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**ALDEHYDE EXPOSURE AND ITS IMPACT
TO PHYSIOLOGICAL ATTRIBUTES:
A SCOPING LITERATURE REVIEW**

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1.0 SUMMARY

The Air Force needs information detailing the potential for chemical exposure in an Air Force environment, the performance attributes impacted, and the dose-response relationship between the amount of chemical and level of impact. A program sponsored by the Air Education and Training Command (AETC) Surgeon General developed performance attributes for vision, audiology, physiology, and psychology. A list of relevant Air Force chemicals in occupational environments was developed in order to conduct systematic literature reviews to determine their impact on performance attributes of concern. The first class of chemicals reviewed were the aldehydes which are a large class of organic compounds that are formed by the oxidation of alcohols.

Given the large number of chemicals and performance attributes to review, the commercial software DistillerSR with its artificial intelligence (AI) function, was selected because it eliminates duplicate articles and can automatically select the articles of interest based upon criteria specified by the review team. Abstracts were then screened by two or more individuals and studies selected based upon the inclusion or exclusion criteria developed by the team. Final selection of research articles involved screening articles based on inclusion or exclusion criteria also developed by the team. Data was then extracted into a template created in Distiller, saved and downloaded to an Excel file to compile and analyze. The information was then extracted from the Excel files into the tables in the results section of this report. A risk of bias checklist was used to score both human and animal studies and provide an overall score for each study that addressed the quality of the article as well as internal validity (bias and confounding), power and also external validity. Articles for each of the attribute categories were then summarized in the results.

The primary aldehyde for which articles and research was found was formaldehyde. Low levels of formaldehyde are found in combustion products and in building materials, so Airmen can be exposed on the flight line, traveling to work or in a new or renovated building. A primary impact of formaldehyde is irritation which can affect vision, the upper respiratory system (physiology) and a number of cognitive functions (psychology). The literature search failed to find any references for aldehydes affecting the auditory attributes. Due to the limited dose-response data available for most attributes, additional research and model development is recommended. Non-occupational and short-term exposures can induce transient impacts on performance attributes.

2.0 INTRODUCTION

2.1 Performance Attributes of Concern

Mission success is predicated on the human weapon system operating at peak performance. Airmen are exposed to a wide variety of chemicals in their complex and challenging operating environments. Because chemical exposures within Air Force operating environments can result in decreased performance, accurate and timely risk assessment is crucial to support mission success and protect Airmen. Even small decrements in key attributes, like cognition, can impact mission outcomes (Amitai *et al.*, 1998; Chen *et al.*, 2009; Gatto *et al.*, 2014; Mohammed *et al.*,

2020). Currently, predicting risks associated with occupational exposure is difficult and time-consuming because the necessary information is located across multiple databases, evaluation tools, and the scientific literature. The Air Force needs a centralized source of information detailing the potential for chemical exposure in an Air Force environment, the performance attributes impacted, and the dose-response relationship between the amount of chemical and level of impact. This report is the first systematic literature review of chemicals found in Air Force occupational environments and their impact on performance attributes of concern.

The process to develop performance attributes began with the Optimization of Human Capital (OHC) program sponsored by the AETC Surgeon General. The OHC was created to address a capability gap in the objective alignment of airmen for maximum fit in a specific career field. The Precision-Based Airman Optimization (PBAO) portion of the OHC was to support development and transition of a system for measuring human characteristics early in the airman accession process for the purpose of improving alignment of Airmen to occupational specialties. By answering the question of how much of a particular ability is truly needed to successfully perform a specific job, the Air Force could make informed placement decisions to better support mission effectiveness and broaden the population of those considered fit for duty. Also knowing the attributes of ability allows the monitoring of job performance so there is no loss of capability due to various stressors such as chemical exposure.

Scientists and subject matter experts (SMEs) collaborated in the development of a set of basic performance resources (BPRs) and individual attributes (such as agility and visual acuity) that could be utilized as measurable indicators of potential performance success within a given career field (Scheiman *et al.*, 2020). They used General Systems Performance Theory (GSPT) and the Elemental Resource Model (ERM; Kondraske, G.V., 2011) as the conceptual basis for measurement and modeling of human performance. BPRs are a key GSPT construct. All aspects of system performance possess performance resources.

The process for defining and selecting BPRs used multiple sources of information including government-recommended tests and measures, occupational data from the U.S. Department of Labor's Occupational Information Network (O*NET; U.S. Department of Labor 2019), literature searches, and a working group from two Air Force Specialty Codes. Knowledge gained through each of these sources informed the development of a PBAO BPR list across four basic human performance resources (vision, audiology, physiology, and psychology) with multiple attributes for each. There was a total of 101 performance attributes chosen divided into 11 for vision, 9 for audiology, 37 for physiology, and 44 for psychology. The list of attributes was then reviewed by the authors to determine which ones could be most directly affected by chemical exposure. These attributes were added to the search terms in Table 2.

2.2 Aldehydes Overview

Aldehydes are a large class of organic compounds that are formed by the oxidation of alcohols. Aldehydes have a carbon atom that shares a double bond with an oxygen atom (carbonyl group), a single bond with a hydrogen atom, and a single bond with another atom or group of atoms. They are colorless, flammable liquids that are less dense in water and mostly soluble in water. Aldehydes have diverse properties that depend on the remainder of the molecule. Formaldehyde (CH₂O and acetaldehyde (C₂H₄O) are smaller molecules that are completely soluble in water.

Many volatile aldehydes have a pungent odor. Sampling methods for aldehydes include using a personal sampling pump with DNPH-coated glass fiber filters or sorbent tubes with DNPH-coated silica gel. Direct reading instruments can be used to sample ambient air and combustion gas mixtures to characterize workplace air.

2.3 Potential Sources in the Air Force

All of the aldehydes reviewed made the chemical list (Steele *et al.*, 2021) for this effort because they have been measured in the field either in the hardened aircraft shelter study or in the F-22 cockpit study. Kobayashi and Kikukawa (2000) reported formaldehyde in the exhaust of F-4 aircraft using JP-8 as the jet fuel. Aldehydes are also a byproduct of cigarette smoke and the combustion of fuels in general, making them a constituent of photochemical smog. Therefore, aldehydes are formed as combustion byproducts. Others may be in cleaning products or used as a disinfectant. Aldehydes are used as preservatives. They are also used to manufacture resins, are found in composites, engineered wood products and wall board in homes and offices. It is known that formaldehyde is a common contaminant in building environments.

3.0 METHODS

3.1 Systematic Review

A systematic literature review is a comprehensive analysis of all available literature on a topic to make data-driven decisions (Higgins and Thomas, 2019). This process first came to prominence in the medical community as a way to determine the efficacy of different treatment methods. Other communities, including the National Toxicology Program (NTP) and the U.S. Environmental Protection Agency (EPA), have adopted this rigorous process for their own needs (EPA, 2018; NTP, 2019).

Regardless of discipline, systematic reviews are published using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format (Moher *et al.*, 2009). Systematic reviews must document all decision points in their review, including where the literature was sourced (e.g. databases, grey literature, conference proceedings), the inclusion and exclusion criteria for a paper, the number of papers included and excluded in each phase, and what meta-data were collected from each paper. It is common for researchers to screen thousands of abstracts during a single review which translates to hundreds of man-hours.

The first step in implementing a systematic review is defining the review question by: 1) specifying the population of interest or participants, 2) specifying the types of interventions (if referring to a pharmaceutical, however, chemicals of occupational exposures are used in this review); 3) identifying the control or comparison population, and 4) identifying the types of outcomes that are of interest. In this review, outcomes are considered physiological effects that can result from acute/sub-chronic or periodic exposures and impact human performance. This process of identifying the question is typically referred to as population, intervention(s), controls, outcome (PICO), in the medical community. The team modified this process, replacing pharmaceutical/therapeutic interventions with AF-specific occupational exposures. Hence population, exposure(s), controls, and outcome (PECO), as shown in Table 1. These components,

with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for studies selected using the software.

Table 1. PECO statement formulated by Exposure Health team to guide scoping literature review

Population	Healthy human population between ages 18 - 65, animals
Exposure	Exposure to chemicals included in list of top 125 chemicals of interest to the Air Force
Comparator/Control	Health human population between ages 18 - 65 not exposure to chemical of interest, animals not exposed to chemicals of interest
Outcome(s)	Outcomes related to the attributes list

3.1.1 Search Terms

The list of chemicals chosen for this review is comprised of the highest priority chemicals used across the Air Force by mass and by chemicals identified in Air Force specific exposure assessments. There were three primary sources used to identify chemicals that fit this profile.

The first source was the chemical inventories pulled from the Air Force’s Enterprise Environmental, Safety, and Occupational Health Management Information System (EESOH-MIS). For each major command (MAJCOM), a representative base was identified (See Table 2). An EESOH-MIS expert generated a 2020 chemical inventory report for each base. Within the reports, the chemical name, Chemical Abstract Services (CAS) number, industrial process, and quantity used per operation were captured. For each base, the top 100 chemicals consumed in 2020 by mass were considered for inclusion in the final list.

Table 2. Representative Air Force Base (AFB) by Major Commands

MAJCOM	Representative Base
Air Combat Command (ACC)	Nellis AFB
Air Education and Training Command (AETC)	Joint Base San Antonio
Air Force District of Washington (AFDW)	Joint Base Andrews
Air Force Materiel Command (AFMC)	Wright-Patterson AFB
Air Force Global Strike Command (AFGSC)	Minot AFB
Air Mobility Command (AMC)	Joint Base McGuire-Dix-Lakehurst
Air Force Special Operations Command (AFSOC)	Cannon AFB
Pacific Air Forces (PACAF)	Kadena AB
United States Air Forces Europe/Africa (USAFE)/(AFRICOM)	Ramstein AB
United States Space Force (USSF)	Vandenberg AFB

The second source was a list of chemicals identified in a hardened aircraft shelter (HAS) during engine runs of an F-35 (McKinley *et al.*, 2016). These chemicals were unique in that they represented combustion by-products and therefore were unlikely to appear in any chemical inventory found in EESOH-MIS. All 76 chemicals discovered during the HAS study were included in the final list.

The third source was a list of chemicals identified during sampling of cockpit air in an F-22. This list numbered over 300 chemicals, so a subset of those chemicals that overlapped with the HAS list or two or more Air Force bases were selected for further review.

When first compiling the top 100 chemicals at each base, the HAS list, and the F-22 chemical list, 882 unique chemicals were present. Researchers used a combination of anticipated severity of health effects due to exposure, frequency of occurrence across bases, and estimated the potential for exposure to winnow the list down.

Within the Bioenvironmental Engineering (BE) career field, the consulting branch, USAF School of Aerospace Medicine Consultative Services Division (USAFSAM/OEC), developed a chemical hazard evaluation tool (CHET), in which 2279 chemicals were assigned health effect ratings (HER) for exposure via inhalation, dermal contact, and ingestion. For those chemicals on the list of 800+ that also appeared in the CHET, the health effect ratings for the three exposure routes were included in our consideration for inclusion. For those chemicals which did not appear in the CHET, health effects reported in the literature were copied from haz-map.com.

In the first pass, 178 chemicals were removed from the list of 882 since they did not appear on the HAS list and were only reported as being used at one base. The second pass removed 24 chemicals that were not on the HAS list and had a combined HER rating across the three exposure routes of less than or equal to 2. Forty-seven additional chemicals were removed for only appearing on two bases and not on the HAS list. Twenty-one chemicals were combined into a single, representative CAS based on all 21 chemicals having a product description of petroleum distillates. Finally, four chemicals did not appear on the HAS list and were reported as having minimal health effects by haz-map.com. In total, 273 chemicals were removed from further consideration.

All 76 chemicals appearing on the HAS list were included for the reasons mentioned above. Once HAS chemicals were removed from consideration, the remaining list of 533 chemicals was sorted by the number of bases reporting their use. The top 40 chemicals used across bases were captured and added to the final list.

One-hundred and sixteen (116) chemicals were identified for further review. This list was sent out to other researchers within RH for review. Suggestions were made to include chemicals on the Occupational Safety and Health Administration (OSHA) expanded standard list, of which five chemicals were selected. Trimethylsilanol is of interest among Navy IHs due to its presence during pilot breathing air studies, so it was added to the list. 1-Decene dimer, a known component in polyalphaolefin (PAO) coolant, did not initially make the round of cuts based on its reported frequency of use, but was re-added as it has been identified as an Air Force contaminant of concern. Respirable particles and elemental carbon were added as they are

aerosols with documented health effects and known to occur as a byproduct of combustion. Finally, a potential neurotoxin, PIP 3.1 oil, was added on the recommendation of a team member. In total, 126 chemicals (Steele *et al.*, 2021) were chosen for review.

As described in Section 2.1, Performance Attributes of Concern, SMEs have identified many performance attributes of interest. For this project, the search terms selected were narrowed down from the list of 101 to those pertaining specifically to performance attributes that could be impacted by chemical exposure and are listed in Table 3.

Table 3. Complete list of search terms chosen for attributes and chemicals of Air Force interest

Attribute Category	Search Terms
General terms for exposure studies	Chemical name and CAS# plus each of the following: exposure, inhalation, dermal/skin, oral/ingestion/gavage, toxicity, acute health effects, neurotox*. Then chemical name and CAS# plus each of the following terms in each of the four categories of attributes
Auditory	hearing, hearing loss, auditory, auditory threshold, auditory cutoff frequency, central auditory system, auditory temporal processing, auditory + temporal lobe, auditory cortex, word recognition + noise, sound localization, sentence recognition + noise, speech recognition + noise, spatial release from masking (SRM), tinnitus, vestibular, balance, auditory frequency shift, speech + differentiation, speech + recognition
Physiology	respiratory, respiration, respiratory rates, respiratory volume, motor activity, response to stimuli, body composition of fat/adipose, range of motion, extreme(s) of motion, functional movement, functional movement screen, mobility, flexor strength, grip strength, neuromuscular strength, core strength test, neuromuscular endurance, upper extremity steadiness, lower extremity steadiness, steadiness, dexterity, coordination, whole body agility, aerobic endurance, anaerobic performance capacity, chronotype
Psychology	behavior, neurobehavioral, neuroticism, cognition, cognitive function, activity level, motor activity, coordination, functional observational battery/FOB, neuropathologic, problem solving, mental ability, fear, anxiety, aggression, depression, CNS depression, acoustic startle, active avoidance, water maze, conditioned fear, force swim test, Morris water maze, inhibitory/passive avoidance, novel object recognition, light-dark box, rotor-rod, radial-arm water maze, social preference, Wisconsin Card Sorting Test (WCST), discrimination, prefrontal cortex, hippocampus, hippocampal, hallucination, risk-taking, mental focus, openness to experience, mental fatigue, OCEAN model, mental rotation, Verbal Intelligence, Performance Intelligence, working memory, N-back
Vision	vision, eye toxicity, eye irritation, ocular toxicity, achromatic contrast sensitivity, chromatic color contrast sensitivity, visual acuity, depth perception, binocular fusion range, field of view, blindness

3.1.2 Study Selection

Given the large number of chemicals and performance attributes to review, both open-source and commercial software which automates portions of the systematic literature review process were

evaluated. DistillerSR, with its AI function, Daisy, was selected because it eliminates duplicates and performs both a means of systematically selecting articles and mining qualitative and quantitative data from our literature searches, based upon criteria specified by the review team.

The selection of research articles to include in the final review involved multiple levels of screening. Initially abstracts were screened by two or more individuals and selected based upon the inclusion or exclusion criteria listed in Table 4. The list of selection criteria questions (Table 4) was established by team members. When there was disagreement in the selection of an abstract(s), both reviewers re-read the abstract to determine if agreement could be reached. Distiller's AI capabilities (DAISY) learns from multiple choice questions for inclusion/exclusion criteria and associates the terminology in the text with these criteria. Through this process the reviewers can run DAISY for the abstracts which were already reviewed by the researchers to determine if DAISY yielded good agreement. If satisfactory agreement was demonstrated, then the DAISY AI function was used to select/deselect the remaining abstracts.

Table 4. Inclusion and exclusion criteria used during study screening

Inclusion Criteria	Exclusion Criteria
-Appropriate model	-Inappropriate living model not easily extrapolated to humans (e.g. <i>in vitro</i> cell assays)
-Attribute related	-Not related to a health-based attribute of interesting (e.g. carcinogenicity/genotoxicity study, dermal effects, developmental toxicity) -Attribute related but a chronic outcome (e.g. asthma is a chronic outcome related to physiological attributes)
-Correct chemical	-Wrong chemical (e.g. ethylene vs ethylene glycol) -Chemical is in experiment but not explicitly studied (e.g. cumene is used to elicit a response but cumene exposure is not under study)
-Appropriate exposure scenario	-Exposure concerns related to ecotoxicity -Study concerned with chemical transport within the environment -Study focused on development of a material or transport of a material through media -Study focused on developing/characterizing sensors, detectors, or probes -Study focused on developing analytical chemical method for detection
-Original research	-Study a review of research -Study an opinion on policy
-Appropriate endpoints studied	-Study focused on biomarkers -Study focused on exposure assessment but not health effect

3.1.3 Data Extraction

The list of data extraction questions and responses (Table 5) were also developed by the team. Key information was pulled by team members from each study that Distiller saved and could be downloaded to an Excel file to compile and analyze. The information was then extracted from the Excel files into the tables in the Results section of this report.

Table 5. Data extraction fields used when evaluating included studies

Extraction Question	Responses
What type of study is this?	-Human --Epidemiology --Exposure assessment --Medical case study -Animal --Mice --Rat --Primate --Chinchilla --Swine --Dog --Rabbit --Guinea Pig -In silico model -Other
What size was the study population per group?	*Group identification *Exposure chemical *N for group *Female N *Male N
Was this study qualitative or quantitative?	-Qualitative -Quantitative -Semi-quantitative
What performance attribute category was studied?	-Vision --Vision --Eye/ocular toxicity --Eye irritation --Achromatic contrast sensitivity --Chromatic contrast sensitivity --Visual acuity --Depth perception --Binocular fusion range --Field of view --Blindness --Other not listed (specify*) -Auditory

Extraction Question	Responses
	<ul style="list-style-type: none"> --Hearing loss --Central auditory system/temporal processing --Auditory threshold shift --Cutoff frequency --Word/sentence recognition --Sound localization --Spatial release from masking (SRM) --Tinnitus --Vestibular impact/balance --Speech differentiation/recognition --Other not listed (specify*) -Psychology <ul style="list-style-type: none"> --Neuroticism --Cognition/cognitive function --Activity level/motor activity --Coordination --Neuropathology --Problem solving --Fear --Anxiety --Aggression --Depression --CNS depression/impact --Inhibitory/passive avoidance --Novel object recognition --Social preference --Discrimination --Hallucinations --Risk-taking --Focus --Openness to experience --Mental fatigue --Verbal intelligence --Performance intelligence --Working memory --Other not listed (specify*) -Physiology <ul style="list-style-type: none"> --Respiration/respiration rate --Respiratory volume --Response to stimuli --Motor activity/activity level --Body composition of fat/adipose --Coordination/functional movement/dexterity --Grip/flexor strength --Mobility/range of motion

Extraction Question	Responses
	<ul style="list-style-type: none"> --Core strength --Aerobic endurance --Anaerobic performance capacity --Chronotype --Cardiovascular impact: blood pressure --Cardiovascular impact: heart rate --Other not listed (specify*)
Outcomes	<ul style="list-style-type: none"> *What chemical does this outcome relate to? *What performance attribute category was studied? *Which study group did this outcome relate to? *What concentrations were tested? *Units of concentration -What relevant concentration category does it fall into? <ul style="list-style-type: none"> --LD50/IDLH --Significantly above OEL (>1.5x OEL) --OEL +/- 50% of value (ACGIH > NIOSH >OSHA) --Sub-OEL (<1.5x OEL) --EPA population/non-occupational exposure *What effect was observed? *How long did the exposure take place before an effect was noted? *At what concentration was the effect observed? -Should this be considered for meta-analysis <ul style="list-style-type: none"> --Yes --No
Epidemiology Risk Estimate Data	<ul style="list-style-type: none"> *What chemical does this relate to? *Which group does this apply to? *What is the reference group? *What is the health effect? *What range of concentrations were studied? *Units for concentration. *Defining concentration (if given) *How long did the exposure occur? -What kind of risk estimate is this? <ul style="list-style-type: none"> --Odds ratio --Relative risk --Other *What is the OR or RR? *What is the confidence interval? *What is the percentile for the CI (e.g. 95th)?
Comments	Free text

- = check boxes; * = free text

ACGIH American Conference of Governmental Industrial Hygienists

3.1.4 Risk of Bias (RoB)

Literature reviews must be comprehensive in terms of the study's they examine. But more importantly the data in the study must be judged objectively. This starts with examining the design of the study to ensure that biases are minimized or excluded. Checklists have been used to judge the quality of the methodology in a study and to address potential biases. A checklist by Downs and Black (1998) was chosen because it was developed for epidemiology studies and this effort is interested in human data. The checklist provides the strengths and weaknesses of the design and methods. Weaknesses can be selection bias, confounders and low power for human studies. Another limitation can be external validity which involves the ability to be able to generalize the data beyond the study population. The checklist was modified by the team so it could also be used for animal studies. The objective of the checklist was to be able to score both human and animal studies and provide an overall score for each study that addressed the quality of the article as well as internal validity (bias and confounding), power and also external validity (Table 6). Since a "Yes" is scored as a 1, a RoB score that is lower means a study has a lower bias. A perfect score for a human study varies depending on the type of study. A perfect case control study score would be 29 out of 29. Since four of the question do not pertain to animal studies a perfect score is 25 out of 25. To compare animal and human studies equally, a perfect score was considered to be 0% and higher scores became a higher percent. For examples, 25/25 = 0% for a perfect score and 31/25 = 24% for a score where 3 questions had values of 2.

Table 6. Modified Downs & Black risk of bias form used to evaluate individual studies for bias. The points for each response are: Yes = 1 point; No = 2 points; Not applicable = 0 points; Unable to determine = 2 points

	Question	Response
Reporting	Is the hypothesis/aim/objective of the study clearly described?	-Yes -No -Not applicable
	Are the main outcomes to be measured clearly described in the Introduction or Methods sections?	-Yes -No -Not applicable
	Are the characteristics of the subject/animal model included in the study clearly described?	-Yes -No -Not applicable
	Are the types of exposure of interest clearly described?	-Yes -No -Not applicable
	Are the distributions of principal confounders in each group of subjects to be compared clearly described? <i>A list of principal confounders is provided. Not relevant for laboratory animal studies (Not relevant for animal studies.)</i>	-Yes -No -Not applicable
	Are the main findings of the study clearly described?	-Yes -No -Not applicable

	Does the study provide estimates of the (non)normality of the distribution and variability in the data for the main outcomes?	-Yes -No -Not applicable
	Have all important adverse events that may be a consequence of the intervention (exposure) been reported?	-Yes -No -Not applicable
	Have the characteristics of subjects lost to follow-up or animals that died or were removed from the study been described?	-Yes -No -Not applicable
	Have the actual probability values been reported (e.g. 0.035 instead of <0.5) for the main outcomes expect where the probability value is less than 0.0001?	-Yes -No -Not applicable
External Validity	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? Was the animal model representative and relevant for the study?	-Yes -No -Unable to determine -Not applicable
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	-Yes -No -Unable to determine -Not applicable
	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	-Yes -No -Unable to determine -Not applicable
Internal Validity-- Bias	Was an attempt made to blind study subjects to the intervention they have received? Or for animal studies, were personnel blinded to the animal groups and exposure conditions?	-Yes -No -Unable to determine -Not applicable
	Was an attempt made to blind those measuring the main outcomes of the intervention?	-Yes -No -Unable to determine -Not applicable
	If any of the results of the study were based on “data dredging”, was this made clear?	-Yes -No -Unable to determine -Not applicable
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of subjects, or in case-control studies, is the time period between the exposure and outcome the same for cases and controls? (Not relevant for animal studies.)	-Yes -No -Unable to determine -Not applicable
	Are the control groups appropriately designed for the study (e.g. plain control, sham control, combination)?	-Yes -No -Unable to determine -Not applicable

	Were the statistical tests used to assess the main outcomes appropriate?	-Yes -No -Unable to determine -Not applicable
	Was compliance with exposure reliable?	-Yes -No -Unable to determine -Not applicable
	Were the main outcome measures used accurate? (e.g. standard methods/tests, established bias if using questionnaires, quantitative)?	-Yes -No -Unable to determine -Not applicable
Internal Validity-- Confounding (Selection Bias)	Is the population under study relevant to the endpoints being examined?	-Yes -No -Unable to determine -Not applicable
	Were study animals in an appropriate number of exposure groups (controls + 3 exposures)?	-Yes -No -Unable to determine -Not applicable
	Were the cases and controls (case-control studies) recruited over the same period of time? (Not relevant for animal studies.)	-Yes -No -Unable to determine -Not applicable
	Were the study subjects/animals randomized to exposure groups?	-Yes -No -Unable to determine -Not applicable
	Was the randomized exposure assignment (or randomization of animals to group) concealed from both subjects and study personnel until study start was complete and irrevocable?	-Yes -No -Unable to determine -Not applicable
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (Not relevant for animal studies.)	-Yes -No -Unable to determine -Not applicable
	Were losses of subjects to follow-up (death or removal of animals from study) taken into account?	-Yes -No -Unable to determine -Not applicable
	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	-Yes -No -Unable to determine -Not applicable

4.0 RESULTS

Like any study design, the review began with the formulation of a question. In this case, the format was structured to ask multiple PECO (population affected, exposure/chemical, criteria, and outcome/performance affected) questions regarding multiple performance attributes and how they may be affected by each chemical both in healthy humans and animals. These questions formed the protocol, establishing the inclusion and exclusion criteria and details about the methods that were used throughout the review process.

From the protocol, a comprehensive search of the literature was conducted based upon the PECO format. The more specific the question is, the better the search and process will be. The search was performed through several databases, with the help of an experienced librarian and resulted in 5068 articles (Figure 1), which were uploaded into DistillerSR. Before the screening of articles, DistillerSR removed duplicate articles, bringing the total number to 4751 articles. Screening of articles through the inclusion/exclusion criteria was performed in three parts. The first level of screening was performed by looking at the titles and abstracts. Two independent team members read the titles and abstracts and decided, based upon the criteria, whether to include the articles. Most articles did not meet the criteria. The Daisy AI also simultaneously trained on screening these titles and abstract and when it reported a F1 score of 61% or higher (a measure of test accuracy of how well the AI agreed with the reviewers), the AI was used to assist in completing the first level of title and abstract screening (Figure 1). The second level of screening was performed by an individual reviewer and Daisy reading the full articles to determine if they actually answered the criteria questions and had potential data to extract. The third level was data extraction and RoB assessment, which again was done using one independent reviewer on the final 47 studies selected (Figure 1). The data extracted was collected and summarize to identify acute or subchronic exposure levels that may impact performance in a number of ways. Meta-analysis could not be conducted from the extracted data, as it pertained to multiple different chemicals (exposures) and multiple different performance attributes (outcomes). The resulting data for each attribute category, RoB analysis are presented in the following sections.

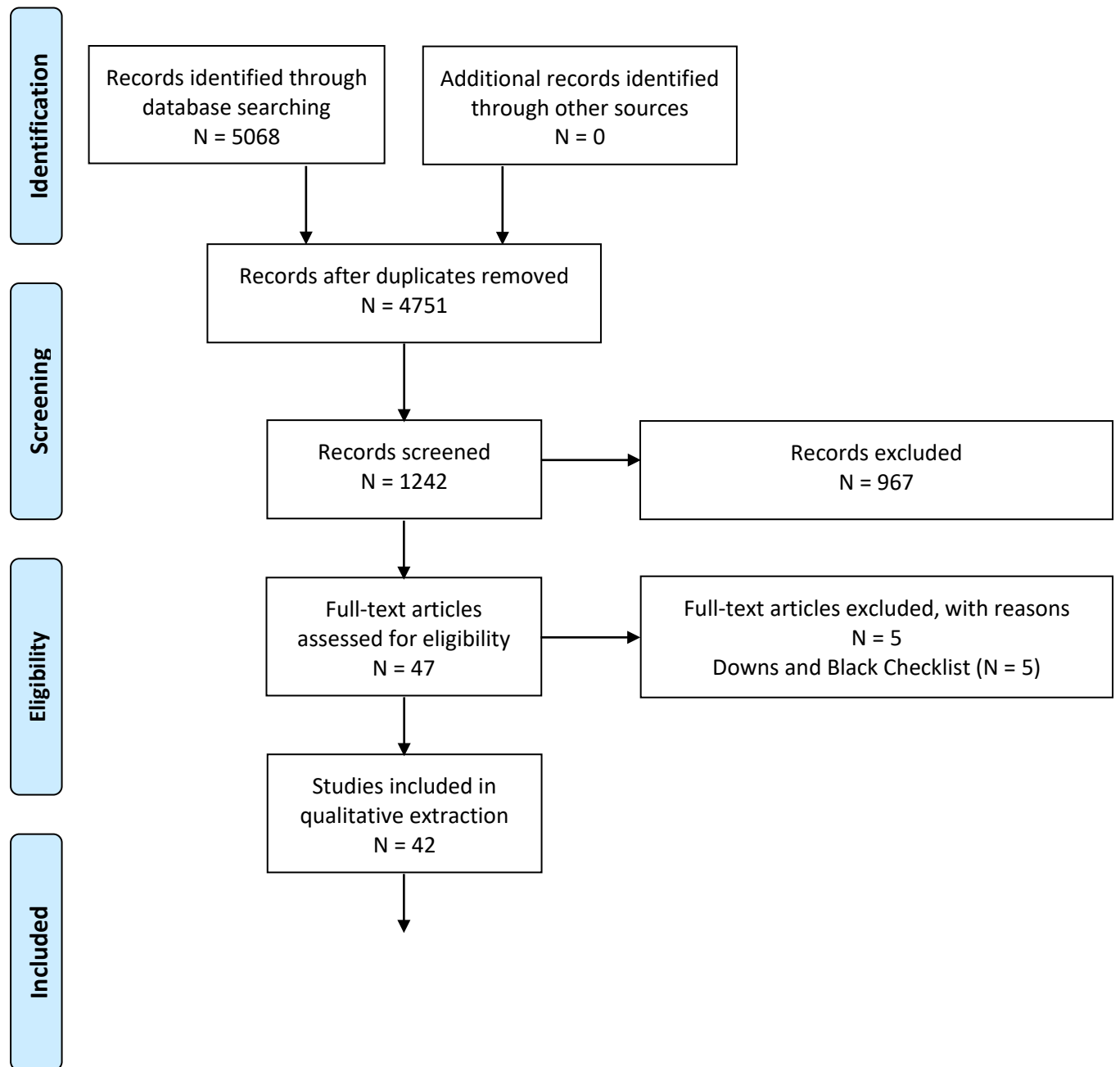


Figure 1. PRISMA format describing the systematic screening and selection of studies for analysis

4.1 Visual Attributes

Table 7 lists a summary of 12 studies, which met the selection criteria and indicated an impact on vision. Exposure to aldehydes occurs mainly through airborne concentrations and the main effect on vision is eye irritation. In fact, eye irritation and increased lacrimation are typically the first symptoms experienced from exposure to this class of compounds. Eye irritation was seen at formaldehyde concentrations as low as 1.0 parts per million (ppm) for 6 minutes (Bender *et al.*, 1983; Arts *et al.*, 2006).

Direct contact of the eye with liquid formaldehyde has lasting effects. In rabbits with eyes exposed to small round paper filter disks soaked in 0, 20, 100, 200, and 300 ppm of formaldehyde for 5 minutes, increased tear production was noted for several days following exposure (Lai *et al.*, 2013). In one case study, involving eye surgery, the solution used to minimize trauma to the corneal epithelium, sodium hyaluronate, was contaminated with formaldehyde causing corneal haze and complete ptosis (closed eyelid) (Sekeryapan *et al.*, 2011). The result was restricted vision.

Table 7. Summary of Studies Evaluating Chemical Exposures that Impact Visual Attributes

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Vazques-Ferreiro et al. 2019 [94] Human epidemiological study	Formaldehyde [50-00-0]	0.006 -2.44 mg/m ³	Eye irritation	Eye irritation present at 2.44 mg/m ³ (2 ppm)	N/A
Lai et al. 2013 [413] rabbits	Formaldehyde [50-00-0]	20 ppm; 100 ppm; 200 ppm; 300 ppm for five minutes each exposure; outcomes measured at 1, 3, 7, and 10 days after exposure	Eye toxicity; eye irritation; blindness	Tear production increased	30%
Mueller et al. 2013 [500] Human exposure assessment	Formaldehyde [50-00-0]	0.7 ppm for four hours; 0.4 ppm for four hours with 15 min peaks of 0.8 ppm	Eye irritation	No chemosensory effect	21%
Sekeryapan et al. 2011 [515] Human medical case study	Formaldehyde [50-00-0]	Exposure of undetermined amount during surgery, due to disinfectant	Eye toxicity; eye irritation; visual acuity	Corneal haze and ptosis	54%
Löfstedt et al. 2011 [573] Human epidemiology study	Formaldehyde [50-00-0]	>37 µg/m ³ with an average working history of 8.1 years (±8.2 years)	Eye irritation	Ocular irritation increased	20%
Arts et al. 2006 [827] Human exposure assessment	Formaldehyde [50-00-0]	1 ppm; 1.7 ppm	Eye irritation	Subjective eye irritation increased; objective eye irritation increased	43%
Kim et al. 1999 [1071] Human exposure assessment	Formaldehyde [50-00-0]	3.736 mg/m ³ (0.194 - 11.2 mg/m ³) during cadaver dissections	Eye irritation and lacrimation	Eye soreness and lacrimation increased	50%
Green et al. 1987 [1471]	Formaldehyde [50-00-0]	3 ppm for 1 hour	Eye irritation	Eye irritation increased	16%

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Human exposure assessment Bender et al. 1983 [1666] Human exposure assessment	Formaldehyde [50-00-0]	0.35 ppm for 268 s, 0.56 ppm for 217 s, 0.70 ppm for 72 s, 0.90 for 119 s, and 1.0 ppm for 78 s	Eye irritation	Steadily increasing eye irritation	27%
Alexandersson et al. 1982 [1707] Human exposure assessment	Formaldehyde [50-00-0]	0.36 ppm for one working day	Eye irritation	Increased eye irritation	19%
Nøjgaard et al. 2005 [2859] Human exposure assessment	Methacrolein [78-85-3]	286 ppb for 20 minutes	Blink frequency	18% increase in blink frequency	16%
Kulle et al. 1987 [3080] Human exposure assessment	Formaldehyde [50-00-0]	0, 1, 2, and 3 ppm recorded at 180 minutes	Eye irritation	Dose response increase in eye irritation starting at 1 ppm	24%

Vazques-Ferreiro et al. (2019)

The aim of a meta-analysis conducted by Vazques-Ferreiro *et al.* (2019) was to calculate the eye irritation dose of formaldehyde. Eye irritation is a highly sensitive predictor of toxic levels of formaldehyde and could be used as a marker of exposure risk. A systematic literature review was conducted from selected databases. All cohort, cross-sectional, and clinical studies that compared eye irritation in patients exposed and not exposed to formaldehyde were included. Data was extracted and a risk of bias checklist was used to assess the quality of the data. Odds ratios were calculated for each study. Eighteen of 2561 articles met the meta-regressions model. The threshold for eye irritation from exposure to formaldehyde relative to non-exposure was established at an odds ratio (OR) of 2, correlating with an expected exposure limit of 0.0014 mg/m³.

Lai et al. (2013)

Fifteen healthy New Zealand rabbits were used by Lai *et al.* (2013) in the *in vivo* Schirmer's Test after exposure to formaldehyde. Small round paper filter disks soaked in 0, 20, 100, 200, and 300 ppm of formaldehyde were applied to the rabbit eye and the eye was then closed for 5 minutes. The eye was subsequently washed with balance salt solution (BSS) to remove residual formaldehyde (FA). Gentamycin ointment was applied to the eye two times daily during the experimental period. At 1, 3, 7, and 10 days after exposure, a filter strip was inserted into the eye for five minutes. The amount of moisture on the test strip was measured by how far a blue dye traveled on the test strip. Both eyes were tested at the same time, with one eye as a control, and the other as the test site. Increased tear production was observed regardless of the formaldehyde concentration or number of days after exposure.

Mueller et al. (2013)

Healthy, non-smoking male adults (n =41) with an average age of 32 ± 9.9 were exposed for 4 hours per day to formaldehyde on five consecutive days and to five different exposure conditions: air alone, 0.5 and 0.7 ppm for 4 hours and to 0.3 and 0.4 ppm for 4 hours with peaks of 0.6 or 0.8 ppm for 15 minutes, respectively. Subjects were tested to determine if they were hypo- or hypersensitive individuals. The parameters and chemosensory effects examined were subjective rating of symptoms and complaints (Swedish Performance Evaluation System), conjunctival redness, eye-blinking frequency, self-reported tear film break-up time and nasal flow rates. There were no effects associated with either hypo- or hypersensitive males. A no observable adverse exposure level (NOAEL) of 0.7 ppm for a 4 hour constant exposure and a no-effect level (NOEL) of 0.4 ppm with peaks of 0.8 ppm were the results of this study (Mueller, Bruckner, Triebig, 2013).

Sekeryapan et al. (2011)

A 45-year-old woman with preoperative visual acuity of 20/200 in the right eye and 20/20 in the left eye underwent primary strabismus surgery to correct her right eye. Adult strabismus (crossed eyes) is when your eyes are not lined up properly and they point in different directions. Her past medical history was unremarkable and she did not report the use of any medication. During surgery, the cornea was covered with sodium hyaluronate to minimize the trauma to the corneal epithelium. The sodium hyaluronate was used in a cataract surgery the previous day and was disinfected in a container in which paraformaldehyde tablets are used to produce formaldehyde.

On the first postoperative day, there was complete ptosis of the right upper eyelid. Ptosis is when the upper eyelid droops, restricting or blocking vision. It is believed that formaldehyde diffused from the cornea to the muscles of the eyelid to cause the ptosis. The cornea was edematous which was also thought to be caused by formaldehyde contamination of the sodium hyaluronate. Three months postoperatively, the right eyelid ptosis was still present but with mild improvement. There was still a grade 2 stromal haze seen on the anterior segment of the cornea. Formaldehyde contamination must be avoided in all steps of eye surgery (Sekeryapan *et al.*, 2011).

Löfstedt et al. (2011)

Lofstedt *et al.* (2011) investigated the prevalence of nasal and ocular symptoms and nasal signs in foundry workers exposed to isocyanic acid, methyl isocyanate, formaldehyde, and total dust during the Hot Box method to produce cores for hollow castings. Forty-three foundry workers and 69 control subjects completed questionnaires and were examined for symptoms. Exposures were divided into unexposed, low and high. The level of formaldehyde measured was $51 \mu\text{g}/\text{m}^3$ with a standard deviation of 49 and a range of 13 to 190. The incidence of ocular irritation in the week immediately preceding testing was found to be correlated with the high formaldehyde exposures. No other correlations were found. Irritation of the eyes is one of the first symptoms of formaldehyde exposure and may vary rapidly in reply to changes of exposure levels (Lofstedt *et al.*, 2011).

Arts et al. (2006)

Arts *et al.* (2006) summarized eye irritation results from 9 publications representing 10 studies. For studies in which subjects reported irritation, formaldehyde concentrations equal to 1 ppm or higher caused the beginning of eye irritation. A confounding result in these studies is the fact that there were responders up to 22% at the control concentration of just air (0 ppm formaldehyde). Only one study used an objective measurement of eye-blinking frequency where 1.7 ppm was the concentration of formaldehyde in which eye irritation was reported to begin.

Kim et al. (1999)

Kim *et al.* (1999) studied 167 Korean medical students, aged 23.8 ± 2.5 years (mean \pm standard deviation). They were exposed to formaldehyde in anatomy and pathology laboratory classes. A control group of 67 premedical students, aged 20.1 ± 2.8 years (mean \pm standard deviation) were not exposed to formaldehyde. Concentrations of formaldehyde at 48 locations in the laboratory ranged from 0.194 to 11.245 mg/m^3 with a mean \pm standard deviation of $3.736 \pm 3.478 \text{ mg}/\text{m}^3$. The most-commonly reported symptoms induced by formaldehyde exposure during cadaver dissection were eye soreness (92.8%) and lacrimation (74.9%). Exposure to formaldehyde did not produce either IgG or IgE antibodies to this chemical.

Green et al. (1987)

Green *et al.* (1987) studied 22 healthy and 16 asthmatic subjects who were exposed to 3 ppm formaldehyde for 1 hour. The healthy subjects underwent intermittent heavy exercise (minute ventilation = 65 L/minute), whereas the asthmatics performed intermittent moderate exercise (minute ventilation = 37 L/minute). Symptoms and pulmonary function were assessed during exposure. No normal or asthmatic subject reported eye irritation or odor perception above a mild level with the clean air exposure. At 3 ppm, 82% of the volunteers reported detecting an

odor and experienced general irritation. Also, 27% responded with moderate or above eye irritation. The individual scores for odor and eye irritation ranged from zero to severe (score of 5). There were no differences between the healthy and asthmatic groups. The (normalized) average severity rating score for the healthy subjects was 1.1.

Bender et al. (1983)

Bender *et al.* (1983) was one of the studies reviewed by Arts *et al.* (2006). Volunteers were first tested for their sensitivity to eye irritation by formaldehyde using 1.3 and 2.2 ppm. About half of the original volunteers either reported eye irritation from clean air or were unresponsive to the test system and were rejected. The sensitive volunteers (5–28 per group) were then exposed using eye ports for 6 minute exposures to formaldehyde concentrations between 0 and 1.0 ppm (0.35, 0.56, 0.7, 0.9 and 1.0). The subjects were asked to give a subjective rating of eye irritation. The severity was scored when irritation was first noted and again at the end of the 6-minute exposure period. The results, when irritation was first reported, indicate that only at 1.0 ppm was there a significant difference between formaldehyde and clean air exposure (control concentration). Only the 1.0 ppm exposure averaged a slightly to moderately irritating rating (between 1 and 2). All other levels averaged less than slightly irritating (<1). In addition, severity ratings at the end of the 6 minute exposure period were lower than when irritation was first mentioned. The 1.0 ppm level is consistent with the 1.0 ppm summarized by Arts *et al.* (2006).

Alexandersson et al. (1982)

Air concentrations of FA were obtained from 47 males exposed to formaldehyde and 20 controls carrying sampling pumps in their breathing zone. Subjects were employed for at least 1 year in a Swedish carpentry shop producing chip board. Formaldehyde exposure occurred in an area where sawdust and wood chips were cemented together under high pressure. The controls were not exposed to formaldehyde. Interviews were conducted with employees using a standardized questionnaire. Three out of four exposed employees expressed eye discomfort during the work day. The mean sampling concentration of FA was 0.36 ppm, with a range of 0.04 ppm – 1.25 ppm. The mean concentration is below the Swedish National Board of Occupational Health and Safety Threshold Level of 1.0 ppm (Alexandersson *et al.*, 1982).

Nøjgaard et al. (2005)

Nøjgaard *et al.* (2005) exposed ten male subjects averaging 43 (standard deviation 10.5) years of age for 20 minutes to limonene oxidation products (LOPs), methacrolein, and clean air, respectively. Blink frequency (BF) was used as a measure of trigeminal stimulation of the human eye which changes when exposed to an irritant. A baseline BF was measured prior to and following each exposure (8 and 4 minutes, respectively). The subjects were exposed locally in the non-dominant eye only at 20% relative humidity (RH), while viewing an educational film. Blinking was video recorded and evaluated for full sessions of 36 minutes. The mean BF increased significantly during exposure to LOPs and methacrolein compared to the baseline of clean air, and the findings coincided with weak eye irritation symptoms. The lowest observed effect level was 286 ppb methacrolein. Effects may be exacerbated by low RH.

Kulle et al. (1987)

In a study by Kulle *et al.* (1987), 19 subjects (10 males and 9 females) were randomly exposed for 3 hour intervals to formaldehyde at 0, 1.0 and 2.0 ppm at rest plus at 2.0 ppm formaldehyde

including exercise. Ten of these volunteers were also exposed to 0.5 ppm, whereas the other nine were also exposed to 3.0 ppm formaldehyde. Symptom questionnaires were completed before, shortly after and 24 hour after exposure. Incidences and symptom scores were reported for all volunteers with data presented in Kulle (1993). All mean scores were below the score of 1 (present but not annoying) except for odor detection (1.00) and eye irritation at 3.0 ppm (1.44) formaldehyde. A linear concentration–response relationship was observed for odor and eye irritation. Exercise did not enhance the eye irritant effect. No symptoms were reported 24 hours following exposure at rest or following the exercise exposures. In a second paper, Kulle (1993) re-examined the symptomatic response data and using additional statistical methodology, estimated the threshold levels for odor and irritant responses. Estimated thresholds were less than 0.5 ppm for odor and 0.5–1.0 ppm for eye irritation. No differences were seen between the male and the female symptom responses.

4.2 Auditory Attributes

The literature search failed to find any references for aldehydes effecting the auditory attributes. There was one 2021 article about acrolein as an ototoxicant but the study did not test for hearing loss or functional changes in the auditory pathway but both are potentially impacted based on the biochemical and histopathological changes observed after exposure to acrolein.

Erhan et al. (2021)

Acrolein is a reactive aldehyde that forms during the burning of wood, fuels and cigarettes. It is known to cause oxidative stress and inflammatory nerve tissue damage. A previous study also reported that acrolein damaged cochlear nucleus neurons by triggering reactive oxygen species production and lipid peroxidation (Qu et al., 2018). Erhan et al. (2021) studied the effect of acrolein on the vestibulocochlear nerve in Wistar rats. The rats were divided into three groups (n = 6, for each group) a control group, an acrolein group and a lutein and acrolein group. The lutein group was administered 1 mg/kg lutein daily via oral gavage. The acrolein and control groups received saline via oral gavage. Then, 1 hour after the administration of lutein and saline, the lutein and acrolein groups were treated with 3 mg/kg of acrolein via oral gavage once a day for 30 days. Biochemical experiments showed that in the vestibulocochlear nerve tissues of the animals treated with acrolein, the levels of malondialdehyde, total oxidants, nuclear factor kappa b, tumor necrosis factor alpha and interleukin 1 beta significantly increased, while the levels of total glutathione and total antioxidants decreased compared to those in the control and lutein groups. Severe histopathological damage was seen in vestibulocochlear nerve tissue of the acrolein group. This damage was prevented in the lutein group by the antioxidant and anti-inflammatory properties of lutein.

4.3 Physiological Attributes

Thirty articles met the criteria for review based on the effects of aldehydes on physiological attributes, and formaldehyde was the most studied aldehyde (Table 8). The most common route of exposure for aldehydes is inhalation. Due to its high reactivity and water solubility, formaldehyde is easily absorbed in the nose and throat, causing irritation and potentially causing damage to the upper respiratory tract (Wei et al., 2007; Ritchie et al., 1987; Kamata et al., 1996; and Edling et al., 1987). Although many studies showed a decrease in respiratory function, inhaled formaldehyde does not readily penetrate deep into the lungs. (Jin et al., 2021; Larsen et

al., 2013 and 2000, Vandenplas et al., 2004, Green et al., 1987; Murphy and Ulrich, 1964; Alexandersson et al., 1982).

No observed effects in mice were seen at concentrations below 0.3 ppm for formaldehyde when exposed for 30 minutes, which is close to the NOEL of 0.08 ppm in humans (Nielsen et al., 1999). No observed effects from exposure to acetaldehyde were observed at concentrations of up to 10 ppm (Jin et al., 2021). Low concentrations of formaldehyde above 0.3 ppm can cause nasal discharge and preexisting allergic symptoms can be exacerbated by formaldehyde exposure (Fló-Neyret et al., 2001; Morgan et al., 1986; Hisamitsu et al., 2011; Löfstedt et al., 2011; Priha et al., 2004). Significant neurotoxic effects such as memory and learning disabilities were also shown to occur for acute exposures of formaldehyde at low concentrations (Usanmaz et al., 2002).

In addition to nose and throat irritation, formaldehyde was shown to decrease vascular function (Augenreich et al., 2020; Zhang et al., 2018; Tani et al., 1986), impair olfactory function (Zhang et al., 2014), and change lung surfactant production (Kamata et al., 1996) at high concentrations. Although there is no permissible exposure limit (PEL) for methacrolein, a concentration of 10.4 ppm was shown in one study to decrease the respiratory rate in mice by 50 percent (Larsen et al., 2000).

Table 8. Literature pertaining to physiological attributes of interest to the AF

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Jin et al. 2021 [1] Mice study	Formaldehyde [50-00-0]	5 – 10 ppm during two 9-minute sessions	Respiratory rates	Respiratory depression at 10 ppm	42%
	Acetaldehyde [75-07-0]	5 – 10 ppm during two 9-minute sessions	Respiratory rates	No decrease in respiration observed at max exposure level	
Augenreich et al. 2020 [8] Human exposure assessment	Formaldehyde [50-00-0]	197 ± 79 ppb for 90 minutes	Passive limb movement	Decrease in brachial artery flow	26%
Zhang et al. 2018 [155] Rat study	Formaldehyde [50-00-0]	0.5 mg/m ³ for 7 days for 4 hours/day	Blood pressure (BP)	No effect observed;	37%
		3 mg/m ³ for 7 days for 4 hours/day	Blood pressure (BP)	Decreased BP at day 8	
		18 mg/m ³ for 7 days for 4 hours/day	Blood pressure (BP)	Acute decrease in BP	
Zhang et al. 2014 [351] Rat study	Formaldehyde [50-00-0]	13.5 ± 1.5 ppm 2x/day for 30 min/day for 14 days	Olfactory function	1 in 6 tests resulted in significant increase in the latency time to find food	32%
Larsen et al. 2013 [442] Mice study	Formaldehyde [50-00-0]	60-minute exposures for: 1.8 ppm formaldehyde at <10% relative humidity + OVA; 4 ppm formaldehyde at <10% relative humidity + OVA;	Respiratory rate	Expiratory flow rate decreased	33%

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Hisamitsu et al. 2011 [548] Human epidemiological study	Formaldehyde [50-00-0]	0.44 – 0.67 ppm formaldehyde over a dissection course that lasted 3 months	Sensory irritation	35/41 students complained of odors, eye irritation, ocular pain, and burning in the throat. 15/41 complained of headaches and heavy-headedness	30%
Löfstedt et al. 2011 [573] Human epidemiological study	Formaldehyde [50-00-0]	< 37 µg/m ³ with average worker exposure of 8.1 years (±8.2 years) >37 µg/m ³ with average worker exposure of 8.1 years (±8.2 years)	Nasal irritation Nasal irritation	Increased sneezing (OR: 3.9; CI 1.4 – 10.4) Increased nasal discharge (OR: 4.2; CI 1.7 -10.8) Itchiness in nose (OR: 5.1; CI: 1.2-22.0) Evidence of dry mucosa, with or without crusts (OR: 2.8; CI: 1.1 – 6.9)	20%
Wei et al. 2007 [748] Human exposure assessment	Formaldehyde [50-00-0]	238, 763.3, and 891 µg/m ³ up to 8 hours a meeting for 3-month class.	Irritation, non-specific ill feeling	23% of students experienced nose irritation, 15.1% throat irritation, 13.7% mouth irritation, 35.7% eye irritation, 4.1% headaches, 8.2% felt ill, 5.4% had eczema; 28% felt strong stress	42%
Priha et al. 2004 [877] Human exposure assessment	Formaldehyde [50-00-0]	0.17 mg/m ³ [no time frame specified]	Irritation	Of the medium density fiberboard (MDF) group, 5% had eye irritation, 36% had nasal irritation, 5% had throat irritation, and 14% experienced skin irritation	10%
Vandenplas et al. 2004 [926] Human exposure assessment	Formaldehyde [50-00-0]	Unknown but estimated to be well above the ACGIH OEL	Respiratory capacity	Decreased FEV at 1 day post (60%) and at 8 days (81%)	9%
Fló-Neyret et al. 2001 [1010] Frog study	Formaldehyde [50-00-0]	1.25 ppm; 2.5 ppm; 5.0 ppm for 60 minutes	Respiration rates	ciliary beat frequency decreased and mucociliary clearance decreased for all concentrations	30%
Nielsen et al. 1999 [1062] Mice study	Formaldehyde [50-00-0]	0.3 ppm for 30 minutes 4.0 ppm for 30 minutes	Respiration rate Respiration rate	No effect level Reduced respiration rate due to sensory irritation	22%
Akbar-Khanzadeh et al. 1997 [1113] Human exposure assessment	Formaldehyde [50-00-0]	1.88 ppm (average) for 1 and 3 hours	Respiration rate	Increase in respiratory function of the exposed subjects was significantly less than that of the control subjects.	22%

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Riedel et al. 1996 [1161] Guinea pig study	Formaldehyde [50-00-0]	0.25 ppm for 5 days	Respiration rate	Increased bronchial sensitization to an allergen	32%
Kamata et al. 1996 [1162] Rat study	Formaldehyde [50-00-0]	15 ppm for 6 hours	Nasal irritation	Slight increase in nasal mucosa damage	22%
		15 ppm for 6 hours	Lung irritation	Increase in lung surfactant production	
		145.6 ppm for 6 hours	Nasal irritation	Increase in nasal mucosa damage	
		145.6 ppm for 6 hours	Lung irritation	Decrease in lung surfactant production	
Edling et al. 1987 [1461] Human exposure assessment	Formaldehyde [50-00-0]	0 mg/m ³ for 10.5 years (avg) [range: 1-30 years]	Rhinoscopic biopsy	Normal values (score = 1.8)	14%
		0.5 – 1.1 mg/m ³ for 10.5 years (avg) [range: 1-30 years]	Rhinoscopic biopsy	Elevated values (score = 2.8)	
		0.5 – 1.1 mg/m ³ for 10.5 years (avg) [range: 1-30 years]	Sensory irritation	66% of workers reported running eyes, 50% running nose, and 53% a sore throat	
Green et al. 1987 [1471] Human exposure assessment	Formaldehyde [50-00-0]	3 ppm for 1 hour during heavy exercise	Respiratory changes	3.8% lower FEV1, 2.6% lower FVC, and 2.8% lower FEV3	16%
Ritchie et al. 1987 [1481] Human exposure assessment	Formaldehyde [50-00-0]	Groups were broken out into exposures of <0.1 ppm, 0.1 – 0.3 ppm, and ≥0.3 ppm. Each for an average of 12 hours	Sensory irritation	All groups saw an increase in nose and throat irritation, headaches, and skin rash above 0.3 ppm	11%
Tani et al. 1986 [1524] Rabbit study	Formaldehyde [50-00-0]	10 ppm for less than 10 minutes	Respiratory rate	Changes in respiratory movements but only shown in figure	59%
			Heart rate	Decrease in heart rate from 300 to 169 beats/min	

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
			Blood pressure	No changes in blood pressure	
Morgan et al. 1986 [1536] Rat study	Formaldehyde [50-00-0]	0.5 ppm for 6h/day for 9 days	Mucociliary escalator (MCE) performance	No detectable impact to MCE	21%
		2.0 ppm for 6h/day for 9 days	Mucociliary escalator (MCE) performance	Minimal impact to MCE	
		6.0 ppm for 6h/day for 9 days	Mucociliary escalator (MCE) performance	“Much less severe” impact to MCE	
		15.0 ppm for 6h/day for 9 days	Mucociliary escalator(MCE) performance	Severe impact to MCE	
Rusch et al. 1983 [1673] Rat, hamster, and primate study	Formaldehyde [50-00-0]	3 ppm in last 13 weeks of 26 week study of Cynomolgus monkeys	Hoarseness and congestion	Marked increase in hoarseness and congestion	29%
Alexandersson et al. 1982 [1707] Human exposure assessment	Formaldehyde [50-00-0]	0.36 ppm for one working day	Airway irritation	Upper airway irritation decreased, lower lung function decreased	19%
Murphy & Ulrich 1964 [1879] Guinea pig study	Formaldehyde [50-00-0]	0 ppm for 1 hour	Respiration rate	Normal function (>80 breaths per minute)	N/A
		3.9 ppm for 1 hour	Respiration rate	Respiration rate only 73% of normal value	
		12.5 ppm for 1 hour	Respiration rate	Respiration rate only 83% of normal value	

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Larsen et al. 2000 [2874] Mice study	Methacrolein [78-85-3]	13.9 ppm for 30 minutes	Respiration rate	Decrease in respiration rate	N/A
		26.3 ppm for 30 minutes	Respiration rate	Decrease in respiration rate	
Bos et al. 1992 [3075] Mice study	Formaldehyde [50-00-0]	3.2 ppm	RD50 value	Swiss Webster mouse (Confirmed in Steinhagen and Barrow (1984)	N/A
		4.9 ppm	RD50 value	B6C3F1 mouse	
		5.3 ppm	RD50 value	Swiss OF1 mouse	
	Acetaldehyde [75-07-0]	4,946 ppm	RD50 value	Swiss Webster mouse	
	Propionaldehyde	2,052 ppm	RD50 value	Swiss Webster mouse (Confirmed in Steinhagen and Barrow (1984)	
Kulle et al. 1987 [3080] Human exposure assessment	Formaldehyde [50-00-0]	0 ppm 3h exposures x 5	Pulmonary function	No change to pulmonary function observed at any concentration, with or without exercise	24%
		0.5 ppm 3h x5	Pulmonary function		
		1.0 ppm 3h x 5	Pulmonary function		
		2.0 ppm 3h x5	Pulmonary function		
		3.0 ppm 3h x5	Pulmonary function		
Usanmaz et al. 2002 [4244] Mice study	Formaldehyde [50-00-0]	0, 1.8, 3.2, 6.4, 9.7, and 14.8 ppm, each for 3 hours.	Ambulatory activity	Decreased ambulatory activity in a dose response manner	50%
			Vertical activity	Vertical activity decreased in a dose response manner, though 3.2, 4.5, and 6.4 were essentially the same level	

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
			Wet dog shake (WDS) as a proconvulsive sign	Increased from 1.8 to 6.4 ppm but not in a dose response manner and then decreased at 9.7 and 14.8 ppm, indicating a different MOA	
Vyas et al. 2000 [4268] Human epidemiology study	Glutaraldehyde as a disinfectant [111-30-8]	Endoscopy nurses Mean time on the job was 2.2 years (1 month to 19 years; 74% < 5 years) and those who left within the last 5 years	Pulmonary function	The mean percentage predicted forced expired volume in 1 second (ppFEV1) for ex-employees (93.82, 95% confidence interval (95% CI) 88.53 to 99.11) was significantly lower (p<0.01) than that of current workers exposed to GA (104.08, 95% CI 102.35 to 105.73).	N/A
Kriebel et al. 1993 [4450] Human exposure assessment	Formaldehyde [50-00-0]	One 3h exposure for 10 weeks with an average exposure of 0.73 ±1.22 ppm	Respiratory volume	10 L/min drop in pre-lab FEV and general trend of lower FEVs when comparing post-lab values to pre-lab values	23%
Swiecichowski et al. 1993 [4462] Guinea pig study	Formaldehyde [50-00-0]	0.3 ppm for 8 hours	Respiration rate	Airway reactivity significantly increased	26%

Jin et al. (2021)

In order to examine the role of acetaldehyde and formaldehyde in the effects of electronic cigarettes, male C57BL/6J mice were exposed by inhalation to filtered air or formaldehyde (FA) or acetaldehyde (AA) for two 9-min sessions at 5-10 ppm (Jin *et al.*, 2021). Mice were instrumented with pressure transmitters to detect changes in pleural cavity pressure. Pressure waveforms were analyzed for respiratory rate (breaths per min), expiratory, and inspiratory times, and peak amplitude (mmHg, a measure of respiratory effort). Onset of exposure to FA (n=2 mice per group) had modest effect at 5 ppm but greater than 5 ppm provoked rapid and robust changes in respiratory rate and expiratory time. Less noticeable changes occurred in inspiratory time and peak amplitude. Onset of exposure to AA (n = 3 mice per group) had no noticeable effect at 5 or up to 10 ppm on respiratory rate, expiratory time, inspiratory time, and peak amplitude (Jin *et al.*, 2021).

Augenreich et al. (2020)

Augenreich *et al.* (2020) was the first to investigate acute formaldehyde exposure on vascular function. Nine female students with little previous exposure to formaldehyde were studied before and immediately after a 90-minute formaldehyde exposure in cadaver dissection laboratories. The subjects wore formaldehyde sensors on a chest harness to measure individual exposure levels to formaldehyde. Levels of formaldehyde in the rooms were below the OSHA PEL of 750 ppm for an 8-hour time weighted average. Macrovascular function in the arm (flow mediated dilation) was measured in the brachial artery using Doppler ultrasound after exposure to formaldehyde. Doppler ultrasound was also used to measure microvascular function in the arm (artery reactive hyperemia) and leg (passive limb movement). The average formaldehyde exposure during 90 minutes was 197 ± 79 ppm, with a 30-minute average ranging from 20 to 356 ppm formaldehyde. There was no change in artery reactive hyperemia and passive leg movement. A 3% reduction of flow mediated dilation in the brachial artery was observed. This indicates a potential negative impact of acute formaldehyde exposure on vascular function in the arms of females.

Zhang et al. (2018)

Formaldehyde (FA) has been linked to adverse cardiovascular effects. Male Wistar rats were exposed to 0.42 ± 0.03 , 2.50 ± 0.20 or 15 ± 0.31 ppm FA for 4 hours per day for 7 days and compared to controls exposed to air alone for the same times Zhang *et al.* (2018). Blood pressure was measured 20 minutes after each exposure. The final blood pressure value for each rat was the mean of 6 continuous measurements. Rat aortic tissues were harvested for analysis after the last exposure. The blood pressures of rats was significantly lower in the 15 ppm group for all 7 days but was only lower than controls on days 6 and 7 for the 2.5 ppm group. The expression levels of calcium activated potassium channel (BK_{Ca}) subunits α and $\beta 1$ and inducible nitric oxide synthase (iNOS) of the aortas were up-regulated by FA *in vivo*. Formaldehyde markedly reduced the levels of Ca_v1.2 and Ca_v1.3, which are the subunits of the L-Ca²⁺ (calcium) channel. However, the amount of nitric oxide, cGMP and iNOS in the aortas were increased by FA. The change in blood pressure appears to be the result of FA regulating ion channels and signaling pathways.

Zhang et al. (2014)

To investigate the effect of repeated formaldehyde inhalation exposure on olfactory function male Sprague-Dawley rats were exposed to 13.5 ± 1.5 ppm formaldehyde by inhalation twice for 30 minutes per day for 14 days (Zhang *et al.*, 2014). The buried food pellet test and the time to find the food pellet (latency) were used to detect olfactory function and locomotion (locomotive activity searching for the pellet). To examine potential mechanisms of action western blots were used to evaluate synaptosomal-associated protein 25 (SNAP25) protein levels in the olfactory bulb (OB) lysate and synaptosome, as well as mature and immature olfactory sensory neuron markers, olfactory marker protein (OMP), and Tuj-1. Real-time polymerase chain reaction (PCR) was used to detect SNAP25 mRNA amounts. Repeated formaldehyde inhalation exposure impaired olfactory function but not locomotion. SNAP25 protein decreased significantly in the OB, but not in the occipital lobe. Formaldehyde inhalation exposure did not affect mature or immature olfactory sensory neurons or mRNA in the OB. The results suggest that a decrease of SNAP25 protein in the OB and its synaptosomal fraction may contribute to olfactory function impairment after repeated formaldehyde inhalation exposure.

Larsen et al. (2013)

Thirty male mice, in groups of 5, were challenged with the immunogen ovalbumin (OVA) and housed at low (less than 10% relative humidity) or high humidity (85 – 89% relative humidity). Control mice were challenged with saline and exposed to saline mist. The mice were exposed to 0.4 ppm, 1.8 ppm, or 5.7 ppm formaldehyde for 60 minutes. Five mice were also exposed to 4.0 ppm in a low humidity environment. Sensory irritation in the upper airway was not affected by changes in levels of relative humidity. Exposure flow rate decreased in mice exposed to 5.7 ppm at high relative humidity compared to the saline control mice. This is in accordance with high concentrations of irritants such as formaldehyde causing upper airway irritation in environments with high relative humidity. Saline control mice had decreased exposure flow rate and more upper airway irritation than mice exposed to 1.8 ppm and 4.0 ppm in low relative humidity. No effect was seen in formaldehyde exposure and humidity for the degree of upper airway and lung irritation Larsen *et al.* (2013).

Hisamitsu et al. (2011)

Hisamitsu *et al.* (2011) studied students (total 41, 26 male, 15 female), ranging in age from 21 to 25 years in a 3 month cadaver dissection course. They were divided into groups based on their type of allergic rhinitis. Eleven students were in the non-allergy group. All subjects were evaluated by a careful medical examination, Nagashima jet nebulizing olfaction test, intranasal examination for nasal secretions and nasal mucosal sensitivity to histamine immediately before and after the course and 6 months after the completion of the course. The olfaction test was repeated 12 months after the end of the course. Formaldehyde was measured using passive aldehyde samplers worn by the students. Levels of formaldehyde ranged from 0.51 to 0.97 ppm in the center of the laboratory, with an average concentration of about of 0.67 ppm. The concentrations in the corners, ranged from 0.22 to 0.70 ppm with an average of 0.44 ppm. An increase in the olfactory cognition threshold was observed in 13 of 41 (32%) subjects and increased nasal mucosal hypersensitivity to histamine was observed in 17 of 41 (41%) during and immediately after completion of the course. These subjects had evidence of preexisting allergic rhinitis. Six out of 41 (15%) other students with no prior evidence of allergic rhinitis also exhibited formaldehyde associated clinical symptoms during the dissecting course. However,

nasal symptoms disappeared upon completion of the course in all subjects indicating that these effects appeared to be transient. The olfactory thresholds were returning towards normal at 6 months and were mostly recovered at 12 months.

Löfstedt et al. (2011)

Lofstedt *et al.* (2011) investigated the prevalence of nasal and ocular symptoms and nasal signs in foundry workers exposed to isocyanic acid, methyl isocyanate, formaldehyde, and total dust during the Hot Box method to produce cores for hollow castings. Forty-three foundry workers and 69 control subjects completed questionnaires and were examined for symptoms. Exposures were divided into unexposed, low and high. The level of formaldehyde measured was $51 \mu\text{g}/\text{m}^3$ with a standard deviation of 49 and a range of 13 to 190. Compared to the controls, a greater proportion of all the members of the exposed group experienced nasal symptoms during the week immediately preceding the nasal examination (74% vs 39%, OR = 4.6, 95% CI: 2.0 to 10.7). Specific symptoms such as nasal discharge (OR = 3.0, 95% CI: 1.3 to 7.2) and sneezing (OR = 3.1, 95% CI: 1.2 to 7.8) were more prevalent among all the exposed individuals than the controls. There were significant associations between most exposures and symptoms when the exposed individuals were divided into low- and high-exposed groups. A dose-response relationship between the prevalence of any nasal symptom and exposure to formaldehyde was observed. Dry mucosa with or without crusts was more prevalent among all the exposed individuals than the controls (OR = 2.6, 95% CI: 1.2 to 5.7) but there was no dose response for formaldehyde. An increased prevalence of nasal symptoms and signs was observed among exposed workers, suggesting a link with monoisocyanates and other airway irritants, such as formaldehyde and dust, in the foundry environment (Lofstedt *et al.*, 2011).

Wei et al. (2007)

Male (n = 52-67) and female (n = 27) students aged 21.4 ± 3.1 (average \pm SD) were exposed to formaldehyde in an anatomy dissection class. The geometric mean concentrations were 238 (at the end), 763.3 (in the middle), and 891 (at the beginning of the course) $\mu\text{g}/\text{m}^3$. The results based on questionnaire responses found that 23% of students experienced nose irritation, 15.1% throat irritation, 13.7% mouth irritation, 35.7% eye irritation, 4.1% headaches, 8.2% felt ill, 5.4% had eczema; and 28% felt strong stress Wei *et al.* (2007).

Priha et al. (2004)

Priha *et al.* (2004) recruited workers from 3 factories using medium-density fiber (MDF) board and who were exposed to dust and formaldehyde that off-gassed from the boards. There were 22 members in the MDF group, all men, with an average age of 38 years (range 25–56 years), of whom 45% were smokers. The unexposed control group consisted of 15 office workers of the Finnish Institute of Occupational Health, all men, with an average age 39 years (range 29–57), 13% of whom were smokers. Formaldehyde levels in the factories averaged 0.19 ± 0.11 SD mg/m^3 . The prevalence of reported symptoms at the end of shift were 5% had eye irritation, 36% had nasal irritation, 5% had throat irritation, and 14% experienced skin irritation and the findings did not correlate with smoking. Cell counts and cytokine levels of nasal lavage fluid samples did not show statistically significant differences between the workers exposed to MDF board dust and those exposed to other wood dusts. Two MDF-exposed workers had a considerable increase in the proportion of eosinophils and cytokine levels.

Vandenplas et al. (2004)

Vandenplas *et al.* (2004) reported about a 31-year-old male who had been accidentally exposed for about 2 hours to formaldehyde that leaked from a malfunctioning reactor gasket while working in a chemical plant producing urea-formaldehyde resins. Over the following hours, he developed asthma symptoms and was admitted to a local emergency room. He reported no history of pre-existing respiratory disease. Pulmonary function tests showed a decreased FEV₁ at 1 day post (60%) and at 8 days (81%) but returned to normal at 26 days (106%). Although pulmonary function remained normal the subject continued to experience asthma symptoms. In this subject, the strong temporal relationship between accidental high-level exposure to formaldehyde and the rapid onset of asthma symptoms that were persistent is consistent with a non-immunological form of asthma, most often referred to as reactive airways dysfunction syndrome (RADS) or irritant-induced asthma (Vandenplas *et al.*, 2004).

Fló-Neyret et al. (2001)

Fló-Neyret *et al.* (2001) studied the effects of formaldehyde on the ciliated epithelium of the mucus membrane of the respiratory tract. The palates of American bullfrogs were removed and exposed for 60 minutes to either diluted Ringer's solution (control, n=8) or 1.25 ppm, 2.5 ppm, 5.0 ppm in diluted Ringer's solution (n=10 for each group). A short-term toxicity assay was developed and ciliary beat frequency and the mucociliary clearance rate (ability of the cilia to clear mucus from the respiratory tract) was determined as estimators of formaldehyde toxicity. Statistical analysis showed that both the ciliary beat frequency and mucociliary clearance decreased significantly at formaldehyde concentrations of 2.5 ppm and 5.0 ppm. This evidence suggests that low concentrations of formaldehyde can cause impairment of mucociliary function.

Nielsen et al. (1999)

Nielsen *et al.* (1999) investigated concentration and time-effect relationships of formaldehyde and ozone on the airways in BALB/c mice. They monitored continuously respiratory rate, tidal volume, expiratory flow rate, time of inspiration, time of expiration, and respiratory patterns. Mice were exposed to 0.3 to 4 ppm formaldehyde for 30 minutes. The 4 ppm formaldehyde level was the RD₅₀ value which compared with other strains of mice such as Swiss Webster and showed mainly sensory irritation effects of the upper airways that decrease the respiratory rate due to a trigeminal reflex. The NOEL was essentially 0.3 ppm which is close to the human NOEL of 0.08 ppm. The upper airway irritant, formaldehyde, showed the same types of respiratory effects in humans and in BALB/c mice.

Akbar-Khanzadeh et al. (1997)

Akbar-Khanzadeh and Mlynek (1997) measured the respiratory function of 50 (25 men and 25 women) nonsmoking medical students exposed to formaldehyde in a gross anatomy laboratory and compared them with the respiratory function of 36 (8 men and 28 women) non-exposed, non-smoking physiotherapy students. Formaldehyde concentrations were measured in the breathing zone of each exposed subject and in the middle of the laboratory for 157 (42) and 160 (29) mean \pm (SD) minutes. Formaldehyde concentrations in the breathing zone of exposed subjects averaged 1.88 (0.96) ppm and 0.97 (0.28) ppm in the laboratory and exceeded recommended exposure standards. On average, the variables of respiratory function (FVC, FEV₁, FEV₃) of both the exposed and the control subjects increased significantly within one hour and from one to three hours after exposure. The increase in respiratory function of the exposed

subjects was significantly less than that of the control subjects. There was no meaningful correlation between concentration of formaldehyde in the breathing zone and changes in the respiratory function of exposed subjects. The exposure to formaldehyde may have inhibited the normal diurnal variation in respiratory function.

Riedel et al. (1996)

The influence of formaldehyde exposure on bronchial allergic sensitization was studied in female guinea pigs by Riedel *et al.* (1996). Twelve guinea pigs each were exposed to either clean air, 0.13ppm of formaldehyde, or 0.25 ppm of formaldehyde for 5 days. The guinea pigs were then exposed to 0.5% OVA as a sensitizing agent. When further challenged with 1% ovalbumin for 1 minute to test for bronchial sensitization, there was no enhanced sensitization in the group exposed to 0.13ppm FA compared to the control group. In the group exposed to 0.25 ppm of formaldehyde, 10/12 were sensitized or experienced a positive reaction compared to 3/12 in the control group. The researchers were able to demonstrate an increased bronchial sensitization to an allergen after short-term exposures to low concentrations of formaldehyde.

Kamata et al. (1996)

Kamata *et al.* (1996) measured lung surfactant and lipid peroxide (LPO) changes in rats given a single acute inhalation exposure to formaldehyde. LPO compromises the integrity of the cell membrane in both the nose and lungs. Male Fisher-344 rats were divided into 3 groups. Two groups of 15 rats each were subjected to a single inhalation exposure of low (15 ppm) and high (150 ppm) concentrations of formaldehyde for 6 hours. A control group (n=15) was subjected to a single inhalation exposure of distilled water mixed with air. Changes to LPO were slight in the nasal mucosa of both exposure groups. There was a slight increase in nasal mucosa damage in the low exposure group, and a greater increase in damage in the high exposure group. Lung surfactant production increased in the low exposure group, and decreased in the high exposure group.

Edling et al. (1987)

Edling *et al.* (1987) evaluated the cytotoxic effect of formaldehyde on the nasal mucosa in 38 men with an average age of 38 years and average exposure time of 10.5 years who processed laminae. All men passed a medical examination and a nasal biopsy. The histological findings were scored, 0-8, according to a system proposed by Torjussen. The findings were compared with a non-exposed reference group of 25 men (mean age 35 years). Smokers comprised 35% of the exposed compared to 48% of the non-exposed. The average histological biopsy score was 2.8 for the exposed versus 1.8 for the non-exposed (p less than 0.05, Wilcoxon). The more common findings in the exposed were loss of cilia, goblet cell hyperplasia and squamous metaplasia. In four cases (11%) there was a mild dysplasia. Smoking had a slight modifying effect histologically. The results indicate that the suspected precancerous findings in animal studies after exposure to formaldehyde might be present in workers exposed to formaldehyde at relatively low levels.

Green et al. (1987)

Green *et al.* (1987) studied 22 healthy and 16 asthmatic subjects who were exposed to 3 ppm formaldehyde for 1 hour. The healthy subjects underwent intermittent heavy exercise

(Minute ventilation = 65 L/min), whereas the asthmatics performed intermittent moderate exercise (minute ventilation = 37L/min). Symptoms and pulmonary function were assessed during exposure. The healthy group had statistically significant ($p < 0.02$) lower pulmonary functions after 55 minute of exposure to formaldehyde as compared to clean air: 3.8% in FEV₁, 2.6% in FVC₂, and 2.8% in FEV₃. The asthmatic group showed no statistically significant decreases in pulmonary function. Decrements in FEV₁ greater than 10% were seen in five of 38 subjects. Acute exposure to 3 ppm formaldehyde produced consistent irritant symptoms in both normal and asthmatic subjects, small decreases in pulmonary function in normal subjects doing heavy exercise, and clinically significant decrements in FEV₁ greater than 10 in 13% of the study population.

Ritchie et al. (1987)

The Minnesota Department of Health (MDH) investigated over 900 cases of possible formaldehyde exposure between 1979 and 1981 offering a free testing service as a diagnostic aid to physicians and for all Minnesota residents who were concerned about possible exposure. The MDH required each person who wanted a residence tested to be screened by a family physician. When the examining physician made a written request the MDH tested for formaldehyde in those homes. During each home visit, an MDH technician collected formaldehyde samples in two rooms. An adult was interviewed from the household using a standard questionnaire. A standard collection protocol was used for both sample collection and analysis. Residents were requested to close doors and windows of the homes 12 hours before the testing was conducted. Measurements were obtained from two rooms in the home, usually the living room and a bedroom, at a height of about 50 cm above the floor. Values were classified as below 0.1 ppm, between 0.1 and 0.3 ppm, and 0.3 ppm and above and were the average of both rooms. Actual levels were not reported. The effects of formaldehyde levels above 0.3 ppm were greater than for levels below 0.3 ppm. Reports of eye irritation were most frequent, followed by nose and throat irritation, headaches, and skin rash. Mobile homes were compared to conventional homes. The effects of formaldehyde exposure in both mobile and conventional homes were consistent (Ritchie and Lehnen, 1987).

Tani et al. (1986)

Tani *et al.* (1986) exposed male rabbits to 10 ppm formaldehyde for 10 minutes and measured blood pressure in the femoral artery, heart rate and respiratory movements (qualitative evaluation of traces on the polygraph). Exposure of the nasal cavities and lungs to formaldehyde decreased heart rate from 300 to 160 beats per minute after two minutes and as low as 100 after 10 minutes. Blood pressure was essentially the same throughout the exposure based on tracings as exact values were not reported. Respiratory movement traces indicated irregular rhythmicity followed by a decrease in respiratory rate.

Morgan et al. (1986)

Morgan *et al.* (1986) exposed F-344 male rats to 0, 0.5, 2, 6, and 15 ppm formaldehyde for 6 hours once or up to multiple times for 3 weeks. After euthanasia of rats within one hour of exposure, nasal mucocilliary function was evaluated. Defects in mucocilliary function were readily detected in certain regions of the nasal cavities. The effects on mucostasis, cessation or severe slowing of mucus flow, ciliastasis, loss of ciliary activity, and altered mucus flow patterns were related to formaldehyde concentration and duration of exposure in a dose response manner.

Variation was minimal between rats in each exposure group. Mucostasis was more extensive than ciliastasis but in some areas mucus was observed flowing over areas of ciliastasis. The no effect concentration was 0.5 ppm. Mucociliary function was a more sensitive indicator of toxicity than histopathology.

Rusch et al. (1983)

Rusch *et al.* (1983) exposed by inhalation five groups of 6 male Cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Syrian golden hamsters for 22 hours per day, 7 days per week for 26 weeks to formaldehyde gas. The cumulative mean exposure concentrations were 0, 0, 0.19, 0.98, and 2.95 ppm for the two control groups, low-, mid-, and high-level exposure groups, respectively. There was no treatment-related mortality during the study. The most significant findings in the monkeys were hoarseness and congestion in the 2.95 ppm exposure group with 0.98 ppm as the no effect concentration. In the rat, squamous metaplasia in the nasal turbinates, decreased body weights starting during the second week of the study, and decreased liver weights were the effects in the 2.95 ppm exposure group. In contrast to monkeys and rats, hamsters did not show any significant responses to exposure even at 2.95 ppm. The monkey and rat were more sensitive to formaldehyde exposure than the hamster.

Alexandersson et al. (1982)

Air concentrations of FA were obtained from 47 males exposed to formaldehyde and 20 controls carrying sampling pumps in their breathing zone. Subjects were employed for at least 1 year in a Swedish carpentry shop producing chip board. Asthmatics were excluded from both groups. Formaldehyde exposure occurred in an area where sawdust and wood chips were cemented together under high pressure. The controls were not exposed to formaldehyde. Interviews were conducted with employees using a standardized questionnaire. More than one-third of the exposed workers complained of symptoms involving the throat. Lung function testing (spirometry) was conducted on the exposed group on Monday morning prior to work, and immediately in the afternoon after work. Half of the controls were studied in the morning and half in the afternoon. There were no significant differences in lung function between exposed groups and controls studied in the morning. At the end of the day, forced expiratory volume and maximum mid-expiratory flow decreased in the exposed group. Control subjects studied in the afternoon displayed a normal lung function. The mean sampling concentration of FA was 0.36 ppm, with a range of 0.04 ppm – 1.25 ppm. The mean concentration is below the Swedish National Board of Occupational Health and Safety Threshold Level of 1.0 ppm. The findings are consistent with an airway obstruction which could subside over a night or weekend of non-exposure, and occur after short term exposure to formaldehyde levels below the regulatory level.

Murphy & Ulrich (1964)

As part of testing and validating a new exposure system, Murphy & Ulrich (1964) exposed G. pigs (n=10, n=9, respectively) for one hour to either 3.9 or 12.5 ppm formaldehyde and measured respiratory rate. The 3.9 ppm concentration resulted in a respiratory rate that was 73% of the normal pre-exposure values while the 12.5 ppm concentration was 63% of normal.

Larsen et al. (2000)

The study assessed the acute effects of methacrolein on the respiratory system. Twenty-four BALB/cA mice were grouped into 6 exposure concentrations (2.0 ppm, 4.4 ppm, 6.6 ppm, 10.2

ppm, 13.1 ppm, 26.3 ppm). After a 15 minute baseline period, the mice were exposed for 30 minutes to methacrolein, followed by a 15 minute recovery period. Results showed a concentration-dependent decrease in respiratory rate. The time between the end of inspiration and the beginning of expiration, or time of break also increased in a concentration-dependent manner. The tidal volume and expiratory rate also decreased but not in a consistent concentration-dependent manner. The relationship between the decrease in respiratory rate and the exposure concentration was calculated, and 10.4 ppm was the concentration of methacrolein that decreased the respiratory rate by 50% (RD₅₀). The increase in time of break and decrease in respiratory rate indicates that methacrolein is a potential sensory irritant.

Bos et al. (1992)

Bos *et al.* (1992) wrote a review of the sensory irritation test which determines the 50% decrease in respiratory rate (RD₅₀) during exposure to a chemical irritant. The authors questioned the ability of the test to be used for assessments of occupational exposure limits. However, they examined data from the rat and multiple strains of mice. The Sensory Irritation Test as developed by Alarie (1966) and now developed into a standardized test by ASTM (this is not an acronym) requires the use of only male Swiss Webster Mice in a very strict weight range. Based on studies using the Swiss Webster Mouse, the sensory irritation RD₅₀ values are 3.2 ppm for formaldehyde, 4,946 ppm for acetaldehyde and 2,052 ppm for propionaldehyde. According to Steinhagen and Barrow (1984) there is good correlation between RD₅₀ values and occupational exposure limits.

Kulle et al. (1987)

In a study by Kulle *et al.* (1987), 19 subjects (10 males and 9 females) were randomly exposed for 3 hour intervals to formaldehyde at 0, 1.0 and 2.0 ppm at rest plus at 2.0 ppm formaldehyde including exercise. Ten of these volunteers were also exposed to 0.5 ppm, whereas the other nine were also exposed to 3.0 ppm formaldehyde. Symptom questionnaires were completed before, shortly after and 24 hour after exposure. Incidences and symptom scores were reported for all volunteers with data presented in Kulle (1993). Pulmonary function was measured in all subjects at rest and with exercise. There were no significant decrements in pulmonary function (FVC, FEV₁, FEF_{25-75%}, SG_{aw}) nor increases in bronchial reactivity to methacholine (log PD_{35SGaw}) as a result of acute 3 hour exposures to 0.5-3.0 ppm formaldehyde at rest or with exercise (2.0 ppm), including 24-hour post exposure measurements.

Usanmaz et al. (2002)

Usanmaz *et al.* (2002) studied the effects of acute and subacute FA exposures on spontaneous locomotor activity (SLMA), and wet dog shake (WDS) in both sexes of BALB/c mice. SLMA, both horizontal or ambulatory activity and standing up on the rear feet (vertical activity) is a first-tier behavioral technique which indicates the presence of neurotoxicity. An increase in WDS is a pre-convulsive sign. The SLMA was reduced in a concentration dependent manner after acute FA exposures at 1.8, 3.2, 4.5, 6.4, 9.7, and 14.8 ppm. The incidence of WDS behavior was increased only after acute FA exposures at 1.8, 3.2 and 6.4 ppm but not in a dose response manner and then decreased at 9.7 and 14.8 ppm, indicating a different mechanism of action. SLMA was also reduced after subacute FA exposure at 2.0 ppm for 3 weeks. The inhibitory effects were significant after 1-week exposure at this concentration, but a tolerance developed at the end of the second week. As the concentration increased to 3.2 ppm, SLMA has found to be

reduced after 2-week exposure. There was no change in the incidence of WDS due to the subacute exposures of FA at the respective concentrations. Based upon these data, acute and subacute exposures of FA produce a significant behavioral depression in mice. The data also suggest that acute FA exposures at low concentrations (such as 1.8 ppm) may increase the excitability of central nervous system.

Vyas et al. (2000)

Vyas *et al.* (2000) studied endoscopy nurses in the United Kingdom who were apparently exposed to glutaraldehyde as a disinfectant. Exposure assessment found that glutaraldehyde in the endoscopy units ranged from less than 0.001 to 1.08 mg/m³. The mean time on the job was 2.2 years with a range of 1 month to 19 years and 74% who worked less than 5 years. They were compared to those who left within the last 5 years with 38.2% leaving for health reasons. Spirometry was performed with recordings of forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). The FEV₁ was converted to predicted forced expired volume in 1 second (ppFEV₁) which takes into account each subject's age, sex, and height. There was no significant difference in ppFEV₁ between non-smokers and smokers nor in symptomatic compared with asymptomatic workers. The mean ppFEV₁ for ex-employees (93.82, 95% confidence interval (95% CI) 88.53 to 99.11) was significantly lower (p<0.01) than that of current workers exposed to glutaraldehyde (104.08, 95% CI 102.35 to 105.73).

Kriebel et al. (1993)

Epidemiologic studies of irritants are difficult to perform using standard epidemiologic methods for several reasons, including the reversible nature of the health outcomes, the selection of sensitive individuals from the study population, and the wide heterogeneity in normal responses to irritants (Kriebel *et al.*, 1993). The authors examined the feasibility of using reported symptoms and repeated measurements of peak expiratory flow (PEF) to study respiratory irritants and effects in students exposed to formaldehyde during a clinical anatomy laboratory course. There were 24 physical therapy students dissecting cadavers for 3 hour per week over a 10-wk period. Each student measured their PEF at the beginning and end of each laboratory session with the supervision of an investigator. Formaldehyde exposures in the breathing zone ranged from 0.49 to 0.93 ppm (geometric mean \pm geometric SD, 0.73 \pm 1.22). Irritant symptoms increased strongly over the course of the average laboratory period, but this effect was stronger at the beginning than at the end of the semester. PEF measured before each laboratory session declined over the semester by an average of about 10 L/minute (2% of baseline), a trend that was statistically significant in random-effects regression models. After 14 weeks away from the laboratory, the group's mean baseline PEF had returned to its preexposure level. Mean PEF also declined over each laboratory period, although this effect was attenuated over the course of the semester. Other important predictors of cross-laboratory PEF decrements were asthma and reporting throat irritation during the laboratory. It appears that mild irritant effects can be detected in naive subjects using a repeated monitoring design and relatively simple instrumentation.

Swiecichowski et al. (1993)

To study the effect on the lower respiratory tract and determine whether formaldehyde induces airway hyperreactivity, guinea pigs were exposed to formaldehyde or filtered air (sham control) for 2 or 8 hour (hr) by Swiecichowski *et al.* (1993). Airway smooth muscle responsiveness was

evaluated *in vivo* and *in vitro*. Specific pulmonary resistance and airway reactivity (to infused acetylcholine) increased with formaldehyde exposure. Formaldehyde exposure caused bronchoconstriction and hyperreactivity at lower concentrations when exposure duration was extended from 2 to 8 hr. Exposure to ≤ 0.3 ppm formaldehyde for 8 hr was sufficient to produce a significant increase in airway reactivity, while similar effects only occurred after > 9 ppm formaldehyde for 2 hr. Formaldehyde exposure also heightens airway smooth muscle responsiveness to acetylcholine *in vitro*. These effects occurred with no evidence of epithelial damage or inflammation up to 4 days after formaldehyde exposure. At concentrations relevant to environmental exposure, formaldehyde alters airway smooth muscle reactivity in guinea pigs. These findings suggest that the duration of exposure is important to the induction of airway hyperreactivity and that prolonged, low-level exposures may generate abnormal physiological responses in the airways not detectable after acute exposures.

4.4 Psychological Attributes

Seven articles researching aldehyde impacts on psychological attributes were selected for data extraction, based upon the inclusion/exclusion criteria (Table 9). These were predominantly animal studies assessing impacts on cognitive performance, using behavioral tests for measuring working memory and spatial memory. In rats, injection with 0.45 mM FA significantly increased blood glucose levels and hippocampal formaldehyde levels compared to controls and it also significantly impacted synaptic plasticity, reducing excitatory hippocampal long-term potentiation (LTP). This was manifested in a marked increase in escape latency in the Morris Water Maze test (MWM) (Tan *et al.*, 2018). However, no differences were seen in the visible platform tests between FA-injected and control rats. Other studies support a negative effects on LTP and learning. Specific proteins associated with synaptic plasticity (SNAP25 and VAMP2) were significantly decreased in rats exposed to 13.5 ± 1.5 ppm FA by inhalation, twice for 30-minute each day for up to 14 days (Liu *et al.*, 2010). In addition, the exposed rats demonstrated memory impairment based upon the escape latency and probe trials in MWM tests. Using a food maze, Pitten *et al.* (2000) assessed formaldehyde's impact on behavior, orientation and memory. Thirteen rats in each of 2 groups inhaled either 2.6 ppm or 4.6 ppm FA 10 minute/day, 7 days/week for 90 days, while control rats (n=14) inhaled water steam for the same periods. Rats were trained in a maze by placing each rat at the entrance and finding their way to the end where food was placed. No significant difference was seen between the 3 groups during training. However, during the exposure period, exposed rats needed more time to find food and made more mistakes along the way than the control group. The control group became slightly more proficient running the maze throughout. Post-exposure, rats in the two exposed groups still had a tendency to make more mistakes in the maze compared to controls. There was no significant differences between the exposed groups.

In mice, similar cognitive deficits were reported. Liu *et al.* (2018) intra-nasally instilled formaldehyde (0, 0.155, 1.55 and 15.5 mg/kg/day) for 1 week, during which the MWM test was performed on Days 1-5. After 5 days mice exhibited slower Escape Latency. The mice were not tested on Day 6, to allow time to forget details of the test, but retested on Day 7. On Day 7 the two higher dose groups swam less time in the platform quadrant than control mice and their swimming routes were irregular. Brain histology revealed a compromised blood brain barrier, pathological alterations, and the presence of proteins associated with Alzheimer's disease (AD), oxidative stress and inflammation. Lu *et al.* (2008) also used the MWM to study spatial learning

and memory in 15 mice divided into three test groups (n=5 each): 0, 1, and 3 mg/m³ inhaled formaldehyde, released from wood baseboards, 6 hrs/day for 7 days. Mice were trained in the MWM 30 minutes after each exposure by placing each mouse in one of the four quadrants of a round pool and recording the escape latency (time it took for the mice to reach a platform). To test spatial learning, the mice learned to swim from different quadrants of the pool directly to the platform, presumably by using spatial cues from the room as a reference, and time to find platform was recorded. Spatial memory was tested by taking the platform away and placing the mice in a designated point in the pool. The time to swim to where the platform had been located was recorded. Mice exposed to 3 mg/m³ formaldehyde showed confusion and a decrease in spatial learning and spatial memory. Li *et al.* (2016) studied the effects of inhaled formaldehyde on anxiety (using open field and elevated plus-maze test), depression (using a forced swim test), and cognitive capacity (using the novel recognition task) in 45 mice, randomly divided into 3 groups (0, 1 or 2 ppm of gaseous formaldehyde for 2 hrs/day for 7 days). The rats in the 2 ppm formaldehyde group had significantly increased levels of depression-like behavior, reduced locomotor activity and impaired cognitive behavior.

One human study which met the review criteria was found. Medical students exposed to a mean indoor concentration of formaldehyde and phenol of 0.265 mg/m³ and 4.65 mg/m³, respectively, during dissection classes for 43 days reported increased incidence in dizziness and headaches at the end of the 10 weeks compared to all medical students at the beginning of the course (Wantke *et al.*, 2000).

Table 9. Literature related to psychological attributes of interest to the AF.

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Tan et al. 2018 [142] Rat study	Formaldehyde [50-00-0]	0.45 mM	Cognition activity level	Using the water maze test, there was a marked increase in escape latency plus less time in target quadrant. Hippocampal long-term potentiation was depressed.	30%
	Formaldehyde [50-00-0]	endogenous	Cognition activity level	Morris water maze resulted in marked increase in escape latency plus less time in target quadrant. Hippocampal long-term potentiation was depressed	
Liu et al. 2018 [167] Mice study	Formaldehyde [50-00-0]	0.155 mg/kg/day and 15.5 mg/kg/day administered via intranasal instillation daily for 7 days	Working memory	Significant reduction in escape latency and average EL at day 5 (cognition) and decreased time in platform quadrant at day 7 (spatial memory)	21%
Liu et al. 2010 [604] Rat study	Formaldehyde [50-00-0]	13.5 ± 1.5 ppm, twice a day for 30 minutes, up to 28 days	Working memory Short- and long-term memory	Increased escape latency times and probe trials without mobility disturbances in Morris water maze test Evidence of difficulty forming memories	33%
Lu et al. 2008 [734] Mice study	Formaldehyde [50-00-0]	1 mg/m ³ 6h/day for 7 days	Spatial learning	No adverse effect observed	33%
			Spatial memory	No adverse effect observed	
		3 mg/m ³ 6h/day for 7 days	Spatial learning	Impaired spatial learning observed	
		Spatial memory	Impaired spatial memory observed		
Pitten et al. 2000 [1042] Rat study	Formaldehyde [50-00-0]	2.6 and 4.6 ppm for 10 min/day, 7 days/week for 90	Working memory	Time to find food increased Number of mistakes made in the maze increased	5%

Reference [RefID] and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
		days with 30 days post-observation	Time to complete a task		
Wantke et al. 2000 [1043] Human exposure assessment	Formaldehyde [50-00-0]	0.265 mg/m ³ for 10 weeks during a dissection class	Dizziness and headache	Increased incidence of dizziness and headache among medical students	23%
Li et al. 2016 [3778] Mice study	Formaldehyde [50-00-0]	2 ppm	Depression Novel object recognition	Mice demonstrated less spontaneous locomotor activity, indicating depression Mice performed poorly in the novel object recognition tests compared to the control and 1 ppm exposed group	22%

Tan et al. (2018)

To examine the effect of FA on glucose metabolism and cognitive function, healthy adult male Sprague-Dawley rats were injected with 0.45 mM FA, a pathologic concentration previously reported in STZ-induced diabetes rat models (Tong *et al.*, 2013). An intraperitoneal injection of FA for 7 days had no effect on body weight but significantly increased blood glucose levels ($p = 0.0047$) as well as blood ($p = 0.0075$) and hippocampal FA levels ($p = 0.0058$) compared to controls. To examine the effect of FA on synaptic plasticity, hippocampal LTP was assessed *in vivo*. Intra-cerebroventricular injection of 0.45 mM FA markedly reduced average field excitatory postsynaptic potential amplitudes of LTP in the injected SD rats ($n = 10$) compared with control rats ($P < 0.01$). Rats in the Morris water maze test had no differences in vision and mobility between the FA-injected rats and control rats in the visible platform tests. The FA-injected rats exhibited a marked increase in escape latency on acquisition days 3 through 6 compared with control rats ($P < 0.01$). In the probe trial on the last day of testing, the FA-injected rats spent less time and had a shorter distance in the target quadrant than control rats ($P < 0.01$). These results indicate that an injection of 0.45 mM FA induces hyperglycemia and cognitive deficits in healthy rats (Tong *et al.*, 2013). Extrapolation to the inhalation route of exposure and determination of dose response need to be conducted next.

Liu et al. (2018)

Liu *et al.* (2018) conducted a study to determine if formaldehyde contributes to the development of Alzheimer's disease (AD). They exposed C57BL/6 mice by intranasal instillation daily to formaldehyde (0, 0.155, 1.55 and 15.5 mg/kg/day) for 1 week. The MWM was performed to evaluate the cognitive ability of the mice after exposure. From Day 1 to Day 5, the hidden-platform acquisition test was conducted to assess the spatial memory ability of the mice after exposure. No MWM test was performed on Day 6 to allow the mice a period of time to forget the details of the test. The test was conducted again on Day 7. After 5 days, each of the exposure group mice exhibited a slower Escape Latency. Only the mice exposed to 1.55 and 15.5 mg/kg/day formaldehyde had significantly slower decreases. On the 7th day the time spent swimming in the platform quadrant was significantly less in the 1.55 and 15.5 mg/kg/day groups than the controls and the 0.155 mg/kg/day group. In the two higher exposure groups the swimming routes were irregular and showed no purpose. In addition to these cognitive deficits, blood brain barrier damage, pathological alterations, the presence of proteins associated with AD, oxidative stress and inflammation were found in the mouse brain.

Liu et al. (2010)

Liu *et al.* (2010) exposed male Sprague–Dawley rats to 13.5 ± 1.5 ppm FA by inhalation, twice for 30-minute each day for up to 14 consecutive days. The effects on learning and memory were tested in a Morris water maze. The formaldehyde-treated rats showed learning and memory impairment compared to controls in escape latency and probe trials, but there was no disturbances in the mobility of the rats in the Morris water maze. Using western blot assays, SNARE proteins were measured in hippocampal synaptosomes with decreases in both SNAP25 and VAMP2 after formaldehyde exposures. The decrease in these two proteins in the hippocampus is a potential contributing mechanism to the learning and memory impairments seen in the Morris Water Maze tests after formaldehyde exposures.

Lu et al. (2008)

Fifteen male mice were used to study the neurotoxic effects of formaldehyde in the brain. *Lu et al. (2008)* divided mice into three inhalation test groups (n=5 each): 0, 1, and 3 mg/m³ formaldehyde, released from wood baseboards, 6 hrs/day for 7 days. The Morris water maze test was used to evaluate spatial learning and memory and evaluate the central nervous system toxicity of formaldehyde. Mice were trained in the Morris water maze 30 minutes after each exposure by placing each mouse in one of the four quadrants of a round pool and recording the escape latency (time it took for the mice to reach a platform). To test spatial learning, the mice learned to swim from different quadrants of the pool directly to the platform, presumably by using spatial cues from the room as a reference. The escape latency was recorded. Spatial memory was tested by taking the platform away and placing the mice in a designated point in the pool. The time it took for the mice to swim to where the platform had been located was recorded. Mice exposed to 3 mg/m³ formaldehyde showed confusion and a clear decrease in spatial learning and spatial memory. Inhalation of formaldehyde can affect learning and memory by damaging the neurons, and can partially explain the distraction of concentration and memory loss in occupationally exposed populations.

Pitten et al. (2000)

Pitten et al. (2000) studied whether inhalation of formaldehyde was a neurotoxicological agent and could have an impact on behavior, orientation and memory. Thirteen rats in each of 2 groups inhaled either 2.6 ppm or 4.6 ppm formaldehyde 10 minute/day, 7 days/week for 90 days. Rats in the control group (n=14) inhaled water steam for the same exposure period. Assignment to the groups was random and with no regard to the gender. Rats were trained in a maze by placing each rat at the entrance and finding their way to the end where food was placed. The time required to find food (memory) and the number of mistakes made in the maze on the way to find food (orientation) were recorded. A mistake was counted when the rat pointed in the wrong direction while finding its way to the end. At the end of the training period, all the rats were able to find food in the maze. Every 7th day during the exposure period, the rats went through the maze prior to being exposed on that day. After the 90-day exposure period, the rats were observed for an additional 30 days and went through the maze every 10th day. There was no significant difference between the 3 groups during training. The control group made almost the same number of mistakes during the exposure and post-exposure observational period. During the exposure period, the exposed rats needed more time to find food and made more mistakes along the way to the food than the control group when going through the maze. The control group became slightly faster running the maze during the exposure period. Post-exposure, rats in the two exposed groups had a tendency to make more mistakes in the maze compared to the control group. There was no significant difference in behavior between the exposed groups, and therefore, no dose-response relationship was established.

Wantke et al. (2000)

Wantke et al. (2000) studied the sensitizing potential of formaldehyde and phenol during anatomy dissecting classes. Twenty-seven medical students (12 female, 15 male) were assessed for symptoms and complaints such as dizziness, headache, burning eyes, oral or pharyngeal itch, and paresthesia of the hands. Nine females and nine males not occupationally exposed to formaldehyde or phenol served as controls. Symptoms and complaints were assessed by questionnaires daily. Students were exposed to a mean indoor formaldehyde level of 0.265

mg/m³ and a mean indoor phenol level of 4.65 mg/m³ for 43 days. After 10 weeks, only male students in the last observation period experienced dizziness. Thirteen students experienced headache after 10 weeks, compared with no students at the beginning of classes. The symptoms experienced by the students were primarily the irritating effects of formaldehyde and phenol.

Li et al. (2016)

Li et al. (2006) investigated the effects of inhaled formaldehyde on anxiety, depression, and cognitive capacity in mice. Forty-five mice, randomly divided into 3 groups, were exposed to 0, 1 or 2 ppm of gaseous formaldehyde for 2hrs/day for 7 days. Two hours after the final exposure, the mice were used for the behavior tests. Anxiety-like behavior was measured using open field and elevated plus-maze tests, and depression-like behavior was measured using a forced swim test. Learning and memory was measured using the novel recognition task, which is a non-spatial, non-aversive memory test used to test cognitive capabilities. Time spent in various quadrants in an open-field chamber and total distance traveled around the chamber was recorded during the open field and elevated plus-maze tests. The duration of immobility was recorded during the last 5 minutes of the 6-minute test. The novel object recognition test measured retention of the exploration of two objects. Later, one of the familiar objects was replaced with a novel object and the ability to explore the objects and discriminate between the 2 was calculated. Inhalation of 1 ppm formaldehyde reduced levels of anxiety-like behavior. Inhalation of 2 ppm formaldehyde increased levels of depression-like behavior, reduced locomotor activity and impaired cognitive behavior.

4.5 Analysis of RoB

The range of percent values for the RoB scores was 5 to 59%. There were no studies that had a perfect RoB score but there was one study with a score of only 5%, which indicates low bias for this study. The most biased study was at 59%. The average RoB was 28%. Analysis of the RoB showed that many studies have a degree of bias and that it is hard to design and conduct a perfect study.

4.6 Aldehydes Not Identified in Literature

Despite extensive searching, eight of the aldehydes on the list did not appear in conjunction with the physiological attributes: benzaldehyde, butyraldehyde, glyoxal, isovaleraldehyde, valeraldehyde, p-tolualdehyde, o-tolualdehyde, and methylglyoxal. Three aldehydes remain on the list of 125 that will be covered in subsequent reviews due to overlapping chemical features: acrolein, crotonaldehyde, and m-tolualdehyde.

5.0 DISCUSSION

5.1 Vision

Of the 12 articles that met the study's inclusion criteria for impacts on vision attributes, 11 focused on chemosensory irritation as the critical endpoint. The remaining study was a medical case reporting the development of corneal haze and ptosis in a patient exposed to an unknown amount of formaldehyde used during surgical instrument sterilization. Within the 10 studies focused on chemosensory irritation from formaldehyde, subjective eye irritation was consistently

reported at 1.0 ppm (Arts *et al.*, 2006; Bender *et al.*, 1983; Kulle *et al.*, 1987) while objective measures of eye irritation, such as increased blink frequency and lacrimation, were reported at 1.7 ppm (Arts *et al.*, 2006). One study on methacrolein found increased blink frequency among volunteers at 286 ppb, nearly six times lower than the concentration found to trigger objective eye irritation among those exposed to formaldehyde (Nøjgaard *et al.*, 2005). This finding is noteworthy, as it suggests large variability in irritative effect may exist in the same chemical class (aldehydes). In the absence of studies focused specifically on other aldehydes, *in silico* methods such as read-across or quantitative structure–activity relationship (QSAR) may be appropriate to extrapolate known effects from formaldehyde exposure. Despite the dearth of studies of the impact to visual attributes from exposure to aldehydes, there is enough suggestive evidence to warrant future studies into AF-specific compounds and their impact on Airmen and Guardians. Occupations which require prolonged visual focus may be most sensitive to the impact to productivity brought on by irritation from aldehyde exposure.

5.2 Physiology

Many of the studies exposed subjects to levels of formaldehyde over 1 ppm, which is now above the OSHA PEL of 0.75 ppm. The ACGIH threshold limit value time weighted average for an eight hour working day is 0.1 ppm. The ACGIH short term exposure limit for 15 minutes of exposure to formaldehyde is 0.3 ppm. This is equal to the no observed effects level in mice but can still cause irritating effects in the upper respiratory tract of humans.

Occupational exposure to formaldehyde can occur in a variety of situations. Pilots and aircraft personnel can be exposed to combustion by-products. Laboratory technicians can be exposed during tissue biopsies and histopathology evaluations. Additional exposure to the general Airmen population can potentially occur from disinfecting cleaners and newly installed walls or flooring both at home and at work at their computer. The symptoms of nasal and throat irritation can be minor annoyances at most, but these effects can cause distractions, loss of focus and attention to detail for a wide range of job classes during mission critical tasks.

For the aldehydes, there were only fourteen articles that met the inclusion criteria that involved human exposure or epidemiological studies and they were all for formaldehyde. The only other aldehydes in this section were acetaldehyde and methacrolein. There is no ACGIH threshold limit value time weighted average for acetaldehyde and methacrolein but acetaldehyde has a short term exposure limit of 25 ppm. There is no OSHA PEL for methacrolein but acetaldehyde has a PEL of 200 ppm. Based on respiratory rate depression studies in mice methacrolein is expected to be about 3 times less irritating than formaldehyde while acetaldehyde is expected to be two to three orders of magnitude less irritating than formaldehyde. There were no studies identified for propionaldehyde but in the course of reviewing respiratory rate depression data a value was found and added to Table 8 which indicates that it would be much less irritating than formaldehyde and methacrolein.

It is not clear the potential impact of formaldehyde on vascular function. More studies are needed to be able to understand the effects on physiological performance attributes. Although smell is not one of the performance attributes of concern it is an interesting effect that formaldehyde effects this sense.

5.3 Psychology

The only aldehyde for which articles were found that addressed impacts on psychological attributes was formaldehyde. All but one of the studies used animals. The lone human study found that while attending a class dissecting preserved tissues, dizziness could also be an effect of formaldehyde exposure in addition to irritation (Wantke *et al.*, 2000). In the animal studies low levels of formaldehyde in rodents produced negative impacts on a number of cognitive attributes such as spatial learning, spatial memory, working memory, short and long-term memory and increased number of mistakes (Pitten *et al.*, 2000; Lu *et al.*, 2008; Liu *et al.*, 2010; Li *et al.*, 2016; Liu *et al.*, 2018). In one study, depression of long-term potentiation in the hippocampus was seen in both rats and mice (Tan *et al.*, 2018). This could explain the effects on memory because the hippocampus is the major center in the brain for memory formation. In another study, mice were determined to be depressed based on a change in their activity level. All of these effects could influence performance. Also in the process of examining the effects of formaldehyde on cognitive attributes, it was determined that formaldehyde affects glucose metabolism by causing hyperglycemia (Tan *et al.*, 2018). Somerfield *et al.* (2004) found that hyperglycemia can impair the speed of information processing without affecting accuracy; can also impact working memory; and causes changes in mood such as feelings of agitation, anxiety, lethargy and decrease in happiness. The hyperglycemia could be part of the mechanism of action of formaldehyde but also has its own impacts on performance. In addition, formaldehyde exposure can lead to the development of Alzheimer's disease (Liu *et al.*, 2018). Development of Alzheimer's is not a short-term effect so its impact on performance attributes is not an immediate concern but can be added to the long-term concerns, such as the potential development of asthma and/or cancer caused by formaldehyde exposure.

5.4 Gaps and Recommendations

There is a need for human dose-response data for exposures to aldehydes of interest to the AF and their impacts on attributes. The attributes described in Table 3 are unique to the military environment which means they are not commonly studied endpoints in general research. In order to best serve Airmen and Guardians, the Air Force may need to conduct key studies.

The bulk of the research cited in this report pertains to formaldehyde. In order to predict potential effects of other aldehydes, identified as AF-relevant but lacking available data in published literature, *in silico* QSAR models providing nearest neighbor analysis could be used for extrapolating effects based upon chemical structure similarities with formaldehyde. Without nearest neighbor analysis, it is not currently possible to determine how relevant the lowest observable adverse exposure level (LOAEL) formaldehyde concentrations are compared to other aldehydes. Lhasa's commercial software, Derek Nexus, uses nearest neighbor analysis to predict dozens of endpoints. Licenses are being purchased for another funded project, so this resource will be available for future work.

Risk management in industry and academia has predominantly focused on identifying life-threatening exposures. In recent years attention has been given to irritative effects as they are recognized as having a negative impact on worker wellbeing. In deference to this, ACGIH has recommended lower TLVs based on avoiding irritative effects. However, small decrements to performance attributes such as cognition or vision have not yet garnered wider attention, even though there is evidence negative impacts begin at low levels. In a military environment, where

small decrements to performance attributes can have disproportionate impacts on mission success, the Air Force may not be able to rely on their industrial and academic partners to spearhead research in this area.

In the absence of human dose-response data, there are risk mitigation strategies the Air Force can undertake to reduce Airmen and Guardian exposure to aldehydes. As part of an exposure reduction strategy, low volatile organic compound (VOC) emitting building materials and furnishings should be chosen for indoor environments.

A systematic review of the scientific literature was conducted on 126 chemicals found in Air Force occupational environments and their impacts on four performance attribute categories: hearing, vision, psychology, and physiology. To help link chemical exposure to the performance attributes, relevant toxicity search terms were used. The list of chemicals selected for review were derived from multiple bioenvironmental engineering inventories and narrowed down based upon the anticipated severity of health effects due to exposure (based upon HER ratings), the frequency of the chemicals' occurrence across bases and confirmations of potential for exposure.

Artificial Intelligence (AI) capabilities were required to complete the analyses of over 5000 articles, collected from multiple literature databases within a reasonable time frame. DistillerSR was selected from an internal review of both open source and commercial systematic review software packages, due to its AI feature, Daisy, which uses the PRISMA format (Figure 1). Unlike typical systematic reviews of a unique pharmaceutical or therapy intervention, which cover a set of standard PICO study questions, this review was unique in that questions covering multiple different performance attributes or outcomes and how multiple different chemical exposures may affect them, in humans and animals were used to form the protocol's inclusion and exclusion criteria. Similar systematic reviews on such a broad range of exposures and effects were not found in the literature. It is well known that the more specific the study question, the better the search process and results will be. Therefore, this review represents a novel approach of using AI for "scoping" multiple related topics simultaneously, which may not have identified as much published data/information as would be collected, if each chemical and attribute was reviewed separately. In addition, due to the AF's interest in performance impacts resulting from only short-term exposures, it should be noted that effects from chronic exposures were not included. Short term exposures can induce transient effects that are not well documented for many performance attributes and which the AI was not trained on, based upon the review criteria. Future research may be warranted in this area.

In the aldehyde class, literature meeting the criteria was found predominantly on formaldehyde. Data was found supporting potential impacts upon all four categories of attributes (vision, auditory, psychology/cognition, and physiology). Many of the vision and physiological effects were from irritation of eyes and respiratory track, respectfully. Effects on psychology/cognition and auditory attributes suggest impacts on synaptic plasticity, which affect memory and learning. In addition, non-occupational exposure of formaldehyde (such as traffic exposure, exposure from furnishings in the home, etc.) can impact performance attributes at work. The AF may not be able to rely on their industrial and academic partners to spearhead research in low levels of aldehydes causing small decrements to performance attributes such as in cognition or balance. In

order to extrapolate potential effects of other aldehydes from the data available in literature on formaldehyde, in silico QSAR models incorporating nearest neighbor analysis could be used. Analysis of the RoB showed that many studies have a degree of bias and that it is hard to design and conduct a perfect study. The average RoB of the articles selected for data extraction and qualitative assessment was 28%, which was satisfactory for the purpose of this study. Bias assessments are important in systematic reviews, however it is not a replacement for scientific judgement. Most of the studies selected were not designed as randomized control trials (RCTs). Several were in vivo observational studies, as most environmental and occupational exposures are not possible, as one cannot ethically randomize people to potentially harmful exposures with no perceived benefit. Meta-analysis could not be conducted from the extracted data, as it pertained to multiple different chemicals (exposures) and multiple different performance attributes (outcomes), which are not comparable and therefore this review was limited to scoping for relevant data.

During the review process, the researchers noted a number of items that the technology in Distiller SR could be improved upon. One issue that was apparent during the downloading of full articles, is that software did not automatically process a pdf file into structured text that can be searched. This had to be done by the reviewer, for a number of articles. Also, the Daisy AI did not include linguistic translations, although few articles were found in foreign languages. Yet, this could be improved by the algorithm developers to prevent relevant articles from exclusion. Lastly, tasks that are not currently amenable to automation such as data extraction and critical appraisal should be future goals of AI software.

Given the amount of literature growing each day, the future will necessitate the need to develop feasible workflows for combining the tools into an information pipeline, so that researchers seeking to assimilate data from different types of study designs, for example, from preclinical and/or observational experiments in vivo animals to predict outcomes.

For evidence-based researchers, AI has enormous potential as a way to keep pace with the AF's increasing demand for timely evidence. The AF's focus on medical devices and new materials, will rely on manufacturers and researchers to conduct rigorous and thorough literature reviews to comply with new regulations. The increased workload can be overwhelming, and AI is often discussed as a possible solution. There is much research underway to develop AI to the point where it can be completely automating the systematic review process, but further development and testing in real-world applications is required. AI today is most effective when used to augment the researcher's toolbox, not replace it altogether. Transparency of AI algorithms and validation are still required before AI can be trusted in critical decision making. Acknowledging these limitations, however, can guide the improvement of machine learning tools and algorithms to ensure that AI eventually fulfills its potential in the area of evidence generation. This project demonstrated that current AI can still facilitate unusual systematic reviews, but –it isn't ready to tackle it alone and the AI requires sufficient training by independent reviewers.

6.0 CONCLUSIONS

Non-occupational exposure of formaldehyde (such as traffic exposure, exposure from furnishings in the home, etc.) can impact attributes at work.

Short term exposures can induce transient effects that are not well documented for many performance attributes. Future research is warranted in this area.

Because of bias, it is hard to design and conduct a perfect study.

The Air Force may not be able to rely on their industrial and academic partners to spearhead research in low levels of aldehydes causing small decrements to performance attributes such as in cognition or balance.

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APPENDIX: Aldehyde Occupational Exposure Limits

Full CAS #	Chemical Name	ACGIH TLV	NIOSH REL	OSHA PEL	AIHA & OARS WEELs
50-00-0	formaldehyde	0.1 ppm	0.016 ppm	0.75 ppm	
75-07-0	acetaldehyde	25 ppm (ceiling)		200 ppm	
100-52-7	benzaldehyde				2 ppm
123-72-8	butyraldehyde				25 ppm
107-22-2	glyoxal	0.1 mg/m ³ IFV			0.1 mg/m ³
590-86-3	isovaleraldehyde				
123-38-6	propionaldehyde	20 ppm			20 ppm
110-62-3	valeraldehyde	50 ppm	50 ppm		
104-87-0	p-tolualdehyde				
529-20-4	o-tolualdehyde				
78-85-3	methacrolein				
78-98-8	methylglyoxal				

abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; AIHA = American Industrial Hygiene Association; CAS = chemical abstract services; IFV = inhalable fraction and vapor; NIOSH = National Institute of Occupational Safety and Health; OARS = Occupational Alliance for Risk Science; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; WEEL = Workplace Environmental Exposure Levels

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AA	acetaldehyde
ACGIH	American Conference of Governmental Industrial Hygienists
AD	Alzheimer's disease
AF	Air Force
AIHA	American Industrial Hygiene Association
AETC	Air Education and Training Command
AI	artificial intelligence
BE	Bioenvironmental Engineering
BF	Blink frequency
BL	blink frequency
BP	Blood Pressure
BPRs	Basic performance resources
CAS	chemical abstract services
CHET	chemical hazard evaluation tool
CI	confidence interval
CNS	central nervous system
DAISY	Distiller's AI capabilities
EESOH-MIS	Enterprise Environmental, Safety, and Occupational Health Management Information System
EPA	Environmental Protection Agency
FA	formaldehyde
FEV	Force Expiration Volume
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
GSPT	General Systems Performance Theory
HAS	hardened aircraft shelter
HER	health effect ratings
IDLH	Immediately Dangerous to Life and Health
IFV	inhalable fraction and vapor
iNOS	inducible nitric oxide synthase
LD50	Lethal dose 50%
LPO	lipid peroxide
LOPs	limonene oxidation products
LTP	long-term potentiation
MAJCOM	Major Command
MDF	medium density fiberboard
MWM	Morris water maze
MCE	mucociliary escalator
MDH	Minnesota Department of Health
NIOSH	National Institute of Occupational Safety and Health
NOEL	No-Effect Level
NTP	National Toxicology Program
OARS	Occupational Alliance for Risk Science

OHC	Optimization of Human Capital
OL	olfactory bulb
O*NET	Occupational Information Network (U.S. Department of Labor)
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OVA	ovalbumin
PBAO	Precision-based Airman Optimization
PCR	polymerase chain reaction
PECO	population, exposure(s), controls, and outcome
PEF	peak expiratory flow
PEL	permissible exposure limit
PICO	population, intervention(s), controls, outcome
ppFEV ₁	predicted forced expired volume in 1 second
ppb	parts per billion
ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QSAR	Quantitative Structure-Activity Relationship
RD50	Respiratory Depression 50%
REL	recommended exposure limit
RoB	risk of bias
RR	relative risk
SD	Sprague-Dawley
SMEs	subject matter experts
SLMA	spontaneous locomotor activity
SRM	spatial release from masking
TLV	threshold limit value
WDS	wet dog shake
WEEL	Workplace Environmental Exposure Levels