.3-3.1)	1.73 (1.44)	-	area	30
		< 0-6.36 (< 0.5-3)	1.87 (1.56)	-	area	16
Fertilizer manufacturing	-	0.24-2.28 (0.2-1.9)	1.08 (0.9)	-	personal, area	11
Mushroom farming	-	< 0.61-12+ (0.51-10+)	3.22 (2.68)	-	area	12
		ND-3.24 (ND-2.7)			personal	3

		ND-5.92 (ND-4.93)	-	-	area	3
Funeral homes	embalmers	0.1-6.3 (0.09-5.26)	0.89 (0.74)	-	area	187
		0.24-4.79 (0.20-3.99)	1.32 (1.1)	0.65 (0.54)	area personal	8
		1.56-4.72 (1.30-3.99)	3.24 (2.7)	2.99 (2.49)	area personal	5
Pathology	autopsy room	0.07-9.5 (0.06-7.9)	5.76 (4.8)	-	area	10
		2.64-9.5 (2.20-7.9)	5.22 (4.35)	-	area	6

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitoring	Number of observations
Biology teaching	laboratory	3.30-17.76 (2.75-14.8)	9.96 (8.3)	-	area	8
Hospital	laboratory	2.64-2.76 (2.2-2.3)	2.70 (2.25)		personal	2
		2.28 (1.9)	-		personal	1
		2.64 (2.2)	2.4 (2)		area	2
Government	laboratory	2.88 (2.4)	-		personal	1
		0.96 (0.8)	-		area	1
Hospital	dialysis unit	ND-1.08 (ND-0.90)	0.50 (0.42)		area	9
		0.32-0.76 (0.27-0.63)	0.49 (0.41)		personal	5
		0.05-0.60 (0.04-0.50)	0.61 (0.51)		area	
Animal dissection	laboratory	< 0.46-1.25 (< 0.38-1.04)	-		personal	15
		0.06-0.48 (0.05-0.40)	0.18 (0.15)		area	6
		0.13-0.22 (0.11-0.29)	0.22 (0.18)		area	3
Garment manufacturing (3 plants)	-	< 0.17-0.76 (< 0.14-0.63)	0.28-0.40 (0.23-0.33)		personal	40
		< 0.04-0.48 (< 0.03-0.40)	0.23-0.31 (0.19-0.26)		area	43
		0.04-0.48 (0.03-0.40)	0.25 (0.21)		area	43

Table 22 (contd).

Garment manufacturing (contd)		0.06-1.34 (0.05-1.2)	0.55 (0.46)		area	42
Chemical manufacturing	-	0.05-1.92 (0.04-1.6)	0.66 (0.55)	-	personal	3
		0.04-0.52 (0.03-0.43)	0.20 (0.17)	-	area	5
Glass manufacturing	-	0.50 (0.42)	0.50 (0.42)	-	personal	1
		0.54-0.80 (0.45-0.64)	0.65 (0.54)	-	area	2
Hospital work	-	0.44-0.88 (0.37-0.73)	0.66 (0.56)	-	area	2
Paraformaldehyde packaging	-	< 0.30-1.02 (< 0.25-0.85)	0.66 (0.55)	-	personal	10
		0.34-4.08 (0.28-3.4)	1.40 (1.17)	-	area	8
Office work (3 locations)	-	0.02-0.14 (0.02-0.12)	0.07 (0.06)	-	area	39
		< 0.05 (< 0.04)	< 0.05 (< 0.04)	-	area	9

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitoring	Number of observations
Autopsy rooms	resident	-	1.90[d] (1.58)		personal	10
	pathologist	-	1.50[d] (1.24)		personal	9
	technician	-	0.68[d] (0.57)		personal	2
	assistants	0.16-16.28 (0.13-13.57)	0.86 (0.72)		area	23

[a] From: Consensus Workshop on Formaldehyde (1984).

[b] *Abbreviations for analytical procedures:*

AA = acetylacetone.
BI = bisulfite impingers.
CA = chromotropic acid procedure.
CL = chemiluminescence procedure.
CO = colorimetric analysis.
CT = charcoal tubes.
SS = solid sorbents.
DT = Draeger tubes.
FS = Fourier transform spectrometer.
GC = gas chromatography.
IC = ion chromatography.

MB = MBTH procedure.
SP = spectrophotometric procedure.
CEA = CEA instruments Model 555.

[c] TWA = time-weighted average.

[d] Average.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 Inhalation

6.1.1.1 Animal data

Eight male F-344 rats were exposed to 17.3 mg formaldehyde/m^3 (14.4 ppm) by nose only inhalation for 2 h, and the blood was collected immediately after exposure. Formaldehyde concentrations in the blood were determined by gas chromatography/mass spectrometry. The blood of 8 unexposed rats was collected and analysed in the same manner. Measured formaldehyde concentrations (mg/kg blood) were: exposed, 2.25 ± 0.07; controls, 2.24 ± 0.07 (mean ± SE) (Heck et al., 1985).

Under normal conditions, absorption is expected to occur in the upper respiratory tract (nasal passages in obligate nose-breathers; trachea, bronchi in oral breathers) where first contact occurs (Heck et al., 1983).

Absorption through the upper respiratory tract was estimated to be 100% at all respiratory rates tested. Detailed studies on the distribution of ^{14}C-formaldehyde in the rat nasal cavity have confirmed that it is absorbed primarily in the upper respiratory system. Following a 6-h exposure by inhalation, the amount of ^{14}C-formaldehyde absorbed appeared to be approximately proportional to the airborne concentration. The amount retained did not appear to vary following pre-exposure (Heck et al., 1982).

Chang et al. (1983) reported studies on the effects of inhaled formaldehyde vapour on respiratory minute volumes in mice and rats. The results showed that both rats and mice responded to formaldehyde inhalation by a reduction in their respiratory rates and minute volumes. However, mice responded to lower formaldehyde concentrations than rats. For example, respiratory rates were reduced by 50% at 7.2 mg/m^3 (6 ppm) in mice and 18 mg/m^3 (15 ppm) in rats. Rats developed some tolerance to formaldehyde during exposure. Both rats and mice pretreated with 18 mg formaldehyde/m^3 (15 ppm) were slightly more sensitive to respiratory-rate depression, but pretreated rats compensated for the decrease in respiratory rate by an increase in tidal volume. Thus, following pretreatment, the difference in sensitivity between the two species became more marked. As a result, mice were able to minimize the inhalation of formaldehyde more efficiently than rats, so that, at 18 mg/m^3 (15 ppm), the nasal mucosa in mice was exposed to approximately one-half of the dose of formaldehyde to which the rats were exposed. This species difference contributes to the differences in respiratory tract toxicity from inhaled formaldehyde.

The respiratory retention of inhaled formaldehyde (0.15-0.35 µg/ml) was studied in 4 sedated dogs by enforced ventilation (Egle, 1972). The percentage uptake was calculated by determining the amount inhaled by means of a respirometer and the amount recovered after exhaling into a collection bag (Method: MBTH, Hauser & Cummins, 1964). Absorption was determined to be near 100%, even when the ventilation rate of the dogs was increased to 20 litre/min.

6.1.1.2 Human Data

In human volunteers exposed to 2.3 mg formaldehyde/m^3 (1.9 ppm) for 40 min, there was no significant difference between pre- and post-exposure formaldehyde levels in the blood (2.77 ± 0.28 µg and 2.61 ± 0.14 µg/100 ml, respectively). Individual human subjects differed in terms of their blood-formaldehyde levels and, in some subjects, there were significant differences between formaldehyde concentrations in the blood before and after exposure suggesting that blood-formaldehyde concentrations may vary with time (Heck et al., 1985).

In an earlier study, Einbrodt et al. (1976) measured the formate levels in blood and urine following formaldehyde inhalation. They concluded that the determination of formic acid is appropriate for estimating previous formaldehyde exposure. This could not be confirmed using modern analytical methods (Triebig et al., 1980, 1986; Bernstein et al., 1984). It has been demonstrated that biological monitoring of formaldehyde exposure is not a feasible technique for exposure levels of less than 0.6 mg/m^3 (0.5 ppm) (Gottschling et al., 1984).

6.1.2 Dermal

In in vitro experiments, Usdin & Arnold (1979) studied the transfer of ^{14}C-formaldehyde into guinea-pig skin. Aqueous ^{14}C-formaldehyde (0.20 µg) was applied in diffusion cells (area, 2 cm^2), and some were occluded to avoid uncontrolled evaporation of formaldehyde.

Under both occluded and non-occluded conditions, ^{14}C was found on and in the dehaired skin (up to 0.8% of the initial dose), and small amounts (0.4% of the initial dose) were excreted in the urine. However, the labelled material found was not identified, and it is not known whether or not it was formaldehyde.

In another in vitro experiment, the permeability of human skin to formaldehyde was examined using excised skin in a flow-through diffusion cell. The rate of resorption was determined by measuring the amount of substance found in the receptor fluid beneath the skin at steady-state. The rates of resorption were: formaldehyde from a concentrated solution of formalin, 319 µg/cm^2 per h, formaldehyde from a solution of 10% formalin in phosphate buffer, 16.7 µg/cm^2 per h (Loden, 1986).

An ointment containing 0.1% of ^{14}C-formaldehyde was applied to the shaved backs of rats by Bartnik et al. (1985). Three to 5% of the ^{14}C-formaldehyde was found to have been absorbed within 48 h.

^{14}C-formaldehyde or dimethyloldihydroxyethyleneurea (DMDHEU) were incorporated into cotton. Patches were applied to the shaved backs of rabbits for a period of 48 h; 0.09-2.61% of the total ^{14}C contained in the patches was found in the skin. Other tissues and organs showed only low levels of radioactivity (0.001-0.005% of the total ^{14}C (Robbins et al., 1984).

Twenty-four hours after dermal application of 0.4-0.9 µg ^{14}C-formaldehyde/cm^2 in 5 male monkeys, most of the dose had been lost, mainly by evaporation from the skin (52%) or was bound (34%) to the surface layers of the skin at the application site. Percutaneous penetration was very low, calculated to be, at the most, 0.5% of the applied dose. The total body burden of a necropsied monkey, 24 h after dermal dosing, was 0.2% of the dose, confirming that aqueous formaldehyde does not penetrate the skin to any appreciable degree, even when applied directly to it (Jeffcoat, 1984).

6.1.3 Oral

Following oral exposure (gavage) of 5 anaesthetized dogs to formaldehyde (70 mg/kg), formate levels in the blood increased rapidly. However, fifteen minutes after treatment, all the dogs vomited making quantitative determinations impossible (Malorny et al., 1965).

6.2 Distribution

The normal values of blood-formaldehyde have been determined in both rats and human beings. In rats, the analyses were performed by gas chromatography/mass spectrometry using a stable isotope dilution technique (Heck et al., 1982); values of 2.24 ± 0.07 mg/kg (mean ± SE) were found.

The mean formaldehyde concentration in the blood of 6 human volunteers (4 males, 2 females) was 2.61 ± 0.14 mg/kg (mean ± SE) (Heck & Casanova-Schmitz, 1984) (see section 6.1.1.2).

Malorny et al. (1965) intravenously infused 0.2 mol formaldehyde into dogs and cats; McMartin et al. (1977) performed similar infusions in cynomolgus monkeys. There was no accumulation of formaldehyde in the blood, because of its rapid conversion to formate.

The disposition of radioactive formaldehyde was studied in A/J mice to determine its elimination and to assess its accumulation in tissues. Mice were dosed ip with $^{14}CH_2O$ at 6 mg/kg or 100 mg/kg body weight. Most of the dose (70-75%) was excreted as $^{14}CO_2$ within 4 h, but an additional 10% of the dose was eliminated as $^{14}CO_2$ in 24 h. The rate of $^{14}CO_2$ excretion in mice given $^{14}CH_2O$ was slower than the rate of $^{14}CO_2$ excretion in mice given an equivalent dose (100 mg/kg) of formate (HCOOH), the obligatory intermediate in the oxidation of formaldehyde to carbon dioxide. These results suggest that formaldehyde might accumulate in tissues. To assess this possibility, whole-body levels of $^{14}CH_2O$ were determined by the dimedone precipitation method following a dose of 100 mg/kg. The elimination half-time of formaldehyde was calculated to be 100 min, with a rate constant of 0.42/h. However, several rate constants were observed, 80% of the dose being recovered as formate at 30 min. At 2 h, the level of $^{14}CH_2O$ in the plasma was 1.07 ± 0.25 mg/litre, and the liver level was 1.7 ± 0.87 mg/kg. Levels of $^{14}CH_2O$ in other tissues were similar to that in the liver. This level of $^{14}CH_2O$ is at least 50% lower than the endogenous level of formaldehyde that has been reported. These results suggest that there is more than a single formaldehyde pool in mice but that, nevertheless, it does not accumulate in tissues at levels that are significant relative to the endogenous tissue level (Billings et al., 1984).

Whole-body autoradiography of mice, sacrificed 5 min after an iv injection of ^{14}C-formaldehyde, showed localization of radioactivity, primarily in the liver and, to a lesser extent, in the kidneys. Following a survival time of 30 min or more, radioactivity appeared in the tissues with a high cell turnover (blood-forming organs, lymphoid system, gastrointestinal mucosa) and in those with a high rate of protein synthesis (exocrine pancreas, salivary glands) (Johansson & Tjalve, 1978).

Following a 6-h inhalation exposure of rats to up to 18 mg/m^3 (15 ppm) ^{14}C-formaldehyde, radioactivity was extensively distributed in other tissues, the highest concentrations occurring in the oesoph-

agus, followed by the kidney, liver, intestine, and lung, indicating that absorbed ^{14}C-formaldehyde and its metabolites were rapidly removed by the mucosal blood supply. Studies on distribution and kinetics indicated that inhaled formaldehyde is extensively metabolized and incorporated (Heck et al., 1982).

DNA, RNA, protein, and lipid fractions of liver and spleen tissues of rats showed significantly elevated levels of ^{14}C incorporation after a single ip injection of 72 mg ^{14}C-formaldehyde (14.7 µCi/kg) (Upreti et al., 1987).

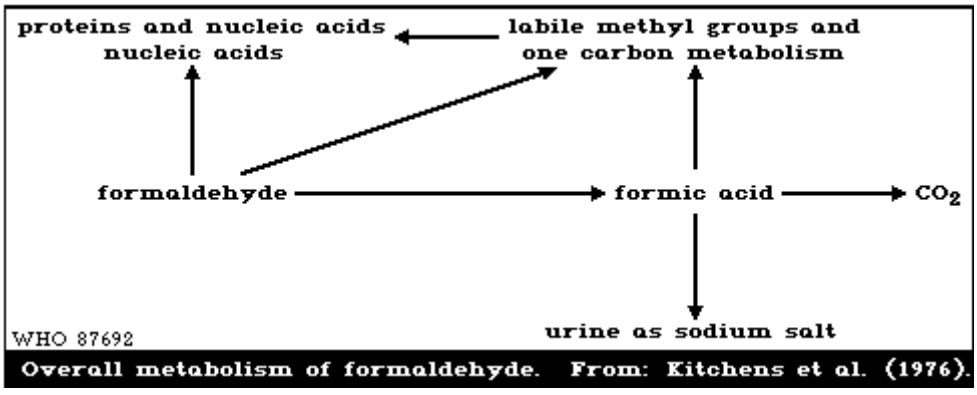
The retention of formaldehyde gas in the nasal passages of anaesthetized male F-344 rats exposed in a nose-only system to ^{14}C-formaldehyde at 2.4-60 mg/m^3 for 30 min was studied by Patterson et al. (1986). More than 93% was retained, regardless of airborne concentrations.

In order to localize absorption and distribution within the nasal cavity, rats and mice, not previously exposed or pretreated, were exposed to 18.0 mg ^{14}C-formaldehyde/m^3 (15 ppm) for 6 h and prepared for whole-body autoradiography. Formaldehyde-associated ^{14}C was heavily deposited in the anterior nasal cavity in both rats and mice. The amount of radioactivity was well correlated with the distribution of lesions in exposed animals. However, the radioactivity may represent metabolically incorporated material rather than covalently bound formaldehyde. No differences in the distribution of formaldehyde were observed between rats and mice (Swenberg et al., 1983).

6.3 Metabolic Transformation

The overall metabolism of formaldehyde is summarized in Fig. 3.

The oxidation into formic acid and carbon dioxide, the reaction with glutathione, and the covalent linkage with proteins and nucleic acids, which are partly reversible, are of importance. The covalent linkage to formaldehyde cannot be directly determined, since radioactive formaldehyde is also incorporated into the DNA via the one-carbon metabolism.



Overall metabolism of formaldehyde. From: Kitchens et al. (1976).

In studies on several species, including human beings, formaldehyde underwent rapid biotransformation, immediately after resorption, and, therefore, could not be traced in tissue (Simon, 1914; Malorny et al., 1965; Rietbrock, 1965; Einbrodt et al., 1976; Delbrück et al., 1982). Heck & Casanova-Schmitz (1984) showed that blood-formaldehyde concentrations did not rise in human volunteers even immediately after inhalation exposure.

Kitchens et al. (1976) summarized the chemical reactions in biological systems as: (a) hydration in the presence of water; (b) reactions with the active hydrogen of ammonia, amines, or amides, resulting

in the formation of stable methylene bridges; such reactions are important, because of the ubiquity of nitrogen compounds; and (c) reactions with active hydrogen (thiols, nitroalkanes, hydrogen cyanide, phenol).

Formaldehyde may be formed endogenously (Hutson, 1970) after contact with xenobiotics; 18 chemicals have been shown to be metabolized by the nasal microsomes of rats to produce formaldehyde (Dahl & Hadley, 1983). Formaldehyde is a normal metabolite in mammalian systems. It is rapidly metabolized to formate (Malorny et al., 1965), which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide. Formaldehyde also reacts with proteins (French & Edsall, 1945) and nucleic acids (Haselkorn & Doty, 1961; Lewin, 1966; Collins & Guild, 1968; Feldman, 1973; Chaw et al., 1980); it reacts with single-strand DNA, but not with double-stranded DNA. This link is reversible. Only formaldehyde cross-links of DNA and protein are stable (Brutlag et al., 1969) (section 8.5). The biological reactions and metabolism of formaldehyde are shown in Fig. 4.

The oxidation of absorbed formaldehyde to formic acid is catalyzed by several enzymes (Strittmatter & Ball, 1955). The most important enzyme is the NAD-dependent formaldehyde dehydrogenase, which requires reduced glutathione (GSH) as a cofactor. Thus, exogenous formaldehyde becomes a source for the so-called one-carbon pool in intermediary metabolism. Sources of formate are presented in Fig. 5.

There are at least 7 enzymes that catalyze the oxidation of formaldehyde in animal tissues, namely aldehyde dehydrogenase, xanthinoxidase, catalase, peroxidase, glycerinaldehyde-3-phosphate dehydrogenase,

aldehyde oxidase, and a specific DPN-dependent formaldehyde dehydrogenase (Cooper & Kini, 1962).

6.4 Elimination and Excretion

As discussed in section 6.3, absorbed formaldehyde is metabolized rapidly to formate or enters the one-carbon pool to be incorporated into other molecules. Besides this, there are two pathways of final elimination via exhalation or renal elimination (Fig. 3). Du Vigneaud et al. (1950) administered ^{14}C-formaldehyde subcutaneously to rats and found 81% of the radioactivity as carbon dioxide; a small amount was found in choline. Neely (1964) administered formaldehyde intraperitoneally to rats; 82% of the radiolabel was recovered as carbon dioxide and 13-14% as urinary methionine, serine, and a cysteine adduct.

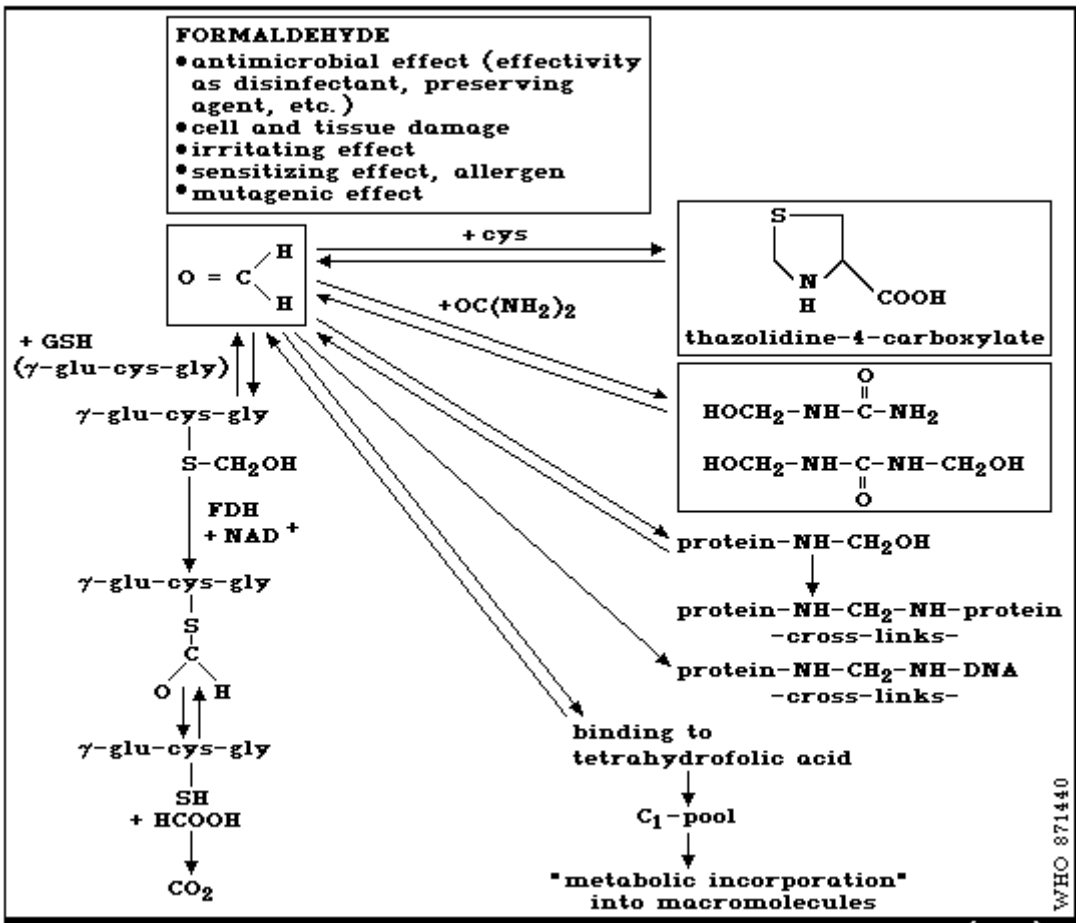
Even after high formaldehyde uptake, the elimination of formate via the kidneys of rats is virtually negligible (Delbrück et al., 1982). Robbins et al. (1984) injected ^{14}C-formaldehyde (100 µCi in a volume of 1 ml) in rabbits. Four hours after administration, 28.5% of the total dose of radioactivity was expired and 37%, after 48 h. By 48 h, 4.1% of the radioactivity had been excreted in the urine; significant levels or radioactivity were detected in the liver (2.4%), kidney (0.6%), and blood (2.2%).

6.5 Retention and Turnover

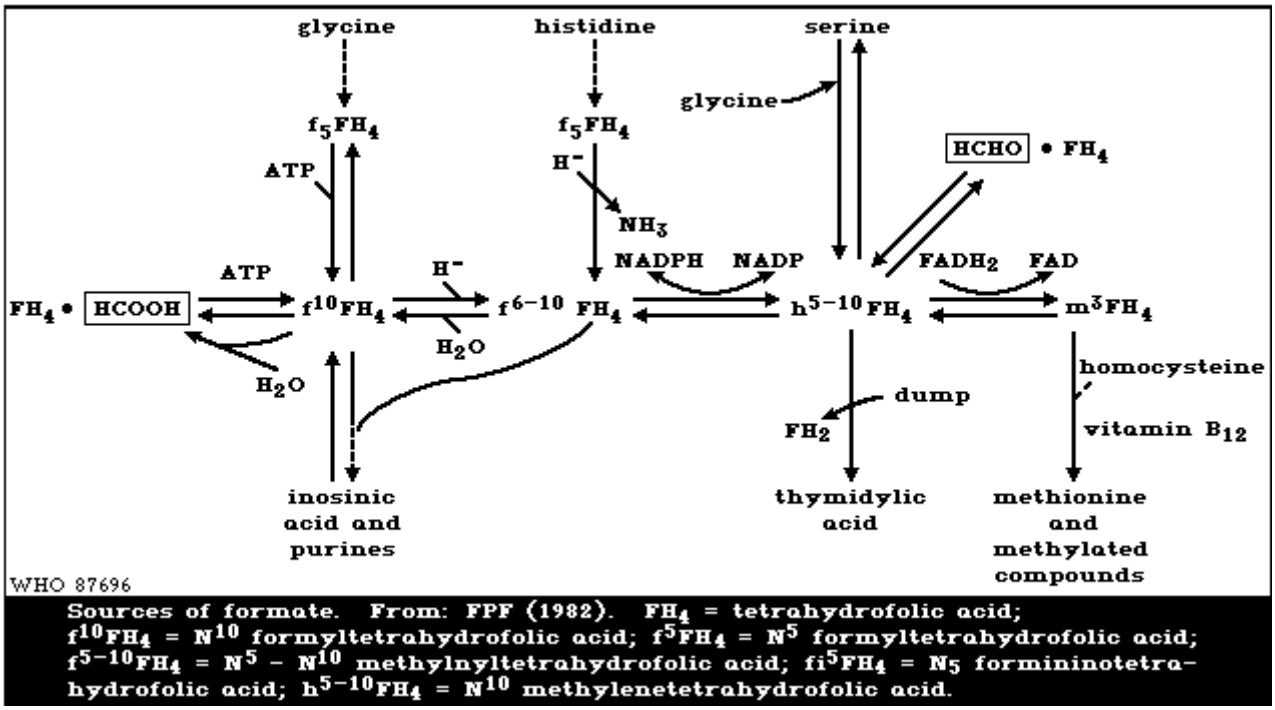
Elimination of formate is slower than its formation from absorbed formaldehyde and depends on the species. Stratemann et al. (1968) found a relationship between folate level shown in two biological test systems and the half-life of formic acid in the plasma of some mammals (Table 23).

Malorny et al. (1965) infused 0.2 mol formaldehyde intravenously

into dogs; the plasma half-life for formate ranged between 80 and 90 min, and formaldehyde could not be detected. In similar studies on cynomolgus monkeys, by McMartin et al. (1979), infusing intravenously 1 mmol/kg over a 3-4 min period the blood half-life of formaldehyde was estimated to be 1.5 min. Rietbrock (1969) administered 1.17 mmol formaldehyde/kg iv to rats, guinea-pigs, rabbits, and cats, and found the plasma half-life to be 1 min. The half-life of formate in human beings given 50-60 mg Na-formate/kg, body weight orally, was 45 min (Malorny 1969).



Biological reactions and metabolism of formaldehyde. From: Bolt (1987).



Sources of formate. From: FPF (1982). FH_4 = tetrahydrofolic acid; $f^{10}FH_4$ = N^{10} formyltetrahydrofolic acid; f^5FH_4 = N^5 formyltetrahydrofolic acid; $f^{5-10}FH_4$ = N^5 - N^{10} methylnyltetrahydrofolic acid; fi^5FH_4 = N_5 formininotetrahydrofolic acid; $h^{5-10}FH_4$ = N^{10} methylenetetrahydrofolic acid.

Table 23. Relationship between folate level and the half-life of formic acid in plasma[a]

Species	Number of analyses	Folate activity (ng/ml) *L. casei*	Folate activity (ng/ml) *Strept. faec.*	Formate half-life (min)
Man	11	15.5 ± 2.2	6.6 ± 0.7	55
Dog	37	15.5 ± 1.7	6.1 ± 0.9	77
Rabbit	17	49.2 ± 6.9	15.2 ± 1.4	32
Rat	21	126 ± 16.6	37.8 ± 8.9	12

[a] From: Stratemann et al. (1968).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Microorganisms

Formaldehyde is used as a disinfectant to kill viruses, bacteria, fungi, and parasites and has found wide use as a fumigant (section 3.2.2).

It produces mutagenic effects in prokaryotic and lower eukaryotic test systems (Table 31, and section 8.6).

In a population of *Aerobacter aerogenes*, treatment with 50 µg formaldehyde/ml of medium produced a reversible change in the base ratio of non-ribosomal RNA and induced enzymes capable of metabolizing formaldehyde at an increased rate (Neely, 1966).

Approximately 20-40% of the total nitrogen in most surface soils is in the form of amino acids. Because of the importance of amino acids as a nitrogen source for plant and microbial growth, Frankenberger & Johanson (1982) studied the enzyme (EC 4.3.1.3) that catalyzes the deamination of L-histidine in soils; treatment with formaldehyde markedly inhibited its activity. Negative effects on the biological properties of the soil owing to increased doses of urea-formaldehyde fertilizers have been reported by Rakhmatulina et al. (1984).

Berestetskii et al. (1981) found that formaldehyde was one of the volatile compounds formed in the early stages of plant residue decomposition in the soil. Kanamura et al. (1982) isolated a microorganism (genus *Hyphomicrobium*) from the soil that can use formaldehyde as the only source of carbon. Furthermore, formaldehyde has a significant role in the complex batch growth behaviour of a methanol-utilizing bacterium (*Methylomonas*) (Agrawal & Lim, 1984).

The bacterial content of the soil near industrial enterprises polluted with formaldehyde was 28-40 million bacteria/kg polluted soil; the level in control areas was 900 million bacteria/kg soil. There is no information on other pollutants or concentrations (Zhuravliova, 1969). Species of *Pseudomonas* were able to assimilate formaldehyde and formate (Grabinska-Loniewska, 1974). Hingst et al. (1985) studied the microorganism contents of sewage samples; species of *Pseudomonas* survived a 30-min exposure to formaldehyde at 5 g/kg (admixture to sewage samples).

Exposure to 2.4 mg formaldehyde/m^3 for 24 h killed all spores from pure cultures of various species of *Aspergillus* , *Scopulariopsis* , and *Penicillium crustosum* (Dennis & Gaunt, 1974).

The phytopathogenic fungi *Fusarium oxysporum* , *lycopersici* , and *Rhizoctonia solani* were completely eradicated after exposure for 30 min to an aqueous solution of formaldehyde at 4-5 g/litre. When tested in tuff (a granular plant growth medium of volcanic rock origin), the effectiveness of formaldehyde was lower compared with the corresponding amounts in aqueous solutions (Sneh et al., 1983).

7.2 Aquatic Organisms

The acute toxicity of formaldehyde for various species of aquatic organisms is shown in Table 24.

Many early studies conducted to determine the toxicity of formaldehyde and safe levels for therapeutic treatment against fungal infections and ectoparasites have been reported. This type of study is difficult to evaluate with respect to environmental hazard because of very short exposure periods and the way the data are presented.

From the data shown in Table 24, it appears that formaldehyde has a relatively low toxicity for fish, 96-h LC_{50} values being higher than 10 mg/litre in all cases.

The toxic effects of formaldehyde on fresh-water trout and salmon included changes in gill function, hypochloraemia, depressed plasma-calcium and carbon dioxide, reduced blood pH, and decreased oxygen consumption (Wedemeyer, 1971). Effects in rainbow trout occurred rapidly after a 1 h exposure at 200 mg/litre, and ca. 24 h was required for recovery (Wedemeyer & Yasutake, 1974). In rainbow trout and Atlantic salmon, formalin treatment caused increased blood-haemoglobin, packed cell volume, blood-glucose levels, and plasma-protein concentrations (Nieminen et al., 1983). The toxicity of formaldehyde for rainbow trout was increased by high water temperature, soft water, and high pH levels (Bills et al., 1977).

Algae and some invertebrates seem to be more susceptible to formaldehyde. Acute toxicity occurs in green algae at formaldehyde concentrations of 0.3-0.5 mg/litre (*Scenedesmus sp.*), in several species of protozoa, at 4.5-22 mg/litre, in *Daphnia* , at 2-20 mg/litre (EC_{50}) and in *Cyprinodopris* species at 0.42 mg/litre (96-h EC_{50}). Other invertebrates differ widely in their responses to formalin (Table 25).

For amphibia, the 24-, 48-, and 72-h LC_{50} values for larva of the

frog, *Rana pipiens*, were 8.4, 8.0, and 8.0 mg formaldehyde/litre, with a 72-h LC_{100} at 11.4 mg/litre. Tadpoles of the bullfrog, *Rana catesbeiana*, were more resistant, having 24-, 48-, and 72-h LC_{50} values of 20.1, 17.9, and 17.9 mg/litre, respectively, with a 72-h LC_{100} of 30.4 mg formaldehyde/litre. In toad larvae (*Bufo sp.*) the 72-h LC_{50} and LC_{100} values were 17.1 and 19.0 mg/litre, respectively (Helms, 1964). Carmichael (1983) exposed tadpoles of *Rana berlandieri* to formalin for 24 h and found that no mortality occurred at concentrations $\leq$ 6.0 mg formaldehyde/litre, but at 9.2, 13.6, 20.4, and 30.5 mg formaldehyde/litre, mortality was 13, 35, 78, and 100%, respectively.

7.3 Terrestrial Organisms

Persson (1973) studied the influence of formalin on the eggs and larvae of the cattle parasites *Ostertagia ostertagia* and *Cooperia oncophora* in liquid cattle manure. A 1% solution destroyed the eggs and a 5% solution affected the larvae. It also had a negative effect on the germination and growth of crops fertilized with the manure.

Table 24. Acute toxicity of formaldehyde for some aquatic organisms (static bio

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre
Algae					
Scenedesmus quadricauda	-	7.5	12	-	0.3
Scenedesmus	27	7.5-7.8	12	24	0.4
Bacteria					
Escherichia coli	25	7.5-7.8	-	-	1
Pseudomonas fluorescens	25	7.5-7.8	-	-	2
Protozoa					
Chilomonas paramaecum	-	6.9	-	48	4.5
Mikroregma	27	7.5-7.8	12	24	5
Uronema parduczi	-	6.9	-	20	6.5
Entosiphon sulcatum	25	6.9	-	72	22
Water fleas					
Daphnia magna	27	7.5-7.8	12	24	2
Daphnia magna	23	7.5	12	48	2

Table 24 (contd).

Water fleas (contd).					

Daphnia magna (IRCHA)	-	8	16	24	42
Daphnia magna	20-22	7.6-7.7	16	24	52
Daphnia magna	-	-	-	24	100-1000
Fish					
Black bullhead - fingerling -	12	6.5-9.5	8	96	62.1[a]
Channel catfish - fingerling -	12	6.5	8	96	65.8[a]
Bluegill - fingerling -	12	6.5	8	96	100[a]
Lake trout - fingerling -	12	6.5	8	96	100[a]
Smallmouth bass (*M. dolomieuri*) - fingerling -	12	6.5	8	96	136[a]
Largemouth bass (*M. salmoides*) - fingerling -	12	6.5	8	96	143[a]
Atlantic salmon	12	6.5	-	96	173

Table 24 (contd).

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre
Fish (contd).					
Atlantic salmon	12	6.5	8	3	564[a]
(fingerling)	12	6.5	8	6	336[a]
	12	6.5	8	24	156[a]
	12	6.5	8	96	69.2
Green sunfish	12	-	-	96	173
Green sunfish	12	6.5	8	24	129[a]
(fingerling)	12	6.5	8	96	69.2[a]
	-	-	-	72	> 34.2
Rainbow trout (green egg)	12	6.5-9.5	46-48	96	565-1020
Rainbow trout (eyed egg)	12	6.5-9.5	-	96	198-435
Rainbow trout (sac larvae)	12	6.5-9.5	-	96	89.5-112
Rainbow trout	12	6.5-9.5	-	96	61.9-106

(fingerling)					
Rainbow trout	12	6.5	8	3	492[a]
(fingerling)	12	6.5	8	6	262[a]
	12	6.5	8	24	120[a]
	12	6.5	8	96	47.2[a]
Rainbow trout	12	-	20	96	118

Table 24 (contd).

Fish (contd).					
Rainbow trout	12	7.5	40-48	24	214-7200
Rainbow trout	12	7.5-8.2	30-245	96	440-618
Rainbow trout	-	-	-	48	59.2
	-	-	-	24	76.6
	-	-	-	48	62.2
Brown trout	-	-	-	24	120.3
	-	-	-	48	68.5
Brook trout	-	-	-	24	72.5
	-	-	-	48	58.1
Lake trout	-	-	-	24	81.4
(fingerling)	-	-	-	48	61.8
	12	6.5	8	6	241[a]
	12	6.5	8	24	56.4[a]
	12	6.5	8	96	40.0[a]
Bluegill sunfish	-	-	-	24	68.5
(fingerling)	-	-	-	48	51.8
	-	-	-	72	30.4
	12	6.5	8	3	916[a]
	12	6.5	8	6	640[a]
	12	6.5	8	24	84.4[a]
	12	6.5	8	96	40.0[a]
	-	-	-	24	53.7
	-	-	-	48	34.0
	-	-	-	96	25.2
Largemouth bass	-	-	-	72	38
(fingerling)	12	6.5	8	6	412[a]
	12	6.5	8	24	113[a]
	12	6.5	8	96	57.2[a]

Table 24 (contd).

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre
Fish (contd).					

Smallmouth bass	12	6.5	8	24	88.8[a]
(fingerling)	12	6.5	8	96	54.4[a]
Striped bass	-	-	-	24	31.8
	-	-	-	48	11.8
	-	-	-	96	6.7
Channel catfish	-	-	-	24	50.7
	-	-	-	48	35.5
	-	-	-	96	25.5[b]
(fingerling)	12	6.5	8	3	198[a]
	12	6.5	8	6	92.8[a]
	12	6.5	8	24	48.8[a]
	12	6.5	8	96	26.3[a]
Black bullhead	-	-	-	72	17.1
(fingerling)	12	6.5	8	24	69.2[a]
	12	6.5	8	96	24.8[a]
Golden shiner				72	23.6
American eel					31.1
glass stage	-	-	-	96	
black stage	-	-	-	96	83.1
yellow stage	-	-	-	96	122.1

Table 24 (contd).

Fish (contd).					
Carp	-	-	-	72	> 26.6
	-	-	-	2	74[a]
Zebrafish	-	-	-	96	41
Golden orfe	-	-	-	48	22
	-	-	-	48	32.4[b]
	-	-	-	48	15.0[b]
Harlequin fish	-	-	-	24	76
	-	-	-	48	50
Tilapia	-	-	-	72	> 38.0

[a] Flow through bioassay.
[b] Method not stated.

Table 25. Toxicity of formalin (37% formaldehyde) for selected aquatic invertebrates in soft water at 16 °C[a]

Species	LC_{50} and 95% confidence interval (µlitre

	1 h	3 h	6 h	24
Seed shrimp (ostracods)[b]	9.00	6.40	1.20	1.1
Cypridopsis sp.	6.83-11.9	4.91-8.34	0.664-2.17	0.690
Freshwater prawn[b]	-	2150	1900	1105
Palawmonetes kadiakensis	-	1948-2373	1588-2273	896
Bivalves[c]				800
Corbicula sp.	-	-	-	638
Snail[d]	3525	1340	780	710
Helisoma sp.	3201-3881	953-1883	629-967	544
Backswimmer[d]	-	-	-	4500
Notonecta sp.				3006

[a] From: Bills et al. (1977).

[b] Toxicity based on immobility.

[c] Toxicity based on ability to resist attempts to open valves and respond t

[d] Toxicity based on ability to respond to tactile stimulus.

Nematodes in peat were killed by application of 370 g formaldehyde/litre solution at 179 ml/m^3 (Lockhart, 1972).

Changes in populations of the cereal cyst nematode *Heterodera avenae* and in crop growth in a sandy loam soil were studied in 1974-78 (Kerry et al. 1982). Fungal parasites attack *H. avenae* females and eggs resulting in poor multiplication of the nematode. The number of cysts containing nematode eggs, after harvest, was not affected by formalin (380 g formaldehyde/litre) applied as a drench at 3000 litre/ha in 1977. However, fecundity doubled in treated soil, and nematode multiplication increased 18.6 times compared with 3.8 times in untreated plots. When the plots were irrigated in 1978, the numbers of cysts and fecundity increased in formalin-treated soils, resulting in a 0.3- to 14.6-fold increase due to suppression of fungal parasites.

The yellow rice borer (*Tryporyza incertulas*) (*Lepidoptera*) is one of the most serious pests of rice. To obtain sterile males, it has to be mass-reared on an artificial diet containing formaldehyde (Wang et al., 1983); the same has been reported for the pink borer (*Sesamia inferens*) (Siddiqui et al., 1983).

In ruminants, deamination of dietary proteins by rumen microorganisms is of importance, because of loss of essential nitrogen from the rumen as ammonia. Formaldehyde protects dietary-protein from microbial proteolysis in the rumen by reacting with free amino groups in the protein, forming inter- and intramolecular methylene bridges (Siddons et al., 1982). Thus, there is an increase in the efficiency of utilization of amino acids for wool (10 g formaldehyde/kg protein) and body growth in sheep and other ruminants (Faichney, 1970; Ferguson, 1970; Hemsley et al., 1973). Differences in nitrogen retention were found, but no significant differences in wool growth or live-weight gain, when sheep were fed formaldehyde-treated linseed meal and meatmeal (2.5% formalin) (Rattray & Joyce, 1970). Mills et al. (1972) showed that ^{14}C-formaldehyde bound to a sodium caseinate-oil mixture was rapidly metabolized by sheep and goat tissues and eliminated via expired air, urine, and faeces, but was not accumulated in the milk or in the carcass. To study the digestion in the small intestine of young bulls of the protein of rapeseed meal, treated or not treated with formaldehyde, Kowalczyk et al. (1982) fitted each bull with cannulae in the rumen and abomasum. Formaldehyde-treated rapeseed meal was poorly digested. The nutritional value of soybean meal that had been treated

with 3 g formaldehyde/kg was investigated by Crooker et al. (1983). Analysis of covariance revealed that the digestibility of dietary crude protein by cows fed formaldehyde-treated meal was lower than that in the controls (62.4% versus 65.4%) as was the milk-protein content. Erfle et al. (1986) fed lactating cows with formaldehyde-treated soybean meal and found that milk-protein levels were significantly decreased. After treatment with formaldehyde, lysine and tyrosine were lost from the soybean meal.

Grenet (1983) studied the utilization of grass-silage nitrogen in growing sheep and found that formic acid had a beneficial effect (decreased urinary-nitrogen loss). However, the addition of 1.5 litre formalin/tonne of green forage did not improve nitrogen-retention; higher quantities of formaldehyde tended to have an unfavourable effect, particularly with lucerne silage.

7.4 Plants

A study was carried out by Sangines et al. (1984) to examine the protective effects of formaldehyde on ensilaged whole peanut plant protein. Formaldehyde (50, 100, 150, and 200 g/litre) was added at the rate of 5 litres/tonne. A control without any formaldehyde was included. There were no significant differences in pH among treatments (5.56-5.70). The ammonia concentration dropped significantly in all treatments, a finding that suggests a protective effect against protein-nitrogen degradation to non-protein nitrogen (NH_3). Lactic acid fermentation was observed, without any difference between treated and control silage. Nevertheless, there was a reduction in the propionic acid and ethanol concentrations in all the silages. It was concluded that there was an inhibition of the fermentation process in all the silages treated, and that the addition of formaldehyde at the 5% level is a satisfactory way of protecting this type of feed.

In agriculture, urea-formaldehyde fertilizers are used to improve crops. At concentrations of up to 0.3 g/kg soddy podsolic soil, formaldehyde did not change the nitrogen and carbohydrate metabolism in barley plants (Lebedeva et al., 1985). However, increased doses of the fertilizer caused negative effects on the biological properties of the soil (Rakhmatulina et al., 1984).

Doman et al. (1961) studied the conversion of gaseous formaldehyde absorbed by leaves of kidney beans and barley plants from the atmosphere, using 14C tracing. The activity appeared first in phosphate ester fractions and later in the amino acids alanine, serine, aspartic acid and unidentified products, especially when the experiments were conducted in the dark. Zemlianukhin et al. (1972), also using 14C tracing, studied the metabolism in 12-day-old maize seedlings, of formic acid, which was oxidized to carbon dioxide or metabolized to cellular constituents.

Pollen germination has been shown to be sensitive to various air pollutants. Masaru et al. (1976) sowed lily pollen grains (*Lilium longiflorum*) on culture medium. After being exposed to formaldehyde in a fumigation chamber, for 24 h, pollen tube length was measured. A 5-h exposure to formaldehyde at 0.44 mg/m^3 (0.37 ppm) resulted in a significant reduction in pollen-tube length, whereas a 1- or 2-h exposure was innocuous. When the formaldehyde concentration was increased to 2.88 mg/m^3 (2.4 ppm), a 1-h exposure caused a decrease in tube length. The investigators observed that, with respect to pollen, the activity of formaldehyde was comparable with that of nitrogen dioxide. To test combinations of pollutants, pollen grains were exposed to sulfur dioxide at 1.79 mg/m^3 (0.69 ppm) for 30 min or to nitrogen dioxide at

0.28 mg/m^3 (0.15 ppm) for 30 or 60 min. This treatment led to slight inhibition of tube elongation. A second exposure to formaldehyde at 0.3 mg/m^3 (0.26 ppm) led to significant inhibition of pollen tube length (about 30-40% of the length of control pollen-tubes).

A sealed Plexiglas chamber with temperature and humidity control and illuminated externally with wide spectrum grow lights was used to evaluate the ability of golden pothos (*Scindapsus aureus*), nephthytis (*Syngonium podophyllum*), and the spider plant (*Chlorophytum elatum var. vittatum*) to remove formaldehyde from contaminated air at initial concentrations of 18-44 mg/m^3. Under the conditions of this study, the spider plant proved most efficient by sorbing and/or removing up to 2.27 µg formaldehyde/cm^2 leaf surface area in a 6-h exposure (Wolverton et al., 1984).

Various factors influence the response of a plant receptor to formaldehyde exposure. These include genetic factors, stage of plant development, age of tissue, climatic factors, such as temperature, relative humidity, light quality, light intensity, photoperiod, rate of air movement, and soil factors, such as moisture, aeration, and nutrients. Most studies dealing with the influence of formaldehyde exposure on plants suffer from lack of such information.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Concern about the toxicological effects of formaldehyde is related to effects resulting from single or repeated exposures including irritation, cytotoxicity, cell proliferation, and sensitization, and effects resulting from long-term exposures, particularly cancer.

The most significant properties of formaldehyde are its potential to cause irritation and, at high concentrations after long-term exposure, nasal tumours in rats and statistically not significant nasal tumours in mice.

8.1 Skin and Eye Irritation, Sensitization

Formaldehyde is known to be a primary skin and eye irritant, the local tissue reaction increasing with increased dose. However, this is based on anecdotal evidence rather than animal studies. The only report is that of Carpenter & Smyth (1946) who found formaldehyde to be an eye irritant for rabbits.

The sensitizing potential of aqueous formaldehyde was evaluated with the guinea-pig maximization test (GPMT) in two laboratories (Copenhagen and Stockholm) using different guinea-pig strains (Andersen et al., 1985). Six intradermal (0.1-30 g/litre) and 6 topical (5-200 g/litre) concentrations were used for induction, and formaldehyde at 10 and 1 g/litre was used for challenge. The incidence of contact sensitivity depended on the intradermal, but not on the topical, induction dose. Statistical analyses showed a non-linear dose-response relationship. The estimated maximal sensitization rate in Copenhagen was 80% after intradermal induction with 0.65% formaldehyde; in Stockholm, it was 84% after induction with 0.34%. The data from the two laboratories gave parallel displaced dose-response curves, suggesting that the guinea-pig strain used in Stockholm was significantly more susceptible to formaldehyde than the strain used in Copenhagen. The EC_{50} (formaldehyde concentration at which 50% of the guinea-pigs were sensitized at 72 h) at a 10 g/litre challenge concentration was 0.6 g/litre in Copenhagen and 0.24 g/litre in Stockholm.

Other studies are summarized in Table 26. The results show that aqueous formaldehyde solution is a sensitizer for the skin.

Lee et al. (1984) exposed guinea-pigs to formaldehyde at 7.2 mg/m^3 or 12 mg/m^3, for 6 or 8 h/day, on 5 consecutive days. The animals were evaluated for skin sensitivity (production of anti-formaldehyde antibody) and respiratory sensitivity (both immediate and delayed-onset) to formaldehyde, which was shown to be a skin sensitizer without causing detectable pulmonary hypersensitivity.

8.2 Single Exposures

Acute toxicity has been studied in several animal species (Table 27).

Table 26. Contact allergy predictive tests in guinea-pigs

Induction dose (%)	Challenge dose (%)	Sensitization (number positive/ number tested)	Test	Reference
30	1	2/7	open epicutaneous	Maibach (1983)
10	1	5/8		
3	1	3/8		
1	1	2/6		
0.3	1	2/6		
0.1	1	0/6		
5	5	7/20	epicutaneous maximization	Guillot & Gonnet (1985)
10	5	3/10	cumulative contact enhancement test	Tsuchiya et al. (1985)
5	5	2/10		
1	5	0/10		
0.2	5	0/10		
10	1	4/10		Tsuchiya et al. (1985)
5	1	2/10		
1	1	0/10		
0.2	1	0/10		
10	0.2	1/10		Tsuchiya et al. (1985)
5	0.2	0/10		
1	0.2	0/0		
0.2	0.2	0/0		

Table 27. Acute toxic effects of formaldehyde on laboratory animals

Species	Route	Dose (duration)	Effect/response	Reference
Rat	oral	800 mg/kg body weight	LD_{50}	Smyth et al. et al. (197
	subcutaneous	420 mg/kg body weight	LD_{50}	Skog (1950)
	intravenous	87 mg/kg body weight	LD_{50}	Langecker (1
	inhalation	984 mg/m^3 (30 min)	LC_{50}	Skog (1950)
	inhalation	578 mg/m^3 (4 h)	LC_{50}	Nagorny et a

Mouse	subcutaneous	300 mg/kg body weight	LD_{50}	Skog (1950)
	inhalation	497 mg/m^3 (4 h)	LC_{50}	Nagorny et a
Rabbit	dermal	270 mg/kg body weight	LD_{50}	Lewis & Tatk
	dermal	0.1-20%	skin irritation: mild to moderate	NRC (1981)
	eye	0.5 ml	eye irritation: grade 8 on a scale of 10	Carpenter &
Guinea-pig	oral	260 mg/kg body weight	LD_{50}	Smyth et al.
	dermal	0.1-20%	skin irritation: mild to moderate	Colburn (19
	dermal	1% (open application)	sensitization: positive	US CPSC (19
		3% (open application)	sensitization: positive	US CPSC (19
		1% (intradermal)	sensitization: positive	Colburn (19

The odour and irritant properties of formaldehyde serve as repellents. Kane & Alarie (1977) used the decrease in respiratory rate of mice as an index of irritation. At 0.6 mg formaldehyde/m^3 air, an irritant effect on the eyes, nose, and throat occurred, and tolerance to the irritant effects of formaldehyde did not develop.

Exposure to high concentrations of formaldehyde vapour (> 120 mg/m^3) caused hypersalivation, acute dyspnoea, vomiting, muscular spasms, and can finally lead to the death of test animals (Skog, 1950; Horton et al., 1963; Bitron & Aharonson, 1978).

8.3 Short-term Exposures

8.3.1 Inhalation studies

Inhalation studies are summarized in Table 28.

A range finding study was conducted in which rats and mice were exposed to atmospheres containing 4.8, 15, or 46 mg formaldehyde/m^3 (4, 12.7, or 40 ppm). Exposures were for approximately 6 h/day, 5 days/week, for 13 weeks, except for the high dose level, which was terminated after 2 weeks (Mitchell et al., 1979). Exposure of both mice and rats to concentrations of inhaled formaldehyde of 46 mg/m^3 (40 ppm) resulted in ulceration or necrosis of the nasal turbinate mucosa in a significant number of animals of each species. Both sexes of rats had a high incidence of tracheal mucosal ulceration and necrosis, whereas only a few male mice exhibited this lesion. Pulmonary congestion was prominent in both male and female rats and in male mice at the highest dose level. Female mice of both the control and high-dose group had a similar incidence of pulmonary congestion. Secondary lesions encountered in rats exposed to this dose of formaldehyde seemed to be related to bacterial septicaemia due to a damaged respiratory mucosa.

Groups of 10 male and 10 female B6C3F1 mice were exposed to 2.4, 4.8, 12, 24, or 48 mg formaldehyde vapour/m^3 (2, 4, 10, 20, or 40 ppm) for 6 h/day, 5 days/week, over 13 weeks (Maronpot et al., 1986).

Clinical abnormalities (dyspnoea, listlessness, and hunched posture), significant mortality, and body weight loss were observed in the 48 mg/m^3 groups. Pathological changes were observed in the nose, larynx, trachea, and bronchi of treated males and females, and in the uterus and ovaries of treated females. Squamous metaplasia and inflammation were present in the nasal tissues of both male and female mice in the 12-48 mg/m^3 (10, 20, 40 ppm) groups and in the larynx of both males and females in the 24 and 48 mg/m^3 (20, 40 ppm) groups. In some mice, epithelial-lined, irregular connective tissue bands spanned the tracheal lumen. Metaplasia of the bronchial epithelium was confined to the groups exposed to 48 mg/m^3. The effects on the respiratory system were more prevalent in male than in female mice. Hypoplasia of the uterus and ovaries, probably secondary to body weight loss, was confined to the 48 mg/m^3 (40 ppm) exposure group.

Table 28. Short-term formaldehyde inhalation studies

Species	Exposure	Concentration mg/m^3 (ppm)	Effect
	Nose-only inhalation		
Rat	6 h/day, 5 days/week, for 4 weeks	3.6 (3)	no adverse findi
	6 h/day, 5 days/week, for 4 weeks	19, 73, 120 (16, 61, 99)	antibody inhibit
	Inhalation		
Rat	8 h/day (continuous), 5 days/week, for 4 weeks	6, 12 (5, 10) (equivalent to 40 ppm x h or 80 ppm x h)	slightly increas ation of nasal e slight hypermeta nasal epithelium
	8.5 h/day (interrupted), 5 days/week, for 4 weeks	12, 24 (10, 20) (equivalent to 40 ppm x h or 80 ppm x h)	strongly increas ation of nasal e moderate hyperme nasal epithelium
Rat	22 h/day, for 90 days	1.9 (1.6)	no adverse findi
	22 h/day, for 45 days	5.4 (4.55)	decreased weight
	22 h/day, for 60 days	9.6 (8.07)	decreased liver eye irritation
	6 h/day, 5 days/week, for 13 weeks	4.8 (4)	no adverse effec

Table 28 (contd).

	Inhalation (contd).		

Rat	6 h/day, 5 days/week, for 13 weeks	15	(12.7)	nasal erosion
	6 h/day, 5 days/week, for 2 weeks	48	(40)	nasal ulceration
	8 h/day (continuous), 5 days/week, for 13 weeks	1.2 9.6	(equivalent to 8 ppm x h)	no adverse effec
	8.5 h/day (intervals), 5 days/week, for 13 weeks	2.4 9.6	(equivalent to 8 ppm x h)	no adverse effec
	8 h/day, 5 days/week, for 13 weeks	2.4 19.2	(equivalent to 16 ppm x h)	no adverse effec
	8.5 h/day, 5 days/week, for 13 weeks	4.8 19.2	(equivalent to 16 ppm x h)	hyper- and metap nasal respirator
	6 h/day, 5 days/week, for 13 weeks	0.36	(0.3)	transient, sligh in cell turnover nasal respirator
	6 h/day, 5 days/week, for 13 weeks	1.2	(1)	transient, sligh in cell turnover the nasal respir epithelium
	6 h/day, 5 days/week, for 13 weeks	3.6	(3)	5- to 10-fold in cell turnover ra squamous metapla nasal respirator

Table 28 (contd).

Species	Exposure	Concentration mg/m^3	(ppm)	Effect
	Inhalation (contd).			
Rat	6 h/day, 5 days/week, for 13 weeks	1.2	(1)	questionable hyp of the nasal res epithelium
	6 h/day, 5 days/week, for 13 weeks	12	(10)	squamous metapla respiratory epit
	6 h/day, 5 days/week, for 13 weeks	24	(20)	transient excita uncoordinated lo growth retardati creased level of protein; increas of several plasm squamous metapla nasal respirator tory epithelium; metaplasia of la epithelium
	6 h/day, 5 days/week,	2.4-48	(2-40)	12-48 mg/m^3: hist

	for 13 weeks			lesions in the u tory system; 48
	22 h/day, 7 days/week, for 26 weeks	1.2	(1)	no adverse findi
	22 h/day, 7 days/week, for 26 weeks	3.6	(3)	squamous metapla sion in body wei

Table 28 (contd).

	Inhalation (contd).			
Mouse	6 h/day, 5 days/week, for 13 weeks	4.8	(4)	no adverse findi
	6 h/day, 5 days/week, for 13 weeks	15	(12.7)	no adverse findi
	6 h/day, 5 days/week, for 2 weeks	48	(40)	nasal ulceration
Hamster	22 h/day, 7 days/week, for 26 weeks	1.2 and 3.6	(1 and 3)	no adverse findi
Guinea-pig	6 h/day, 5 days/week, for 8 weeks	1.2	(1)	hyperkeratosis i (reversible afte mucus flow eleva squamous metapla piratory epithel
Monkey (cynomolgus)	22 h/day, 7 days/week, for 26 weeks	1.2	(1)	metaplasia in na ates in 1/6 expo
	22 h/day, 7 days/week, for 26 weeks	3.6	(3)	metaplasia in na ates in 6/6 expo
Monkey (rhesus)	6 h/day, 5 days/week, for 1 or 6 weeks	7.2	(6)	mild degeneratio squamous metapla passages, trache in 6/6 exposed. nasal surface ar was greater in 6 group

Groups of 6 male cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Syrian golden hamsters were exposed to 0, 0.24, 1.2, or 3.7 mg/m^3 (0, 0.2, 1, or 3 ppm) formaldehyde vapour (98.8% pure) for 22 h/day, 7 days/week, over 26 weeks. Squamous metaplasia of the nasal turbinates was evident in 6/6 monkeys exposed to 3.7 mg/m^3 (3 ppm) and in 1/6 exposed to 1.2 mg/m^3 (1 ppm). Squamous metaplasia and basal cell hyperplasia of the respiratory epithelium of the nasal cavity were significantly increased in rats exposed to 3.7 mg/m^3 (3 ppm). The same group exhibited marked depressions in body weight gain. No exposure-related effects were demonstrated in hamsters (Rusch et al., 1983).

Two groups of 3 adult (aged 4-5 years) male rhesus monkeys were exposed to 7.2 mg/m^3 (6 ppm) formaldehyde in inhalation chambers. One group was exposed 6 h/day for 5 days; the other group was exposed for 6 h/day, 5 days/week for 6 weeks. A control group of 3 monkeys was sham

exposed to filtered room air for 6 h/day, 5 days/week for 6 weeks. Both exposed groups showed mild degeneration and early squamous metaplasia in parts of the transitional and respiratory epithelium of the nasal passages and respiratory epithelium of the trachea and major bronchi. The nasal surface area involved was significantly increased in the 6 week exposure group. Cell proliferation rates were significantly increased and remained elevated 6 weeks after the termination of exposure (Monticello et al., 1989).

Fifteen-week-old male Hartley guinea-pigs were exposed for 6 h/day, 5 days/week, for 8 weeks, to 0.12, 1.2, or 12 mg formaldehyde/m^3 (Marshall et al., 1983). Animals were sacrificed at 1 and 30 days after the end of exposure, and tissue samples were taken to study the histology and lung biochemistry. Body weight, nasal mucous clearance velocity, and airway sensitivity to inhaled histamine were measured after 2, 4, and 8 weeks of exposure and 2 and 4 weeks after completion of exposure. Nasal mucous clearance velocity increased by 25% after 4 weeks of exposure to 12 mg/m^3, but returned to control values 2 weeks after the end of exposure. Dose-related histological findings included hyperkeratosis and squamous metaplasia of the respiratory epithelium occurring in foci in the anterior half of the nasal cavities. Thirty days after exposure, squamous metaplasia had resolved; however, slight hyperkeratosis of respiratory epithelium was still present in guinea-pigs exposed to 12 mg formaldehyde/m^3. Altered airway sensitization to inhaled histamine was not noted in exposed guinea-pigs. No differences were observed in body weights and lung biochemical end-points between control and exposed guinea-pigs.

The acute effects of inhaled formaldehyde on the nasal mucociliary apparatus of male F-344 rats were studied by Morgan et al. (1986) using whole-body exposures. Formaldehyde exposures ranged from a single 6-h period up to repeated 6-h exposures daily for 3 weeks, with exposure concentrations of 18, 7.2, 2.4, or 0.6 mg/m^3. Within 1 h of the last exposure, the rats were killed and the nasal passages examined for effects on nasal mucociliary function. Exposure to 18 mg formaldehyde/m^3 induced inhibition of mucociliary function in specific regions of the nose, and mucostasis was generally more extensive than ciliastasis. These effects, which were initially confined to the anterior regions of the nose, became progressively more extensive

for up to 2 weeks of exposure with only very slight progression during the third week. Inhibition of mucociliary function was much less severe with exposure to 7.2 mg/m^3, minimal at 2.4 mg/m^3, and not detected in rats following exposure to 0.6 mg/m^3.

Woutersen et al. (1987) exposed male and female rats to 0, 1.2, 12, or 24 mg formaldehyde/m^3 for 6 h/day, 5 days/week, over 13 weeks; definite adverse effects were observed at 12 and 24 mg/m^3, but the study was inconclusive with respect to whether 1.2 mg/m^3 was a cytotoxic effect level for the nasal epithelium.

The possibility of the hepatotoxicity of formaldehyde for rats was investigated by Woutersen et al. (1987). It was concluded that formaldehyde was not hepatotoxic at concentrations as high as 12 mg/m^3 (10 ppm). At 24 mg/m^3 (20 ppm), there was a slight increase in the levels of certain plasma-enzymes suggesting a hepatotoxic effect, however, histopathological examinations did not reveal any liver damage, and there were no changes in liver weight or liver-glutathione concentrations. The slight increase in plasma-enzyme levels may have been caused by growth retardation (Woutersen et al., 1987).

Zwart et al. (1987) exposed rats (50 per sex and group) to 0, 0.36,

1.2, or 3.6 mg formaldehyde/m^3 for 6 h/day, 5 days/week, over 13 weeks. Definite adverse effects on the nasal epithelium were observed at 3.6 mg/m^3. The authors concluded there was some indication that formaldehyde at levels of 0.36 and 1.2 mg/m^3 challenged the nasal mucociliary and regenerative defence systems at the beginning, but not at the end, of the study.

In a 13-week inhalation study, male rats were exposed for 5 days per week to 0, 1.2, or 2.4 mg formaldehyde/m^3, continuously (8 h per day), or to 2.4 or 4.8 mg formaldehyde/m^3 intermittently (8 successive 1-h periods a day, each consisting of 30 min of exposure and 30 min of non-exposure) (Wilmer et al., 1986). The only adverse effect (hyperplasia of the nasal respiratory epithelium) was found in animals exposed to 4.8 mg/m^3. This study showed that the concentration is more important than the total dose for the cytotoxic effects of formaldehyde on the nose.

A 4-week inhalation study on male rats was carried out by Wilmer et al. (1987) in which the animals were exposed for 5 days/week to 0, 6, or 12 mg formaldehyde/m^3, continuously for 8 h/day, or 12 or 24 mg formaldehyde/m^3 intermittently (8 successive 1-h periods per day, each consisting of 30 min of exposure and 30 min of non-exposure). This study also showed that the concentration rather than the total dose of formaldehyde determined the severity of the cytotoxic effects on the nasal epithelium.

Fifteen male rats were exposed to vapourizing 10% formalin solution (3.7% formaldehyde) by inhalation for 2-22 weeks; their tracheas were removed and examined microscopically after various periods of exposure; a wide spectrum of morphological changes in the epithelium and underlying connective tissues was observed. In addition to chronic inflammation, metaplastic changes, including squamous metaplasia and dysplasia of the epithelium, were induced by formaldehyde (Al-Abbas et al., 1986).

The immunotoxicity of formaldehyde was studied in mice by Dean et al. (1984). Female B6C3F1 mice underwent inhalation exposure to 18 mg/m^3 for 6 h/day, 5 days/week, over 3 weeks. Most immune functions involving T and B lymphocytes and macrophages were not impaired and there was an enhanced resistance to *Listeria monocytogenes*. In a later study by the same group (Adams et al., 1987), exposure of mice to 18 mg formaldehyde/m^3 (15 ppm) for 6 h daily over 3 weeks caused an increased (approximately two-fold) competence for release of hydrogen peroxide (H_2O_2) from the peritoneal macrophages. Enhanced function of the macrophages may be responsible for the enhanced lost resistance reported by Dean et al. (1984).

8.3.2 Oral studies

In a 4-week, drinking-water study on rats, using formaldehyde levels of 0, 5, 25, or 125 mg/kg body weight per day, adverse effects attributable to formaldehyde were encountered in the high-dose group only, and comprised decreased plasma-protein levels and hyperkeratosis and gastritis in the fore- and glandular stomach, respectively (Til et al., 1987).

Administration of formaldehyde in the drinking-water to Sprague-Dawley rats at a dose of 150 mg/kg body weight per day and in the diet to beagle dogs at a dose of 100 mg/kg body weight per day for a period of 13 weeks was found to result in a slightly depressed growth rate; no effects on the stomach were observed (Johannsen et al., 1986).

During an 18-day study, rats were fed a diet of soybean meal

treated with formaldehyde (Schmidt et al., 1973). The use of more than 2 ml formalin (40%)/100 g soybean protein reduced growth, and also nitrogen retention in nitrogen balance studies.

8.4 Long-Term Exposure and Carcinogenicity

8.4.1 Inhalation

Exposure of B6C3F1 mice and Fischer 344 rats to 2.4, 7.2, or 18 mg formaldehyde vapour/m^3 (2, 6, or 15 ppm) for up to 24 months resulted in chronic toxicity. The survival of mice did not appear to be related to the concentration of formaldehyde to which they were exposed; however, exposure to a level of 17.6 mg/m^3 resulted in reduced body weight. Several lesions were seen in the nasal cavities of mice exposed to concentrations of 7.2 or 18 mg/m^3 (6 or 15 ppm), including dysplasia and squamous metaplasia of the respiratory epithelium, purulent or seropurulent rhinitis, and atrophy of the olfactory epithelium. Three months after exposure was discontinued (27 months), the nasal lesions had regressed. In the rats, several lesions occurred in the nasal cavities at the low concentration of 2.4 mg/m^3 (2 ppm); these increased in extent and severity with increasing concentrations. The lesions included dysplasia and squamous metaplasia of the respiratory epithelium, goblet-cell hyperplasia, and purulent or seropurulent rhinitis. Rats exposed to 18 mg/m^3 (15 ppm) also exhibited goblet-cell metaplasia of the olfactory epithelium, respiratory epithelial hyperplasia, squamous epithelial hyperplasia, squamous atypia, and papillary hyperplasia; dysplasia and squamous metaplasia of the tracheal epithelium were also detected. The incidence of squamous metaplasia in rats exposed to 2.4 or 6.7 mg/m^3 (2 or 5.6 ppm) regressed within 3 months of the termination of exposure (Swenberg et al. 1980; Kerns et al., 1983) (see Table 30). Male Syrian golden hamsters exposed to diethylnitrosamine by sc injection (0.5 mg, once per week, for 10 weeks) and to formaldehyde (36 mg/m^3 via inhalation, 48 h/week prior to each injection, and subsequently continued for the life-time of each animal) developed tracheal carcinomas (Dalbey, 1982). Male Syrian golden hamsters exposed to up to 12 mg formaldehyde/m^3 (10 ppm) for 5 h/day and 5 days per week for their life-time did not show any tumours but 5% showed hyperplastic and metaplastic areas on the nasal epithelium. The author concluded that formaldehyde may act as a cofactor in carcinogenesis in the trachea.

Following exposure of Sprague-Dawley rats to formaldehyde 17 mg/m^3 (14 ppm) alone, or in combination (pre-mixed or non-pre-mixed) with HCl 14 mg/m^3 (10 ppm), for 6 h/day, 5 days/week, for life (Table 29), rhinitis, hyperplasia, and squamous metaplasia in laryngeal-tracheal segments and nasal mucosa were observed (Albert et al., 1982; Sellakumar et al., 1985).

Albert et al. (1982) exposed rats to a mixture of gaseous formaldehyde (17.9 mg/m^3) and hydrogen chloride (16.9 mg/m^3) for 6 h/day, 5 days/week, for life. In the exposure chamber, a bis-chloromethyl-ether (BCME) concentration of 0.5-2 µg/m^3, due to the chemical reaction of formaldehyde and hydrogen chloride, was estimated. Sellakumar et al. (1985) calculated levels of BCME under similar conditions of 0.5-2.05 µg/m^3 (0.1-0.4 ppb). Nasal squamous cell carcinomas were found in 25/99 rats and papillomas in 3/99 rats; squamous metaplasia of the nasal epithelium was found in 64/99 of the exposed rats.

A subsequent report (Sellakumar et al., 1985) of studies on combined exposure to hydrogen chloride and formaldehyde showed that the

carcinogenic response to formaldehyde does not result from the BCME formed by the mixture of the gases.

Tobe et al. (1985) exposed male F-344 rats for 6 h/day, 5 days/week, over 28 months, to 0.36, 2.4, or 17 mg formaldehyde/m^3. Rhinitis accompanied by desquamation was found in all groups. In all formaldehyde-exposed groups, nasal epithelial hyperplasia and squamous metaplasia with hyperplasia were seen. In the 17 mg/m^3 group, squamous cell carcinoma was recognized in 14 rats and papilloma in 5 of 32 rats exposed.

Table 29. Summary of carcinogenicity studies of formaldehyde on animals

Species/ Strain	Number of animals (sex)	Route of exposure	Dosage	Findings
Mouse	42-60	inhalation	0, 50, 100, or 200 mg/m^3; three l-h periods/week, for 35 weeks	no pulmonary tur 0-100 mg/m^3
Mouse	36	inhalation	50 mg/m^3 for 35 weeks + 150 mg/m^3 for 29 weeks; three l-h periods/week in addition	no pulmonary tur
Mouse	26	inhalation	100 mg/m^3; three 1-h periods/week for 35 weeks followed by a coal-tar aerosol for 35 weeks	formaldehyde dic the pulmonary c of coal-tar
Mouse: B6C3F1	119-121 (male) 119-121 (female)	inhalation	0, 2.4, 6.72, or 17.16 mg/m^3; 6 h/day, 5 days/week, for up to 24 months; 6-month follow-up	squamous cell ca the nasal cavit (at high exposu
Mouse: CTM, SWR +C3Hf	29-99 (male) 27-100 (female)	ingestion	0 or 0.5 HMT in drinking-water for 60 weeks or 5% for 30 weeks (CTM only); follow-up for 110-130 weeks[a]	no increased tu incidence
Mouse: CTM	39 (male) 44 (female)	subcutaneous	5 g/kg on alternate days, for 110-130 weeks[a]	no increased tu incidence
Mouse	60	Injection (route not described)	µl "formol oil" 50 times to the cervix uteri (dose not defined)	no tumours[d]

Table 29 (contd).

Species/ Strain	Number of animals (sex)	Route of exposure	Dosage	Findings
Mouse: SENCAR	30 (female)	topical, back skin	3.7% formaldehyde in acetone once a week, 48 weeks	formaldehyde is not a complete or an initiator (preliminary fi

Mouse: CD-1	30 (female)	subcutaneous	0.1-1.0 mg, 3 times a week for 180 days	no incidence of promotor activi (preliminary fi
Mouse	16 (male) 16 (female)	topical, back skin	200 µg 1% or 10% sol., twice a week, 60 weeks	no tumours
Rat: Sprague Dawley	100 (male)	inhalation	17 mg/m^3 (14.2 ppm); 382 exposures over a 588-day period; 6 h/day, 5 days/week	10 squamous cell of the nasal ca (significantwit to controls (pr findings only)
Rat: Sprague Dawley	99	inhalation	16.80 mg/m^3 (14.7 ppm) formaldehyde + 14.80 mg/m^3 (10.6 ppm) HCl (BCME estima-ted 1 µg/m^3), 6 h/day, 5 days/week, for life	25/99 squamous c carcinomas of th cavity and 3 pa
Rat: Sprague Dawley	100 (male)	inhalation	17.16 mg/m^3 (14.3 ppm) formaldehyde + 14 mg/m^3-(10 ppm) HCl (pre-mixed); 378 exposures over 588 days; 6 h/day, 5 days/week	12 squamous cell of the nasal cavity (signifi with regard to (preliminary re
Rat: Sprague Dawley	100 (male)	inhalation	16.92 mg/m^3 (14.1 ppm) for-maldehyde + 13.30 mg/m^3 (9.5 ppm) HCl (not pre-mixed); 378 exposures over 588 days; 6 h/day, 5 days/week	6 nasal (signifi regardto control (5 squamous cel carcinomas, 1 a (preliminary re

Table 29 (contd).

Species/ Strain	Number of animals (sex)	Route of exposure	Dosage	Findings
Rat: F-344	119-121 (male) 119-121 (female)	inhalation	0, 2.4, 6.72, or 17.16 mg/m^3; for up to 24 months; 6 h/ day, 5 days/week; 6-month follow-up	non-significant adenoma at all (non-significan (significant) s carcinomas of n at the medium a doses, respecti (see also Table
Rat: F-344	32	inhalation	0.36, 2.4, or 17 mg/m^3; 6 h/day, 5 days/week, for 28 months	rhinitis; epithe hyperplasia; sq metaplasia at 1 32 squamous cel (P < 0.01) and papillomas (P <
Rat: Sprague Dawley	100 (male)	inhalation	18.24 mg/m^3 (15.2 ppm) for-maldehyde + 13.86 mg/m^3 (9.9 ppm) HCl (pre-mixed) (BCME,	13 polyps/papil squamous cell ca 1 adenocarcinom

			0.1-0.4 µg/m^3); 6 h/day, 5 days/week, for life	1 fibrosarcoma; neuroepitheliom
Rat: Sprague Dawley	100 (male)	inhalation	17.88 mg/m^3 (14.9 ppm) formaldehyde + 13.58 mg/m^3 (9.7 ppm) HCl (not pre-mixed);6 h/day, 5 days/week for life	27 squamous cell 2 adenocarcinoma polyps/papillom
Rat: Sprague Dawley	100 (male)	inhalation	17.76 mg/m^3 (14.8 ppm) formaldehyde; 6 h/day, 5 days/week, for life	38 squamous cell 1 fibrosarcoma; cinoma
Rat	30	stomach tube	0.4 g/day[a], for 333 days	no treatment-rel

Table 29 (contd).

Rat: Wistar	48 (male) 48 (female)	ingestion	1% HMT in drinking-water for 104 weeks, for 3 years[a]	no increased tu incidence
Rat: Wistar	280 (male) 280 (female)	ingestion	0, 1.2, 15, or 81 mg/kg bw (males); 0, 1.8, 21, or 109 mg/kg bw (females) (drinking-water, 2 years)	no tumours (exc mesenchymoma in male)
Rat: Wistar	80 (male) 80 (female)	ingestion	0, 10, 50, or 300 mg/kg bw; (drinking-water, 2 years)	no significant tumours
Rabbit	6	oral tank	3% formalin, 90 min, 5 times/week for 10 months	2/6 leukoplakia
Syrian golden hamsters	88	inhalation	12 mg/m^3, 5 h/day, 5 day/week, lifetime	no increase in tumour incidenc
Syrian golden hamsters	50	inhalation	36 mg/m^3, 5 h/day, 5 day/week, lifetime (with diethylnitrosamine)	no increase in r tumour incidenc
Rat	10	subcutaneous	1 ml/week for 15 months 0.4% solution	4/10 injection-
Rat	20	subcutaneous	1-2 ml/week till tumour development 9-40%[a]	7/20 injection- 1/20 injection-s
Rat: Wistar	20 (male) 20 (female)	subcutaneous	5 g/kg on alternate days, for 2 years[a]	no increased tu incidence

[a] Hexamethylenetetramine (HMT) (from which formaldehyde is liberated *in vivo*).
[b] Showed "histological features of carcinoma in situ" (Mueller et al., 1978).

[c] Aspartame (sweetener) was administered to rats at a dosage level of 8 g/kg bo
has been assumed to biodegrade (10%) in the animals yielding 800 mg formalde
[d] No tumours, even after treatment with dibenzpyrene and coal tar.

Table 30. Neoplastic changes in the nasal cavities of Fischer 344 rats[a]

Formaldehyde mg/m^3 (ppm)	Sex	Number of nasal cavities evaluated	Squamous cell carcinomas	Nasal carcinomas	Undifferen-tiated carcinomas/ sarcomas	Malignant sarcomas
0 (0)	male	118	0	0	0	0
	female	114	0	0	0	0
2.4 (2)	male	118	0	0	0	0
	female	118	0	0	0	0
6.7 (5.6)	male	119	1	0	0	0
	female	116	1	0	0	0
17.2 (14.3)	male	117	51[c]	1[b]	2[b]	1
	female	115	52[d]	1	0	0

[a] From: Kerns et al. (1983) and BGA (1985).
[b] One animal also exhibited a squamous cell carcinoma.
[c] 36 of these animals were among the 57 that died prematurely.
[d] 15 of these animals were among the 67 that died prematurely.

Male rats were exposed to 0, 12, or 24 mg formaldehyde/m^3 for 4, 8, or 13 weeks (6 h/day, 5 days/week) and were then observed for periods of up to 126 weeks (Feron et al., 1987a). Non-neoplastic histopathological changes in the nasal respiratory epithelium (hyper- and metaplasia) and olfactory epithelium (disarrangement, thinning, and simple cuboidal or squamous metaplasia) occurred at 24 mg/m^3, similar, but less pronounced, changes of the nasal respiratory epithelium were seen at 12 mg/m^3 and a limited and not statistically significant number of nasal tumours occurred at 24 mg/m^3, mainly in rats that had been exposed for 13 weeks (6/132: 3 squamous cell carcinomas, 1 carcinoma *in situ* and 2 polypoid adenomas).

Feron et al. (1987b) carried out an inhalation study on male rats with a severely damaged (by electrocoagulation) or undamaged nasal mucosa. They were exposed to 0, 0.12, 1.2, or 12 mg formaldehyde/m^3 6 h/day, 5 days/week, over periods of either 28 months or 3 months, followed by an observation period of 25 months. A significant number of nasal squamous cell carcinomas (17/60) occurred only in rats with a damaged nose that had been exposed to 12 mg/m^3 for a period of 28 months.

Basal-cell hyperplasia and/or squamous metaplasia were observed in the tracheo-bronchial epithelium of C3H mice exposed to 50, 100, or 200 mg formaldehyde/m^3, for 4 h/day, 3 days/week, over 35 weeks; atrophic metaplasia was also observed in the highest dose group (Horton et al., 1963).

Neoplastic lesions found in the nasal cavities of Fischer 344 rats exposed to formaldehyde gas are summarized in Table 30 (Kerns et al., 1983). Several studies were performed to examine whether formaldehyde acts as a complete carcinogen, a promoter, or an initiator of tumours. Horton et al. (1963) exposed mice to coal-tar aerosol and to formal-

dehyde (48 or 120 mg/m^3, 1 h/day, 3 days/week, over 35 weeks). Coal-tar aerosol exposure resulted in lung tumour formation, but there was no evidence of any co-carcinogenic effect of formaldehyde.

8.4.2 Dermal studies

Studies were carried out on mice (Krivanek et al., 1983a; Spangler & Ward, 1982; Iversen, 1986) to test whether formaldehyde solution applied to the skin induced papilloma or malignant tumours as an initiator, or promoter of cancer, or as a complete carcinogen. Formaldehyde proved to be neither a complete carcinogen, nor an initiator (with phorbolmyristateacetate as a promoter). With respect to promoting activity (with benzo(a)pyrene or dimethylbenyanthracene as an initiator) the results were either negative or inconclusive. Details can be found in Table 29.

8.4.3 Oral studies

Some studies were performed using HMT instead of formaldehyde. It is used as an urinary tract antiseptic and antimicrobial food additive (Della Porta et al., 1968) and owes its activity to its degradation to formaldehyde and ammonia in an acid medium (digestive tract) with conversion of 20% of the theoretical amount of formaldehyde at pH 5 (Goodman & Gilman, 1975).

Slightly reduced growth rate and survival were observed in CTM mice given 5% hexamethylenetetramine (HMT) in the drinking-water for 30 weeks; a slightly reduced growth rate was also observed in SWR mice exposed to 1% HMT in the drinking-water for 60 weeks (Della Porta et al., 1968) (Table 29).

Formaldehyde, and other compounds were tested for tumour-promoting activity in a 2-stage stomach carcinogenesis study (Takahashi et al., 1986). Male Wistar rats were given N-methyl- N'-nitro-N-nitroso-guanidine (MNNG) in the drinking-water (100 mg/litre) and a diet supplemented with 10% sodium chloride for 8 weeks. Thereafter, they were maintained on drinking-water containing 0.5% Formalin for 32 weeks. Formaldehyde increased the incidence of adenocarcinoma in the glandular stomach, after initiation with MNNG and sodium chloride. The incidence of squamous cell papilloma in the forestomach was significantly increased in the groups given formaldehyde, irrespective of prior initiation. The results indicate that formaldehyde induces forestomach papilloma and exerts tumour-promoting activity.

Groups of 70 male and 70 female SPF Wistar rats, 31 days old, were administered formaldehyde at 1.2, 15, or 81 and 1.8, 21, or 109 mg/kg body weight per day, respectively, as a 5% (w/w) solution in the drinking-water for up to two years. A group of 70 males and 70 females served as controls. Groups of 10 rats per sex per group were killed at weeks 53 and 79 and the remaining animals at week 105. Mortality was elevated among mid-dose males by the end of the study but there was no difference among other groups. Mean body weights were lower in high-dose animals; this was accompanied by a decrease in food and liquid intake. The limiting ridge of the forestomach was raised and thickened in most animals of the high-dose group at each interim killing and at the end of the study; a similar effect was observed in some other treated groups and occasionally in controls. Papillary epithelial hyperplasia, hyperkeratosis, and focal ulceration in the forestomach were observed in high-dose animals as were chronic atrophic gastritis, ulceration, and hyperplasia in the glandular stomach. In addition, a higher incidence and degree of renal papillary necrosis was seen in high-dose animals at the end of the study compared to other treated groups and controls. One mesenchymoma of the skin was observed in a high-dose male killed at 52 weeks and two gastric papillomas were observed, one in a

low-dose male and one in a female control, at the end of the study. No other gastric tumours were reported and no treatment-related tumours were found (Til et al., 1988).

A similar study was carried out on Wistar rats administered formaldehyde in the drinking-water (Tobe et al., 1989). Groups of 20 male and 20 female Wistar rats, four weeks old, were administered 10, 50, or 300 mg formaldehyde/kg body weight per day as 0.02, 0.1, or 0.5% solutions, respectively, in the drinking-water for up to 2 years. A group of 20 males and 20 females served as controls. Groups of 6 rats per sex per group were killed at 12 and 18 months and the remaining surviving animals were killed at 24 months. Mortality was elevated in the high-dose group and reached 45% and 55% in males and females, respectively, at 12 months; all animals in this group had died by 21 months (females) and 24 months (males). Body weight gain and food and liquid intake were significantly reduced in high-dose animals.

Erosions, ulcers, squamous cell hyperplasia, hyperkeratosis, and basal cell hyperplasia with submucosal cell infiltration were observed in the forestomach in animals of both sexes in the high-dose group at 12 months. Erosions, ulcers, and submucosal cell infiltration also occurred in the glandular stomach among this group at 12 months and glandular hyperplasia was observed along the limiting ridge of the fundic mucosa. In the mid-dose group, hyperkeratosis occurred in the forestomach in one male and one female among animals killed at 18 and 24 months. No such lesion was found in animals in the low-dose group at any time. There was no significant increase in the incidence of any neoplastic lesion in any treated group compared with controls. The types of tumours observed were similar to those that occur spontaneously in this strain of rats.

8.5 Mutagenicity and Related End-Points

The mutagenic properties of formaldehyde have been studied in different test systems (Tables 31 and 32). Extensive data have resulted from the treatment of *Drosophila* with formaldehyde-treated food (Auerbach et al., 1977).

In general, the available data show that formaldehyde is mutagenic in different test systems, especially when high concentrations act directly on cells (gene and chromosome mutations). Addition of metabolizing systems to the assay system tends to reduce the activity of formaldehyde. The mutagenic effects of formaldehyde in *Drosophila* depend on the route of administration. Inconsistent responses were obtained in *in vitro* mammalian mutagenicity assays, increases in mutation frequency being obtained in the mouse lymphoma assays, but not with Chinese hamster ovary cells.

Positive cell transformation assays have been reported *in vitro*. After inhalation of the compound, local DNA adducts were observed in rats without simultaneous systemic genetic effects (Casanova-Schmitz et al., 1984b).

Table 31. The genetic toxicology of formaldehyde: *in vitro* studies

Assay	Strain/type	Metabolic activation	Result	Comments
Procaryotes				
Escherichia coli	WP2 Hcr+	none	-	
	WP2 Hcr-		+	
Escherichia coli	WP2	± Aroclor	+	

	WP67	induced rat	+	
	CM871	liver S-9	+	
	spot test		+	strain was fied for s was metabo vation use
Escherichia coli	WP2 uvrA	none	-	
Salmonella typhimurium	TM677	± Aroclor induced rat liver S-9	+	toxicity city reduc
Salmonella typhimurium	no strain data		-	
Salmonella typhimurium	Ames; no strain data	± hepatic activation	-	paraforma
Salmonella typhimurium	TA1535,	none	-	
	TA1538,		-	
	TA1537,		-	
	TA97		-	
	TA98		-	
	TA100		-	

Table 31 (contd).

Salmonella typhimurium	TA97	± Aroclor	-	effects o
	TA98	induced rat and	-	given; ass
	TA100	hamster liver S-9	-	abstract a negative
Salmonella typhimurium	TM677	± Aroclor	+	
	TA97	induced rat	+	
	TA98	liver S-9	+	
	TA100		+	
Salmonella typhimurium	TM677	none	+	
	TA100		+	
Salmonella typhimurium	TA98	± Aroclor	+	formaldeh
	TA100	induced rat	+	formalin (
	UTH8414	liver S-9	-	methanol)
	UTH8413		-	
Salmonella typhiurium	TA1535	none	-	formalin
	TA1537		-	
	TA1538		-	
	TA98		-	
	TA100		-	
Salmonella typhimurium	TA98	± KC500	-	negative
	TA100	induced rat liver S-9	+	

Salmonella typhimurium	TA98 TA100	± rat liver microsomes	+ +	activity dehyde was the presen liver micr
Salmonella typhimurium	TA1535 + plasmids 5310002/psk1002	none	+	

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments
Salmonella typhimurium	TA97 TA102	± Aroclor induced rat liver S-9	- +	weak resp
Salmonella typhimurium	TA100 TA102	± Aroclor induced rat liver S-9	+	pre-incub procedure
Salmonella typhimurium	no strain data	± hepatic activation	-	
Salmonella typhimurium	TA100	± clophen A50 induced rat liver S-9	+ (weak)	
Salmonella typhimurium	TA102 TA2638	none	-	
Salmonella typhimurium	TA98 TA100 TA1537	± PCB, KC-100 induced rat liver S-9	- -	formalin; strain TA1 S-9
Salmonella typhimurium	TA98 TA100 TA1535 TA1537	± Aroclor induced rat and hamster liver S-9	- - - -	
Eucaryotes				
Nematode	*Caenorhapolitis elalgans*	-		Point mut unc-22 ge "twitching sure to ni

Table 31 (contd).

Neurospora crassa	H-59 (repair deficient) H-12	-	+ +	

Neurospora crassa	Ade		+	
Drosophila			+	FA genera mutants
Drosophila	-	-	-	not susce mutagenici formaldehy food; muta jection in
Tradescantia (micronucleus)		-	- +	strain ab fumigation
Saccharomyces cerevisiae (recombination)	D4 D3	-	+ +	
Saccharomyces cerevisiae (recombination)	N123		+	mitotic recombina
Mammalian cell mutation				
Mouse lymphoma	L5178Y	± hepatic activation	+	paraformal
Mouse lymphoma	L5178Y TK±	± S-9	+	negative o dition of and NAD+

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments
Mammalian cell mutation (contd).				
CHO cells	HGPRT locus	none	-	
CHO cells	HGPRT locus	± Aroclor induced rat liver S-9	equivocal (without S-9) + (with S-9 very weak)	
CHO cells	AS52 locus		+	
Human lymphoblasts	TK6	none	+	
Cell transformation				
	C3H10T 1/2	none	-	

	hamster embryo	none	+	
	rat kidney cell	none	±	formaldehy formed cel incubated
	Balb/C3T3 1/2	none	+	
	BKH-21/C1.13	± Aroclor induced rat liver S-9	+	

Table 31 (contd).

DNA repair				
	hamster embryo cells (SA7 virus) (enhanced viral transformation)	none	+	
	human diploid fibroblasts		+ -	nick trans not inhibi
DNA cross-linking	CHO-KI	none	+	
DNA assay				
DNA-cell binding		none	?	
Unscheduled DNA synthesis	Hela		+	
DNA damage	L1210 mouse leukaemia cells		+	DNA-protei links
Unscheduled DNA synthesis	rat tracheal epi-thelial cells	none	-	
	bronchial epi-thelial and fibroblast cells	none	+	DNA-protei links; sin breaks in bited rese bition of (UDS)
	human fibroblasts		+	

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments
DNA-protein cross-linking	rat nasal epithelium	none	+	
Unscheduled DNA synthesis	rat nasal epithelium	none	-	
Scheduled DNA synthesis	rat nasal epithelium	none	+	
RNA synthesis	rat nasal epithelium	none	-	
Cytogenetic assays				
Sister chromatid exchange	CHO	hepatic activation	+	paraformal
Chromosome aberration	CHO	hepatic activation	+	
Sister chromatid exchange	V79	± Aroclor induced rat liver S-9 ± hepatocytes	+	FA induced chromatid frequency with S-9 t that of co this was s to metabol ing to mac
Sister chromatid exchange	human lymphocyte		+	
Sister chromatid exchange	human lymphocyte		+	

Table 31 (contd).

	human lymphoblast TK6		+ +	TK locus D protein cr
Chromosome aberration	CHO	± metabolic activation	+	
Sister chromatid exchange	human lymphocytes	none	+	

Sister chromatid exchange	CHO	none	+	
	human lymphocytes	none	+	
Chromosome aberration	embryonic kidney culture	none	-	formalin
Sister chromatid exchange	CHO	± hepatic activation	+	metabolic decreased
Chromosome aberration	CHO		-	which sist exchange a detected
Chromosome aberration	human lymphocyte	± clophen	+	
Sister chromatid exchange	human lymphocyte	A50 induced rat liver S-9	+	
Chromosome aberration	CHO cells	± PCB KC-400 induced rat liver S-9	+ (in absence of S-9)	
Chromosome aberration	CHO	± Aroclor	+	
Sister chromatid exchange	CHO	induced rat liver S-9	+	

Table 32. The genetic toxicology of formaldehyde: *in vivo* studies

Assay	Strain/type	Result	Comments
Cytogenetic assays			
Sister chromatid exchange	mouse	+ in female mice at mid- and higher dose levels	formaldehyde concentrati greater that the target trations of 14.4 and 30
Chromosome aberration	mouse	?	formalin (correct CAS nu given); 24-h and 25-mont caused insignificant inc cells with chromosomal a symmetrical translocatio germ cells found in the cyte stage and increased implantation embryonic m
Chromosome aberration	CBA mouse	-	bone marrow + spleen; 0. at doses of 6.25, 12.5,
Micronucleus	CBA mouse	-	25 mg/kg
Micronucleus	NMRI mouse	-	bone marrow; single ip i of 10, 20, or 30 mg/kg; at 3 and 6 years; 2 male females per group
Sister chromatid exchanges/chromosome aberration	Fischer rat	-	0.6, 7.2, or 18 mg/m^3 (0. 15 ppm); 6 h/day, for 5

Table 32 (contd).

Chromosome aberration	rat	- at week 1 and 32 months bone marrow; + at high dose in lung macrophage at 1 week and 2 months	0, 0.6, 3.6, or 18 mg/m^3 3, or 15 ppm) paraformal 6 h/day, 5 days/week, fo at 4 and 6 months the mi in the lung cells of all including controls had d and the number of cells for scoring was inadequa
Unscheduled DNA synthesis			
	rat (tracheal epithelial cells)	-	0.47, 2, 5.9, or 14.8 mg for 1, 3, or 5 days
Dominant lethal			
	mouse	- (spermatogonial chromosome)	mixture of formaldehyde hydrogen peroxide (30 mg 90 mg/kg)
		weak dominant lethal effects weeks 1 and 6	number of pregnancies no no increase in post-impl lethality; number of liv never decreased below 7. pre-implantation loss si increased during the who except for the 5th and 7
	ICR-Ha Swiss mouse (8- to 10-week-old males)	-	32, 40, 16, or 20 mg/kg for 3 or 8 weeks (female weekly)

Table 32 (contd).

Assay	Strain/type	Result	Comments
Dominant lethal (contd).			
	Q-strain mouse	- (spermatogonial chromosome	50 mg/kg ip
		weak dominant lethal effect	no effect was observed o of pregnant females; an embryonic mortality obse first week after treatme butable to an increase i of pre- and post-implant only in the 3rd week was pre-implantation deaths increased
Spot test			
Somatic cell mutation	C57B1/6J"Ha" mouse	-	6 - 6.1 and 17.8 - 18.1 6 h/day, for 3 days

(T-stock)

DNA-protein cross-links have been studied in cultures of mammalian cells. Some DNA strand breakage was reported, but DNA-DNA cross-links were not observed. Formaldehyde has been shown to induce chromosome aberrations and sister chromatid exchanges in a number of cell lines. The results of studies on the induction of sister chromatid exchanges in human lymphocyte cultures (Kreiger & Garry, 1983) demonstrated that there was no significant sister chromatid exchange response below an apparent "threshold" of 5 ml culture medium.

Craft et al. (1987) exposed human lymphoblasts *in vitro* to various concentrations of formaldehyde (0-150 µmol/litre x 2 h). Both the induction of mutations and the formation of DNA-protein cross-links by formaldehyde are non-linear functions occurring at overlapping concentration ranges. Holding the culture for 24 h resulted in complete removal of the cross-links.

Definite evidence that formaldehyde may induce mutations *in vivo* has not been found. Tests for the induction of sister chromatid exchanges in mouse bone marrow cells gave equivocal results. Dominant lethal tests in ICR-Ha Swiss mice were reported to be negative at doses up to 40 mg/kg; more recent studies on Q-strain mice showed effects, except during the first and third week, after treatment of males with 50 mg formaldehyde/kg. Micronucleus and chromosomal assays failed to reveal any formaldehyde-induced lesions in both exposed rats and mice. The results of a mouse somatic cell mutation assay (spot test) were also negative for formaldehyde.

Formaldehyde damage induced in DNA in different human cell culture systems comprised DNA-protein cross-links and DNA single-strand breaks; these lesions undergo efficient repair by complex mechanisms (Grafstrom et al., 1984). An earlier finding that formaldehyde may inhibit DNA repair (Grafstrom et al., 1983) has not been confirmed (Snyder & van Houten, 1986).

8.6 Reproduction, Embryotoxicity, and Teratogenicity

This topic has been studied in inhalation, feeding, drinking-water, gavage, and dermal studies. The results are summarized in Table 33.

In a dominant-lethal study, formaldehyde did not appear to affect spermatogenesis or fertility in mice at single dose levels up to 40 mg/kg body weight (ip) or produce any increases in fetal death or pre-implantation losses (Epstein et al., 1972).

Yasamura et al. (1983) gave mice doses of 0, 30, 40, or 50 mg formaldehyde/kg per day by intraperitoneal injection on days 7-14 of pregnancy. The mean body weight of treated fetuses was lower than that in the controls, and the incidence of prenatal death was slightly increased in treated mice. There was a significant increase in the frequency of abnormal fetuses from treated dams, the major malformations being cleft palate and malformations of the extremities. Strain differences were observed.

A teratology study on the rat was undertaken by the Formaldehyde Council of Canada (Martin, 1985). Twenty-five mated Sprague-Dawley rats

were exposed through inhalation (whole-body exposure) for 6 h/day to formaldehyde doses of 2.4, 6, or 12 mg/m^3, from day 0 to day 15 of gestation, inclusive. Two control groups were included in the study. The females used for the study were 13 weeks of age and weighed between 221 and 277 g. Proven males of the same strain and source were used for mating. The pregnancy rate in all groups was at least 80%. Uterine

parameters, including numbers of corpora lutea, implantation sites, live fetuses, dead fetuses, and resorptions, fetal weight, sex ratio, and pre- and post-implantation losses, were unaffected by treatment. The overall incidence of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies was not affected by treatment with formaldehyde.

Pregnant hamsters were treated with dermal applications of formaldehyde solution on day 8, 9, 10, or 11 of gestation (Overman, 1985). Fetuses were removed on day 15 and were weighed, measured, and examined for teratogenic effects. The resorption rate increased in the formaldehyde-treated groups, but treatment did not significantly affect weight or length, and no malformations that could be related to treatment appeared. It was concluded that fetal risk due to topical exposure to formaldehyde was minimal in this model system. However, there is no information in this study on the amount of formaldehyde actually absorbed.

Table 33. Reproduction and teratology studies

Species	Route of exposure	Number of animals Female	Male	Dosage	Time of treatment	Effects on offspring/ reproduction
Rat	inhalation	12	3	0.012 mg/m^3	10-15 days before gestation (females)	14-15% increase in duration of gestation; increase in body, heart, and kidney weight; decrease in weight of liver and lungs
		12	3	1 mg/m^3		
Rat	inhalation	12	3	0.012 mg/m^3	10-20 days before gestation embryo; (females)	decrease in ascorbic acid in the whole lower DNA content in fetal liver; increase in liver ascorbic acid[a]
		12	3	1 mg/m^3		
Rat	inhalation	12	3	0.012 mg/m^3	10-20 days before gestation (females)	changes in kidney and liver; decrease in myocardial glycogen; disintegration of lymphocytes[a]; involution of thymic lymphoid tissue[a]
		12	3	1 mg/m^3		
Rat	inhalation	15	-	0.0005 mg/litre	4 h/day, on days 1-19 of gestation	sacrifice on day 20; increase in number of preimplantation deaths; no external malformations; offspring of 6 dams delivered on day 22; at one-month postpartum, females, but not males, were shorter; decrease in mobility of females
		15	-	0.005 mg/litre		

Table 33 (contd).

Rat	combined inhalation and ingestion	6 -	3[b] -	0.005 mg/litre and 0.12 mg/m^3; 0.01 mg/litre and 0.25 mg/m^3; 0.1 mg/litre and 0.5 mg/m^3	6 months; water; 4 h, 5 times/week	no adverse effects on reproduction; decrease in the amount of nucleic acid in the testes
Rat	inhalation	334 in 12 groups		0.4 mg/m^3 6 mg/m^3	4 h/day for 20 days	decrease in susceptibility to adverse effects on pregnant rats (compared with non-pregnant rats); altered renal and hepatic function[a], decrease in blood haemoglobin[a]
Dog	ingestion	9-11	-	125 mg/kg (125 ppm) 375 mg/kg (375 ppm)	4 days after mating to day 56	no adverse findings
Rat	ingestion	16	16	0.16% HMT	parents: from 2 to 5 months of age; offspring: from birth to 123 days of age	no adverse findings
Rat	ingestion	12	6	1% HMT in drinking-water	start: at 8 weeks of age during pregnancy and nursing F1 treated until 20 weeks post-partum	no adverse findings

Table 33 (contd).

Species	Route of exposure	Number of animals Female	Male	Dosage	Time of treatment	Effects on offspring/ reproduction
Rat	ingestion	2	1	1% HMT[c]	F1, F2, and F3; 2.5 years	no adverse findings
Rat	ingestion	5		2% HMT[c]	P and F1; 2.5 years	no adverse findings
Mouse	stomach tube	34	-	74 mg/kg per day; 148 mg/kg per day;	days 6-15 of gestation	no malformations; toxic for 22/34[a]

				185 mg/kg per day		
Mouse	stomach tube	-	7	100 mg/kg	5 days	no effects on sperm
Hamster	dermal	22		0.5 ml of 37% formaldehyde solution (but no information on amount absorbed)	day 8, 9, 10, or 11 of gestation	increased resorptions, but no effects on fetal weight or length and no malformations

[a] Only after exposure to the high dose.

[b] Female untreated, male treated.

[c] Hexamethylenetetramine (HMT) (from which formaldehyde is liberated *in vi*

The results in Table 33 do not show any evidence of the embryo being unusually sensitive to formaldehyde, and there is no information to show that formaldehyde is teratogenic in rodents when administered orally or applied dermally in non-toxic amounts to the dams. Furthermore, the data do not provide any evidence indicating that formaldehyde causes terata at exposure concentrations that are not toxic for the adult.

8.7 Mechanisms of Carcinogenicity

8.7.1 Reactions with macromolecules

Formaldehyde reacts readily with a variety of cellular nucleophiles, including glutathione, forming adducts of varying stability (Feldman, 1973; Uotila & Koivusalo, 1974; McGhee & von Hippel, 1975). The glutathione adduct of formaldehyde is the true substrate of formaldehyde dehydrogenase, which catalyzes the oxidation of the adduct to S-formyl-glutathione (Uotila & Koivusalo, 1974). Reaction products with DNA, which have been demonstrated *in vitro* , include adducts (McGhee & von Hippel, 1975a,b) and DNA protein cross-links (Brutlag et al., 1969; Doenecke, 1978; Ohba et al., 1979).

Investigations in rats exposed to formaldehyde through inhalation have shown that formaldehyde induces the formation of DNA protein cross-links in the nasal respiratory mucosa *in vivo* (Casanova-Schmitz & Heck, 1983; Casanova-Schmitz et al., 1984). The concentration-response curve for DNA protein cross-linking was sublinear below 7.2 mg/m^3 (6 ppm) but apparently linear at higher concentrations (Casanova-Schmitz et al., 1984). In rats depleted of glutathione, either by simultaneous exposure to acrolain (Lam et al., 1985) or by ip injection with phorone (2,6-dimethyl-2,5-heptadien-4-one) (Casanova & Heck, 1987) a significant increase in the yield of formaldehyde-induced DNA protein cross-links was observed, suggesting that the formaldehyde dehydrogenase-catalyzed oxidation of formaldehyde is an important defence mechanism against the covalent binding of formaldehyde with nucleic acids in the nasal respiratory mucosa.

DNA protein cross-links could not be detected in the bone marrow of rats exposed to formaldehyde through inhalation (Casanova-Schmitz et al., 1984; Casanova & Heck, 1987), suggesting that these are formed only at the site of entry. Minini (1985) found DNA protein cross-links in the stomach and beginning of the small intestine of rats that had been administered formaldehyde by gavage. These cross-links were detected only after the administration of a very high dose of formal-

dehyde (750 mg/kg, i.e., about 3/4 of the LD_{50}) (McGhee & von Hippel, 1975a,b).

8.7.2 Cytotoxicity and cell proliferation

Increased cell replication occurs as a result of the cytotoxic effects of formaldehyde on the nasal mucosa.

Morphological changes (acute degeneration, swelling, formation of "dense bodies", and vacuoles in epithelial cells) were described in the respiratory epithelium of rats after a single 6-h exposure to 18 mg formaldehyde/m^3 (Chang et al., 1983; Swenberg et al., 1983). When such exposure was repeated 3-5 times, ulceration was observed in the respiratory epithelium in most experimental animals. After a 9-day exposure, reparative hyperplasia and metaplasia were found. At 7.2 mg/m^3, hyperplasia and slight degenerative changes were still detected. In contrast, morphological changes could not be proved at 0.6 and 2.4 mg formaldehyde/m^3 (Starr & Gibson, 1985).

Further research clarified the dependence of cytotoxic effects on the concentration of formaldehyde and on the length of exposure. After exposing rats to 7.2 or 18 mg formaldehyde/m^3 (6 or 15 ppm) for 6 h per day over 3 days, the rate of incorporation of 3H-thymidine into the DNA of the respiratory epithelium, 2 h after the end of the exposure, was increased by a factor of 20 or 10, respectively, indicating increased cell proliferation. On the other hand, no statistically significant increase in thymidine incorporation compared with that in the controls was found in rats after exposure to 0.6 or 2.4 mg/m^3 (0.5 or 2 ppm) and in mice after exposure to 0.6, 2.4, or 7.2 mg/m^3 (0.5, 2, or 6 ppm) for 6 h/day over 3 days. Exposure to formaldehyde at 18 mg/m^3 (15 ppm) led to thymidine incorporation being increased by a factor of 8, in mice (Swenberg et al., 1983).

Despite nearly equal doses (concentration x time), significantly increased effects were observed with exposure to 18 mg/m^3, (15 ppm) for 6 h/day, 5 days/week (= 448 mg/m^3 (540 ppm) x h/week) (Kerns et al., 1983) compared with exposure to 3.6 mg/m^3, for 22 h/day, 7 days/week (= 460 mg/m^3 (554 ppm) x h/week) (Rusch et al., 1983). This indicates that formaldehyde concentration is more important than the accumulated dose (Swenberg et al., 1985).

A slight increase in cell proliferation (3H-thymidine labelling, 18 h after the end of exposure) was observed after a single 6-h inhalation exposure of rats to 0.6 or 2.4 mg formaldehyde/m^3 (0.5 or 2 ppm), but not after 3 or 9 such exposures carried out on consecutive days (Swenberg et al.,1985). In contrast, exposure to 7.2 mg/m^3 (6 ppm) 6 h/day for 1 or 3 days caused a marked increase in cell turnover, which did not normalize as it did after exposure to 0.6 or 2.4 mg/m^3 (0.5 or 2 ppm).

The results of recent inhalation studies have confirmed that the concentration rather than the dose determines the severity of the cytotoxic effects. In a 4-week study, Wilmer et al. (1987) showed that there were no appreciable differences in the type, degree, and incidence of nasal lesions between rats continuously exposed to 12 mg (10 ppm) formaldehyde/m^3 (66 mg/m^3 (80 ppm)/h per day) and those exposed intermittently to 12 mg/m^3 (10 ppm) (33 mg/m^3 (40 ppm)/h per day). Moreover, intermittent exposure of rats to 12 mg/m^3 (10 ppm) (33 mg/m^3 (40 ppm)/h per day) induced more severe nasal changes than continuous exposure to 6 mg/m^3 (also 48 mg/m^3 (40 ppm)/h per day). From a subsequent 13-week study (Wilmer et al., 1986), it appeared that

hyperplasia and metaplasia of the nasal respiratory epithelium occurred in rats intermittently exposed to 4.8 mg/m^3 (13 mg/m^3 (16 ppm)/h per day) but did not occur in rats continuously exposed to 2.4 mg/m^3 (2 ppm) (also 13 mg/m^3 (16 ppm)/h per day). In a 28-month inhalation study, male rats with severely damaged (by electrocoagulation) or undamaged nasal mucosa were exposed to formaldehyde concentrations of up to 12 mg/m^3 (10 ppm); exposure to 12 mg/m^3 (10 ppm) resulted in a much higher incidence of nasal tumours in rats with a damaged mucosa (17/60) than in rats with an undamaged nose (1/29) (Feron et al., 1987).

Small ultrastructural changes were reported in the cell membrane of nasal ciliated epithelial cells of rats exposed to formaldehyde through inhalation (Monteiro-Riviere & Popp, 1986). Similar changes were also found in the controls, but the significance is unclear.

9. EFFECTS ON MAN

9.1 Sources of Exposure

The general population may be exposed to formaldehyde in tobacco smoke, automobile emissions, from materials used in buildings and home furnishings, in consumer and medicinal products, and in nature (section 3).

9.2 General Population Exposure

A large number of occupations are associated with formaldehyde exposure (Tables 4 and 34).

Table 34. Potential occupational exposure to formaldehyde[a]

Anatomists	Glass etchers
Agricultural workers	Glue and adhesive makers
Bakers	Hexamethylenetetramine makers
Beauticians	Hide preservers[b]
Biologists	Histology technicians (assumed to
Bookbinders	including necropsy and autopsy
Botanists	technicians)
Carpenters	Ink makers
Crease-resistant textile	Lacquerers and lacquer makers
finishers	Medical personnel (assumed to include
Deodorant manufacturers	pathologists)
Disinfectant manufacturers	Mirror makers
Disinfectors	Oil-well workers
Dress shop personnel	Paper makers[b]
Dressmakers	Particle board makers[b]
Drugmakers	Pentaerythritol makers
Dyemakers	Photographic film makers
Electrical insulation makers	Plastic workers
Embalmers	Resin makers
Embalming fluid makers	Rubber makers[c]
Ethylene glycol makers	Soil sterilizers and greenhouse
Fertilizer makers	workers
Fire-proofers	Surgeons
Formaldehyde resin makers	Tannery workers[b]
Formaldehyde employees	Taxidermists
Foundry employees	Textile mordanters and printers
Fumigators	Textile waterproofers
Fungicide workers	Varnish workers[b]
Furniture workers	Wood-based material workers
Fur processors[b]	Zoologists

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[a] From: NIOSH (1976a).
[b] See IARC (1981).
[c] See IARC (1981).

The most predominant effects of formaldehyde exposure usually reported in human beings are various kinds of physical symptoms emanating from the irritation of the mucosa in the eyes and upper airways as well as the sensitivity of the skin. Sensory reactions are apparently the most typical effects in the non-industrial indoor environment. Most human beings are exposed to low concentrations of formaldehyde (less than 0.06 mg/m^3) in the environment and sensory effects (odour and irritation) are by far the most common response; symptoms of hyperactivity in the lower respiratory tract may also be produced.

It should be realized that extrapolation from animal studies to estimate human response is dubious in most cases and, for some effects, impossible. Although some effects, e.g., skin reactions may be comparable between animals and human beings, other effects, such as pulmonary function reactions, are more questionable and others, such as sensory irritation, cannot be compared.

9.2.1 Sensory effects

The odour of formaldehyde is detected and/or recognized by most human beings at concentrations below 1.2 mg/m^3 (1 ppm) (Leonardos et al., 1969; Gemert & Nettenbreijer, 1977; Fazzalari, 1978; Brabec, 1981). The absolute odour threshold is defined as the concentration at which a group of observers can detect the odour in 50% of the presentations (from a series of concentrations) (WHO, 1987) and, for formaldehyde, it has been shown to be between 0.06 and 0.22 mg/m^3 (Feldman & Bonashkevskaya, 1971; Berglund et al., 1985, 1987; Ahlström et al., 1986). However, the individual odour detection thresholds cover a wide concentration range, over two powers of ten, and the distribution is extremely positively skewed. Berglund et al. (1987) showed that over a period of one year, the odour detection and odour strength reports for formaldehyde were consistent for a group of 10 observers. For a group of 50 observers, they also showed that the 50-percentile detection threshold for formaldehyde odour (ED_{50}, method of constant stimuli including blanks) was 180 µg/m^3 (145 ppb), the 10-percentile (ED_{10}) threshold was 25 µg/m^3 (20 ppb), and the 90-percentile (ED_{90}) threshold was 600 µg/m^3 (500 ppb).

If formaldehyde is mixed with contaminated indoor air from a "sick" building, an increase in the odour intensity of the stimulus mixture is found at formaldehyde concentrations of less than 0.25 mg/m^3 while, at higher concentrations, the odour strength remains largely unchanged (Ahlström et al., 1986). At high concentrations, formaldehyde has a distinct and pungent odour.

The difference between odour and irritation concentration may be noticeable, but there is no evidence that there is a threshold at which odour is superceded by irritation. However, for most inhaled odorous compounds, the trigeminal nerve has a higher threshold than the olfactory nerve (Moncrieff, 1955). When the formaldehyde concentration is increased and affects both the eyes and the nostrils, sensory irritation is first experienced in the eyes, then the odour is perceived, and finally nasal irritation occurs (Moncrieff, 1955).

In recent studies with short-term exposures, eye irritation was reported for formaldehyde from a level of 0.06 mg/m^3 and irritation of

the respiratory tract, from 0.12 mg/m^3 (Niemelä & Vainio, 1981; NRC, 1981). Clinical and epidemiological data show substantial variations in individual irritant responses to formaldehyde. The sensory effects of formaldehyde determined for odour and sensory irritation are listed in Table 35. The table only lists the reports that have included information on reasonable experimental control. In evaluating the different studies, it should be noted that many of the reported elevated lower limit values for sensory irritation emanate from studies in which the observers were not exposed to very low concentrations of formaldehyde or clean air was not included as the control condition.

Anderson (1979) showed that eye, nose, and throat irritation were reported by 3 of 16 observers exposed for 5 h daily to 0.288 mg formaldehyde/m^3 and by 15 of 16 observers exposed to 0.96 mg/m^3 in an environment chamber. A direct relationship between concentration and sensory irritation was observed only above 0.96 mg/m^3 and only at the highest concentration, 1.92 mg/m^3, was slight discomfort experienced (18 on a scale of 100). Bender et al. (1983) evaluated eye irritation according to the time of detection of the first trace of irritation as well as according to subjective ranking of severity. Both time and severity appeared to be functions of formaldehyde concentration; severity of response was above "slight" only with the highest test concentration of 1.2 mg/m^3 (28 observers).

In a study by Cain et al. (1986), a group of 33 observers judged the perceived irritation and odour of formaldehyde during 29-min chamber exposures to concentrations ranging from 0.3 to 2.4 mg/m^3. The sensory irritation increased with time for the lower concentrations and decreased with time for the highest. This effect was true for irritation of eyes, nose, and throat and the sensitivity proved to be roughly equal for all three sites. The sensory irritant effect of formaldehyde at 1.2 mg/m^3 was shown to decrease when the chemical pyridine was injected into the chamber; such sensory interactions occur in environmentally realistic situations (see Ahlström et al., 1986). Apart from Cain et al. (1986), Weber-Tschopp et al. (1977) and Bender et al. (1983) have shown sensory adaptation to occur with longer exposure durations.

Weber-Tschopp et al. (1977) exposed healthy volunteers (24 men, 9 women) to formaldehyde concentrations ranging between 0.036 and 4.8 mg/m^3 air (33 volunteers for 35 min, 48 volunteers for 1.5 min). Eye blinking rates as well as subjective irritation effects were determined. The irritation threshold was found to range between 1.2 and 2.4 mg formaldehyde/m^3. A similar threshold (1 mg/m^3) was found in other studies (BGA, 1985). Triebig et al. (1980) noted that 9 out of 53 medical student volunteers exposed to formaldehyde concentrations of between 0.39 and 0.60 mg/m^3 for 8 h/week, over 8 weeks, complained of headaches, a burning sensation in the eyes, sore throat, and annoyance because of the smell.

Formaldehyde has been identified as one of the chemical components of photochemical smog. However, photochemical smog is a complex mixture of chemicals in which not all the components have been identified.

Schuck et al. (1966) showed that eye irritation appeared at 0.012 mg formaldehyde/m^3, but the formaldehyde had been generated by irradiating ethylene or propylene-nitrogen dioxide mixtures. The authors noted that irritating components other than formaldehyde, such as peroyzlacyl nitrate, which is also a potent sensory irritant present in photochemical smog, may have been generated during irradiation. Since formaldehyde usually appears in complex mixtures in the human environment (automobile exhaust, photochemical smog, tobacco smoke, contaminated indoor air), it is evident that the mixture may cause

sensory irritation at much lower formaldehyde concentrations than when formaldehyde is present alone. For example, Weber-Tschopp et al. (1976) showed that, during 29-min chamber exposures, formaldehyde concentrations of 0.3 mg/m^3 in a tobacco smoke environment resulted in moderate, strong, or very strong eye irritation.

It has been shown that sensory irritation is the earliest human reaction to formaldehyde, both in exposure studies and from complaints about indoor environments. An expert committee at the US National Academy of Sciences (NRC, 1980) calculated that less than 20% of an exposed human population would react to concentrations of less than 0.3 mg/m^3 with slight sensory irritation of the eyes, nose, and throat, and possibly also with a slight decrease in mucosal secretion/flow in the nose (Newell, 1983). Since differences in individual reactions to formaldehyde are large in both the normal population and in hyperreactive and sensitized persons, it is difficult to estimate a concentration guaranteed not to produce negative reactions in the general population.

Table 35. Sensory effects of formaldehyde on man

Type of exposure	Exp. control	Method	Site	Conc. range mg/m^3 (ppm)	(No. stimuli) conc. in air mg/m^3 (ppm)	Length of stimulus	No. volunteers (sex)	Irrit and o detect (d) th holds (ppm)
30-m^3 chamber	-	Constant stimuli	Eye	0.04-4.8 (0.03-4)	(4) 0.04; 1.2; 2.4; 3.6; 4.8 (0.03; 1; 2; 3; 4)	1 1/2 min (short exposure)	35 (M) 13 (F)	1.2-2 (1-2
30-m^3 chamber	-	Constant stimuli	Eye	0.04-4.8 (0.03-4)	(4) 0.04; 1.2; 2.4; 3.6; 4.8 (0.03; 1; 2; 3; 4)	37 min (long continuous exposure)	24 (M) 9 (F)	1.2-2 (1-2
17-m^3 aluminium smog chamber equipped with 7 sets of eye ports	-	Constant stimuli	Eye	0.01-1.2 (0.01-1)	(5) 0; 0.4; 0.7; 0.8; 1.1; 1.2 (0; 0.35; 0.56; 0.7; 0.9; 1.0)	6 min	5-28	0.46-1 (0.38 ppm) 1.2 (ppm)
Chamber	23 ± 0.5 °C 50 ± 5% RH	Constant stimuli	Eye throat nose	0.3-2.0	(4) 0.3; 0.5; 1.0; 2.0	5 min	11 (M) 5 (F)	1.0
Exposure hood	22 + 1 °C Pyridine as master stimulus	Limit with forced choice responses	nose	0.06-1.15	(7) 0.06; 0.10; 0.17; 0.28; 0.46; 0.77; 1.15	6 second	8 (M) 14 (F)	0.06 (50% 0.20 (100%

9.2.2 Toxic effects

The clinical features of toxicity are weakness, headache, abdominal pain, vertigo, anaesthesia, anxiety, burning sensation in the nose and throat, thirst, clammy skin, central nervous system depression, coma, convulsions, cyanosis, diarrhoea, dizziness, dysphagia, irritation and necrosis of mucous membranes and gastrointestinal tract, vomiting, hoarseness, nausea, pallor, shock, and stupor. Respiratory system effects caused by high formaldehyde concentrations are pneumonia, dyspnoea, wheezing, laryngeal and pulmonary oedema, bronchospasm, coughing of frothy fluid, respiratory depression, obstructive tracheobronchitis, laryngeal spasm, and sensation of substernal pressure. Coagulation necrosis of the skin, dermatitis and hypersensitivity, lachrymation and corrosion of the eyes, double vision, and conjunctivitis can occur. Acute ingestion may cause renal injury, dysuria, anuria, pyuria, and haematuria, and lead to an increase in formate levels in the urine. Death is due to pulmonary oedema, respiratory failure, or circulatory collapse (Hallenbeck & Cunningham-Burns, 1985).

Kline (1925) reported 12 cases where ingestion of formaldehyde (a few drops to 89 ml of concentrated solution) led to death. The largest amount ingested from which a patient has recovered is 120 ml. A 60-year-old man swallowed 60-90 ml of a 40% formaldehyde solution. Thirty hours after death, the mucosa of the lower part of the oesophagus, stomach, and first portion of duodenum were dark chocolate brown in colour and of the consistency of leather. All organs and tissues in contact with the stomach were "hardened" to a depth of about 8 mm (Levison, 1904).

Allen et al. (1970) reported corrosive injuries of the stomach due to formaldehyde ingestion.

9.2.3 Respiratory effects

No cases of death from formaldehyde inhalation have been published. There are numerous reports that exposure to formaldehyde vapour causes direct irritation of the respiratory tract. However, precise thresholds have not been established for the irritant effects of inhaled formaldehyde but, within the range of 0.1-3.1 mg/m^3, most people experience irritation of the throat (Table 35).

The effects of formaldehyde on ciliary movement and mucociliary clearance were studied by Andersen & Mölhave (1983). They measured nasal mucociliary flow by external detection of the motion of a radiolabelled resin particle placed on the surface of the inferior turbinate. The nasal mucous flow rate in the nose decreased during exposure to formaldehyde, but the response did not increase at concentrations ranging from 0.5 mg/m^3 to 2 mg/m^3 or on prolongation of the exposure period from 3 h to 5 h.

The potential of formaldehyde to produce chronic respiratory tract disease was studied by Yefremov (1970). At a wood-processing plant, the incidence of chronic upper respiratory disease was higher in 278 workers exposed to formaldehyde than in 200 controls. However, formaldehyde concentrations were not measured, and possible confounders were not evaluated.

Forty-seven subjects exposed to formaldehyde (mean air concentration 0.45 mg/m^3) and 20 unexposed subjects, all of whom were employed at a carpentry shop, were studied by Alexandersson et al. (1982) with regard to symptoms and pulmonary function. Symptoms involving the eyes and throat as well as chest oppression were significantly more common in the exposed subjects than in the unexposed

controls. Spirometry and simple breath nitrogen washout were normal on the Monday morning, before exposure to formaldehyde. A reduction in forced expiratory volume in 1 second by an average of 0.2 litres (P = 0.002), percent forced expiratory volume by 2% (P = 0.04), maximum mid-expiratory flow by 0.3 litre/second (P = 0.04) and an increase in closing volume in percentage of vital capacity by 3.4% (P = 0.002) were seen after a day of work and exposure to formaldehyde, suggesting bronchoconstriction. Smokers and nonsmokers displayed similar changes in spirometry and nitrogen washout.

Schoenberg & Mitchell (1975) performed standardized respiratory questionnaire and pulmonary function tests (FVD, FEV1, MEF 50%) on 63 employees in an acrylic-wool filter department (40 production line workers, 8 former production line workers, and 15 employees who had never been on the production line). Formaldehyde levels in the work environment were between 0.5 and 1 mg/m^3, and phenol levels, between 7 and 10 mg/m^3; particles and fibres were not well suppressed. In spite of the high proportion (85%) of subjects reporting acute respiratory symptoms, only small and insignificant changes in pulmonary function were found.

Andersen & Mölhave (1983), in a study of 16 healthy volunteers in a chamber, could not find any increase in airway resistance or any effects on vital capacity and maximum expiratory flow volume from exposure to formaldehyde levels of up to 2.0 mg/m^3 in a 5-h study.

To study pulmonary function during and after exposure to formaldehyde, Schachter et al. (1986) exposed 15 non-smoking healthy volunteers (mean age, 25.4 years) in a double-blind random manner to 0 or 2.4 mg formaldehyde/m^3, for 40 min on one day and again on a second day but with the subjects performing moderate exercise (450 kpm/min) for 10 min. No significant bronchoconstriction was noted (FEV1 test), and subjective complaints following such exposure were confined to irritative phenomena of the upper airways. Post-exposure symptoms (up to 24 h following exposure) were infrequent and confined to headache. Another study by the same group (Witek et al., 1986, 1987) on 15 healthy and 15 asthmatic volunteers resulted in similar findings.

Main & Hogan (1983) examined 21 subjects exposed to formaldehyde (0.14-1.9 mg/m^3) in a mobile home trailer. Eighteen unexposed controls were included. No differences in lung function were found between the 2 groups. However, there were significantly more complaints of eye and throat irritation, headache, and fatigue among the exposed.

In controlled studies, Day et al. (1984) exposed 18 volunteers to a formaldehyde concentration of 1.2 mg/m^3. Nine subjects had previously complained of various non-respiratory adverse effects from the urea formaldehyde foam insulation (UFFI) in their homes. Pulmonary function was assessed before and after exposure in a laboratory. Each subject was exposed, on separate occasions, to formaldehyde at 1.2 mg/m^3 in a environmental chamber for 90 min and to UFFI off-gas yielding a formaldehyde concentration of 1.4 mg/m^3 in a fume hood for 30 min. None of the measures of pulmonary function used showed any clinically or statistically significant responses to the exposure either immediately or 8 h after, commencement of exposure. There were no statistically significant differences between the responses of the group that had previously complained of adverse effects and of the groups that had not. There was no evidence that either formaldehyde or UFFI off-gas behaved as a lower airway allergen or important bronchospastic irritant in this heterogeneous population but, because of the small number of persons under study, it cannot be excluded.

Fifteen non-smoking volunteers (mean age, 25.1 years) who suffered

from substantial bronchial hyperreactivity, were studied by Harving et al. (1986). The mean provocation concentration of histamine producing a 20% decrease (PC_{20}) in peak expiratory flow rate was 0.37 g/litre (standard deviation (SD) = 0.36). All except one patient regularly required bronchodilator treatment. None used methylxanthines or corticosteroids. They were exposed to formaldehyde once a week for 3 consecutive weeks. The studies were carried out in a double-blind random fashion, under controlled conditions, in a climate chamber with particle-free air. All underwent the same 3 treatments, being exposed to mean formaldehyde concentrations of 0.85 mg/m^3 (SD = 0.07), 0.12 mg/m^3 (SD = 0.07), and zero. The mean exposure time at a steady-state concentration was 89.4 min (SD = 9.5). Bronchodilator drugs were withheld for 4 h before the studies. During the exposure, each participant rated his symptoms of asthma every 15 min on a visual analogue scale, and forced expiratory volume in one second was measured on a spirometer every 30 min.

Before and after exposure to formaldehyde, functional residual capacity and airways resistance were determined in a body plethysmograph, and flow-volume curves were measured. Immediately after exposure, a histamine challenge test was performed.

No significant changes in forced expiratory volume in one second, airways resistance, functional residual capacity flow-volume curves, or subjective ratings of symptoms of asthma were found in the group as a whole, or among the 9 participants with high histamine reactivity (PC_{20} < 0.50 mg/ml). Histamine challenge tests were highly reproducible and were unaffected by exposure to formaldehyde. No appreciable symptoms were reported after exposure.

Asthma-like symptoms have been elicited by irritant concentrations of formaldehyde. Precise thresholds have not been established for the irritant effects of inhaled formaldehyde. However, lower airway and pulmonary effects are likely to occur between 6 and 36 mg/m^3, independent of confirmed sensitization.

Several studies have addressed the problem of the mobile home situation, especially in Canada and the USA, without measurements of other confounders (section 9.2.8).

9.2.4. Dermal, respiratory tract, and systemic sensitization

Formaldehyde is a known sensitizer for the skin (DFG, 1987), but no thresholds for induction of dermal, respiratory tract, or systemic sensitization have been reliably determined.

9.2.4.1 Mucosal effects

Wilhelmsson & Holmström (1987) investigated possible mechanisms underlying nasal symptoms in 30 formaldehyde-exposed workers in a factory producing formaldehyde. The mean concentration of airborne formaldehyde was somewhat below 1 mg/m^3, but there were higher peak values. About 40% of the workers had rhinitis with nasal obstruction and discharge associated with the work place. The sera of the subjects were analysed for IgE antibodies by RAST and 2 workers were found to be positive with a high level of IgE.

There is no evidence in the literature of allergic reactivity of the mucous membranes of the eyes being caused by airborne formaldehyde or by formaldehyde solutions. There are only a few case reports about asthmatic symptoms caused by formaldehyde.

9.2.4.2 Skin effects

Allergic sensitization is caused by formaldehyde in solution only, not by gaseous formaldehyde. Prolonged and repeated contact with liquid solutions can cause skin irritation or allergic contact dermatitis, including sensitization. It is not known whether dermal reactions occur in human beings from airborne exposure to formaldehyde.

Formaldehyde allergy may be associated with the use of disinfectants, formaldehyde-based plastics, and contact with textiles impregnated with formaldehyde-based resins. Patch-test studies with different concentrations of formaldehyde have shown that concentrations below 0.05% rarely elicit an allergic reaction, even in sensitive individuals (Schulz, 1983). Marzulli & Maibach (1973) reported that one of 5 sensitized volunteers reacted, under controlled conditions, to a challenge concentration of 0.01% formaldehyde.

Formaldehyde solution is a primary skin-sensitizing agent inducing allergic contact dermatitis (Type IV, T-cell mediated delayed hypersensitivity reaction); it may induce immunological contact urticaria (Type I, perhaps IgE mediated, immediate hypersensitivity reaction).

Patch tests performed with formaldehyde challenge concentrations of 1% or less resulted in positive reactions in about 2% of all patients tested throughout the world; higher formaldehyde challenge concentrations may be irritant (Anon., 1987).

There are geographical and demographical differences in the incidence of contact sensitivity to allergens. The Japanese Contact Dermatitis Research Group (1982) published a study dealing with the results of patch tests performed at 17 Japanese hospitals in 1981. A total of more than 900 patients and healthy volunteer subjects were patch-tested with 2% formaldehyde solution (10 mg formaldehyde/cm^2). This caused irritation in 2.78% and a delayed reaction in 2.62% of the patients.

An allergic contact dermatitis reaction was provoked by a dose of formaldehyde of 0.25 µg/cm^2 skin (challenge dose: 50 µg/cm^2 with 0.5% percutaneous penetration).

In the past, formaldehyde dermatitis provoked by clothing textiles was a problem in certain countries. Modern textile finishing agents contain N-methylol compounds with only low amounts of free formaldehyde, so that formaldehyde allergies due to textiles are no longer expected to occur (Bille, 1981; Edman & Möller, 1982).

Contact eczema caused by formaldehyde may clear within 1-3 weeks, even without treatment, when the cause has been recognized and contact is strictly avoided.

Allergic reactions to cosmetics containing formaldehyde as a preservative, especially shampoos, are unusual (Eckardt, 1966) and appear mostly among those who have been sensitized by occupational exposure.

In a haemodialysis unit where formalin was used as a sterilant, 6 out of 13 staff members developed dermatitis within 3 weeks (Sneddon, 1968); 4 of the 6 were positive in patch tests with 3% formalin.

9.2.4.3 Respiratory tract sensitization

Well-controlled scientific studies on allergic airway responses to formaldehyde are few.

Nordman et al. (1985) gave a total of 230 patients, who suffered from "asthma like" respiratory symptoms, a bronchial provocation test

with formaldehyde. On the basis of the medical and occupational histories of the patients, the specific bronchial provocation test and other tests results, 12 cases were considered to be caused by specific sensitization to formaldehyde.

Burge et al. (1985) reported tests on 15 formaldehyde-exposed workers with symptoms suggesting occupation-related asthma. Bronchial provocation tests with a mean formaldehyde concentration of 4.8 mg/m^3 (range not given) showed 3 subjects with delayed bronchiospasm and 6 with an immediate reduction in forced expiratory volume in one second (FEV1).

In a similar study on 13 patients with asthma suspected of being related to formaldehyde exposure, no significant drop in FEV was seen when bronchial provocation tests with formaldehyde concentrations of up to 3.6 mg/m^3 were carried out. Five of the subjects were on bronchodilator treatment at the time (Frigas et al., 1984).

Eight cases of occupational asthma (3 smokers, 5 non-smokers) were reported among 28 members of the nursing staff at a haemodialysis unit where formalin was used to sterilize the artificial kidney machine (Hendrick & Lane, 1977). In 2 out of 5 subjects with histories of recurrent attacks of wheezing, inhalation provocation tests led to asthmatic attacks similar to those at work.

Hendrick et al. (1982) reinvestigated the nurses of the haemodialysis unit. One nurse had not worked with formaldehyde since 1976 and had had no further symptoms. Her 1981 test (15-min exposure to 7.2 mg formaldehyde/m^3) did not provoke any asthmatic response. The other nurse had continued to work with formaldehyde, though under much improved conditions, and had continued to suffer mild intermittent attacks of asthma. Her test (5-min exposure to 3.6 mg formaldehyde/m^3) provoked a late asthmatic reaction similar to the one observed in 1975.

9.2.4.4 Systemic sensitization

A case report has been described involving an anaphylactic shock reaction after accidental iv application of formaldehyde during haemodialysis treatment due to formaldehyde remaining in the equipment after disinfection. No measurements of the residual formaldehyde in the reconditioned dialyser were given. There was no personal or family history of atopy. Prick tests and radioallergosorbent tests (RAST) with common food and inhalant allergens were negative. Prick tests performed with 0.1 and 1% formaldehyde were positive in the patient, whereas they were negative in control subjects. The RAST with formaldehyde was performed using discs specially prepared and coated with serum-albumin. RAST was strongly positive. RAST to ethylene oxide was negative. A patch test with formaldehyde (concentration 1%) was performed and induced an anaphylactic shock, 26 h after the skin application of formaldehyde. The patient did not present any anaphylactic symptoms with the use of non-reconditioned dialysers. An immediate-type allergy to formaldehyde mediated by IgE may have occurred in this patient (Maurice et al., 1986). Because, after 26 h, the patch test resulted in an anaphylactic, but not delayed allergic contact dermatitis, reaction, the findings seem to be contradictory.

Wilhelmsson & Holmström (1987) investigated possible mechanisms underlying nasal symptoms in 30 formaldehyde workers exposed through inhalation in a formaldehyde-producing factory. Two cases showed a positive RAST with formaldehyde with high total IgE values (177 and 360 kU/litre). One of them suffered from severe rhinitis, the other from nasal and skin symptoms associated with the work place. A skin test with formaldehyde was negative at 15 min but positive at 72 h.

Systemic sensitization arising from the release of formaldehyde into the circulation in chronic haemodialysis patients showed evidence of formaldehyde-dependent immunization. The production of auto-anti-nuclear-like antibodies was dependent on the length (years) of the haemodialysis treatment (Lynen et al., 1983) and on the formaldehyde concentration released from the dialysers (Lewis, 1981).

Auto-anti-nuclear-like antibodies were found in 5 out of 18 patients after 1 year of dialysis; 10 out of 12 patients after 3-5 years, and in all 9 patients exposed to formaldehyde through dialysis for more than 5 years (Lynen et al., 1983).

Auto-anti-nuclear-like antibodies were observed in 30% of the patients when the formaldehyde concentration in the rinse of the dialysers was 8 mg/litre (8 ppm); however, the incidence was zero at a concentration of 0.6-1.2 mg/litre (Lewis et al., 1981).

The presence of auto-anti-nuclear-like antibodies and autoimmune haemolytic anaemia are evidence of Type II autoallergy. Some severe asthmatic reactions suggest Type I allergy in dialysis patients.

Pross et al. (1987), using a wide range of immunological tests, studied the effects of controlled short exposures to formaldehyde. They found a minimal increase in the percent eosinophils, basophils, and T8 positive cells and a reduction in the response of natural killer cells to low-dose human alpha-Interferon. According to the authors, the meaning of these minimal, but statistically significant, changes remains unclear.

The antigenicity of formaldehyde-treated proteins were reported 70 years ago by Landsteiner & Lample (1917). A study by Patterson et al. (1986) demonstrated that sera of human beings exposed to intravenous formaldehyde during dialysis, contained antibodies of various immunoglobulin classes against formaldehyde-serum-albumin, as did sera of two dialysis nurses with histories of formaldehyde-induced asthma.

9.2.4.4.1 Allergic reaction following the dental use of paraformaldehyde

Adverse reactions have been reported following the use of root canal filling materials containing paraformaldehyde. The extrusion of a root canal sealant containing paraformaldehyde beyond the apex may be followed by an allergic reaction in sensitive individuals. The number of cases is very small in relation to the extensive use of such materials. However, 3 cases of allergic angiooedema in response to periapical paraformaldehyde have recently been reported (UK-CSM, 1987).

9.2.5 Skin Irritation

Primary toxic or irritative skin reactions occur through direct contact with formaldehyde solutions.

The concentration of aqueous formaldehyde solution causing irritant contact reactions after application on human skin has not been confirmed. For human skin, a single application of 1% formalin in water with occlusion will produce an irritant response in approximately 5% of the population (Maibach, 1983).

Cosmetics containing a formaldehyde concentration of 0.2% as a preservative and nail hardeners containing at least 5% formaldehyde did not provoke toxic or irritative contact reactions on normal skin.

Other reactions may occur in cases of previously damaged skin surfaces and/or atopic individuals.

There are observations but no published experimental or clinical findings confirming the induction of irritant contact dermatitis by gaseous formaldehyde (Axelson, 1987, Personal Communication).

9.2.6 Genotoxic effects

Studies on pathology staff, occupationally exposed to formaldehyde, failed to demonstrate any increase in the incidence of chromosomal aberrations or the frequency of sister chromatid exchanges (Thomson et al., 1984). Similarly, there were no increases in the incidence of chromosomal aberrations in workers exposed to formaldehyde during its manufacture and processing (Fleig et al., 1982), or in the incidence of sister chromatid exchanges in workers exposed to formaldehyde in a paper factory (Bauchinger & Schmid, 1985).

Yager et al. (1986) reported an increased incidence of sister chromatid exchanges in anatomy students, but the values reported fell within the normal range. Furthermore, the authors reported that the subjects were in a "stress situation" at the time of the study and were also exposed to other agents, including phenol. Bauchinger & Schmid (1985) reported an increased incidence of chromosomal aberrations in a study of workers in a paper factory who were exposed to formaldehyde; the statistical methods used and the relevance of the types of aberrations found have been questioned (Engelhardt et al., 1987).

No increase was found in the mutagenicity of urine of autopsy workers exposed to formaldehyde (Corren et al., 1985). Ward et al. (1984) did not observe any effects on sperm morphology or sperm count attributable to formaldehyde.

Goh & Cestero (1979) studied chromosomal patterns of direct bone marrow preparations from 40 patients undergoing maintenance haemodialysis. Aneuploidies, chromosomal structure abnormalities, and chromosomal breaks were seen in the metaphase. During the period of this study, each patient could have received up to 126 ± 50 mg of formaldehyde during each dialysis.

9.2.7 Effects on reproduction

Shumilina (1975) reported an increased incidence of menstrual disorders, mainly dysmenorrhoea, and problems with pregnancy in 446 women workers using urea-formaldehyde resins (130 exposed to work-place formaldehyde concentrations of 1.4-4.3 mg/m^3 and 316 exposed to concentrations of 0.005-0.67 mg/m^3). There were no differences in fertility between the exposed and control group, but anaemia, toxaemia, and low birth weight of offspring were more frequent in the exposed group. However, possible confounding factors were not evaluated in this study. There is a lack of information on the workers' environment and the socioeconomic conditions of the study and control groups.

Hemminki et al. (1982, 1983) studied spontaneous abortions among hospital staff engaged in sterilizing instruments with chemical agents. They reported that there was no increase in spontaneous abortions associated with the use of formaldehyde.

In a population of hospital autopsy service workers, 11 exposed individuals and 11 matched controls were evaluated for sperm count, abnormal sperm morphology, and 2F-body frequency (Ward et al., 1984). Subjects were matched for age, and use of alcohol, tobacco, and marijuana. Additional information was collected on health, medication, and

other exposures to toxic substances. Ten subjects were employed for 4.3 months (range: 1-11 months) prior to the first sample, and one was employed for several years. Formaldehyde exposures were episodic, but with a time-weighted average of between 0.73 and 1.58 mg/m^3 (weekly exposure range, 3.6-48 mg/m^3 per h). Samples were taken from exposed and control subjects 3 times at 2- to 3-month intervals. No statistically significant differences in the variables were observed between the exposed and control groups. Reduced sperm count was correlated with increased abnormal morphology and 2F-body frequency in the exposed group but not in the control group. Evaluation of the impact of incidental exposures suggests a reduced count with marijuana use and increased abnormal morphology with medications used by controls. No effects on sperm due to formaldehyde or its metabolites were observed in this occupationally-exposed population. However, it was considered that the lack of an effect in this study might be due to a lack of statistical power to detect effects at this exposure level.

9.2.8 Other observations in exposed populations

Dally et al. (1981) measured formaldehyde in the air of 100 homes, containing particle board or urea-formaldehyde foam insulation, in which residents reported symptoms of eye, nose, and throat irritation. They found levels ranging from < 0.12 to 4.42 mg/m^3 (< 0.1 ppm to 3.68 ppm) and concluded that indoor environmental exposure to formaldehyde may exceed occupational exposure levels. Sardinas et al. (1979) studied individuals from 68 households in which 167 complaints related to urea-formaldehyde insulation were being investigated. Twice as many individuals reported eye irritation in homes in which formaldehyde was detected by Draeger tubes (0.5-10 µg/litre) compared with the number in homes in which there was no detectable formaldehyde.

In a study by Woodbury & Zenz (1983), 20 symptomatic infants were followed up, whose mobile home environment was suspected to be related to their illness. The authors noted a relationship between the occurrence of symptoms and the time spent at home. However, no statistically significant association was found between symptoms and air levels of formaldehyde.

All three studies suffer from possible selection bias, the absence of appropriate controls, and no mention of whether other chemical exposures and smoking habits were considered.

In a pilot study, Schenker et al. (1982) studied the health of 24 full-time residents from 6 homes containing urea-formaldehyde foam insulation. The results of standardized allergy skin tests and spirometry tests were normal in all subjects. Memory difficulty was a frequently reported symptom. Memory storage deficits could not be demonstrated, but the results of tests of attention span were abnormal in 11/14 subjects; furthermore, 8 out of the 11 subjects suffered from elevated depression scores. The sample size in this pilot study was small (adults: 9 males, 9 females; children: 2 males, 4 females) and may have been biased by self-referrals; there was no control group.

The Consensus Workshop on Formaldehyde (1984) reviewed several reports linking long-term formaldehyde exposure to a range of psychological or behavioural problems (depression, irritability, memory loss, decreased attentional capacity, sleep disturbances). Most of the studies used subjective self-report symptom inventories. Control data, describing the incidence of such symptoms from unexposed persons are often inadequate or completely absent. Olson & Dossing (1982) administered a standardized questionnaire based on the linear analogue self-assessment method to 70 employees (66 responded) at 7 mobile day-care centres, in which urea-formaldehyde glued particle boards had been

used, and to 34 (26 responded) employees at 3 control institutions, selected at random, which did not contain any particle boards. Mean concentrations of formaldehyde were 0.43 and 0.08 mg/m^3, respectively. Among the staff at the mobile day-care centres, there was a significantly greater prevalence and intensity of symptoms of mucous membrane irritation, headache, abnormal tiredness, menstrual irregularities, and use of analgesics, but there were no differences in terms of memory disturbance and concentration (50% of the cohort were smokers).

Two groups of male workers exposed to formaldehyde (group 1 employed in the phenol-formaldehyde-plastic foam matrix embedding of fibreglass (batt making); group 2, in the fixation of tissues for histology) were studied by Kilburn et al. (1985) for work-related neurobehavioural, respiratory, and dermatological symptoms, and for pulmonary function impairment. Forty-five male fibreglass batt makers were studied during the initial work shift after a holiday, with regard to combined neurobehavioural (impact on sleep, memory, equilibrium, and mood), respiratory, and dermatological symptoms. Average frequencies of 17.8 (for the hot areas of the process) and 14.6 (for the cold areas) were found. Their symptom counts were significantly higher than those for 18 male histology technicians (average 7.3), and those for 26 unexposed male hospital workers (average 4.8).

The fibreglass batt makers were also exposed to numerous other products, such as phenol, surfactants, particulate smoke, glass fibre, etc. The formaldehyde work-place concentrations were not measured. No consideration was given to potential respondent bias in symptoms or exposures or to the socioeconomic differences between the workers and the technicians.

9.2.9 Carcinogenic effects

The evaluation of the risks for human health from occupational or environmental agents relies heavily on the evidence gleaned from epidemiological studies. It is, therefore, important to emphasize the procedures that should be adopted, in order to assess the value of such epidemiological investigations, particularly with reference to the shortcomings inherent in the epidemiological method.

For practical purpose, three types of study are in common use: The cohort, the case-control, and the correlation (surveillance) study.

Cohort and case-control studies relate individual exposure to the agent under study with the occurrence of a health effect (in this case, cancer) in individuals, and provide an estimate of relative risk as the main measure of association. Cohort studies, which follow populations prospectively, are inherently less subject to bias than the more commonly used retrospective (historical) cohort studies as the data on health outcome are not acquired from past records. However, because retrospective cohort studies cannot be based on a well defined population, it is possible to use proportionate mortality (or morbidity) studies which give, by definition, less precise estimates of risk. Case-control studies always rely on retrospective exposure assessments and although such studies are usually easier to execute than cohort studies, they are sensitive to various types of bias that are difficult to eliminate. Correlation (surveillance) studies use whole populations according to geographical area or time period as the initial data base and health outcome (cause-specific deaths or cancer incidence) is related to a summary measure of the population exposure. Individual exposure is not documented, thus causal relationships are difficult to infer from the results.

All epidemiological studies are subject to some extent to factors

that can affect their quality with, as a general rule, cohort studies being superior to case-control studies. Four factors are particularly important: bias, confounding, chance, and qualitative measures of exposure and outcome. Bias means the operation of factors in the design or execution of the study that can lead to erroneous associations between the exposure and the health outcome, because of a failure to estimate these factors independently. Confounding refers to a situation in which the relationship between the exposure and the health outcome is altered by one or more factors that separately and independently influence the outcome. The likelihood that the results of the study could have occurred by chance is estimated by using appropriate statistical analyses. Finally, the accuracy and completeness of the information gathered on exposure and health outcome needs to be reviewed. Cancer is a relatively easy outcome to document but epidemiological studies are often seriously deficient in their assessments of exposure to the agent of interest, i.e., the degree, the duration, and even the misclassification of exposure of individual members of the study population.

Thus, epidemiological studies need to be evaluated, not only for their results, but also for the way in which the investigators have addressed the methodological problem outlined above. Sufficient information should be available in the study reports to make these value judgements.

Thereafter, the reviewer is frequently confronted with a series of studies from which to make an evaluation. Causality, that is the contention that the agent in question causes the disease in question, depends on a number of considerations. The most important are: the size of the relative risk estimate (coupled with a relatively narrow confidence interval), the observation of a putative relationship between agent and disease in a number of studies using similar or different designs in different populations; evidence that the agent acts on specific organ systems which are biologically plausible; and, finally,

that the effect of the agent has been assessed in studies covering an observation period long enough to allow for the latent period and the period of induction of disease. In cancer studies, this may require an observation period of several decades for each study member.

In short, the evaluation of epidemiological studies initially requires value judgements regarding the quality of the design and execution of the study. Thereafter an assessment is needed of groups of studies to estimate the likelihood or otherwise that the relationship between the exposure and the disease is causal. Such evaluation procedures have been adopted here for formaldehyde and human cancer.

Observed and expected deaths for professional and industrial workers exposed to formaldehyde are summarized in Table 36. The occupations studied consisted of professionals who use formaldehyde in the preservation of biological tissues (embalmers, anatomists, pathologists, and zoologists), and industrial workers involved in the production and use of formaldehyde. The pattern and intensity of exposure to formaldehyde differed for both groups.

Table 36. Observed and expected deaths for professional and industrial workers exposed to formaldehyde (with 95% confidence limits)[a]

Cause	*Professional*		*Industrial*	
	Observed/ expected	Confidence limits	Observed/ expected	Confidence limits
Cancer				
Nasal	0/1.7	0-2.17	0/1.3	0-2.84

Mouth	20/23.8	0.51-1.30	12/9.2	0.67-2.28
Brain	40/22.6	1.26-2.41	6/13.2	0.17-0.99
Lymphatic and haematopoietic	80/64.0	0.98-1.53	25/30.6	0.53-1.21
Leukaemia	40/27.2	1.05-2.00	9/11.4	0.36-1.50
Other lymphatic and haematopoietic	40/36.8	0.78-1.48	16/19.2	0.48-1.35
Lung	175/243.6	0.62-0.83	214/227.3	0.82-1.08
Prostate	61/51.6	0.90-1.52	2/0.6	0.40-12.04
Skin	12/11.4	0.54-1.84	0/0.4	0-9.22
Bladder	23/24.3	0.60-1.42	1/0.3	0.18-18.6
Kidney	21/18.6	0.70-1.73	1/0.4	0.06-13.93
Digestive system	211/245.2	0.74-0.98	8/10.4	0.33-1.52
Other causes				
Cirrhosis of liver	83/59.3	1.11-1.74	10/9	0.53-2.04
Non-neoplastic respiratory disease	109/163.7	0.55-0.80	243/241.1	0.88-1.14

[a] From: Consensus Workshop on Formaldehyde (1984).

A summary of epidemiological studies with formaldehyde is presented in Tables 37, 38, and 39. An excess of several forms of cancer, i.e., Hodgkin's disease, leukaemia, cancers of the buccal cavity and pharynx, lung, nose, prostate, bladder, brain, colon, skin and kidney, has been seen in more than one of the epidemiological studies relating to formaldehyde. Some of these excesses may be due to random variation and others may depend on factors other than formaldehyde exposure. Such explanations might be suggested, especially when only a few cases are involved or when the risk ratios are low. Some studies involve the same populations and therefore do not provide completely independent information (Marsh, 1983; Wong, 1983; Liebling et al., 1984).

Table 37. Summary of epidemiological proportional mortality rate (PMR) studies formaldehyde[a]

Author(s) (Year)	Study population	Study period	Site	Risk estimates (PMR)	Dece
Marsh (1982)	chemical workers (USA)	1950-76			136
			respiratory system	80	
			digestive system	127	
			genital system	121	
			lymphatic system	86	
Walrath & Fraumeni (1983)	male embalmers (New York)	1925-80			1010
			buccal and pharyngeal	126	
			nasopharynx	-	
			respiratory	102	
			nasal	-	
			prostate	89	
			bladder	92	
			brain	157	
			leukaemia	132	
			colon	140	
			skin	253	
			Hodgkins	-	
			kidney	170	
			lymphatic and haemato-poietic	115	

Table 37 (contd).

Author(s) (Year)	Study population	Study period	Site	Risk estimates (PMR)	Dece
Walrath & Fraumeni (1984)	embalmers (California)	1925-80			1007
			buccal	131	
			respiratory	94	
			nasal	-	
			prostate	175	
			brain & CNS	194	
			leukaemia	175	
			colon	187	
			skin	59	
			Hodgkins	-	
			bladder	138	
			kidney	100	
			rectum	102	
			gallbladder and liver	85	
			pancreas	135	
			stomach	79	
Stayner et al. (1985)	garment workers	1959-82			25
			buccal	229	
			nasal Pha.	-	
			digestive	126	
			gallbladder and liver	313	
			lung	95	
			skin	179	
			bladder and kidney	92	
			lymphatic	163	
			leukaemia	168	

[a] Exposure characteristics described.

Table 38. Summary of epidemiological case-control studies with formaldehyde

Author(s) (Year)	Study population	Study period	Type of exposure	Cases	Controls	Site
Jensen et al. (1982)	physicians	1943-76	speciality	84	252	lung
Fayer-weather et al. (1983)[a,b]	chemical workers	1957-79	levels and duration	481	481	multiple buccal cavity oesophagus stomach liver, gall-bladder, lung
Coggon et al. (1984)[c]	workers (United Kingdom)	1975-79	occupational	296	472	bronchus
		1975-79	occupational	132	268	bladder

Olsen et al. (1984)	workers (Denmark)	1970-82	exposure assessed	754	2465	nasal nasopharynx
Partanen et al. (1985)[a]	wood workers	1957-80	levels and duration	57	171	respiratory
Bond et al. (1986)[a]	chemical workers	1940-80	ever exposed	308	588	lung
Hayes et al. (1986)[a]	wood workers (Netherlands)	1978-81	levels	91	195	nose and nasal sinuses

Table 38 (contd).

Author(s) (Year)	Study population	Study period	Type of exposure	Cases	Controls	Site
Vaughan et al. (1986a)[a]	Tumour registry	1979-83	occupational	285	552	nasopharynx nasopharynx buccal cavity buccal cavity
Vaughan et al. (1986b)[a]	Tumour registry	1979-83	residential	285	552	nasopharynx nasal cavity buccal cavity
Brinton et al. (1984)[a]	industrial workers	1970-80	occupational	160	290	nasal cavity
Olsen & Asnaes (1986)	Tumour registry Denmark	1970-82	occupational	759	2465	nasal cavity nasopharynx
Roush et al. (1985)	Tumour registry	1940-81	occupational	371	605	nasopharynx nasal cavity
Hardell et al. (1982)[a]	Tumour registry Sweden	1970-79	occupational	44	541	nasal

[a] Study controlled for tobacco use.
[b] Selection criteria < 20 years after first exposure.
[c] Selection criteria male < 40 years.

Table 39. Summary of epidemiological cohort studies with formaldehyde[a]

Author(s) (Year)	Study population	Study period	Site	Risk estimates (SMR)	Study population	Type of exposure
Acheson et al. (1984)	chemical workers	1941-81			7680	levels and duration
			bucco-pharyngeal	109		
			nasopharynx	-		
			lung	95		
			nasal	-		
			digestive	101		
			larynx	88		
Harrington & Oakes (1984)	male pathologists	1974-80			2307	none
			digestive	20		
			lung	41		
			bladder	107		
			brain, CNS	331		
			lymphatics	54		
			leukaemia	90		
Levine et al. (1984)	embalmers, (Canada)	1950-77			1477	none
			bucco-pharyngeal	48		
			lung	94		
			prostate	88		
			urinary organs	54		
			brain, CNS	115		
			colorectal	85		
			leukaemia	160		
			lymphatic	124		
			digestive	75		

Table 39 (contd).

Author(s) (Year)	Study population	Study period	Site	Risk estimates (SMR)	Study population	Type of exposure
Stroup et al. (1986)	anatomists	1925-79			2317	duration special
			bucco-pharyngeal	15		
			nasopharynx	-		
			lung	28		
			nasal	-		
			prostate	100		
			bladder	68		
			brain, CNS	270		
			leukaemia	147		
			colon	108		
			lymphatic	123		
Blair et al. (1986)	industrial workers	1934-80			26 561	levels, duration and peaks
			buccal cavity	96		
			nasopharynx	300		
			lung, pleura	111		
			nasal cavity	91		
			prostate	115		
			bladder	96		

			kidney	123		
			brain	81		
			leukaemia	80		
			colon	87		
			skin	80		
			Hodgkin's	142		
Blair et al. (1987)	industrial workers	1930-80	nasopharynx	384	26 561	none
			oropharynx	167		

Table 39 (contd).

Bertazzi et al. (1986)	resin workers	1959-80	bucco-pharyngeal	-	1332	
			digestive	156		
			oesophagus	-		
			stomach	148		
			lung	236		
			lymphatic	201		
Edling et al. (1987)	abrasive manufacturers	1958-83	bucco-pharyngeal	-	521	
			nasopharynx	-		
			stomach	80		
			colon	100		
			pancreas	180		
			lung	57		
			prostate	85		
			lymphatic	200		
Stayner et al. (1988)	textile workers	1953-77	buccal cavity	343	11 030	
			digestive system	58		
			lung	114		
			bladder	112		
			kidney	55		
			brain	71		
			lymphatic system	91		
			leukaemia	114		

[a] There are no cohort studies with control of tobacco use.

In view of the solubility and rapid metabolism of formaldehyde (section 6.3), it seems that (upper) respiratory tract cancers would be more likely to be causally related to formaldehyde exposure than other forms of cancer. Besides various types of occupational exposure, smoking and other use of tobacco would have to be considered with regard to potential confounding factors, especially when exerting strong effects, such as those of tobacco smoking in relation to lung cancer. Furthermore, because of the formaldehyde contents of mainstream and side-stream smoke, there would be a potential increase in any reference population, and this would mask the effects of formaldehyde with regard to cancers that might be related to occupational or other specified exposure to formaldehyde. Finally, it should be noted, within this general epidemiological context, that there is experimental evidence providing a relatively clear suggestion of a possible cancer risk for human beings from exposure to formaldehyde.

Excess of nasal or nasopharyngeal cancer in relation to formaldehyde exposure was reported in 6 of the case-control studies reviewed (Table 38) (Hardell, 1982; Olsen et al., 1984; Roush et al., 1985; Hayes et al., 1986; Vaughan et al., 1986a,b). In 2 other case-control studies (Fayerweather et al., 1983; Brinton et al., 1984), the question of a relationship with formaldehyde was addressed either by primary design or by reporting formaldehyde exposure for either cases or controls, but no excess risk was demonstrated. None of the cohort or PMR studies listed in Tables 37 and 39 had adequate power to detect even a considerably increased risk though, in aggregate, the studies might have had the power to reveal, at least, a higher risk for nasal cancer. It should also be noted that with regard to nasal and nasopharyngeal cancer, smoking is not likely to exert any particularly strong confounding effect, since the relation of these cancer types to smoking is only moderately strong, i.e., up to a risk ratio of about five (Axelson & Sundell, 1978; IARC 1986) and has been lower in many studies.

Cancers of the buccal cavity and pharynx have either not been included in studies or in some case-control studies the risk has appeared about normal (Fayerweather et al., 1983; Vaughan et al., 1986a,b), There was no excess in the largest cohort (Blair et al., 1986), though an excess appeared in other studies involving small numbers (Stayner et al., 1985, 1988; Walrath & Fraumeni, 1983, 1984).

Table 40. Mortality from subsites of cancer of the buccal cavity and pharynx through cumulative exposure to formaldehyde[a]

Cancer	Mortality after formaldehyde exposure at								
	0 mg/m^3-years			< 0.6 mg/m^3-years			0.6 - 6.6 mg/m^3-years		
	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SI
Lip	0	0.1	-[b]	1	0.2	477	0	0.2	·
Tongue	0	0.5	-[b]	0	1.8	-[b]	2	2.1	9
Salivary glands	0	0.2	-[b]	0	0.5	-[b]	0	0.6	-
Gum, floor, other mouth sites	0	0.4	-[b]	1	1.5	66	0	1.8	·
Nasopharynx	1	0.2	530	2	0.7	271	2	0.8	2
Oropharynx	0	0.3	-[b]	4	0.9	443[c]	1	1.0	9
Hypopharynx	1	0.2	594	1	0.6	172	0	0.7	
Other parts of pharynx	0	0.4	-[b]	1	1.4	73	0	1.6	·

[a] From: Blair et al. (1986).

[b] No deaths.

[c] $P < 0.05$.

Some excess of respiratory cancer has appeared in 3 case-control studies in comparison with low exposures in general (Coggon et al., 1984) or comparable unexposed workers (Partanen et al., 1985) and between physicians in surgery and internal medicine, though these findings were based on small numbers (Jensen et al., 1982). Two other studies have come out as non-positive (Fayerweather et al., 1983; Bond et al., 1986). Of these cohort and PMR studies, which had adequate power and were designed to elucidate the risk of respiratory cancer from formaldehyde, 3 (Walrath, 1983; Bertazzi et al., 1986; Blair et al., 1986) showed an excess (significantly high in the study by Bertazzi et al., 1986). Blair et al. (1986) showed some excess in laryngeal cancer (Table 40). Seven studies with reasonable power were

negative (Harrington & Oakes, 1984; Stroup et al., 1984, 1986) or non-positive with regard to respiratory cancer (Marsh, 1983; Acheson et al., 1984; Levine et al., 1984; Walrath & Fraumeni, 1984; Stayner et al., 1985, 1988). The deviations in both directions from the expected in these studies are explainable by the lack of control for smoking and/or the so-called "healthy worker effect", which means that the study population is not comparable with the general population.

Leukaemia has come out somewhat high in all the studies involving reasonable numbers of cases (Stroup et al., 1984, 1986; Walrath & Fraumeni, 1983) and even significantly high in one study (Walrath & Fraumeni, 1984). Three of these studies involved either embalmers (Walrath & Fraumeni, 1983, 1984) or anatomists (Stroup et al., 1984, 1986), which might suggest some other alternative or contributing etiological factor operating. Similarly, for brain cancer, which was found in significant excess in some studies (Harrington & Oakes, 1984; Stroup et al., 1984, 1986; Walrath & Fraumeni, 1984), a confounding factor may be suspected regarding the relationship between brain cancer and social class (Table 41). An excess of colon cancer among embalmers (Walrath & Fraumeni, 1983, 1984; Stroup et al., 1984, 1986) may perhaps be explained by a recently observed association with sedentary work (Garabrant et al., 1984; Gerhardsson et al., 1986). Of the other cancer forms previously mentioned as appearing in excess in more than one study, cancers of the skin, bladder, kidney, and prostate, as well as Hodgkin's disease are represented by small numbers and/or small excesses, though prostatic cancer was significantly high in one study on embalmers, based on 23 cases (Walrath & Fraumeni, 1984) and skin, but not prostatic cancer was significantly high in the other study on embalmers (Walrath & Fraumeni, 1983).

Table 41. Mortality ratios of men according to social class[a]

Disease	*Population*			*Social class*					*Re*
Place Race	Age (years)	Year	Ratio[b]	High I	II	III	IV	Low V	
Brain cancer									
United Kingdom									
all	15-64	1970-72	SMR	108	101	111, 105	100	92	Regis
all	65-74	1970-72	PMR	225	137	109, 99	85	56	Regis
all	20-64	1949-53	SMR	133	96	104	88	99	Regis
all	65	1949-53	PMR	136	112	105	90	71	Regis
all	35-65	1930-32	SMR	167	92	116	97	66	Regis
all	20-65	1921-23	CMFR	160	160	120	80	60	Regis
USA									
California									
all	20-64	1949-51	SMR	130	127	108	77	58	Buell
Massachusetts									
white	20	1971-73	SMOR	164	97	114	62[c]		Dubrov
USA									
all	20-64	1950	SMR	136	121	109	94	81	Gural
Leukaemia									
United Kingdom									
all	15-64	1970-72	SMR	113	100	107, 101	104	95	Regis
all	65-74	1970-72	PMR	138	124	108, 98	90	77	Regis
all	20-64	1949-53	SMR	123	98	104	93	89	Regis
all	65	1949-53	PMR	202	115	101	78	74	Regis
all	20-65	1930-32	SMR	152	126	97	95	86	Regis

USA California all	20-64	1949-51	SMR	104	116	101	86	104	Buell
Massachusetts white	20	1971-73	SMOR	126	97	108	89[c]	-	Dubrov
USA all	20-64	1950	SMR	117	100	105	89	98	Gural

[a] From: Levine (1985).

[b] SMR = standardized mortality ratio.
PMR = proportional mortality ratio.
SMOR = standardized mortality odds ratio.
CMFR = comparative mortality figure ratio.

[c] Including classes IV and V.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of Human Health Risks

The absolute odour threshold for formaldehyde is between 0.06 and 0.22 mg/m^3 (a group of observers detected the odour in 50% of the presentations, 10% of an untrained population detected a level of 0.03 mg/m^3). There is a low probability that human beings will be able to detect formaldehyde in air at concentrations below 0.01 mg/m^3.

Since interaction and adaptation processes are characteristic of the sensory systems involved in the perception of odour and irritation, the duration of exposure and the other components of environmental air exposure influence the perception. Although sensory adaptation because of length of exposure may weaken the perceptual response, there is a high probability that exposure duration will enhance the perception, especially at low concentrations. In addition, formaldehyde often appears in complex gas mixtures that contain other low concentrations of odorous or irritating components. Examples are photochemical smog, automobile exhaust, environmental tobacco smoke, and contaminated indoor air, with building materials as the source.

There are no data on the absolute irritation threshold for formaldehyde, but sensory irritation has been reported for the eyes at 0.06 mg/m^3 and for the respiratory tract at 0.12 mg/m^3.

Formaldehyde vapour causes direct irritation of the human respiratory tract. However, precise thresholds have not been established for the irritant effects of inhaled formaldehyde. Some people experience throat irritation at 0.1 mg/m^3 and almost everybody will experience it before a level of 3.0 mg/m^3 is reached.

The effects on the nasal cavity, the site of impact for most of the inhaled formaldehyde, is impairment of mucociliary flow at or above a level of 0.5 mg/m^3. This effect may also lead to the secondary complication of respiratory disease. There is a higher incidence of chronic respiratory disease in occupationally-exposed subjects or children living in a formaldehyde-polluted environment. Long-term exposure to 0.45 mg/m^3, independent of tobacco-smoking habits, may cause bronchoconstriction.

Formaldehyde has been shown to cause pulmonary effects on healthy and on asthmatic subjects (not sensitized to formaldehyde) at a concentration that is already irritant. Precise thresholds have not been established for the pulmonary irritant effects of inhaled formaldehyde. However, lower airway and pulmonary effects are likely to occur at

levels above 6 mg/m^3.

There are no data on the exact exposure level at which inhaled formaldehyde has a sensitizing effect, but once sensitization has developed, short-term exposure to concentrations that can be found in occupational or home environments is sufficient to produce an asthma-like response. Asthmatic responsiveness may persist if intermittent exposure to low levels continues. Removal from exposure has a favourable effect on symptoms.

Although few proven formaldehyde-induced asthma patients have been reported, it appears likely that this condition is underreported.

There is a possibility of the induction of sensitisation via haemodialysis, where formaldehyde may enter the circulation through the disinfecting of the dialysis equipment. This can be influenced by the state of health and previous medication of the patient.

Skin sensitisation in human beings is induced by direct contact with formaldehyde solutions, only in concentrations higher than 2%. The lowest patch-test challenge concentration producing a reaction in sensitized persons was 0.05% formaldehyde in an aqueous solution. Patch tests performed with formaldehyde challenge concentrations of < 1% formaldehyde resulted in positive reactions in about 2% of all patch-tested patients throughout the world.

Positive patch tests results with formaldehyde challenge concentrations of 2% or more may be due to skin irritation.

Formaldehyde may induce contact urticarial reactions, but these are rarely observed and have not been confirmed as IgE-mediated Type I reactions.

Cell-mediated allergic dermatitis, arising from systemic exposure, and antibody (IgE)-mediated exanthematous phenomena have not been observed after ingestion of formaldehyde.

Irritant skin reactions occur through direct contact with formaldehyde solutions. A single application of 1% formalin in water with occlusion will produce an irritant response in approximately 5% of the test population.

Mental or behavioural problems at levels present in the home environment have been claimed to be due to long-term formaldehyde exposure, as adjudged by questionnaires, but there were no differences in terms of memory loss, sleep disturbance, and concentration. Possible impaired memory, equilibrium, and dexterity, in some cases has been suggested in relation to long-term, high-level occupational exposure.

Animal data do not indicate that formaldehyde is embryotoxic or teratogenic.

Formaldehyde reacts with macromolecules, including DNA. The genotoxic effects of formaldehyde have been reported in a wide range of mutagenicity tests *in vitro* in the absence of a metabolizing system.

In vivo , most mutagenicity tests are negative. However, DNA-protein cross-links are induced at the site of exposure, after inhaling formaldehyde. The importance of this local genotoxic effect with respect to the induction of cancer requires further evaluation.

The importance of positive mutagenicity findings with regard to germ-cell mutations is limited. In the light of known metabolic mechanisms, it should not be assumed that formaldehyde induces mutations in

germ cells and it is unlikely that formaldehyde leads to a heritable genetic risk.

Formaldehyde is a nasal carcinogen in rats. A highly significant incidence of nasal cancer was induced in rats exposed to a level of 18 mg/m^3, but the concentration-response curve was extremely non-linear, and only a low, not statistically significant, incidence of nasal tumours occurred at 7.2 mg/m^3. The results of this and other studies consistently indicate that, at low concentrations, the risk of cancer is *disproportionately* low. It is likely that defence mechanisms in the respiratory tract, including the mucociliary clearance apparatus, metabolism by formaldehyde dehydrogenase and other enzymes, and DNA repair, are effective at low concentrations, but that, at high concentrations, these defence mechanisms can be overwhelmed and may even be inactivated, thus resulting in tissue damage.

On the basis of these data it can be concluded that the induction of nasal cancer in rats by formaldehyde requires repeated exposure to high concentrations, i.e., concentrations that are very irritating and cause considerable damage to the nasal mucosa followed by regenerative hyperplasia and metaplasia. The increased cell turnover, as well as subsequent cycles of DNA-damage provoked by continuous exposure to formaldehyde, may strongly increase the likelihood of relevant DNA damage, and subsequently may greatly enhance the progression of pre-neoplastic cells to cancer. Formaldehyde, in concentrations not leading to cell damage, probably cannot act as a complete carcinogen, causing initiation, promotion, and progression, and, as a result, is very unlikely to induce cancer by itself. From the above, it appears that the cytotoxic effects are likely to play a highly significant role in the formation of nasal tumours by formaldehyde.

Despite differences in the anatomy and physiology of the respiratory tract between rats and human beings, the respiratory tract defence mechanisms are similar. Therefore, it is reasonable to conclude that the response of the human respiratory tract mucosa to formaldehyde will be qualitatively similar to that of the rat respiratory tract mucosa.

Evidence from rat studies suggests that recurrent tissue damage occurs in conjunction with exposure to high, cytotoxic concentrations of formaldehyde, and that this is necessary for nasal tumours to be produced. If respiratory-tract tissue is not repeatedly damaged, exposure of human beings to low, non-cytotoxic concentrations of formaldehyde can be assumed to represent a negligible cancer risk. However, if exposure were to be accompanied by recurrent tissue damage at the initial site of contact, formaldehyde may be assumed to have carcinogenic potential for man.

Some excess has been shown for several types of cancer in more than one of the epidemiological studies relating to formaldehyde, i.e., Hodgkin's disease, leukaemia, and cancers of the buccal cavity and pharynx, lung, nose, prostate, bladder, brain, colon, skin and kidney. Some of these excesses may be due to random variation and others may depend on factors other than formaldehyde exerting confounding effects. Such explanations might be suggested, especially when only a few cases are involved or when the risk ratios are low.

In view of the solubility and rapid metabolism of formaldehyde, it seems that upper respiratory tract cancers would be more likely to be causally related to formaldehyde exposure than other forms of cancer, especially as there is experimental evidence providing a relatively clear suggestion of a possible cancer risk for human beings from exposure to formaldehyde. Besides various types of occupational exposure, smoking and other use of tobacco would have to be considered

as potentially confounding factors, especially when exerting strong effects, such as those of tobacco smoking in relation to lung cancer. Furthermore, because of the formaldehyde content of mainstream and environmental tobacco smoke, there is exposure of any reference population, and this would mask effects with regard to cancers that might be related to occupational or other specified exposure to formaldehyde.

Some excess of nasal or nasopharyngeal cancer was reported in relation to formaldehyde exposure in 6 of the case-control studies reviewed. In 2 other case-control studies, the question of a relationship with formaldehyde was addressed either by primary design or by reporting formaldehyde exposure, but no excess risk was demonstrated. None of the cohort or PMR studies reviewed had adequate power to detect even a considerable increased risk though, in aggregate, the studies might have had the power to reveal, at least, a higher risk for nasal cancer. It should be noted that, with regard to nasal and nasopharyngeal cancer, smoking is not likely to exert any particularly strong confounding effect, since the relationship between these types of cancer and smoking is only moderately strong, i.e., a risk ratio of up to about five, and considerably less in many studies.

Cancers of the buccal cavity and pharynx have either not been included in studies or else the risk has appeared approximately normal in some case-control studies. There was no excess in the largest cohort, though an excess had appeared in other studies involving small numbers.

Some excess respiratory cancer appeared in 3 case-control studies, but these studies were based on small numbers. Two other studies came out as non-positive. Four of the cohort and PMR studies that had adequate power and were designed to elucidate the risk of respiratory cancer from formaldehyde exposure showed an excess risk (significantly high in workers producing resins containing formaldehyde, Bertazzi et al., 1986). There was an excess of laryngeal cancer in one study. Seven studies with reasonable power were either negative or non-positive with regard to respiratory cancer. The deviations in both directions from the expected in these studies are explicable by lack of control for smoking and/or the so-called "healthy worker effect" due to lack of comparability of the study population with the general population.

The incidence of leukaemia was increased in all the studies with reasonable numbers and was significantly high in one study. Three of these studies involved either embalmers or anatomists, which might suggest the operation of some other alternative or contributing etiological factors. Similarly, a confounding effect from some other factors might be suspected with regard to the relation between brain cancer (which was found in significant excess in some studies) and social class. An excess of colon cancer among embalmers must be considered against a recently observed association between this type of cancer and sedentary work. Of the other cancer forms previously mentioned as appearing in excess in more than one study, cancers of the skin, bladder, kidney, and prostate, as well as Hodgkin's disease, are represented by small numbers and/or small excesses. However, in one study based on 23 cases, prostate cancer was significantly high but not skin cancer, whereas in another study on embalmers, skin cancer was significantly high but not prostate cancer.

The available human evidence indicates that formaldehyde does not have a high carcinogenic potential. There are some studies which indicate an excess of nasal and/or nasopharyngeal tumours in exposed individuals or population though the relative risks are, in general, small.

Given the relative rarity of tumours in the biologically plausible area of the upper respiratory tract, and the widespread past occupational exposures to formaldehyde in various work situations, it can be concluded that formaldehyde is, at most, a weak human carcinogen.

Human exposure to formaldehyde should be minimized, not only for its probable carcinogenic effect, but also for its potential for tissue damage. One practical way of moving towards an effective preventive strategy would be to control the formaldehyde level in the work place below that likely to produce a significant irritant effect.

The epidemiological studies on carcinogenicity that contain some exposure assessments imply that, in the past, working populations showing an excess of nasal epithelial tumours had generally been exposed to formaldehyde levels in excess of the tissue-damage threshold. Such a threshold is probably about 1.0 mg/m^3 (range 0.5-3 mg/m^3).

With regard to atmospheric exposure limit values for odour and sensory irritation for the general population and the non-industrial indoor environment, formaldehyde concentrations should not exceed 0.1 mg/m^3. In the case of specially sensitive groups that show hypersensitivity reactions without immunological signs, formaldehyde concentrations should be kept to a minimum and should not exceed 0.01 mg/m^3.

To avoid strong sensory reactions in work-place environments where formaldehyde is being produced or used, peak concentrations above 1.0 mg/m^3 should not be allowed and mean concentrations should be kept below 0.3 mg/m^3.

10.2 Evaluation of Effects on the Environment

Formaldehyde is present in the environment as a result of natural processes and from man-made sources; the quantities produced by the former greatly exceed those from the latter. Nevertheless, the compound should be considered as an environmental contaminant, because it has been detected at levels higher than background concentrations in areas influenced by man-made sources. Air is the most relevant compartment in the formaldehyde cycle, as most of the formaldehyde produced and/or emitted enters the atmosphere and this is also where most of the degradation processes occur. The half-life of formaldehyde in the air is short, due to photodegradation. Formaldehyde is also biodegraded in water and soil in a relatively short time and does not accumulate in organisms. Data available for ecotoxicological assessment refer almost exclusively to formaldehyde in water. It can be classified as toxic for aquatic biota, with a lowest acute effect level for several aquatic organisms of about 1 mg/litre. However, fish seem to be more tolerant. No long-term toxicity tests have been performed, but the possibility of elimination via biodegradation, the low bioaccumulation factor, and the ability of organisms to metabolize formaldehyde, suggest that its impact on the aquatic environment would be limited, except in the case of massive discharge. With regard to the terrestrial environment, the lack of ecotoxicological data gives rise to concern, because most of the formaldehyde is distributed in the air. However, it should be noted that photooxidation in air is the main degradation process and that the reaction is fast. Data on the effects on plant foliage of exposure to peak concentrations of formaldehyde could be of relevance for a complete evaluation, though the highest concentrations detected have not lasted for very long.

10.3 Conclusions

- Formaldehyde occurs naturally and is a widely produced industrial chemical.

- Formaldehyde is a product of normal metabolic pathways.

- Formaldehyde undergoes rapid decomposition and does not accumulate in the environment.

- Major sources of formaldehyde are:

  - automobile and aircraft exhaust emissions;
  - tobacco smoke;
  - natural gas;
  - fossil fuels;
  - waste incineration; and
  - oil refineries.

- Formaldehyde exposure varies widely because of local variations. Significant levels of formaldehyde have been reported in indoor air. Among the sources are tobacco smoke, building and furnishing materials, and disinfectants.

- In work places, exposure may occur during the production or handling of formaldehyde or products containing formaldehyde.

- The most prominent features of formaldehyde vapour are its pungent odour and its irritant effects on the mucosa of eyes and upper airways. Odour-detection thresholds are generally reported to be in the range of 0.1-0.3 mg/m^3.

- Eye and respiratory-tract irritation generally occurs at levels of about 1 mg/m^3, but discomfort has been reported at much lower levels.

- Direct contact with formaldehyde solutions (1-2%) may cause skin irritation in approximately 5% of patients attending dematological clinics.

- Long-term exposure can lead to allergic contact dermatitis; this has been demonstrated for formaldehyde solution only, not for gaseous formaldehyde.

- Reversible airways obstruction has been produced by irritant concentrations of formaldehyde.

- Long-term exposure to formaldehyde at a level as low as 0.5 mg/m^3 may cause a slight elevation in airway resistance.

- Formaldehyde-related asthma has rarely been reported despite the widespread population exposure to formaldehyde.

- To avoid adverse reactions in dental surgery practice, root canal sealers should not be extruded beyond the apex in short-term exposure situations.

- There is no convincing evidence that formaldehyde is a teratogen, in either animals or human beings.

- Formaldehyde has not produced any adverse effects on reproduction in test animals or in human beings.

- Formaldehyde is positive in a wide range of mutagenicity test systems *in vitro*; results of *in vivo* test systems are conflicting.

- Formaldehyde has been shown to form DNA-protein crosslinks *in vitro* and *in vivo* . *In vivo* , this has been shown to occur at an exposure concentration of 1.1 mg/m^3.

- Formaldehyde interferes with DNA repair in human cells *in vitro* .

- Following inhalation exposure at levels causing cell damage, a significant incidence of squamous cell carcinomas of the nasal cavity was induced in 2 strains of rats.

  Nasal tumours in mice have also been reported, but the incidence was not statistically significant. There were no tumours at other sites.

  A limited number of forestomach papillomas have been reported in rats following administration of formaldehyde in the drinking-water.

  Formaldehyde-related tumours were not observed beyond the initial site of contact.

- Although an excess has been reported for a number of cancers, the evidence for a causal role of formaldehyde is likely only for nasal and nasopharyngeal cancer.

11. RECOMMENDATIONS

11.1 Recommendations for Future Research

- The absolute detection and recognition thresholds for formaldehyde should be determined. Psychophysical function relating the perceived irritation to the concentration of formaldehyde should be determined. Special attention should be given to low-concentration effects on the skin of the face (cheeks, eyes) for both surface exposure and inhaled air mixtures. The possible potentiation of sensory irritation by formaldehyde at low concentrations should be further investigated in mixtures of irritants with different durations of exposure. Sensory effects, when human beings are exposed either to air containing formaldehyde or air without formaldehyde, should be compared.

- The link between the perception of irritation and hyperreactivity and allergic reactions to formaldehyde needs further study, in order to evaluate fully the health implications of sensory effects.

- General interaction effects of physical, environmental factors (humidity, radiant heat, temperature, etc.) and low-concentration formaldehyde exposure should be investigated with regard to odour and sensory irritation.

- The combined effects of skin exposure to formaldehyde vapour and inhalation exposure, on various symptoms, including sensory irritation, feeling of warmth on the skin surface, quality of tactile perception, itching, tickling, and smarting of the eyes, need investigation. Both air and contact exposure of various body skin sites to formaldehyde at low concentrations should be studied for sensory effects and irritant contact dermatitis. The interaction effects of various host factors, such as age, psychological stress, skin disease, skin sensitivity, genetic factors (e.g., atopic), and hormonal balance, should be studied.

- the possible production of antibodies (IgE or other) to formaldehyde should be investigated. The detection of IgE antibodies by RAST should be included.

- Workers, who have undergone long-term exposure to formaldehyde should be examined for immunological effects, including clinical and laboratory findings.

- Animal studies on the induction of antibodies and T-cells specifically reacting with formaldehyde should be undertaken.

- More knowledge is needed about the factors involved in the induction of an irritant contact dermatitis by formaldehyde, dependent on occupational and/or other factors. Research should be directed to the formaldehyde concentrations producing such effects as well as to the skin parameters conditioning the start of the irritative skin contact reaction.

- Mechanisms involved in the carcinogenicity of formaldehyde, such as the effectiveness of mucus as a barrier, the genotoxic consequences of DNA-protein cross-links, and the role of tissue damage, should be studied in more detail.

- More knowledge is needed on the interactions of formaldehyde with other air pollutants.

- Further epidemiological studies are needed including studies on groups of people believed to be susceptible to the effects of formaldehyde.

- There is a need for extensive follow-up studies on working populations already investigated (maybe in excess of 20 years), because a long minimum latent period may be a feature of the response of the human nasal epithelium to cancer-causing agents.

- Epidemiological studies should also be re-evaluated for mortality due to cancers of the buccal cavity and pharynx, (human beings are not obligate nose breathers).

11.2 Recommendations for Preventive Measures

To prevent unacceptable risks, exposure to cytotoxic concentrations of formaldehyde should be avoided.

It is recommended that consumer goods containing formaldehyde should be labelled, in order to protect persons with a formaldehyde allergy.

(a) Indoors:

The formaldehyde air concentration allowed in living, sleeping, and working rooms should not be higher than 0.12 mg/m^3, in order to minimize the risk of repeated or continuous low concentration exposure to formaldehyde.

(b) Occupational areas:

It is recommended that formaldehyde concentrations in the work place air should be reduced to non-toxic concentrations. A no-observed-adverse-effect level in monkeys was 1.2 mg/m^3 (1 ppm). For protective reasons, the concentration at the work place should be below 1.2 mg/m^3 (1 ppm).

The exposure may reach a maximum of 1.2 mg/m^3 (1 ppm) for 5 min with not more than 8 peaks in one working period (up to 8 h).

(c) Cosmetics:

Formaldehyde concentrations in cosmetics (creams) that are higher than 0.05% should be labelled and levels should be limited to 0.1% in oral cosmetics.

The upper-level for the use of formaldehyde as a preservative in cosmetics should be 0.2%, except in nail hardeners, which may contain up to 5% formaldehyde.

(d) Hospitals:

1) Because of the sensitizing effect, skin contact with formaldehyde should be avoided by wearing impermeable gloves.

2) Thermal procedures are preferred for the disinfection or sterilization of appliances and instruments. Closed containers should be used in the disinfection of instruments using formaldehyde. Incubators, scopes, and tubes should not be treated with formaldehyde.

3) Thermal laundering procedures are preferred for the disinfection of clothing. Any "tub-disinfection" of clothing in formaldehyde solution should be exceptional. The tub must be closed with a lid. On handling clothing, gloves (and eventually respirators) should be worn.

4) Steam disinfecting is the method of choice for mattresses; spraying with disinfectants is obsolete. Mattresses covered with synthetic materials can be disinfected by wiping with formaldehyde solution, providing ventilation is sufficient.

5) Area disinfection: Wiping or scrubbing is recommended, while spraying with formaldehyde-containing solutions should be confined to non-accessible places. Direct contact with the disinfectant should be avoided by the use of gloves. Large-area disinfecting, - laboratories etc., should be scheduled for off-work times. Sufficient ventilation is mandatory.

6) Fixation of tissues in formalin baths should be performed in closed containers and/or using an exhaust hood. If possible, tissue slices should be washed with water, to remove superfluous formaldehyde, before viewing them under the microscope.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

In 1983, a WHO Study Group reviewed formaldehyde in order to recommend a health-based occupational exposure limit (WHO, 1984). The recommendations were as follows:

> "The Study Group recommends a short-term (15 minutes), health-based occupational exposure limit for formaldehyde in air of 1.0 mg of formaldehyde per m^3 of air.
>
> "A *tentative* health based exposure limit of 0.5 mg of formaldehyde per m^3 of air is recommended as an 8-hour time-weighted daily average during a 40-hour working week.
>
> "In view of the reported dose-dependent carcinogenic effect of formaldehyde in the rat, and the present inadequate epidemiological data on the cancer risk in man, it is advisable to reduce workplace

exposure to formaldehyde to the lowest feasible level."

The carcinogenic risks for human beings were evaluated by an International Agency for Research on Cancer ad hoc expert group in 1981. The evaluation was updated in 1987 and it was concluded that there was limited evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals (IARC, 1987).

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See Also:
Toxicological Abbreviations
Formaldehyde (HSG 57, 1991)
Formaldehyde (ICSC)

Formaldehyde (CICADS 40, 2002)
Formaldehyde (IARC Summary & Evaluation, Volume 62, 1995)
Formaldehyde (IARC Summary & Evaluation, Volume 88, 2006)

pathology consultants PC

January 23, 2023

Oregon Health Authority
Public Health Division
800 NE Oregon St. Suite 772
Portland, OR 97232

Re: Exemptions for Placenta Removal of Human Pathological Waste, Including Placentas
Senate Bill 189

To Whom It Concerns:

Pathology Consultants would like to thank Oregon Health Authority (OHA) for hosting the SB 189 Rules Advisory Committee on January 9, 2024. We were encouraged by the number of stakeholders who represented the state of Oregon on the release of human pathological waste from a healthcare facility but wish there had been more representation from the healthcare community to highlight the risks of releasing hazardous waste to the public. We fully support Native communities, organizational or religious groups that have a structured plan to appropriately oversee the remains including hazardous waste in a safe and proper way.

As an organization of Oregonians, we feel strongly about the health and safety of our patients, our community, and the health of our environment. This includes caring for specimens within our facilities and patient welfare should they be exposed to reagents that are known to have adverse health effects. In the case of our pathology laboratory, the most common reagent a patient would be exposed to when handling specimens is 10% formalin. Formaldehyde is designated as a hazardous air pollutant and regulated pursuant to national emission standards at Section 112 in the Clean Air Act. Formalin, a name for saturated formaldehyde, is equivalent to 4% formaldehyde. With repeated exposure, it is a carcinogen, causes eye and skin irritation, and should not be ingested or inhaled. Due to these risks, we updated our Release of Human Tissue policy in September 2023 to ensure patients and their representatives would not be exposed to formalin should they request their pathological waste. This update complied with SB 189 but also eliminated the risk of exposure to patients, air quality, to waterways, or to groundwater.

We would like OHA to review the attached Safety Data Sheet around Formalin, 10% Neutral Buffered: https://www.tedpella.com/SDS_html/18510_sds.pdf , please note *Section 12: Ecological Information Ecological Information: Water hazard class 1 (Self-assessment): Slightly hazardous for water. Do not allow undiluted product or large quantities of it to reach ground water, water course or sewage system. Chemical Fate Information: ND* as well as *Section 13 Disposal Considerations RCRA 40 CFR 261 Classification: ND Recommendation: Must not be disposed of together with household garbage.* ***Do not allow product to reach sewage system. Federal, State, and local laws governing****.*

Through due diligence, we learned that competing rules (SB 189 and OAR 340-230-0030 (9)) do not allow for safe disposal of human pathological waste outside of healthcare facilities. In Lane County, patients and their representatives cannot cremate these specimens through a licensed facility and funeral homes are not open

Denis M. McCarthy, M.D., President | Lauren A. Hammock, M.D. | J. Robert McFarlane III, M.D.
Deven L. Smith, M.D. | Brittany L. Pakalniskis, M.D. | Lyle C. Lawnicki, M.D. | Misty M. Payne, M.D. | Colin NewBill, M.D. | Claire Murphy, M.D.
P.O. Box 72059, Springfield, OR 97475-0285 | 541.222.6915 (ph) | 541.222.6908 (fax) | www.pathconsultants.com

to burying tiny amounts of tissue. Burying formalin fixed pathological waste in one's own backyard is harmful to groundwater and waterways and self-cremation is harmful to the clean air act. It must not be disposed of with household garbage and cannot be released into the sewer system. Appropriate methods of disposal are limited for patients and their representatives.

It is our position that allowing the general population of patients to have pathological waste in their possession exposes them to unsafe hazards and does not promote patient safety. Patients do not have a safe way to dispose of these hazardous materials that pose direct health safety issues to people in contact and larger environmental concerns if released into the air or waterways of Oregon. We strongly encourage Oregon Health Authority to reconsider the release of formalin fixed human pathological waste from healthcare facilities. We agree with the spirit of the law regarding spiritual beliefs of community members and support the release of fresh tissue to patients or representatives. We do, however, ask for added regulations around the liability involving the safety concerns we have addressed in this letter.

Sincerely,

Lauren Hammock MD

Lauren Hammock, MD
Laboratory Medical Director
Pathology Consultants, PC

Enclosures:
Safety Data Sheet 10% Formalin
Data Safety Sheet Sigma
Formalin-10—Solution-W-V-4L

CC: Chad Dresselhaus, Oregon Mortuary and Cemetery Board
Steve Siegel, Department of Environmental Quality
Shannon O'Fallon, Department of Justice

TED PELLA, INC.
Microscopy Products for Science and Industry

Safety Data Sheet

Product No. 18510 Formalin, 10% Neutral Buffered
Issue Date (09-11-15)
Review Date (08-31-17)

Section 1: Product and Company Identification

Product Name: Formalin, 10% Neutral Buffered
Synonym: None
Company Name
Ted Pella, Inc., P.O. Box 492477, Redding, CA 96049-2477
Inside USA and Canada 1-800-237-3526 (Mon-Thu. 6:00AM to 4:30PM PST; Fri 6:00AM to 4:00PM PST)
Outside USA and Canada 1-530-243-2200 (Mon-Thu. 6:00AM to 4:30PM PST; Fri 6:00AM to 4:00PM PST)
CHEMTREC USA and Canada Emergency Contact Number 1-800-424-9300 24 hours a day
CHEMTREC Outside USA and Canada Emergency Contact Number +1-703-741-5970 24 hours a day

Section 2: Hazard Identification

2.1 Classification of the substance or mixture

GHS Pictograms

GHS06 GHS08 GHS07 GHS05

GHS Categories

GHS06 – Toxic

Acute Tox. 3	H311: Toxic in contact with skin.
Acute Tox. 3	H331: Toxic if inhaled.

GHS08 - Health

Carc. 2 1B	H350: May cause cancer.
Muta. 2	H341: Suspected of causing genetic defects.
STOT SE 1	H370: Causes damage to organs.

GHS05 – Corrosion

Eye Dam. 1	H318: Causes serious eye damage.

GHS07 - Irritant

Acute Tox. 4	H302: Harmful if swallowed.
Skin Irrit. 2	H315: Causes skin irritation.
Skin Sens. 1	H317: May cause an allergic reaction.

2.2 Label elements

Hazard pictograms

GHS05 GHS06 GHS08

Signal Word: DANGER

Hazard-determining components of labeling: formaldehyde, methyl alcohol

Hazard statements:

H227 Combustible liquid.
H302 Harmful if swallowed.
H311 Toxic in contact with skin.
H315 Causes skin irritation.
H318 Causes serious eye damage.
H331 Toxic if inhaled.
H317 May cause an allergic skin reaction.
H341 Suspected of causing genetic defects.
H350 May cause cancer.
H370 Causes damage to organs.

Precautionary statements:

P201	Obtain special instructions before use.
P202	Do not handle until all safety precautions have been read and understood.
P210	Keep away from heat/sparks/open flames/hot surfaces. - No smoking.
P261	Avoid breathing dust/fume/gas/mist/vapors/spray.
P264	Wash thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P272	Contaminated work clothing must not be allowed out of the workplace.
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P301+P330+P312	If swallowed: Rinse mouth. Call a poison center/doctor if you feel unwell.
P302+P353	If on skin: Wash with plenty of soap and water.
P305+P351+P338	If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308+P313	IF exposed: Call a POISON CENTER or doctor/physician.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P361	Remove/take off immediately all contaminated clothing.
P363	Wash contaminated clothing before reuse.
P370+P378	In case of fire: Use for extinction: CO2, powder or water spray.
P403+P235	Store in a well-ventilated place. Keep cool.
P405	Store locked up.
P501	Dispose of contents/container in accordance with local/regional/national/ international regulations.

2.3 Other Hazards

Classification according to Directive 67/548/EEC or Directive 1999/45/EC
Label: X_n - Harmful
R20/21/22-40: Harmful by inhalation, in contact with skin and if swallowed. Limited evidence of a carcinogenic effect.
Label: X_i; Sensitizing
R43: May cause sensitisation by skin contact.
Hazard-determining components of labeling: formaldehyde 50-00-0
Risk phrases:
20/21/22 - Harmful by inhalation, in contact with skin and if swallowed.
40 - Limited evidence of a carcinogenic effect.

43 - May cause sensitisation by skin contact.
Safety phrases:
9 - Keep container in a well-ventilated place.
23 - Do not breathe gas/fumes/vapor/spray (appropriate wording to be specified by the manufacturer).
36/37 - Wear suitable protective clothing and gloves.
60 - This material and its container must be disposed of as hazardous waste.

Health Effects:
NFPA Hazard Rating: Health: 3; Fire: 2; Reactivity: 0
HMIS® Hazard Rating: Health: 3; Fire: 2; Reactivity: 0
(0=least, 1=Slight, 2=Moderate, 3=High, 4=Extreme)

Results of PBT and vPvB assessment:
PBT: NA
vPvB: NA

Emergency overview
Appearance: Liquid
Immediate effects: ND
Potential health effects
Primary Routes of entry: Inhalation, ingestion and eye and skin contact.
Signs and Symptoms of Overexposure: ND
Eyes: Harmful in contact with eyes.
Skin: May cause sensitisation by skin contact. Harmful in contact with skin.
Ingestion: Harmful if swallowed.
Inhalation: Harmful by inhalation.
Chronic Exposure: ND
Chemical Listed as Carcinogen or Potential Carcinogen: Formaldehyde (50-00-0).
See Toxicological Information (Section 11)
Potential environmental effects
See Ecological Information (Section 12)

Section 3: Composition / Information on Ingredients

Principle Hazardous Component(s) (chemical and common name(s)) (Cas. No)	**%**	**OSHA PEL**	**ACGIH TLV**	**NTP**	**IARC**	**OSHA regulated**
Formaldehyde (50-00-0)	2.5-10	2 ppm	0.37 mg/m^3 0.3 ppm	R	Group 1	Yes
Methyl Alcohol (67-56-1)	2.5-10	260 mg/m^3 200 ppm	328 mg/m^3 250 ppm	No	No	No

---

Section 4: First Aid Measures
If accidental overexposure is suspected

General:	Immediately remove any clothing soiled by the product. Symptoms of poisoning may even occur after several hours; therefore, medical observation for at least 48 hours after the accident.
Eye(s) Contact:	Rinse opened eye for several minutes under running water. Then consult a doctor.
Skin Contact:	Immediately wash with water and soap and rinse thoroughly.

Inhalation: Supply fresh air and to be sure call for a doctor. In case of unconsciousness, place patient stably in side position for transportation.
Ingestion: Immediately call a doctor.

Note to physician

Treatment: ND

Medical Conditions generally Aggravated by Exposure: ND

Section 5: Fire Fighting Measures

Flash Point: 85 °C

Flammable Limits: NE

Auto-ignition point: Product is not self-igniting.

Fire Extinguishing Media: CO_2, extinguishing powder or water spray. Fight larger fires with water spray or alcohol resistant foam.

Special Fire Fighting Procedures: Use mouth respiratory protective device.

Unusual Fire and Explosion Hazards: Product does not present an explosion hazard.

Hazardous combustion products: Oxides of Carbon.

DOT Class: NA

Section 6: Accidental Release Measures

Steps to be Taken in Case Material is Released or Spilled: Do not allow to enter sewers/ surface or ground water. Absorb with liquid-binding material (sand, diatomite, acid binders, universal binders, sawdust). Ensure adequate ventilation.

Waste Disposal Methods: Dispose of waste according to Federal, State and Local Regulations.

Section 7: Handling and Storage

Precautions to be taken in Handling and Storage: Ensure good ventilation/exhaustion at the workplace. Prevent formation of aerosols. Keep receptacle tightly sealed. Protect from heat and direct sunlight.

Storage temperature: Room temperature.

Storage Pressure: NA

Section 8: Exposure Controls / Personal Protection

Components with limit values that require monitoring at the workplace:

50-00-0 formaldehyde	
PEL	Short-term value: 2 ppm Long-term value: 0.75 ppm See 29 CFR 1910.1048(c)
REL	Long-term value: 0.016 ppm Ceiling limit value: 0.1* ppm *15 min; See Pocket Guide App.
TLV	Ceiling limit value: 0.37 mg.m^3, 0.3 ppm (SEN) NIC-DSEN; RSEN
67-56-1 Methyl Alcohol	
PEL	Long-term value: 260 mg/m³, 200 ppm
REL	Short-term value: 325 mg/m³, 250 ppm Long-term value: 260 mg/m³, 200 ppm Skin
TLV	TLV Short-term value: 328 mg/m³, 250 ppm

	Long-term value: 262 mg/m³, 200 ppm Skin; BEI

Ingredients with biological limit values

67-56-1 Methyl Alcohol	
BEI	15 mg/L Medium: urine Time: end of shift Parameter: Methanol (background, nonspecific)

Engineering Controls

Ventilation required: Ensure good ventilation/exhaustion at the workplace.

Personal Protection Equipment

Respiratory protection: In case of brief exposure or low pollution use respiratory filter device. In case of intensive or longer exposure use respiratory protective device that is independent of circulating air.

Skin protection: Protective gloves and clothing.

Eye protection: Tightly-sealed goggles or face shield.

Additional clothing and/or equipment: ND

General protective and hygienic measures: Keep away from foodstuffs, beverages and feed. Immediately remove all soiled and contaminated clothing. Wash hands before breaks and at the end of work. Avoid contact with the eyes and skin.

Exposure Guidelines

See Composition/Information on Ingredients (Section 3)

Section 9 Physical and Chemical Properties

Appearance and Physical State: Liquid, color according to product specification.
Odor (threshold): Characteristic (ND)
Specific Gravity (H_2O=1): 0.98817 g/cm³
Vapor pressure at 20 °C: 23 hPa
Vapor Density (air=1): ND
Percent Volatile by volume: ND

Evaporation Rate (butyl acetate=1): ND
Boiling Point: 100 °C
Freezing point / melting point: ND
pH: 7.1
Solubility in Water: Fully miscible.
Organic solvents: 6.0 %
Water: 84 %
VOC content: 6.0%
Molecular Weight: NA

Section 10: Stability and Reactivity

Stability: Stable.
Conditions to Avoid: Heat, flames and sparks.
Materials to Avoid (Incompatibility): ND
Hazardous Decomposition Products: No dangerous decomposition products known.
Hazardous Polymerization: No dangerous reactions known.

Section 11: Toxicological Information

Results of component toxicity test performed:
Acute toxicity - LD/LC50 values relevant for classification

50-00-0 Formaldehyde	Oral LD50:	>200 mg/kg (rat)
67-56-1 Methyl alcohol	Oral LD50:	5628 mg/kg (rat)
	Dermal LD50:	15800 mg/kg (rat)

Primary irritant effect:
Skin: Irritant to skin and mucous membranes.
Eyes: Strong irritant with the danger of severe eye injury.
Sensitization: Sensitization possible through skin contact.
Additional toxicological information:
The product shows the following dangers according to internally approved calculation methods for preparations: Toxic, Harmful, Irritant, Carcinogenic.
Human experience: ND
This product **does** contain compounds listed by NTP or IARC or regulated by OSHA as a carcinogen. See Section 15.

Section 12: Ecological Information
Ecological Information: Water hazard class 1 (Self-assessment): Slightly hazardous for water. Do not allow undiluted product or large quantities of it to reach ground water, water course or sewage system.
Chemical Fate Information: ND

Section 13 Disposal Considerations
RCRA 40 CFR 261 Classification: ND
Recommendation: Must not be disposed of together with household garbage. Do not allow product to reach sewage system.
Federal, State and local laws governing disposal of materials can differ. Ensure proper disposal compliance with proper authorities before disposal.

Section 14: Transportation Information
US DOT Information: Not regulated.
IATA: Not regulated.
Limitations: Formaldehyde solutions from 10% to 24.9% are regulated by IATA as: UN3334, Aviation regulated, n.o.s. (10%-24.9% Formaldehyde solution). Office of Hazardous Materials Safety Regulations and Interpretations; Refer# 01-0271. Refer to IATA for specific operator regulations.
Marine Pollutant: No
Canadian TDG: Not regulated.
Ground Limitations: Reportable Quantity (RQ): 2500 lbs. At RQ limit is regulated. US DOT, Combustible liquid, n.o.s. (Formaldehyde, Methanol), 3, NA1993.

Section 15: Regulatory Information
United States Federal Regulations
SDS complies with OSHA's Hazard Communication Rule 29, CFR 1910.1200.
SARA: Section 355 (extremely hazardous substances): 50-00-0 formaldehyde
SARA Title III: Section 313 (Specific toxic chemical listings): 50-00-0 formaldehyde. 67-56-1 Methyl Alcohol.
RCRA: ND
TSCA (Toxic Substances Control Act): All ingredients are listed.
CERCLA: Formaldehyde 50-00-0: RQ = 100 lbs (45.4 Kg).
State Regulations
California Proposition 65: Yes; chemicals known to cause cancer: 50-00-0 formaldehyde
Chemicals known to cause reproductive toxicity for females: None of the ingredients is listed.
Chemicals known to cause reproductive toxicity for males: None of the ingredients is listed.
Chemicals known to cause developmental toxicity: 67-56-1 Methyl Alcohol.

Carcinogenic categories:
EPA (Environmental Protection Agency): 50-00-0 formaldehyde - B1
TLV (Threshold Limit Value established by ACGIH): 50-00-0 formaldehyde - A2
NIOSH-Ca (National Institute for Occupational Safety and Health): 50-00-0 formaldehyde
OSHA-Ca (Occupational Safety & Health Administration): 50-00-0 formaldehyde
IARC (International Agency for Research on Cancer): 50-00-0 formaldehyde - 1
NTP (National Toxicology Program): 50-00-0 formaldehyde – K
International Regulations
Canada WHMIS: Canadian substance listings:
Canadian Domestic Substances List (DSL): All ingredients are listed.
Canadian Ingredient Disclosure list (limit 0.1%): 50-00-0 formaldehyde.
Canadian Ingredient Disclosure list (limit 1%): None of the ingredients is listed.
Europe EINECS Numbers: ND

Section 16: Other Information
Label Information: Health Hazard.
European Risk and Safety Phrases: See Section 2.
European symbols needed: X, Harmful.
Canadian WHMIS Symbols:
B3 - Combustible liquid.
D2B - Toxic material causing other toxic effects.
Abbreviations used in this document
NE= Not established
NA= Not applicable
NIF= No Information Found
ND= No Data

Disclaimer
Ted Pella, Inc. makes no warranty of any kind regarding the information furnished herein. Users should independently determine the suitability and completeness of information from all sources. While this data is presented in good faith and believed to be accurate, it should be considered only as a supplement to other information gathered by the user. It is the User's responsibility to assure the proper use and disposal of these materials as well as the safety and health of all personnel who may work with or otherwise come in contact with these materials.

SAFETY DATA SHEET

Version 6.7
Revision Date 08/31/2023
Print Date 01/13/2024

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Formalin solution, neutral buffered, 10%

Product Number : HT501128
Brand : Sigma

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Synthesis of substances

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Inc.
3050 SPRUCE ST
ST. LOUIS MO 63103
UNITED STATES

Telephone : +1 314 771-5765
Fax : +1 800 325-5052

1.4 Emergency telephone

Emergency Phone # : 800-424-9300 CHEMTREC (USA) +1-703-527-3887 CHEMTREC (International) 24 Hours/day; 7 Days/week

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)

Flammable liquids (Category 4), H227
Acute toxicity, Oral (Category 4), H302
Acute toxicity, Inhalation (Category 4), H332
Skin sensitization (Category 1), H317
Germ cell mutagenicity (Category 2), H341
Carcinogenicity (Category 1B), H350
Short-term (acute) aquatic hazard (Category 3), H402

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram	
Signal Word	Danger

Hazard statement(s)

H227	Combustible liquid.
H302 + H332	Harmful if swallowed or if inhaled.
H317	May cause an allergic skin reaction.
H341	Suspected of causing genetic defects.
H350	May cause cancer.
H402	Harmful to aquatic life.

Precautionary statement(s)

P201	Obtain special instructions before use.
P202	Do not handle until all safety precautions have been read and understood.
P210	Keep away from heat/ sparks/ open flames/ hot surfaces. No smoking.
P261	Avoid breathing mist or vapors.
P264	Wash skin thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P271	Use only outdoors or in a well-ventilated area.
P272	Contaminated work clothing must not be allowed out of the workplace.
P273	Avoid release to the environment.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.
P301 + P312 + P330	IF SWALLOWED: Call a POISON CENTER/ doctor if you feel unwell. Rinse mouth.
P302 + P352	IF ON SKIN: Wash with plenty of soap and water.
P304 + P340 + P312	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Call a POISON CENTER/ doctor if you feel unwell.
P308 + P313	IF exposed or concerned: Get medical advice/ attention.
P333 + P313	If skin irritation or rash occurs: Get medical advice/ attention.
P363	Wash contaminated clothing before reuse.
P370 + P378	In case of fire: Use dry sand, dry chemical or alcohol-resistant foam to extinguish.
P403 + P235	Store in a well-ventilated place. Keep cool.
P405	Store locked up.
P501	Dispose of contents/ container to an approved waste disposal plant.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

SECTION 3: Composition/information on ingredients

3.2 Mixtures

Component		Classification	Concentration
formaldehyde			
CAS-No.	50-00-0	Flam. Liq. 4; Acute Tox. 3;	>= 1 - < 5 %

EC-No. Index-No. Registration number	200-001-8 605-001-00-5 01-2119488953-20-XXXX	Acute Tox. 2; Acute Tox. 3; Skin Corr. 1B; Eye Dam. 1; Skin Sens. 1; Muta. 2; Carc. 1B; STOT SE 3; Aquatic Acute 2; H227, H301, H330, H311, H314, H318, H317, H341, H350, H335, H401 Concentration limits: >= 25 %: Skin Corr. 1B, H314; 5 - < 25 %: Eye Irrit. 2, H319; >= 5 %: STOT SE 3, H335; >= 0.2 %: Skin Sens. 1, H317; 5 - < 25 %: Skin Irrit. 2, H315; >= 25 %: Skin Corr. 1B, H314; 5 - < 25 %: Skin Irrit. 2, H315; 5 - < 25 %: Eye Irrit. 2, H319; >= 5 %: STOT SE 3, H335; >= 0.2 %: Skin Sens. 1, H317;	
Methanol			
CAS-No. EC-No. Index-No. Registration number	67-56-1 200-659-6 603-001-00-X 01-2119433307-44-XXXX	Flam. Liq. 2; Acute Tox. 3; STOT SE 1; H225, H301, H331, H311, H370 Concentration limits: >= 10 %: STOT SE 1, H370; 3 - < 10 %: STOT SE 2, H371;	>= 1 - < 3 %

For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
Show this material safety data sheet to the doctor in attendance.

If inhaled
After inhalation: fresh air. Immediately call in physician. If breathing stops: immediately apply artificial respiration, if necessary also oxygen.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower. Consult a physician.

In case of eye contact
After eye contact: rinse out with plenty of water. Call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: immediately make victim drink water (two glasses at most). Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Carbon oxides
Not combustible.
Vapors are heavier than air and may spread along floors.
Forms explosive mixtures with air on intense heating.
Ambient fire may liberate hazardous vapours.

5.3 Advice for firefighters
Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information
Remove container from danger zone and cool with water. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Do not breathe vapors, aerosols. Avoid substance contact. Ensure adequate ventilation. Keep away from heat and sources of ignition.
Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up carefully with liquid-absorbent material (e.g. Chemizorb®). Dispose of properly. Clean up affected area.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on safe handling
Work under hood. Do not inhale substance/mixture. Avoid generation of vapours/aerosols.

Advice on protection against fire and explosion
Keep away from open flames, hot surfaces and sources of ignition.Take precautionary measures against static discharge.

Hygiene measures
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Keep in a well-ventilated place. Keep locked up or in an area accessible only to qualified or authorized persons.

Storage class
Storage class (TRGS 510): 6.1C: Combustible, acute toxic Cat.3 / toxic compounds or compounds which causing chronic effects

7.3 Specific end use(s)

Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

Component	CAS-No.	Value	Control parameters	Basis
formaldehyde	50-00-0	TWA	0.1 ppm	USA. ACGIH Threshold Limit Values (TLV)
	Remarks	Dermal Sensitization Respiratory sensitization Confirmed human carcinogen		
		STEL	0.3 ppm	USA. ACGIH Threshold Limit Values (TLV)
		Dermal Sensitization Respiratory sensitization Confirmed human carcinogen		
		TWA	0.016 ppm	USA. NIOSH Recommended Exposure Limits
		Potential Occupational Carcinogen		
		C	0.1 ppm	USA. NIOSH Recommended Exposure Limits
		Potential Occupational Carcinogen		

		PEL	0.75 ppm	OSHA Specifically Regulated Chemicals/Carcinogens
		OSHA specifically regulated carcinogen		
		STEL	2 ppm	OSHA Specifically Regulated Chemicals/Carcinogens
		OSHA specifically regulated carcinogen		
		PEL	0.75 ppm	California permissible exposure limits for chemical contaminants (Title 8, Article 107)
		STEL	2 ppm	California permissible exposure limits for chemical contaminants (Title 8, Article 107)
		TWA	0.016 ppm	USA. NIOSH Recommended Exposure Limits
		Potential Occupational Carcinogen		
		C	0.1 ppm	USA. NIOSH Recommended Exposure Limits
		Potential Occupational Carcinogen		
Methanol	67-56-1	TWA	200 ppm	USA. ACGIH Threshold Limit Values (TLV)
		Danger of cutaneous absorption		
		STEL	250 ppm	USA. ACGIH Threshold Limit Values (TLV)
		Danger of cutaneous absorption		
		ST	250 ppm 325 mg/m3	USA. NIOSH Recommended Exposure Limits
		Potential for dermal absorption		
		TWA	200 ppm 260 mg/m3	USA. NIOSH Recommended Exposure Limits
		Potential for dermal absorption		
		TWA	200 ppm 260 mg/m3	USA. Occupational Exposure Limits (OSHA) - Table Z-1 Limits for Air Contaminants
		PEL	200 ppm 260 mg/m3	California permissible exposure limits for chemical contaminants (Title 8, Article 107)
		Skin		
		C	1,000 ppm	California permissible exposure limits for chemical contaminants (Title 8, Article 107)
		Skin		
		STEL	250 ppm 325 mg/m3	California permissible exposure limits for chemical contaminants (Title 8, Article 107)
		Skin		

		TWA	200 ppm 260 mg/m3	USA. Table Z-1-A Limits for Air Contaminants (1989 vacated values)
		Skin notation		
		STEL	250 ppm 325 mg/m3	USA. Table Z-1-A Limits for Air Contaminants (1989 vacated values)
		Skin notation		

Biological occupational exposure limits

Component	CAS-No.	Parameters	Value	Biological specimen	Basis
Methanol	67-56-1	Methanol	15 mg/l	Urine	ACGIH - Biological Exposure Indices (BEI)
	Remarks	End of shift (As soon as possible after exposure ceases)			

8.2 Exposure controls

Appropriate engineering controls
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the EC approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
protective clothing

Respiratory protection
Recommended Filter type: Filter type ABEK
The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.
required when vapours/aerosols are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Color: colorless
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	6.5 - 7.5 at 10%
e)	Melting point/freezing point	No data available
f)	Initial boiling point and boiling range	100 °C 212 °F at 1,013 hPa
g)	Flash point	85 °C (185 °F)
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	Upper explosion limit: 70 %(V) Lower explosion limit: 7 %(V)
k)	Vapor pressure	53 hPa at 39 °C (102 °F)
l)	Vapor density	No data available
m)	Density	1.080 g/cm3
	Relative density	No data available
n)	Water solubility	completely misciblesoluble
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	Not applicable

q)	Decomposition temperature	No data available
r)	Viscosity	No data available
s)	Explosive properties	Not classified as explosive.
t)	Oxidizing properties	none

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
Forms explosive mixtures with air on intense heating.
A range from approx. 15 Kelvin below the flash point is to be rated as critical.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Violent reactions possible with:
The generally known reaction partners of water.

10.4 Conditions to avoid
Strong heating.

10.5 Incompatible materials
Strong bases, Acids, Oxidizing agents, Alkali metals, Strong oxidizing agents, Amines, Strong acids, Acid chlorides, Acid anhydrides, Reducing agents, Peroxides, Isocyanates, Phenol, Aniline

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Mixture

Acute toxicity
Oral: No data available

Inhalation: No data available

Dermal: No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitization
Mixture may cause an allergic skin reaction.

Germ cell mutagenicity
Evidence of genetic defects.

Carcinogenicity
Possible carcinogen.

IARC:	1 - Group 1: Carcinogenic to humans (formaldehyde)
NTP:	Known - Known to be human carcinogen (formaldehyde)
OSHA:	OSHA specifically regulated carcinogen (formaldehyde)

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Methyl alcohol may be fatal or cause blindness if swallowed., Cannot be made non-poisonous., Effects due to ingestion may include:, Nausea, Dizziness, Gastrointestinal disturbance, Weakness, Confusion., Drowsiness, Unconsciousness, May cause convulsions. Other dangerous properties can not be excluded.

This substance should be handled with particular care.

Handle in accordance with good industrial hygiene and safety practice.

Liver - Irregularities - Based on Human Evidence

Stomach - Irregularities - Based on Human Evidence

Components

formaldehyde

Acute toxicity
LD50 Oral - Rat - 100 mg/kg
Remarks: (Lit.)
LC50 Inhalation - Rat - male and female - 4 h - < 0.57 mg/l - vapor
(OECD Test Guideline 403)
LD50 Dermal - Rabbit - 270 mg/kg
Remarks: (RTECS)
No data available

Skin corrosion/irritation
Skin - Rabbit
Result: Causes burns. - 20 h

(OECD Test Guideline 404)

Serious eye damage/eye irritation
Remarks: Causes serious eye damage.

Respiratory or skin sensitization
Local lymph node assay (LLNA) - Mouse
Result: positive
(OECD Test Guideline 429)

Germ cell mutagenicity
Suspected of causing genetic defects.

Carcinogenicity
Presumed to have carcinogenic potential for humans

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
May cause respiratory irritation.

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

Methanol

Acute toxicity
Acute toxicity estimate Oral - 100.1 mg/kg
(Expert judgment)
Remarks: Classified according to Regulation (EU) 1272/2008, Annex VI (Table 3.1/3.2)
Symptoms: Nausea, Vomiting
Acute toxicity estimate Inhalation - 4 h - 3.1 mg/l - vapor
(Expert judgment)
Remarks: Classified according to Regulation (EU) 1272/2008, Annex VI (Table 3.1/3.2)
Symptoms: Irritation symptoms in the respiratory tract.
Acute toxicity estimate Dermal - 300.1 mg/kg
(Expert judgment)
Remarks: Classified according to Regulation (EU) 1272/2008, Annex VI (Table 3.1/3.2)

Skin corrosion/irritation
Skin - Rabbit
Result: No skin irritation
Remarks: (ECHA)
Remarks: Drying-out effect resulting in rough and chapped skin.

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation
Remarks: (ECHA)

Respiratory or skin sensitization
Sensitisation test: - Guinea pig
Result: negative
(OECD Test Guideline 406)

Germ cell mutagenicity
Based on available data the classification criteria are not met.
Test Type: Ames test
Test system: Salmonella typhimurium
Result: negative
Test Type: In vitro mammalian cell gene mutation test
Test system: Chinese hamster lung cells
Result: negative
Method: OECD Test Guideline 474
Species: Mouse - male and female - Bone marrow
Result: negative

Carcinogenicity
Did not show carcinogenic effects in animal experiments.

Reproductive toxicity
Based on available data the classification criteria are not met.

Specific target organ toxicity - single exposure
Causes damage to organs. - Eyes, Central nervous system
Remarks: Classified according to Regulation (EU) 1272/2008, Annex VI (Table 3.1/3.2)
Acute oral toxicity - Nausea, Vomiting
Acute inhalation toxicity - Irritation symptoms in the respiratory tract.

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

SECTION 12: Ecological information

12.1 Toxicity

Mixture
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Endocrine disrupting properties
No data available

12.7 Other adverse effects

No data available

Components

formaldehyde

Toxicity to fish	static test LC50 - Morone saxatilis - 6.7 mg/l - 96 h Remarks: (ECHA)
Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia pulex (Water flea) - 5.8 mg/l - 48 h (OECD Test Guideline 202)
Toxicity to algae	static test EC50 - Desmodesmus subspicatus (green algae) - 4.89 mg/l - 72 h (OECD Test Guideline 201)
Toxicity to bacteria	static test EC50 - activated sludge - 19 mg/l - 3 h (OECD Test Guideline 209)
Toxicity to daphnia and other aquatic invertebrates(Chronic toxicity)	semi-static test NOEC - Daphnia magna (Water flea) - >= 6.4 mg/l - 21 d (OECD Test Guideline 211)

Methanol

Toxicity to fish	flow-through test LC50 - Lepomis macrochirus (Bluegill) - 15,400.0 mg/l - 96 h (US-EPA)
Toxicity to daphnia and other aquatic invertebrates	semi-static test EC50 - Daphnia magna (Water flea) - 18,260 mg/l - 96 h (OECD Test Guideline 202)
Toxicity to algae	static test ErC50 - Pseudokirchneriella subcapitata (green algae) - ca. 22,000.0 mg/l - 96 h (OECD Test Guideline 201)
Toxicity to bacteria	static test IC50 - activated sludge - > 1,000 mg/l - 3 h (OECD Test Guideline 209)
Toxicity to fish(Chronic toxicity)	NOEC - Oryzias latipes (Orange-red killifish) - 7,900 mg/l - 200 h Remarks: (External MSDS)

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
Waste material must be disposed of in accordance with the national and local regulations. Leave chemicals in original containers. No mixing with other waste. Handle uncleaned containers like the product itself.

SECTION 14: Transport information

DOT (US)
NA-Number: 1993 Class: NONE Packing group: III
Proper shipping name: Combustible liquid, n.o.s. (formaldehyde, Methanol)
Reportable Quantity (RQ): 2500 lbs
Poison Inhalation Hazard: No

IMDG
Not dangerous goods

IATA
Not dangerous goods

SECTION 15: Regulatory information

SARA 302 Components

	CAS-No.	Revision Date
formaldehyde	50-00-0	2008-11-03

SARA 313 Components
The following components are subject to reporting levels established by SARA Title III, Section 313:

	CAS-No.	Revision Date
formaldehyde	50-00-0	2008-11-03
Methanol	67-56-1	2007-07-01

SARA 311/312 Hazards
Fire Hazard, Acute Health Hazard, Chronic Health Hazard

Massachusetts Right To Know Components

	CAS-No.	Revision Date
water	7732-18-5	
formaldehyde	50-00-0	2008-11-03

Methanol	67-56-1	2007-07-01

Pennsylvania Right To Know Components

formaldehyde	CAS-No. 50-00-0	Revision Date 2008-11-03
Methanol	67-56-1	2007-07-01
disodium hydrogen orthophosphate	7558-79-4	1993-04-24

California Prop. 65 Components

, which is/are known to the State of California to cause cancer, andformaldehyde	CAS-No. 50-00-0	Revision Date 2007-09-28
, which is/are known to the State of California to cause birth defects or other reproductive harm. For more information go to www.P65Warnings.ca.gov.Methanol	CAS-No. 67-56-1	Revision Date 2012-03-16

SECTION 16: Other information

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact misbranding@sial.com.

Version: 6.7 Revision Date: 08/31/2023 Print Date: 01/13/2024

SAFETY DATA SHEET

Creation Date 10-Feb-2010 **Revision Date** 24-Dec-2021 **Revision Number** 6

1. Identification

Product Name **Formaldehyde solution, 3.7%-10%**

Cat No. : **SF96-20; SF98-4; SF98-20**

Synonyms Formalin solution, 10%-27% (Histological)

Recommended Use Laboratory chemicals.
Uses advised against Food, drug, pesticide or biocidal product use.

Details of the supplier of the safety data sheet

Company
Fisher Scientific Company
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Acute oral toxicity	Category 4
Acute Inhalation Toxicity - Vapors	Category 3
Skin Corrosion/Irritation	Category 2
Serious Eye Damage/Eye Irritation	Category 2
Skin Sensitization	Category 1
Germ Cell Mutagenicity	Category 2
Carcinogenicity	Category 1A
Specific target organ toxicity (single exposure)	Category 1
Target Organs - Optic nerve, Respiratory system, Central nervous system (CNS).	
Specific target organ toxicity - (repeated exposure)	Category 1
Target Organs - Kidney, Liver, spleen, Blood.	

Label Elements

Signal Word
Danger

Hazard Statements
Harmful if swallowed
Causes severe skin burns and eye damage
May cause an allergic skin reaction
Toxic if inhaled
May cause respiratory irritation
May cause drowsiness or dizziness
Suspected of causing genetic defects
May cause cancer
Causes damage to organs
Causes damage to organs through prolonged or repeated exposure

Precautionary Statements
Prevention
Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Use personal protective equipment as required
Wash face, hands and any exposed skin thoroughly after handling
Do not eat, drink or smoke when using this product
Use only outdoors or in a well-ventilated area
Do not breathe dust/fume/gas/mist/vapors/spray
Contaminated work clothing should not be allowed out of the workplace
Wear protective gloves
Response
Immediately call a POISON CENTER or doctor/physician
Inhalation
IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing
Skin
IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower
Wash contaminated clothing before reuse
If skin irritation or rash occurs: Get medical advice/attention
Eyes
IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
Ingestion
Rinse mouth
Do NOT induce vomiting
Storage
Store locked up
Store in a well-ventilated place. Keep container tightly closed
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)

Other hazards
Poison, may be fatal or cause blindness if swallowed. Vapor harmful. CANNOT BE MADE NON-POISONOUS.
WARNING. Reproductive Harm - https://www.p65warnings.ca.gov/.

3. Composition/Information on Ingredients

Component	CAS No	Weight %
Water	7732-18-5	84.8 - 94.2
Formaldehyde	50-00-0	3.7 - 10.0
Methyl alcohol	67-56-1	1.0 - 4.1
Odor Mask	NA	0.0 - 1.1

4. First-aid measures

General Advice Immediate medical attention is required. Show this safety data sheet to the doctor in attendance.

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. In the case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Immediate medical attention is required.

Inhalation Remove to fresh air. If breathing is difficult, give oxygen. Do not use mouth-to-mouth method if victim ingested or inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Immediate medical attention is required.

Ingestion Do NOT induce vomiting. Call a physician or poison control center immediately.

Most important symptoms and effects May cause allergic skin reaction. Difficulty in breathing. . Causes burns by all exposure routes. Symptoms of allergic reaction may include rash, itching, swelling, trouble breathing, tingling of the hands and feet, dizziness, lightheadedness, chest pain, muscle pain or flushing: Symptoms of overexposure may be headache, dizziness, tiredness, nausea and vomiting: Product is a corrosive material. Use of gastric lavage or emesis is contraindicated. Possible perforation of stomach or esophagus should be investigated: Ingestion causes severe swelling, severe damage to the delicate tissue and danger of perforation

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media Water spray, carbon dioxide (CO2), dry chemical, alcohol-resistant foam.

Unsuitable Extinguishing Media No information available

Flash Point No information available
Method - No information available

Autoignition Temperature No information available
Explosion Limits
Upper No data available
Lower No data available
Sensitivity to Mechanical Impact No information available
Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. In the event of fire and/or explosion do not breathe fumes.

Hazardous Combustion Products
Carbon monoxide (CO). Carbon dioxide (CO_2). Formaldehyde. Thermal decomposition can lead to release of irritating gases and

vapors.

Protective Equipment and Precautions for Firefighters

As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear. Thermal decomposition can lead to release of irritating gases and vapors.

NFPA

Health	Flammability	Instability	Physical hazards
3	1	0	N/A

6. Accidental release measures

Personal Precautions Use personal protective equipment as required. Ensure adequate ventilation. Evacuate personnel to safe areas. Keep people away from and upwind of spill/leak.

Environmental Precautions Should not be released into the environment. Do not flush into surface water or sanitary sewer system. See Section 12 for additional Ecological Information.

Methods for Containment and Clean Up Soak up with inert absorbent material. Keep in suitable, closed containers for disposal.

7. Handling and storage

Handling Use only under a chemical fume hood. Wear personal protective equipment/face protection. Do not breathe mist/vapors/spray. Do not get in eyes, on skin, or on clothing. Do not ingest. If swallowed then seek immediate medical assistance.

Storage. Keep containers tightly closed in a dry, cool and well-ventilated place. Incompatible Materials. Strong oxidizing agents.

8. Exposure controls / personal protection

Exposure Guidelines

Component	ACGIH TLV	OSHA PEL	NIOSH IDLH	Mexico OEL (TWA)
Formaldehyde	TWA: 0.1 ppm STEL: 0.3 ppm	(Vacated) TWA: 3 ppm (Vacated) STEL: 10 ppm (Vacated) Ceiling: 5 ppm TWA: 0.75 ppm STEL: 2 ppm	IDLH: 20 ppm TWA: 0.016 ppm Ceiling: 0.1 ppm	Ceiling: 0.3 ppm
Methyl alcohol	TWA: 200 ppm STEL: 250 ppm Skin	(Vacated) TWA: 200 ppm (Vacated) TWA: 260 mg/m^3 (Vacated) STEL: 250 ppm (Vacated) STEL: 325 mg/m^3 Skin TWA: 200 ppm TWA: 260 mg/m^3	IDLH: 6000 ppm TWA: 200 ppm TWA: 260 mg/m^3 STEL: 250 ppm STEL: 325 mg/m^3	TWA: 200 ppm STEL: 250 ppm

Legend

ACGIH - American Conference of Governmental Industrial Hygienists
OSHA - Occupational Safety and Health Administration
NIOSH IDLH: NIOSH - National Institute for Occupational Safety and Health

Engineering Measures Use only under a chemical fume hood. Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Tight sealing safety goggles. Face protection shield.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Liquid
Appearance	Colorless
Odor	pungent
Odor Threshold	No information available
pH	No information available
Melting Point/Range	0 °C / 32 °F
Boiling Point/Range	100 °C / 212 °F
Flash Point	No information available
Evaporation Rate	No information available
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	No information available
Vapor Density	> 1.00
Specific Gravity	> 1.00
Solubility	miscible
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	No information available
Decomposition Temperature	No information available
Viscosity	No information available

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Stable under normal conditions.

Conditions to Avoid Incompatible products. Excess heat.

Incompatible Materials Strong oxidizing agents

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2), Formaldehyde, Thermal decomposition can lead to release of irritating gases and vapors

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information

Oral LD50 Category 4. ATE = 300 - 2000 mg/kg.

Dermal LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.

Vapor LC50 Category 3. ATE = 2 - 10 mg/l.

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Water	-	-	-
Formaldehyde	500 mg/kg (Rat)	LD50 = 270 mg/kg (Rabbit)	0.578 mg/L (Rat) 4 h
Methyl alcohol	LD50 = 1187 – 2769 mg/kg (Rat)	LD50 = 17100 mg/kg (Rabbit)	LC50 = 128.2 mg/L (Rat) 4 h

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation Irritating to eyes, respiratory system and skin

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS No	IARC	NTP	ACGIH	OSHA	Mexico
Water	7732-18-5	Not listed	Not listed	Not listed	Not listed	Not listed
Formaldehyde	50-00-0	Group 1	Known	A1	X	A2
Methyl alcohol	67-56-1	Not listed	Not listed	Not listed	Not listed	Not listed
Odor Mask	NA	Not listed	Not listed	Not listed	Not listed	Not listed

IARC (International Agency for Research on Cancer)

IARC (International Agency for Research on Cancer)
Group 1 - Carcinogenic to Humans
Group 2A - Probably Carcinogenic to Humans
Group 2B - Possibly Carcinogenic to Humans

NTP: (National Toxicity Program)

NTP: (National Toxicity Program)
Known - Known Carcinogen
Reasonably Anticipated - Reasonably Anticipated to be a Human Carcinogen

ACGIH: (American Conference of Governmental Industrial Hygienists)

A1 - Known Human Carcinogen
A2 - Suspected Human Carcinogen
A3 - Animal Carcinogen
ACGIH: (American Conference of Governmental Industrial Hygienists)

Mexico - Occupational Exposure Limits - Carcinogens

Mexico - Occupational Exposure Limits - Carcinogens
A1 - Confirmed Human Carcinogen
A2 - Suspected Human Carcinogen
A3 - Confirmed Animal Carcinogen
A4 - Not Classifiable as a Human Carcinogen
A5 - Not Suspected as a Human Carcinogen

Mutagenic Effects Mutagenic effects have occurred in humans.

Reproductive Effects Experiments have shown reproductive toxicity effects on laboratory animals.

Developmental Effects Developmental effects have occurred in experimental animals.

Teratogenicity Teratogenic effects have occurred in experimental animals.

STOT - single exposure Optic nerve Respiratory system Central nervous system (CNS)
STOT - repeated exposure Kidney Liver spleen Blood

Aspiration hazard No information available

Symptoms / effects,both acute and delayed Symptoms of allergic reaction may include rash, itching, swelling, trouble breathing, tingling of the hands and feet, dizziness, lightheadedness, chest pain, muscle pain or flushing: Symptoms of overexposure may be headache, dizziness, tiredness, nausea and vomiting: Product is a corrosive material. Use of gastric lavage or emesis is contraindicated. Possible perforation of stomach or esophagus should be investigated: Ingestion causes severe swelling, severe damage to the delicate tissue and danger of perforation

Endocrine Disruptor Information No information available

Other Adverse Effects Tumorigenic effects have been reported in experimental animals. See actual entry in RTECS for complete information.

12. Ecological information

Ecotoxicity

Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. The product contains following substances which are hazardous for the environment. Contains a substance which is:. Toxic to aquatic organisms.

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Formaldehyde	Not listed	Leuciscus idus: LC50 = 15 mg/L 96h	Not listed	EC50 = 20 mg/L 96h EC50 = 2 mg/L 48h
Methyl alcohol	Not listed	Pimephales promelas: LC50 > 10000 mg/L 96h	EC50 = 39000 mg/L 25 min EC50 = 40000 mg/L 15 min EC50 = 43000 mg/L 5 min	EC50 > 10000 mg/L 24h

Persistence and Degradability Miscible with water Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility . Will likely be mobile in the environment due to its water solubility.

Component	log Pow
Formaldehyde	-0.35
Methyl alcohol	-0.74

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

Component	RCRA - U Series Wastes	RCRA - P Series Wastes
Formaldehyde - 50-00-0	U122	-
Methyl alcohol - 67-56-1	U154	-

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

United States of America Inventory

Component	CAS No	TSCA	TSCA Inventory notification - Active-Inactive	TSCA - EPA Regulatory Flags
Water	7732-18-5	X	ACTIVE	-
Formaldehyde	50-00-0	X	ACTIVE	-
Methyl alcohol	67-56-1	X	ACTIVE	-
Odor Mask	NA	-	-	-

Legend:
TSCA US EPA (TSCA) - Toxic Substances Control Act, (40 CFR Part 710)
X - Listed
'-' - Not Listed

TSCA 12(b) - Notices of Export Not applicable

International Inventories
Canada (DSL/NDSL), Europe (EINECS/ELINCS/NLP), Philippines (PICCS), Japan (ENCS), Japan (ISHL), Australia (AICS), China (IECSC), Korea (KECL).

Component	CAS No	DSL	NDSL	EINECS	PICCS	ENCS	ISHL	AICS	IECSC	KECL
Water	7732-18-5	X	-	231-791-2	X	X		X	X	KE-35400
Formaldehyde	50-00-0	X	-	200-001-8	X	X	X	X	X	KE-17074
Methyl alcohol	67-56-1	X	-	200-659-6	X	X	X	X	X	KE-23193
Odor Mask	NA	-	-	-	-	-		-	-	-

KECL - NIER number or KE number (http://ncis.nier.go.kr/en/main.do)

U.S. Federal Regulations

SARA 313

Component	CAS No	Weight %	SARA 313 - Threshold Values %
Formaldehyde	50-00-0	3.7 - 10.0	0.1
Methyl alcohol	67-56-1	1.0 - 4.1	1.0

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act)

Component	CWA - Hazardous Substances	CWA - Reportable Quantities	CWA - Toxic Pollutants	CWA - Priority Pollutants
Formaldehyde	X	100 lb	-	-

Clean Air Act

Component	HAPS Data	Class 1 Ozone Depletors	Class 2 Ozone Depletors
Formaldehyde	X		-
Methyl alcohol	X		-

OSHA - Occupational Safety and Health Administration

Component	Specifically Regulated Chemicals	Highly Hazardous Chemicals
Formaldehyde	2 ppm STEL 0.5 ppm Action Level 0.75 ppm TWA	TQ: 1000 lb

CERCLA This material, as supplied, contains one or more substances regulated as a hazardous substance under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302)

Component	Hazardous Substances RQs	CERCLA EHS RQs
Formaldehyde	100 lb	100 lb
Methyl alcohol	5000 lb	-

California Proposition 65 This product contains the following Proposition 65 chemicals.

Component	CAS No	California Prop. 65	Prop 65 NSRL	Category
Formaldehyde	50-00-0	Carc. (Gaseous only)	40 µg/day	Carcinogen
Methyl alcohol	67-56-1	Developmental	-	Developmental

U.S. State Right-to-Know Regulations

Component	Massachusetts	New Jersey	Pennsylvania	Illinois	Rhode Island
Water	-	-	X	-	-
Formaldehyde	X	X	X	X	X
Methyl alcohol	X	X	X	X	X

U.S. Department of Transportation

Reportable Quantity (RQ): Y
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security This product contains the following DHS chemicals:
Legend - STQs = Screening Threshold Quantities, APA = A placarded amount

Component	DHS Chemical Facility Anti-Terrorism Standard
Formaldehyde	Release STQs - 15000lb (solution)

Other International Regulations

Mexico - Grade No information available

Authorisation/Restrictions according to EU REACH

Component	REACH (1907/2006) - Annex XIV - Substances Subject to Authorization	REACH (1907/2006) - Annex XVII - Restrictions on Certain Dangerous Substances	REACH Regulation (EC 1907/2006) article 59 - Candidate List of Substances of Very High Concern (SVHC)
Formaldehyde	-	Use restricted. See item 72. (see link for restriction details) Use restricted. See item 28. (see link for restriction details) Use restricted. See item 75. (see link for restriction details)	-
Methyl alcohol	-	Use restricted. See item 69. (see link for restriction details)	-

https://echa.europa.eu/substances-restricted-under-reach

Safety, health and environmental regulations/legislation specific for the substance or mixture

Component	CAS No	OECD HPV	Persistent Organic Pollutant	Ozone Depletion Potential	Restriction of Hazardous Substances (RoHS)
Water	7732-18-5	Listed	Not applicable	Not applicable	Not applicable
Formaldehyde	50-00-0	Listed	Not applicable	Not applicable	Not applicable
Methyl alcohol	67-56-1	Listed	Not applicable	Not applicable	Not applicable
Odor Mask	NA	Not applicable	Not applicable	Not applicable	Not applicable

Component	CAS No	Seveso III Directive (2012/18/EC) - Qualifying Quantities for Major Accident Notification	Seveso III Directive (2012/18/EC) - Qualifying Quantities for Safety Report Requirements	Rotterdam Convention (PIC)	Basel Convention (Hazardous Waste)
Water	7732-18-5	Not applicable	Not applicable	Not applicable	Not applicable
Formaldehyde	50-00-0	5 tonne	50 tonne	Not applicable	Not applicable
Methyl alcohol	67-56-1	500 tonne	5000 tonne	Not applicable	Not applicable
Odor Mask	NA	Not applicable	Not applicable	Not applicable	Not applicable

16. Other information

Prepared By Regulatory Affairs
Thermo Fisher Scientific
Email: EMSDS.RA@thermofisher.com

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Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS