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**CHEMICALS OF INTEREST TO THE AIR FORCE AND THEIR
POTENTIAL IMPACT ON VISUAL PERFORMANCE ATTRIBUTES**

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1.0 SUMMARY

The Air Force (AF) Operational Based Vision Assessment lab requested information detailing the potential for chemical exposure in AF occupational environments, the visual performance attributes impacted, and the available information tying the amount of chemical exposure to the level of impact. A program sponsored by the Air Education and Training Command Surgeon General developed key performance attributes for visually-based tasks in addition to attributes that contribute to optimal human performance in the areas of audiology, physiology, and psychology. A list of 126 relevant AF chemicals in occupational environments was developed in order to conduct systematic literature reviews to determine their impact on performance attributes of concern. The classes of chemicals reviewed were aldehydes, solvents, toxic gases and vapors, metals, aliphatics and miscellaneous.

Systematic literature reviews were conducted for aldehydes, toxic gases and vapors, and metals. Given the large number of chemicals and performance attributes to review, the commercial software DistillerSR with its artificial intelligence function was utilized to assist with screening of literature search results. Two or more individuals screened the abstracts of the search results, and studies were selected for the review based upon the inclusion or exclusion criteria developed by the team. Final selection of research articles then involved screening the full text versions of the selected articles based on the same inclusion or exclusion criteria. 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, internal validity (bias and confounding), power and external validity. Articles relating to the impact of each class of chemicals on visual performance attributes were then summarized in the results. Additionally, for solvents, aerosols, aliphatics and miscellaneous chemicals on the list, the ACGIH documentation was reviewed for any studies pertaining to short-term transient effects on visual attributes.

Across all classes of chemicals, eye irritation was the most commonly cited effect of exposure. Although not specifically associated with a single listed visual attribute of interest, irritation of the eyes could potentially impact multiple attributes through vision blurring and eye discomfort. Occupations that require prolonged visual focus may be most sensitive to productivity decrements brought on by eye irritation from chemical exposure. Neurotoxicity was the other major effect of exposure shared between multiple classes of chemicals, with specific solvents, metals, and miscellaneous chemicals associated with neurotoxic effects that impair certain aspects of the visual sensory system. Damage to neural structures including the retina and central visual pathway can impact color vision as well as contrast sensitivity.

In the absence of truly comprehensive data on the effects of all 126 chemicals of AF interest on visual performance attributes, this report can be a first step in the development of risk mitigation strategies the AF can undertake to reduce Airmen and Guardian exposure to chemicals of concern. With the identification of the effects on visual attributes in this report and recent exposure assessments, exposure scenarios can be more readily investigated and mitigation strategies developed to reduce effects where impacts on visual performance are anticipated.

2.0 INTRODUCTION

2.1 Visual 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 (AF) 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 attribute categories 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. Recently, a series of reports developed a centralized source of information detailing the potential for chemical exposure in AF occupational environments, the audiology, physiology, psychology and visual performance attributes impacted, and the available information tying the amount of chemical exposure to the level of impact. The Operational Based Vision Assessment (OBVA) lab requested a compilation of the results for just the visual attributes. This report provides a literature review of chemicals found in AF occupational environments and their impact on visual performance attributes of concern.

The process to develop performance attributes began with the Optimization of Human Capital (OHC) program sponsored by the Air Education and Training Command (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 created 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 AF could make informed placement decisions to better support mission effectiveness and broaden the population of those considered fit for duty. Knowing the attributes that are characteristic of a specific ability allows the monitoring of job performance so there is no loss of capability due to various stressors, including chemical exposure.

Scientists and subject matter experts 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 (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 (U.S. Department of Labor 2019), literature searches, and a working group from two AF 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 were a total of 101 performance attributes chosen, which were divided into 11 for vision, 9 for audiology, 37 for physiology, and 44 for psychology. The list of vision attributes was then reviewed by the authors to determine which ones could be most directly affected by chemical exposure. The 11 vision-specific attributes are listed in Table 1, and these attributes were used to derive the search terms listed in Table 5.

Table 1. List of Air Force Performance Attributes for Vision

BPR Name/Foundation	Definition
Contrast sensitivity - achromatic - 1.25-arc minute (arcmin) gap	Contrast sensitivity for features having a specified spatial frequency and retinal illuminance.
Contrast sensitivity - achromatic - 2.5-arcmin gap	Contrast sensitivity for features having a specified spatial frequency and retinal illuminance.
Contrast sensitivity - achromatic - 16.7-arcmin gap	Contrast sensitivity for features having a specified spatial frequency and retinal illuminance.
Visual acuity - far	See details at a distance.
Contrast sensitivity - LWS cones - 16.7-arcmin gap	Match or detect differences between colors, including shades of color and brightness.
Contrast sensitivity - MWS cones - 16.7-arcmin gap	Match or detect differences between colors, including shades of color and brightness.
Contrast sensitivity - SWS cones - 16.7-arcmin gap	Match or detect differences between colors, including shades of color and brightness.
Depth perception - static - near	Judge which of several objects is closer or farther away from viewer, or judge the distance between viewer and an object.
Binocular fusion range - horizontal	Horizontal range over which a viewer can fuse stereoscopic images presented at a fixed focus distance.
Binocular fusion range - vertical	Vertical range over which a viewer can fuse stereoscopic images presented at a fixed focus distance.
Useful field of view	See objects or movement of objects to one's side when the eyes are looking ahead.

2.2 Chemicals of Interest to the Air Force

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

The first source was the AF'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. The top 100 chemicals consumed by mass in 2020 at each base 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 only a subset of those chemicals that overlapped with the HAS list, or two or more AF bases, were selected for further review.

Upon the initial compilation of 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 to only the highest priority chemicals.

Within the Bioenvironmental Engineering 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, 0-5 scale with 5 being the most hazardous) 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 consideration for inclusion. For

those chemicals that did not appear in the CHET, health effects reported in the literature were copied from the online database haz-map.com.

A total of 178 chemicals were removed from the list of 882 during the first pass screening because 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. Furthermore, 47 additional chemicals were removed for only appearing on two bases and not on the HAS list. A total of 21 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.

The penultimate list included 116 chemicals, and 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 was of interest among Navy IHs due to its presence during pilot breathing air studies, so it was also added to the list. The chemical 1-Decene dimer, a known component in polyalphaolefin 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 AF 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.

Chemicals of interest to the AF were grouped into classes based on structural similarity. Each class is described in the subsequent sections:

Aldehydes

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, and 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 dinitrophenylhydrazine (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.

All of the aldehydes reviewed made the final chemical list (Steele *et al.*, 2021) for this effort because they had been measured in the field either in the hardened aircraft shelter study or in the

F-22 cockpit study. The list of all aldehydes reviewed is provided in Appendix A1. Kobayashi and Kikukawa (2000) reported formaldehyde in the exhaust of F-4 aircraft using JP-8 as jet fuel. Aldehydes are also byproducts of cigarette smoke, the combustion of fuels in general, and are constituents of photochemical smog. Others may be in cleaning products or used as a disinfectant. Aldehydes are used as preservatives and 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.

Toxic Gases and Vapors

Toxic gases and vapors produce deleterious effects through the inhalation exposure route. Some are simple asphyxiants, those gases which displace oxygen (e.g. carbon dioxide (CO₂), propane), while others are primary irritants that interact with the upper or lower respiratory tract and cause inflammation (e.g. sulfur dioxide, nitrogen dioxide), while other agents cause direct toxic effects (e.g. carbon monoxide).

Fourteen toxic gases and vapors were identified as important potential exposures in AF occupations based on EESOH-MIS data (Appendix A2). These chemicals were chosen for the list based on their use across the AF or their presence during comprehensive exposure assessments of AF environments (Steele *et al.*, 2021). Those chemicals which had individual occupational exposure limits (OELs) vacated (propane, acetylene, argon, and ethane; Appendix A2) were regrouped under a “minimal oxygen content” recommendation, as their primary action is through displacing oxygen in air rather than specific toxic effects (ACGIH, 2022). Exposed Airmen may be impacted by these toxic gases and vapors on this list if they are present in quantities sufficient to drive oxygen’s ambient partial pressure of 159.6 torr to below 120 torr (less than 16 percent (%)). Lack of oxygen can lead to hypoxia, a condition with many performance attribute-relevant impacts, including fatigue, impaired vision, impaired thought processes, and decreased coordination (ACGIH, 2022).

Metals

Metals are a group of naturally occurring substances that share a number of properties including high density, electrical conductivity, and a tendency to form cations (Jaishankar *et al.*, 2014). Although many metals are involved in normal biological processes, exposure to elevated levels of these metals or metals that serve no inherent biological function can cause impacts on human health (Tchounwou *et al.*, 2012). Occupational metal exposure primarily results from activities such as metal working and machining United States Army Public Health Center ((USAPHC), 2019) but can also occur via exposure to products of combustion and various industrial processes (Tchounwou *et al.*, 2012).

Eleven metals were identified out of the list of 126 chemicals of importance to the AF (Steele *et al.*, 2021). In reviewing EESOH-MIS data for the ten representative AF bases, several commonalities were noted. Most of the metals studied were found in maintenance activities, with corrosion control operations such as painting referencing several metals (Appendix A3). Some of the selected metals do not appear as raw ingredients in a Safety Data Sheet, so they did not appear in EESOH-MIS. Three of these metals were included due to their inclusion on the OSHA expanded standards list. The AF samples for these metals as required by OSHA; therefore, a risk

of exposure exists. The final chemical on the list, trimethylsilanol, was identified as a chemical of interest by the Navy though it does not appear in EESOH-MIS.

Solvents

According to the American Chemical Society (2022) solvents are chemicals that dissolve solutes and form solutions. They are used for everything from extractions to dry cleaning to painting and various other occupational tasks. Solvents can be as benign as water or as hazardous as dichloromethane. Because they are so ubiquitous, using toxic solvents affects millions of workers every year and has implications for consumers and the environment as well. Products containing solvents include oil-based paints, paint strippers, adhesives, wood finishes, shoe polish, cosmetics, markers, aerosols, nail polish remover, garment dry cleaning, sealants, and household/commercial cleaners.

The list of 126 chemicals of importance to the AF developed by Steele *et al.* (2021), contained 37 chemicals that had a primary classification of solvent. Solvents on the list with existing ACGIH (2022) OELs and documentation were the focus of this report.

Aerosols

Aerosols are small particles that are suspended in the air that come in a variety of sizes, composition, and from a number of different sources. Particles do not have CAS numbers as they are physical descriptors of particulate matter (PM), not specific references to chemical composition. The aerodynamic diameters of aerosols can range from the hundreds of micrometers (μm) down to nanoparticles that can be as small as a few nanometers wide. Particle size ranges are typically characterized by where the particles deposit in the respiratory system as described in Table 3.

Table 3. Categorization of Particle Size Based on How Far Into the Respiratory System the Particles Deposit, Adapted from Lippmann (1999)

Region of Respiratory System	Corresponding Particle Size Selective Sampler Name	Structures in Respiratory System where Particles Primarily Deposit
Gas exchange	Respirable	Alveoli and respiratory bronchioles
Tracheobronchial	Thoracic	Throat and upper airway, to include the terminal bronchioles
Head airways	Inhalable	Nose, mouth but excludes throat

There are size-selective aerosol samplers designed to capture particles of varying size. To be considered a size selective sampler, the sampler must adhere to a mathematical expression that describes the portion of particles that penetrate the specified area of the respiratory system (Hinds, 1999). For the inhalable fraction, samplers must collect 50% of particles with any aerodynamic diameter of $100 \mu\text{m}$ (Hinds, 1999). For thoracic samplers, 50% of particles with aerodynamic diameters of $10 \mu\text{m}$ must be captured, and for respirable samplers, 50% of particles with aerodynamic diameters of $4 \mu\text{m}$ must be collected (Hinds, 1999).

Consideration is given to particle size, not just composition for particle OELs, as the toxicity and bioavailability of airborne particles can vary with their aerodynamic diameter. ACGIH (2022) defines multiple threshold limit values (TLVs) based on particle size for some chemicals that can exist as airborne particulate matter. Separate TLVs can be listed for the inhalable, thoracic, or respirable size fractions for a single chemical. ACGIH (2022) also recommends that airborne concentrations of insoluble and poorly soluble particles with no other existing TLV should be kept below 3 milligrams per cubic meter (mg/m^3) for respirable particles and $10 \text{ mg}/\text{m}^3$ for inhalable particles. Similarly, the USAPHC developed Military Exposure Guidelines (MEGs) for PM with aerodynamic diameters of ≤ 10 and $\leq 2.5 \text{ }\mu\text{m}$, PM_{10} and $\text{PM}_{2.5}$, respectively (USAPHC, 2014).

Particulate matter/aerosols are a major Department of Defense (DoD) concern in some deployment regions, notably Southwest Asia, where ambient particle concentrations are more commonly present at much higher levels than within the United States. The sources of these particles can be short-term dust storms, motor vehicle disturbance of the desert floor, local industries (e.g., brick factories) near base camps and military operations (e.g., burnpits, vehicles) (Garshick *et al.*, 2019). The list of 126 chemicals of importance to the AF developed by Steele *et al.* (2021) contained three line items categorized as aerosols: nanoparticles, respirable particulate, and carbon black.

Aliphatics and Miscellaneous

Aliphatic hydrocarbons are carbon-based compounds that have hydrocarbon rings or straight chains, can be saturated or unsaturated, but are not aromatic (IUPAC, 2022). The simplest aliphatic hydrocarbon is methane (CH_4). Aliphatic hydrocarbons are formed through petroleum cracking and distillation and are commonly found in fuels. Aliphatic hydrocarbons that were not included in other categories (e.g. some aliphatics were included under the “Solvent” category) are grouped with this category.

The miscellaneous chemicals are those which did not fall into the following categories: aerosols, aliphatic hydrocarbons, aldehydes, toxic gases and vapors, solvents, or metals. While their heterogeneity makes general statements on the category difficult, it includes classes of chemicals of importance to the AF such as ethylene glycols, plastics and rubber, petroleum distillates, nitrogen compounds, and naphthalenes.

Aliphatics and miscellaneous chemicals on the list of 126 chemicals of interest to the AF (Steele *et al.*, 2021) with existing ACGIH (2022) OELs and documentation were the focus of this report.

3.0 METHODS

3.1 Systematic Review (Aldehydes, Toxic Gases and Vapors, Metals)

A systematic literature review is a comprehensive analysis of all available literature on a topic to make data-driven decisions (Higgins *et al.*, 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).

Across multiple disciplines, 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 person-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. The description of the population, exposure(s), controls, and outcome (PECO) process is shown in Table 4. 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 for the final review.

Table 4. 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 126 chemicals of interest to the AF
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

In total, 126 chemicals (Steele *et al.*, 2021) were chosen for inclusion in the literature review. Each of these chemicals were included in the literature search by their name and CAS#, along with specific routes of exposure and visual attributes as described in Table 5. The vision search terms in Table 5 were chosen to pertain to visual performance attributes described in Section 2.1, Visual Performance Attributes of Concern.

Table 5. Complete List of Search Terms Chosen for Attributes and Chemicals of Air Force Interest

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 associated with visual attributes
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 were evaluated to determine if portions of the systematic literature review could be automated. DistillerSR, with its artificial intelligence (AI) function (DAISY), was selected because it automatically eliminated duplicate results and provided both a means of systematically selecting articles and mining qualitative and quantitative data from the literature searches using 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 that were established by team members and listed in Table 6. When there was a preliminary disagreement on the selection of an abstract(s), both reviewers re-read the abstract to determine if agreement could be reached. Distiller’s DAISY learns from multiple-choice questions for inclusion/exclusion criteria and associates the terminology in the text with these criteria. The reviewers evaluated DAISY using abstracts that were already reviewed by the researchers to determine if DAISY yielded good agreement with their selections. Once satisfactory agreement was demonstrated, then the DAISY function was used to select/deselect the remaining abstracts.

Table 6. 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)

Inclusion Criteria	Exclusion Criteria
-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

A list of data extraction questions and responses (Appendix B) was developed by the team in order to acquire key information from each study. Team members initially saved this information using the Distiller software, and then downloaded the data to an Excel file for compilation and analysis. The information was then extracted from the Excel files into the tables found in the “Results” section of this report. The full literature review process from literature search through data extraction is displayed in the flow chart in Figure 1.

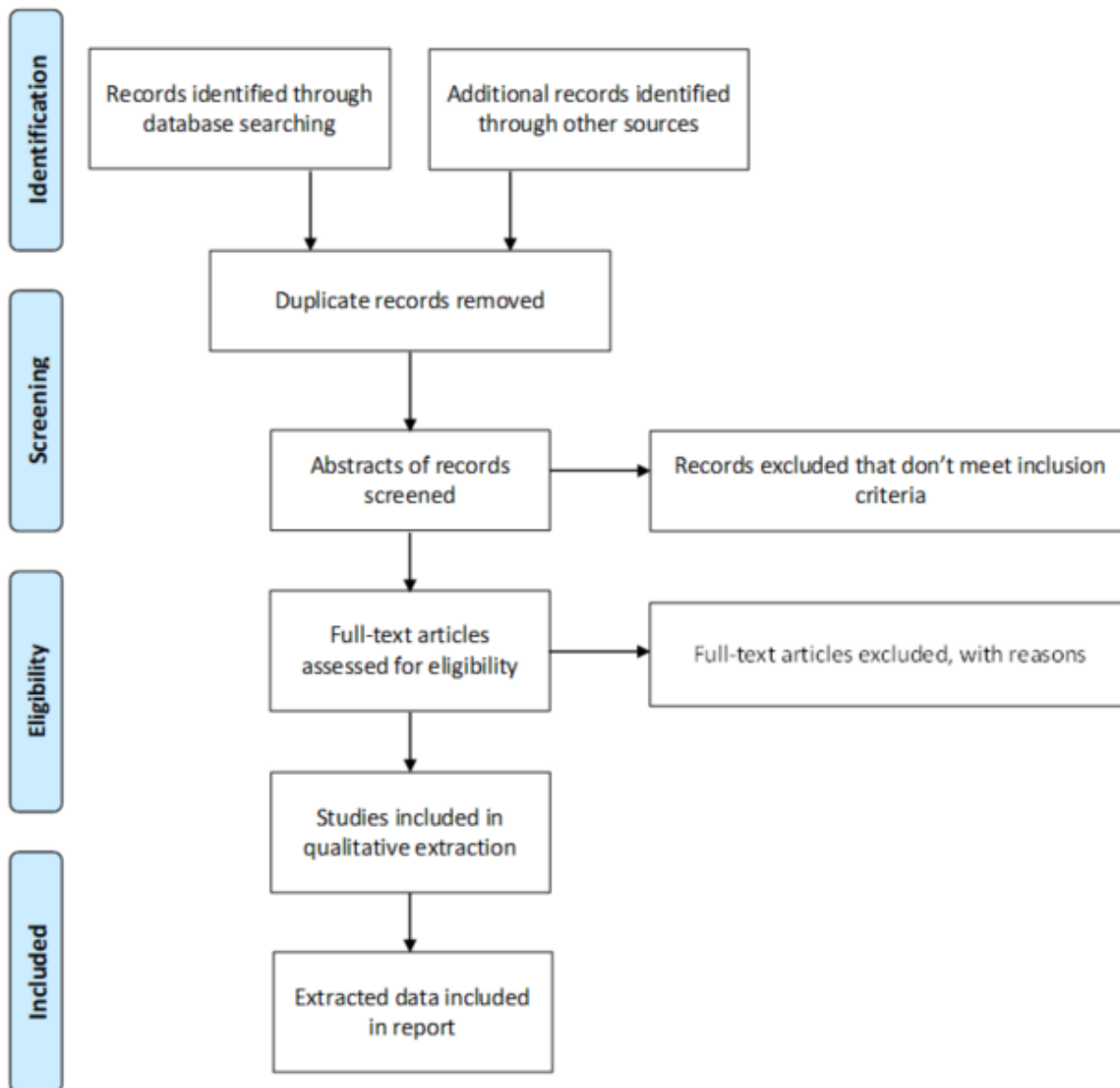


Figure 1. PRISMA Format Describing the Systematic Screening and Selection of Studies for Analysis

3.1.4. Risk of Bias (RoB)

Systematic literature reviews are characteristically comprehensive in terms of the studies they examine, but just as importantly an attempt is typically made to objectively judge the extracted data in order to draw appropriate conclusions from the findings. This judgment starts with an examination of 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 for use in this review

because it was developed for epidemiology studies, and a major portion of the review focused on results of human research studies.

The checklist provided evaluation criteria for the strengths and weaknesses of the design and methods. Design and methodological shortcomings could have been related to the internal validity of the study including factors such as selection bias, confounders, and low statistical power. Each study's external validity, defined as the ability to be able to generalize the data beyond the study population, was also evaluated. The review team modified the checklist so it could also apply to animal studies.

The objective of the modified 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, internal validity (bias and confounding), power, and external validity (Appendix C). Because a "Yes" was scored as a 1, and a "No" was scored as a 2, a lower RoB score meant that a study had a lower bias. A perfect score varied depending on the type of study. A perfect case-control study score would have been 29 out of 29. Because four of the questions do not pertain to animal studies, a perfect animal study score would have been 25 out of 25. To compare animal and human studies equally, a perfect score was considered to be 0% and higher scores equated to 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.

3.2 Threshold Limit Value Review (Solvents, Aerosols, Aliphatics and Miscellaneous)

Solvents, aerosols, aliphatics and miscellaneous chemicals that had an ACGIH (2022) OEL and corresponding documentation were selected for review from the list of 126 chemicals of importance to the AF developed by Steele *et al.* (2021). ACGIH provides recommendations for OELs as TLVs based solely on scientific evidence. A TLV is an 8-hour time weighted average (TWA) for a typical occupational worker shift. A short-term exposure limit (STEL) is a 15-minute exposure that should not be exceeded at any time during a worker's shift. These recommendations are not legally binding, but the AF adopts and uses OELs that are applicable to its mission. In the results section of this report, the current ACGIH information is listed that is relevant to potential impacts on visual performance attributes. ACGIH bases their TLVs on both long-term toxic effect (e.g. cancer) and short-term transient effects (e.g. eye irritation). In identifying scientific literature for this report, ACGIH documentation was reviewed for any studies pertaining to short-term transient effects. MEGs were also consulted, where applicable. MEG values are low-confidence effects range estimates considered protective bounds of the hazard severity concentration ranges.

4.0 RESULTS

4.1 Aldehydes

Table 7 lists a summary of 12 studies that met the selection criteria and indicated an impact of aldehydes on vision. Ocular exposure to aldehydes occurs mainly through contact with the chemical in the air, and the main effect on vision is eye irritation. In fact, eye irritation and increased lacrimation are typically the first symptoms experienced from airborne 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). See Appendix A1 for the full list of aldehydes of interest to the AF based on field data and chemical inventory usage. Three of the thirteen aldehydes listed in the appendix are identified as eye irritants by ACGIH: formaldehyde, acetaldehyde and valeraldehyde.

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 eyelid ptosis (closed eyelid) (Sekeryapan *et al.*, 2011). The functional result was restricted vision, and the haze and ptosis lasted for at least three months with only mild improvement.

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

Reference and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Vazquez-Ferreiro et al. 2019 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 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 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 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 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 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 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	Formaldehyde [50-00-0]	3 ppm for 1 hour	Eye irritation	Eye irritation increased	16%

Reference and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Human exposure assessment Bender et al. 1983 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 Human exposure assessment	Methacrolein [78-85-3]	286 ppb for 20 minutes	Blink frequency	18% increase in blink frequency	16%
Kulle et al. 1987 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%

Vazquez-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 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 balanced salt solution to remove residual formaldehyde. 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 ratings 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 observed adverse effect level (NOAEL) of 0.7 ppm for a 4-hour constant exposure and a no observed effect level (NOEL) of 0.4 ppm with peaks of 0.8 ppm were the results of this study (Mueller *et al.*, 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) occurs when the eyes are not lined up properly and point in different directions. The woman's 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 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 were used to produce formaldehyde. On the first postoperative day, there was complete ptosis of the right upper eyelid. Ptosis occurs 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. The authors concluded that 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 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) with a standard deviation of $49 \mu\text{g}/\text{m}^3$ and a range of 13 to $190 \mu\text{g}/\text{m}^3$. 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 response 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 began to cause eye irritation at concentrations equal to 1 ppm or higher. A confounding result in these studies was the finding 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, for which 1.7 ppm was the concentration of formaldehyde at 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 $11.245 \text{ mg}/\text{m}^3$ 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 Liters/minute), whereas the asthmatics performed intermittent moderate exercise (minute ventilation = 37 Liters/minute). Symptoms and pulmonary function were assessed during exposure. No normal or asthmatic subject reported eye irritation or odor perception above a mild level during the clean air exposure. At 3 ppm formaldehyde, 82% of the volunteers reported detecting an odor and experiencing 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. When irritation was first reported, the 1.0 ppm concentration was the only concentration at which there was significant difference in severity between formaldehyde-exposed subjects and clean air-exposed controls. 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 noticed. The 1.0 ppm level was consistent with the 1.0 ppm summarized by Arts *et al.* (2006).

Alexandersson et al. (1982)

Air concentrations of formaldehyde were obtained from personal samplers carried by 47 males exposed to formaldehyde in their workplace and 20 non-exposed controls. The pumps collected samples from each subject's 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 formaldehyde was 0.36 ppm, with a range of 0.04 ppm – 1.25 ppm. The mean concentration was 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, 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, 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 limonene oxidation products 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 parts per billion (ppb) methacrolein, however, low relative humidity may have exacerbated the effects.

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 hours 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 male and female symptom responses.

4.2 Toxic Gases and Vapors

Table 8 lists a summary of five studies that met the selection criteria and indicated an impact of toxic gases and vapors on vision. Eye irritation was the focus of all five studies, with this effect associated with carbon dioxide exposure in two studies and acrolein in two studies. Carbon dioxide exposure resulted in eye irritation at levels above 800 ppm in an acute epidemiology study (Tsai, Lin and Chan, 2012), whereas a concentration of at least 2% carbon dioxide was sufficient to cause eye irritation in human subjects during a two-minute exposure (Hempel-Jørgensen, Kjærgaard and Mølhav, 1997). Studies related to chemical warfare indicate acrolein causes eye irritation and lacrimation in humans at 0.25 ppm (Prentiss, 1937). Humans experience intense irritation from acrolein exposure at 5.5 ppm and death after a short time at levels above 10 ppm (Henderson and Haggard, 1943). In the fifth study, BF, a measure which can be associated with increased eye irritation in human subjects, was not changed by a four-hour exposure to sulfur dioxide at concentrations up to 2 ppm (Van Thriel *et al.*, 2010)

Table 8. Summary of Studies Evaluating Toxic Gases and Vapors Exposure that Impact Visual Performance Attributes

Reference and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Tsai, Lin and Chan 2012 Human epidemiological study	Carbon Dioxide [124-38-9]	CO ₂ concentrations monitored in indoor office air	Eye irritation	Eye irritation more likely at concentrations >800 ppm	ND
Hempel-Jørgensen, Kjærgaard and Mølhave 1997 Human exposure assessment	Carbon Dioxide [124-38-9]	Five increasing concentrations (2%,4%,8%,16%, 32%) for two minutes. Tested both unilaterally and bilaterally with 15 minutes in between tests.	Eye irritation	Increasing irritation with increasing CO ₂ concentration for both uni- and bilateral; Decrease in eye sensitivity during second test	ND
van Thriel et al. 2010 Human exposure assessment	Sulfur Dioxide [7446-09-5]	0.5 ppm, 1 ppm, 2 ppm for four hours	Blink frequency	No effect of exposure at any concentration	ND
Prentiss 1937 Human case reports	Acrolein [107-02-8]	Acute 0.25-10 ppm	Eye irritation	Eye and conjunctiva irritation as low as 0.25 ppm	ND
Henderson and Haggard 1945 Human case reports	Acrolein [107-02-8]	Acute 1-24 ppm	Eye irritation	Intensely irritating to the eyes at 5 ppm	ND

Tsai, Lin and Chan (2012)

Sick building syndrome (SBS) is associated with multiple environmental factors, including higher temperatures, lower relative humidity, and air contaminants, such as PM and microbiological allergens. Poor ventilation appears to be the most frequently cited factor associated with low productivity among office workers and with a high prevalence of SBS. Tsai, Lin and Chan (2012) attempted to determine whether any association exists between SBS and indoor CO₂ concentrations. They evaluated SBS among 111 office workers in August and November 2003. The environmental conditions in the office, including CO₂ concentrations, temperature, relative humidity, and fine particulate matter (PM_{2.5}), were monitored continuously. Workers were given a SBS questionnaire based on the National Institute for Occupational Safety and Health (NIOSH) Indoor Air Quality and Work Environment Symptoms Survey which contained questions related to 17 symptoms plus they added one extra symptom related to muscular pain, including shoulder, neck, or back pain or numbness. The symptoms listed in the SBS questionnaire were categorized into the following five SBS groups 1) the Eye Irritation group included tired or strained eyes and dry, itching, or irritated eyes; 2) the Nonspecific Symptoms group included headache, unusual tiredness, fatigue, or drowsiness, tension, irritability, or nervousness, difficulty in remembering things or in concentrating, dizziness or lightheadedness, feeling depressed, and nausea or upset stomach; 3) the Upper Respiratory Symptoms group included sore or dry throat, stuffy or runny nose, or sinus congestion, cough and sneezing; 4) the Lower Respiratory Symptoms group included wheezing, chest tightness, and shortness of breath, and 5) the Skin Irritation group included symptoms of dryness or rash. The SBS was defined under the following two criteria: whether the symptoms appeared when the workers entered the study office and disappeared when they left it, and the other was whether such symptoms occurred at least once per week. The most prevalent symptoms of the five SBS groups were eye irritation and nonspecific and upper respiratory symptoms. The generalized estimating equation models were used to estimate the effects of the November period compared with the effects of the August period. The generalized estimating equation models showed that workers exposed to indoor CO₂ levels greater than 800 ppm were likely to report more eye irritation or upper respiratory symptoms.

Hempel-Jørgensen, Kjærgaard, and Mølhave (1997)

Hempel-Jørgensen, Kjærgaard, and Mølhave (1997) sought to create an objective sensory irritation scale for the eye. Knowing CO₂'s irritative effect via production of carbonic acid in the cornea, researchers exposed ten health subjects' eyes (seven men, three women) to five increasing concentrations of CO₂ on four occasions, both unilaterally and bilaterally with at least fifteen minutes between the two exposure methods. CO₂ exposures occurred over ten minutes (2%, 4%, 8%, 16%, and 32%) with each exposure level lasting two minutes. Subjects were blinded to the exposure concentrations. Each subject was tested twice in one week. If a subject was exposed bilaterally first on one day, they were exposed unilaterally first the next test day. No statistically significant difference was found among severity of irritation between unilateral and bilateral tests. Subjects reported increasing eye irritation with increasing CO₂ concentration, regardless of whether exposure was uni- or bilateral. There was a statistically significant decrease in eye sensitivity on the second set of exposure tests in a single day (e.g., when going from uni- to bilateral exposure).

van Thriel et al. (2010)

Eye BR, rhinomanometry, spirometry and symptom ratings of acute health effects were assessed before, during, and after exposures of 16 humans (8 females/8males) to 0.5, 1, and 2 ppm sulfur dioxide (SO₂) for 4 hours and compared to a control condition using clean air. Participants performed light physical exercise, simulated with bicycle ergometry, during exposures. Eye BF, nasal airflow, and lung function were not affected by the acute SO₂ exposure investigated and not significantly affected by gender. Only odor annoyance ratings increased in a dose-dependent manner, but the average magnitudes were labeled weak to moderate. In healthy volunteers, without hyper responsiveness to SO₂, no dose-dependent effects of acute SO₂ exposures up to 2 ppm for 4 hours could be measured.

Prentiss (1937)

Acrolein, an unstable irritant, acts on the eyes and respiratory system simultaneously when exposure occurs. As low as 0.25 ppm results in lacrimation, conjunctiva irritation, and mucous membrane irritation. Around 5 ppm, the irritation becomes “intolerable” and exposure to as little as 10 ppm for ten minutes can result in death Prentiss (1937).

Henderson and Haggard (1945)

According to Henderson and Haggard (1945) acrolein can be detected by humans at 1 ppm and becomes intensely irritating to the eyes and respiratory tract at 5.5 ppm. Acrolein can kill an exposed individual in 10 minutes at concentrations of 10 ppm and above, and is “unbearable” at 24 ppm even for a brief time. At sufficiently high concentrations, acrolein can induce pulmonary edema.

4.3 Metals

Only one study met the selection criteria and indicated a potential effect of one of the eleven metals of interest on a visual performance attribute (Table 9). The study by Sárközi *et al.* (2009) indicated that intratracheal exposure to manganese dioxide over 9 weeks at a concentration of 5.26 milligrams per kilogram (mg/kg) had an effect on the visual cortex in rats.

Table 9. Summary of Studies Evaluating Metals Exposure that Impacts Visual Performance Attributes

Reference and study population	Chemical [CAS]	Exposure Parameters	Outcome Evaluated	Result	RoB Score
Sárközi <i>et al.</i> 2009 Wistar rats	Manganese Dioxide [1313-13-9]	2.63 mg/kg, 5.26 mg/kg intratracheal instillation for 3, 6, and 9 weeks	Evoked potentials in visual cortex	Increased latency of evoked potentials after 9 weeks of receiving 5.26 mg/kg manganese dioxide dose	33%

Sárközi et al. (2009)

Sárközi *et al.* (2009) instilled a nanosuspension of manganese dioxide (MnO₂) into the trachea of adult male Wistar rats for 3, 6, and 9 weeks. The doses of the MnO₂ particles with an approximate 23 nanometers nominal diameter were 2.63 and 5.26 milligrams manganese per kilogram (mg Mn/kg). The weekly body weight gain was normal in control rats but, the treated rats ceased to grow after week 6. At the end of treatment, the rats' spontaneous motor activity was tested in an open field box. Under urethane anesthesia electrophysiology of the primary vision areas of the brain was conducted to record spontaneous and stimulus-evoked cortical activity. Action potentials in the tail nerve were also recorded under urethane anesthesia. Manganese (Mn) was detected in the lung and brain samples of exposed rats. In the open field motor activity test, the percentage of ambulation and rearing decreased while local activity and immobility increased. The latency of the evoked potentials was lengthened in brain areas, and the conduction velocity of the tail nerve decreased. These results indicate that the Mn content of instilled nanoparticles had access from the airways to the brain, and the resulting effects on behavioral and neurophysiology endpoints could impact multiple visual and psychological attributes.

4.4 Solvents

A total of 19 solvents were identified that have ACGIH TLVs and documentation of short-term impacts on visual performance attributes (Table 10). There is evidence that all of these solvents can cause at least some level of eye irritation at sufficiently high exposure concentrations. ACGIH (2022) specifically cited irritancy to the eyes as a basis for the TLVs of the alcohols, acetates, ketones, xylenes, and Stoddard solvent that were identified as solvents of interest to the AF. In addition to eye irritancy, exposure to methanol can also cause damage to the ganglion cells of the retina. This same effect is also seen with methyl acetate exposure because the chemical is rapidly metabolized to methanol in the body. Exposure to toluene has been linked to changes in color vision in multiple occupational studies. One study was obtained by a different search and is summarized below and in Table 10.

Costa et al. (2012)

Costa *et al.* (2012) evaluated the visual outcome of chronic occupational exposure to a mixture of organic solvents by measuring color discrimination, achromatic contrast sensitivity and visual fields in a group of gas station workers. They tested 25 workers (20 males) and 25 controls with no history of chronic exposure to solvents (10 males). All participants had normal ophthalmologic exams. Subjects had worked in gas stations on an average of 9.666.2 years. See Table 10 for the list of fuel to which they were exposed. Color vision was evaluated with the Lanthony D15d and Cambridge Colour Test (CCT). Visual field assessment consisted of white-on-white 24–2 automatic perimetry (Humphrey II-750i). Contrast sensitivity was measured for sinusoidal gratings of 0.2, 0.5, 1.0, 2.0, 5.0, 10.0 and 20.0 cycles per degree (cpd). Results from both groups were compared using the Mann–Whitney U test. The number of errors in the D15d was higher for workers relative to controls ($p < 0.01$). Their CCT color discrimination thresholds were elevated compared to the control group along the protan, deutan and tritan confusion axes ($p < 0.01$), and their ellipse area and ellipticity were higher ($p < 0.01$). Genetic analysis of subjects with very elevated color discrimination thresholds excluded congenital causes for the visual losses. Automated perimetry thresholds showed elevation in the 9, 15 and

21 degrees of eccentricity ($p < 0.01$) and in mean deviation and pattern standard deviation indexes ($p < 0.01$). Contrast sensitivity losses were found for all spatial frequencies measured ($p < 0.01$) except for 0.5 cpd. Significant correlation was found between previous working years and deutan axis thresholds ($\rho = 0.59$; $p < 0.05$), indexes of the Lanthony D15d ($\rho = 0.52$; $p < 0.05$), perimetry results in the fovea ($\rho = 0.51$; $p < 0.05$) and at 3, 9 and 15 degrees of eccentricity ($\rho = 0.46$; $p < 0.05$).

Table 10. Summary of ACGIH TLVs and Documentation for Solvents with Short-Term Effects on Visual Performance Attributes

Chemical Name [CAS]	TLV	References	Notes
methanol [67-56-1]	200 ppm (TWA) 250 ppm (STEL)	<ul style="list-style-type: none"> • Henson EV. 1960. The toxicology of some aliphatic alcohols, Part II. J Occup Med 2: 497-502. • Morgan RL, SS Sorenson, TR Castles. 1987. Prediction of ocular irritation by corneal pachymetry. Food Chem Toxicol 25: 609-613. • Agency for Toxic Substances and Disease Registry (ATSDR). 1993. Methanol toxicity. Am Fam Physician 47: 163-171. • Cook WA. 1945. Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14: 936-946. • Browning E. 1965. Toxicity and Metabolism of Organic Solvents. pp 311-323. Elsevier Publishing Co, Amsterdam. • Kingsley WH & FC Hirsch. 1955. Toxicologic considerations in direct process spirit duplicating machines. Compen Med 40: 7-8 	TLV from 2009. Basis is for eye irritation, up to and including damage of the ganglion cells in the retina, headache, dizziness, and nausea. Rodents don't metabolize methanol like primates so rodent animal studies are not good dose-response benchmarks.

<p>toluene [108-88-3]</p>	<p>20 ppm TWA No STEL OTO*</p>	<ul style="list-style-type: none"> • Gobba F, Cavalleri A. 2003. Color vision impairment in workers exposed to neurotoxic chemicals. <i>Neurotoxicology</i> 24: 693–702. • Muttray A, Wolters V, Jung D, <i>et al.</i> 1999. Effects of high doses of toluene on color vision. <i>Neurotoxicol Teratol</i> 21: 41–45. • Muttray A, Wolters V, Mayer-Popken O, <i>et al.</i> 1995. Effect of subacute occupational exposure to toluene on color vision. <i>Int J Occup Med Environ Health</i> 8: 339–345. • Nakatsuka H, Watanabe T, Takeuchi Y, <i>et al.</i> 1992. Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. <i>Int Arch Occup Environ Health</i> 64: 113–117. • Campagna D, Stengel B, Mergler D, <i>et al.</i> 2001. Color vision and occupational toluene exposure. <i>Neurotoxicol Teratol</i> 23: 473–480. • Cavalleri A, Gobba F, Nicali E, <i>et al.</i> 2000. Dose-related color vision impairment in toluene-exposed workers. <i>Arch Environ Health</i> 55: 399–404. • Paramei GV, Meyer-Baron M, Seeber A. 2004. Impairments of colour vision induced by organic solvents: a meta-analysis study. <i>Neurotoxicology</i> 25: 803–816. • Zavalic M, Mandic Z, Turk R, <i>et al.</i> 1998. Quantitative assessment of color vision 	<p>TLV basis from update in 2020 is for avoiding central nervous system impairment, visual impairment, hearing impairment, pregnancy loss, and effects on the female reproductive system.</p> <p>There are several tests for color vision: Lanthony’s new color test, Farnsworth-Munsell 100 hue, and Lanthony desaturated panel D-15. It is the latter that is the most sensitive to changes in color vision due to chemical exposure (Gobba and Cavalleri, 2003). Acute exposures to toluene for less than an hour (Muttray <i>et al.</i>, 1999) and a workweek (Muttray <i>et al.</i>, 1995) do not show changes in color vision during the exposure. Color vision changes were also not found in 63 men and 111 women currently ex-posed to 46 ppm of toluene (Nakatsuka <i>et al.</i>, 1992).</p> <p>Subclinical blue-yellow color vision changes have been found in photogravure printers and rubber workers exposed at 36 and 42 ppm, respectively. In a study of a rotogravure plant in France, color vision changes occurred in 72 printers and 34 other workers in the plant when compared to a group (N = 19) of non-exposed bookbinders (Campagna <i>et al.</i>, 2001). Eight-hour personal air sampling in the breathing zone showed that the printers were exposed to an average of 36 ppm. These printers had an average employment time in this plant of 18 years. The authors found that reduction in color vision correlated to current exposure, cumulative exposure, and past total hydrocarbon exposure. A study of 33 rubber workers exposed at 42 ppm</p>
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Chemical Name [CAS]	TLV	References	Notes
		<p>impairment in workers exposed to toluene. Am J Ind Med 33: 297–304.</p>	<p>(based on urinary levels) who worked in the plant for less than 10 years compared with 16 controls also showed impairment of color vision that correlated with cumulative solvent exposure but not the levels of toluene in the urine (Cavalleri <i>et al.</i>, 2000). Both studies suggest that the loss of color vision is progressive and requires continued exposure. However, a meta-analysis of four studies that used the Lanthony D-15 color discrimination test failed to show consistent negative effects on color vision, due to variability in response (Paramei <i>et al.</i>, 2004).</p> <p>An earlier study of rotogravure and shoe factory workers exposed at 66 to 250 ppm toluene showed that color vision changes correlated with the level of toluene in the air, toluene in the blood, and o-cresol or hippuric acid in urine after work shift (Zavalic <i>et al.</i>, 1998).</p>

Chemical Name [CAS]	TLV	References	Notes
1. Ethanol fuel (92.6% to 93.8%) and water (6 - 8%) 2. Gasoline and diesel with organic solvents benzene, toluene and xylene (octane boosters) 3. gasoline + 20% ethanol	N/A due to mixtures and multiple fuel exposures	<ul style="list-style-type: none"> • Costa <i>et al.</i> 2012. Long-Term Occupational Exposure to Organic Solvents Affects Color Vision, Contrast Sensitivity and Visual Fields. PLoS ONE 7(8): e42961. doi:10.1371/journal.pone.0042961 	<p>This paper was the initial paper that ultimately led to the full literature search for all attributes.</p> <p>Summary: Occupational exposure to a mixture of solvents by gas station workers may impair visual function in many aspects of color vision. Changes in parvo-, magno- and koniocellular pathway functions are suggested by the study along with significant correlations between the number of previous working years and sensory loss.</p>
isopropanol [67-63-0]	200 ppm (TWA) 400 ppm (STEL)	<ul style="list-style-type: none"> • Laham S, M Ptovin, K Schrader, <i>et al.</i> 1980. Studies on inhalation toxicity of 2-propanol. Drug Chem Toxicol 3: 343-360. • Gill MW, HD Burleigh-Flayer, DE Strother, <i>et al.</i> 1995. Isopropanol acute vapor inhalation neurotoxicity study in rats. J Appl Toxicol 15: 77-84. • Fairhall Lt. 1949. Industrial toxicology, p. 248. Williams & Wilkins, Baltimore. • Nelson KW, JF Ege Jr, M Ross, <i>et al.</i> 1943. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 24-282-285. • Sethre T, T Laubli, M Berode, H Krueger. 2000. Neurobehavioral effects of experimental isopropanol exposure. Int Arch Occup Environ Health 73: 105-112. 	TLV from 2003, name updated in 2006 from IPA to 2-propanol. Basis is to avoid central nervous system depression and irritation to the nose, eyes, and throat.

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Smeets MAM, C Maut, PH Dalton. 2001. Acute sensory irritation from exposure to isopropanol at TLV in workers and controls: objective vs subjective effects. Report submitted to ACGIH from the Monell Chemical Senses Center. On file at ACGIH, Cincinnati, OH. • Smeets MAM, PH Dalton. 2001. Perceived odor and irritation of isopropanol in occupationally exposed workers. Report submitted to ACGIH from the Monell Chemical Senses Center. On file at ACGIH, Cincinnati, OH. • Burleigh-Flayer H, MW Gill, DE Strother, <i>et al.</i> Isopropanol 13-week vapor inhalation study in rats and mice with neurotoxicity evaluation in rats. <i>Fundam Appl Toxicol</i> 23: 421-428. 	
ethanol [64-17-5]	1000 ppm (STEL)	<ul style="list-style-type: none"> • Bevan C. 2001. Monohydric Alcohols—C1 to C6. In: <i>Patty's Toxicology</i>, 5th ed, Vol 6. John Wiley & Sons Inc, New York. • Seeber A, M Blaszkewicz, K Golka, <i>et al.</i> 1997. Solvent exposure and ratings of well-being: dose-effect relationships and consistency of data. <i>Environ Res</i> 73: 81-91. 	TLV from 2009. Basis is avoiding irritation to upper respiratory tract and eyes.
2-methylpentane (hexane isomers other than n-hexane)	500 ppm (TWA) 1000 ppm (STEL)	<ul style="list-style-type: none"> • Sandmeyer EE. 1981. Aliphatic Hydrocarbons. In: <i>Patty's Industrial Hygiene and Toxicology</i>, 3rd Rev. ed., Vol 2B, Toxicology, pp. 3178-3179, 3188. G.D. Clayton and F.E. Clayton, Eds. John Wiley & Sons, New York. 	<p>NOTE: If a mixture contains >5% n-hexane, use the n-hexane TLV (50 ppm TWA).</p> <p>TLV from 1982. Basis for central nervous system (CNS) impairment, upper respiratory and eye irritation.</p>

Chemical Name [CAS]	TLV	References	Notes
[107-83-5]			
xylenes (mixed isomers) [1330-20-7]	100 ppm (TWA) 150 ppm (STEL) A4 — Not Classifiable as a Human Carcinogen OTO*	<ul style="list-style-type: none"> • Berenblum, I.: The Cocarcinogenic Action of Croton Oil. <i>Cancer Res.</i> 1:44 (1941). • Carpenter, C.P.; Kinkead, E.R.; Geary, Jr., D.L.; <i>et al.</i>: Petroleum Hydrocarbon Toxicity Studies V. Animal and Human Response to Vapors of Mixed Xylenes. <i>Toxicol. Appl. Pharmacol.</i> 33:543-558 (1975). • Gamberale, F.; Annwall, G.; Hultengren, M.: Exposure to Xylene and Ethylbenzene. III. Effects on Central Nervous Functions. <i>Scand. J. Work Environ. Health</i> 4:204-211 (1978). • Hastings, L; Cooper, G.P.; Burg, W.: Human Sensory Response to Selected Petroleum Hydrocarbons. In: <i>Advances in Modern Environmental Toxicology</i>, Vol. 6, pp. 255-270. H.N. MacFarland, <i>et al.</i>, Eds. Princeton Scientific, Princeton (1986). • Matthaus, W.: Corneal Lesions in Workers Dealing with Surface Varnishing in the Furniture Industry. <i>Klin Monatsbl. Augenhelik.</i> 144:713-717 (1964). • Nelson, K.W.; Ege, J.F.; Ross, M.; <i>et al.</i>: Sensory Response to Certain Industrial Solvent Vapors. <i>J. Ind. Hyg. Toxicol.</i> 25:282-285 (1943). • Patel, J.M.; Harper, C.; Gupta, B.M.; Drew, R.T.: Changes in Serum Enzymes after 	TLV from 2001. Basis is irritation of the eyes, mucous membranes, and skin and narcosis at high concentrations. There is no substantive difference in the toxicity of the individual isomers or mixed isomers of xylene. Liquid xylene is a skin irritant and causes erythema, dryness, and defatting (Wolf <i>et al.</i> , 1956). Following exposure to doses sufficient to induce overt poisoning and unconsciousness, transient hepatic and renal toxicity have been reported. Controlled studies in volunteers inhaling 64 to 150 ppm (USNTP, 1986) or up to 300 to 400 ppm (Gamberale <i>et al.</i> , 1976; Hasting <i>et al.</i> , 1986) failed to show any evidence for neurologic impairment. No concentration-response relationship was found between eyes closed:eyes open ratio for volunteers exposed at 64 to 400 ppm xylene (Matthaus, 1964). Humans exposed at 200 ppm xylene for 3 to 5 min complained of ocular and upper respiratory tract irritation (Carpenter, 1975). A concentration of 100 ppm for 8 hours was considered a satisfactory air concentration (Nelson, 1946). Accordingly, a TLV-TWA of 100 ppm and a TLV-STEL of 150 ppm are recommended for mixed isomers of xylene and its individual isomers. It is believed that irritant effects will be minimal and that neither significant narcosis nor chronic injuries will result from continued occupational exposure at the recommended values. The Skin notation was deleted in 1983 because repeated percutaneous

Chemical Name [CAS]	TLV	References	Notes
		<p>Inhalation Exposure of p-Xylene. Bull. Environ. Contam. Toxicol. 21:17-24 (1979).</p> <ul style="list-style-type: none"> • U.S. National Toxicology Program: Toxicology and Carcinogenesis Studies of Xylenes (Mixed) (60% m-Xylene, 14% p-Xylene, 9% o-Xylene, and 17% Ethyl Benzene) (CAS No. 1330-20-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 327. DHHS (NIH) Pub. No. 87-2583; NTIS Pub. No. PB-87-189-684. U.S. National Technical Information Service, Springfield, VA (1986). • Wolf, M.A.; Rowe, V.K.; McCollister, D.D.; <i>et al.</i>: Toxicological Studies of Certain Alkylated Benzenes and Benzene. Arch. Ind. Health 14:387—398 (1956). 	<p>absorption was low and did not contribute substantially to that otherwise received by inhalation at the TLV (Patet <i>et al.</i>, 1979). Insignificant evidence for a carcinogenic notation (Berenblum, 1941) (USNTP, 1986).</p>
ethyl benzene [100-41-4]	5 ppm (TWA) No STEL OTO*	<ul style="list-style-type: none"> • Wolf MA; Rowe VK; McCollister DD; <i>et al.</i>: Toxicological studies of certain alkylated benzenes and benzene; experiments on laboratory animals. AMA Arch Ind Health 14:387-398 (1956). • Nielsen GD; Alarie Y: Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Toxicol Appl Pharmacol 65:459-477 (1982). • Yant WP; Schrenk HH; Waite CP; <i>et al.</i>: Acute response of guinea pigs to vapors of 	<p>TLV from 2011. Basis upper respiratory tract irritation; cochlear impairment. Slight dermal and eye irritant (Wolf <i>et al.</i>, 1956). Respiratory Depression 50% (RD₅₀) = 4046 ppm (Nielsen and Alarie, 1982). Guinea pigs at 1000 ppm for 8 hours had slight nasal irritation within first 3 minutes of exposure; some lacrimation also within 8 minutes with both disappearing by 30 minutes; At 2000 ppm, moderate eye and nasal irritation were noted within one minute; 5000 and 10,000 ppm produced immediate, intense irritation of the conjunctiva and nasal mucous membranes followed by unsteadiness, staggering, apparent unconsciousness, intermittent tremors and</p>

Chemical Name [CAS]	TLV	References	Notes
		<p>some new commercial organic compounds. Public Health Rep 45:1241-1250 (1930).</p>	<p>twitching of the extremities, and changes in respiration (Yant <i>et al.</i>, 1930)</p>
<p>cumene [98-82-8]</p>	<p>5 ppm (TWA) No STEL</p>	<ul style="list-style-type: none"> • Standring, P.: Toxicity Review 25: Cumene. Health and Safety Executive, London (1990). • Wolf, M.A.; Rowe, V.K.; McCollister, D.D.; <i>et al.</i>: Toxicological Studies of Certain Alkylated Benzenes and Benzene. AMA Arch. Ind. Health 14:387-398 (1956). • Monsanto Co.: TSCA Section 8(d) Submission. Cumene Health Studies Y-78-213. Acute Toxicity, Eye and Skin Irritation. EPA/OTS Document No. 40-8592034. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (1978). • Nielsen, G.D.; Alarie, Y.: Sensory Irritation, Pulmonary Irritation, and Respiratory Stimulation by Airborne Benzene and Alkylbenzenes: Prediction of Safe Industrial Exposure Levels and Correlation with Their Thermodynamic Properties. Toxicol. Appl. Pharmacol. 65:459-477(1982). • Huels Report No. 1219 (unpublished) (1988). As reported in Dossier prepared by ICI Chemicals and Polymers, Limited (May 27, 1994). • Cushman, J.R.; Norris, J.C.; Dodd, D.E.; <i>et al.</i>: Subchronic Inhalation Toxicity and Neurotoxicity of Cumene in Fisher 344 Rats. J. Am. Coll. Toxicol. 14:129-147 (1995). 	<p>TLV from 2020. Basis upper respiratory tract adenoma; neurological effects. According to Standring (1990) is a nervous system depressant, producing behavioral changes at low doses and ataxia, narcosis, unconsciousness, and respiratory depression at high doses. Slightly irritating to the skin and eyes in the Draize test (Wolfe <i>et al.</i>, 1956; Monsanto Co, 1978). RD₅₀ = 2490 ppm (Nielsen and Alarie, 1982)</p>

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Tegeris, J.S.; Blaster, R.L.: A Comparison of the Acute Behavioral Effects of Alkylbenzenes Using a Functional Observational Battery in Mice. <i>Fund. Appl. Toxicol.</i> 22:240-250 (1994). 	
n-butyl acetate [123-86-4]	50 ppm (TWA) 150 ppm (STEL)	<ul style="list-style-type: none"> • Bernard LG, David RM. n-Butyl acetate: acute inhalation neurotoxicity study in the rat. <i>Toxicological Sciences Laboratory, Eastman Kodak Company, Rochester, NY</i> (1994). • Cain WS; Schmidt R: Can we trust odor databases? Example of t- and n-butyl acetate. <i>Atmospheric Environment</i> 43(16):2591 —601 (2009). • Iregren A; Lof A; Toomingas A; <i>et al.</i>: Irritation effects from experimental exposure to n-butyl acetate. <i>Am J Ind Med</i> 24(6):727-742 (1993). • Nelson KW; Ege JF; Ross M; <i>et al.</i>: Sensory response to certain industrial solvent vapors. <i>J Ind Hyg Toxicol</i> 25:282-285(1943). 	<p>NOTE: TLV applies to all isomers of butyl acetates. References listed specifically address n-butyl acetate exposure.</p> <p>TLV from 2016. The TWA was set to mitigate risk of irritation. Iregren <i>et al.</i> (1993) found that volunteers exposed to 147 ppm of n-butyl acetate for four hours reported eye and respiratory irritation. Cain and Schmidt (2009) determined the ten second eye irritation threshold was between 113 – 177 ppm n-butyl acetate. When 10 human volunteers were exposed to 200 ppm of n-butyl acetate, the majority complained of throat irritation and at 300 ppm, most also experienced eye and nose irritation (Nelson <i>et al.</i>, 1943). Sprague-Dawley rats showed “decreased activity and response to stimulus” to n-butyl acetate starting at 1500 ppm (Bernard and David, 1994)</p>
methyl acetate [79-20-4]	200 ppm (TWA) 250 ppm (STEL)	<ul style="list-style-type: none"> • Browning E: Toxicity and metabolism of industrial solvents, pp 311-323. Elsevier Publishing Co, Amsterdam (1965). • Gosselin RE; Smith RP; Hodge HC: <i>Clinical Toxicology of Commercial Products</i>, 5th ed. Section III Therapeutics Index, 275-279. Williams and Wilkins, Baltimore, MD (1984). 	<p>TLV from 2013. Basis: Headache; dizziness; nausea; eye damage (degeneration of ganglion cells in the retina). TLV is based on its metabolite, methanol. Methyl acetate is rapidly and proportionally metabolized to methanol in the body. Methanol causes sensory irritation, headaches, nausea and visual disturbances, as well</p>

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Henson E: The toxicology of some aliphatic alcohols Part II. <i>J Occup Med</i> 2:497-502 (1960). • Hofmann T: Methyl Acetate: 28 Days Inhalation Toxicity Study in Rats. Hoeschst Marion Roussel Deutschland GmbH, Report No 99.0011. National Technical Information Service, Springfield, VA (1999). • McNally WD: Toxicology. <i>Industrial Medicine</i>, p 615. Chicago, IL (1937). • Schmid E: Die Augenhornhauterkrankung der Mobelpolierer. <i>Archiv fuer Gewerbepathologie und Gewerbehygiene</i> 15:37-44 (1956). • US National Institute for Occupational Safety and Health (US NIOSH): Criteria for a Recommended Standard — Occupational Exposure to Methanol. DHEW (NIOSH) Pub No 76-148 1976. NTIS Pub No PB-5022-08. Online at: http://www.cdc.gov/niosh/76-148.html. Accessed: 8/30/10 (1997). 	<p>as optic neuropathy, metabolic acidosis, narcosis, and respiratory depression at high exposure levels (1000 to 10,000 ppm from chronic studies) (U.S. NIOSH, 1997; Gosselin <i>et al.</i>, 1984; McNally, 1937; Browning, 1965; Henson, 1960). These values should protect against the upper respiratory tract irritation observed in animals where the authors identified a NOAEL of 350 ppm (1057 mg/m³) (Hofmann, 1999) and in exposed workers (Schmid, 1956). Sufficient data were not available to recommend Skin, DSEN, or RSEN notations or a carcinogenicity designation.</p>
ethyl acetate [141-78-6]	400 ppm (TWA)	<ul style="list-style-type: none"> • U.S. National Institute for Occupational Safety and Health: Occupational Safety and Health Guideline for Ethyl Acetate. In: <i>Occupational Safety and Health Guidelines for Chemical Hazards</i>. DHHS (NIOSH) Pub. No. 89-104, Suppl. II-OHG. U.S. Government Printing Office, Washington, DC (1988). 	<p>TLV from 2001. Basis is irritation of the eyes, nose, and upper airways. Other than the irritant effect, data from animal studies and worker exposure experience indicate that ethyl acetate is a substance with a low order of toxicity (Nelson <i>et al.</i>, 1943; Lehman and Flury, 1943; Patty, 1963). Sufficient data not available to recommend Skin, SEN, or carcinogenicity notations or a TLV-STEL (U.S. NIOSH, 1988)</p>

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Nelson, K.W.; Ege, Jr., J.F.; Ross, M.; <i>et al.</i>: Sensory Response to Certain Industrial Solvent Vapors. J. Ind. Hyg. Toxicol. 25:282-285 (1943). • Patty, F.A.: Potential Exposures in Industry: Their Recognition and Control. In: Industrial Hygiene and Toxicology, 2nd ed., Vol. II, Toxicology, p. 2278. F.A. Patty, Ed. John Wiley & Sons, New York (1963). • Lehmann, K.B.; Flury, F.: Toxicology and Hygiene of Industrial Solvents, p. 224. Williams & Wilkins, Baltimore, MD (1943). 	
ethyl ether [60-29-7]	400 ppm (TWA) 500 ppm (STEL)	<ul style="list-style-type: none"> • Kirwin, Jr., C.J.; Sandmeyer, E.E.: Ethers. In: Patty's Industrial Hygiene and Toxicology, 3rd Rev. ed., Vol. 2A, Toxicology, pp. 2491-2511. G.D. Clayton and F.E. Clayton, Eds. John Wiley & Sons, New York (1981). • Nelson, K.W.; Ege, J.F.; Ross, M.; <i>et al.</i>: Sensory Response to Certain Industrial Solvent Vapors. J. Ind. Hyg. Toxicol. 25:282-285 (1943). • Henderson, Y.; Haggard, H.W.: Noxious Gases, 2nd ed., p. 195. Reinhold Publishing Corp., New York (1943). 	TLV from 1976. Basis CNS impairment and upper respiratory tract irritation. The primary physiologic effect of ethyl ether is narcosis and general anesthesia (100,000 to 150,000 ppm); range may produce fatalities due to respiratory arrest. Maintenance of anesthesia at approx. 50,000; lowest anesthetic limit is 19,000 ppm; also an eye irritant (Kirwin and Sandmeyer, 1981). Nasal irritation of volunteer subjects began at 200 ppm and 300 ppm was still objectionable (Nelson <i>et al.</i> , 1943). Inhalation of 2000 ppm at equilibrium could cause dizziness (Henderson and Haggard, 1943).
ethylene glycol [107-21-1]	25 ppm (TWA) 50 ppm (STEL, vapor)	<ul style="list-style-type: none"> • Wills JH; Coulston F; Harris ES; <i>et al.</i>: Inhalation of aerosolized ethylene glycol by man. Clin Toxicol 7:463-476 (1974). • McDonald TO; Roberts MD; Borgman AR: Ocular toxicity of ethylene chlorohydrin and 	TLV from 2017. Basis upper respiratory tract irritation. 188 mg/m ³ could only be tolerated for 15 minutes; 244 mg/m ³ could not be tolerated after 1 or 2 minutes; 308 mg/m ³ was intolerable, even briefly (Wills <i>et al.</i> , 1974). Irritating to the eyes of rabbits (McDonald <i>et al.</i> , 1972). More acutely toxic

Chemical Name [CAS]	TLV	References	Notes
	10 mg/m ³ (STEL, Inhalable particulate matter, Aerosol only)	ethylene glycol in rabbit eyes. Toxicol Appl Pharmacol 21:143-150 (1972). <ul style="list-style-type: none"> • Cavender FL; Sowinski EJ: Glycols. In: Patty's Industrial Hygiene and Toxicology, 5th ed., Vol 8, Toxicology, pp 1-12. E Bingham, C Cohrssen, CH Powell (Eds). John Wiley & Sons, New York (2001). 	to humans than to laboratory animals by ingestion; causes acute CNS depression and renal damage in humans with males more susceptible (Cavender and Sowinski, 2001).
2-butoxyethanol [111-76-2]	20 ppm (TWA) No STEL	<ul style="list-style-type: none"> • Gingell R; Boatman RJ; Bus JS; <i>et al.</i>: Glycol ethers and other selected glycol derivatives. In: Patty's Industrial Hygiene and Toxicology, 4th ed., Vol. II, Part D, Toxicology, pp. 2761-2966. G.D. Clayton and F.E. Clayton, Eds. John Wiley & Sons, New York (1994). • Tyler TR: Acute and subchronic toxicity of ethylene glycol monobutyl ether. Environ Health Perspect 57:185-191 (1984). • Kane LE; Dombroske R; Alarie Y: Evaluation of sensory irritation from some common industrial solvents. Am Ind Hyg Assoc J 41:451-455 (1980). 	TLV from 2003. Basis is eye and upper respiratory tract irritation. In rabbit eyes, produced pain, conjunctival irritation, and moderate to severe, transient corneal injury (Gingell <i>et al.</i> 1994; Tyler, 1984); RD ₅₀ = 2825 ppm (95% CL: 1695 to 7278 ppm) (Kane, Dombroske, Alarie, 1980).
acetone [67-64-1]	250 ppm (TWA) 500 ppm (STEL)	<ul style="list-style-type: none"> • Dick RB; Setzer JV; Taylor BJ; <i>et al.</i>: Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br J Ind Med 46:111-121 (1989). • Matsushita T; Goshima E; Miyagaki H; <i>et al.</i>: Experimental studies for determining the MAC value of acetone (Translated from Japanese). 2. Biological reaction of the "Six-Day Exposure" to acetone. Sangyo Igaku 11:507-511 (1969). 	TLV from 2015. When 16 men were exposed to 900 ppm for four hours, complaints of eye, nose, and throat irritation were elevated compared to the control group (Seeber <i>et al.</i> , 1992). Male and female volunteers were exposed to 250 ppm acetone in two sessions for two hours each session and their performance on psychomotor tests observed (Dick <i>et al.</i> , 1989). Exposed volunteers took 11% longer in their "response time in the auditory tone discrimination task and [there was an

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Seeber A; Kiesswetter E; Vangala RR; <i>et al.</i>: Combined exposure to organic solvents: An experimental approach using acetone and ethyl acetate. <i>Appl Psychol Int Rev</i> 41:281-292 (1992). 	<p>increase] in the rate of incorrect responses”, though no other psychomotor impacts were observed (Dick <i>et al.</i>, 1989). Mastushita <i>et al.</i> (1969) reported that among male volunteers, those exposed to 250 ppm acetone reported mild increases in nose and throat irritation while those exposed to 500 ppm experienced strong irritation. Those volunteers exposed to 500 ppm had significantly longer reaction times to visual stimulus, though the results were “highly variable” (Matsushita <i>et al.</i>, 1969). Significant differences in odor and irritant perception exist among those routinely exposed and naïve subjects. Acetone exposure habituation has been noted in several studies and the TLV was designed to minimize irritative symptoms those not routinely exposed.</p>
2-butanone (in ACGIH as methyl ethyl ketone; MEK) [78-93-3]	200 ppm (TWA) 300 ppm (STEL)	<ul style="list-style-type: none"> • Krasavage, W.J.; O'Donoghue, J.L.; Divincenzo, G.D.: Ketones. In: Patty's Industrial Hygiene and Toxicology, 3rd Rev. ed., Vol. 2C, Toxicology, pp. 4728-4733. G.D. Clayton and F.E. Clayton, Eds. John Wiley & Sons, New York (1982). • Patty, F.A.; Schrenk, H.H.; Yant, W.P.: Acute Response of Guinea Pigs to Vapors of Some New Commercial Organic Compounds — VIII. Butanone. U.S. Public Health Rep. 50:1217-1228 (1935). • Altenkirch, H.; Stoltenburg, G.; Wagner, H.M.: Experimental Studies on Hydrocarbon Neuropathies Induced by Methyl Ethyl 	<p>TLV from 1992. Basis upper respiratory tract irritation; CNS and PNS impairment. Signs of eye and nasal irritation developed rapidly in guinea pigs exposed at 10,000 ppm; narcosis occurred after 5 hours (Krasavage <i>et al.</i>, 1982). Patty <i>et al.</i> (1935) found that guinea pigs tolerated 3000 ppm for several hours, whereas humans found this concentration irritating to the nose and eyes. Subchronic animal studies did not see neuropathy.</p>

Chemical Name [CAS]	TLV	References	Notes
		<p>Ketone (MEK). J. Neurol. 219:159-170(1978).</p> <ul style="list-style-type: none"> • Spencer, P.S.; Shaumberg, H.H.: Feline Nervous System Response to Chronic Intoxication with Commercial Grades of Methyl n-Butyl Ketone, Methyl Isobutyl Ketone, and Methyl Ethyl Ketone. Toxicol. Appl. Pharmacol. 37:301-311 (1976). 	
2-heptanone [110-43-0]	50 ppm (TWA)	<ul style="list-style-type: none"> • Johnson, B.L.; Setzer, J.V.; Lewis, T.R.; Hornung, R.W.: An Electrodiagnostic Study of the Neurotoxicity of Methyl n-Amyl Ketone. Am. Ind. Hyg. Assoc. J. 39:866-872(1978). • Specht, H.; Miller, J.W.; Valaer, P.J.; Sayers, R.R.: Acute Response of Guinea Pigs to the Inhalation of Ketone Vapors. U.S. National Institutes of Health Bulletin No. 176. U.S. Public Health Service, Washington, DC (1940). 	TLV from 1980. At the time of the TLV derivation, little to no human data existed and data from animals was thin. When Johnson <i>et al.</i> (1978) measured motor conduction velocities in the sciatic-tibial and ulnar nerves in 2-heptanone exposed rats and monkeys, they found no evidence of negative health impacts. The exposure occurred for 6 hours/day, 5 days/week for nine months at 0, 131, and 1025 ppm (Johnson <i>et al.</i> , 1978). When guinea pigs were exposed to 1500 ppm of methyl n-amyl ketone, they showed signs of mucous membrane irritation while at 2000 ppm they showed signs of narcosis (Specht <i>et al.</i> , 1940). A TLV was conservatively assigned at 50 ppm to avoid eye and skin irritation.
methyl isobutyl ketone (MIBK) [108-10-1]	20 ppm (TWA) 75 ppm (STEL)	<ul style="list-style-type: none"> • Armeli G; Linari F; Martorano G: Clinical and hematochemical examinations in workers exposed to the action of a ketone (MIBK) repeated after five years (in Italian). Lav Umano 20:418^123 (1968). • Iregren A; Tesarz M; Wigaeus-Hjelm E: Human experimental MIBK exposure: 	TLV from 2010. Twelve volunteers (six male, six female) were exposed to 49 ppm MIBK for two hours with 1.5 hours of exercise and half an hour of rest (Iregren <i>et al.</i> , 1993). Volunteers were evaluated for changes in their heart rate, their simple reaction time, their ability to solve simple arithmetic problems, their self-reported mood, and asked to respond to an acute symptom

Chemical Name [CAS]	TLV	References	Notes
		<p>effects on heart rate, performance and symptoms. Environ Res 63:101-108 (1993).</p> <ul style="list-style-type: none"> Linari F; Perrelli G; Varese D: Clinical observations and blood chemistry tests among workers exposed to the effect of a complex ketone—methyl isobutyl ketone (in Italian). Arch Sci Med (Torina) 117:226-237 (1964). Silverman L; Schulte HF; First MW: Further studies on sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 28:262-266 (1946). 	<p>questionnaire (Iregren, <i>et al.</i>, 1993) Volunteers reported more intense central nervous system symptoms) but no other endpoint had statistically significant results when compared to controls' responses (Iregren <i>et al.</i>, 1993). Subjects reported 200 ppm of MIBK was irritating to the eyes and concentrations over 200 ppm irritated the nose and throat (Silverman <i>et al.</i>, 1946). Workers exposed to 500 ppm MIBK for 20 – 30 minutes a day reported eye, nose, and throat irritation (Linari <i>et al.</i>, 1964). Five years later when the same lab was resampled, peak exposures were measured at 100 ppm and only 1/19 of the original cohort reported continuing eye irritation (Armeli <i>et al.</i>, 1968).</p>
Stoddard solvent [8052-41-3]	100 ppm (TWA)	<ul style="list-style-type: none"> U.S. National Institute for Occupational Safety and Health/U.S. Occupational Safety and Health Administration: Occupational Health Guideline for Stoddard Solvent (September 1978). In: Occupational Health Guidelines for Chemical Hazards. F.W. Mackison, R.S. Stricoff, L.J. Partridge, Jr., Eds. DHHS (NIOSH) Pub. No. 81-123; NTIS Pub. No. PB-83-154- 609. U.S. National Technical Information Service, Springfield, VA (1981). U.S. National Institute for Occupational Safety & Health: Criteria for a Recommended Standard - Occupational Exposure to Refined Petroleum Solvents. DHEW (NIOSH) Pub. No. 77-192; 1977. In: NIOSH Criteria Documents Plus CD-ROM. 	<p>TLV from 2001. Basis, from toxicity data of the major ingredients of Stoddard solvent, is the irritative and narcotic effects of its vapors (U.S. NIOSH, 1981, 1997). Data from controlled inhalation of Stoddard solvent by Carpenter <i>et al.</i> (1975) and Nelson <i>et al.</i>(1943) tend to confirm this value. Reports of renal injury in rats from repeated exposures at 330 ppm provide additional evidence for a TLV-TWA of no more than 100 ppm. Sufficient data were not available to recommend Skin, SEN, or carcinogenicity notations or a TLV-STEL.</p>

Chemical Name [CAS]	TLV	References	Notes
		<p>DHHS (NIOSH) Pub. No. 97-106; NTIS Pub. No. PB-502-082. U.S. National Technical Information Service, Springfield, VA (1997).</p> <ul style="list-style-type: none"> • Carpenter, C.P.; Kinkead, E.R.; Geary, Jr., D.L.; et al.: Petroleum Hydrocarbon Toxicity Studies. III. Animal and Human Response to Vapors of Stoddard Solvent. Toxicol. Appl. Pharmacol. 32:282-297 (1975). • Nelson, K.W.; Ege, J.F.; Ross, M.; et al.: Sensory Response to Certain Industrial Solvent Vapors. J. Ind. Hyg. Toxicol. 25:282-285 (1943). 	

*OTO indicates ototoxicity, when a chemical can cause hearing loss either by itself or in combination with noise. For chemicals identified as ototoxins, exposed individuals may need enrolled in hearing conservation programs even in the absence of noise in excess of 85 dBA

4.5 Aerosols

Information on the effect of aerosols on visual performance attributes was limited. Aerosol size-specific effects for individual chemicals, such as metals, are typically captured in the TLVs for those chemicals as shown in Appendix A3. However, there are some recommendations for general aerosol exposure that are relevant to visual performance. USAPHC developed MEGs for particulate matter with aerodynamic diameters of ≤ 10 and ≤ 2.5 μm , PM_{10} and $\text{PM}_{2.5}$, respectively (USAPHC, 2014).

For short term exposures (24 hours), the hazard severity is ranked as follows:

- Critical at PM_{10} ($500 \mu\text{g}/\text{m}^3$) and at $\text{PM}_{2.5}$ ($600 \mu\text{g}/\text{m}^3$). Above these levels, personnel are expected to experience very notable eye, nose, and throat irritation and respiratory effects. Visual acuity is impaired, as is overall aerobic capacity. Some personnel will not be able to perform duties or aerobic activities.
- Marginal at PM_{10} ($250 \mu\text{g}/\text{m}^3$) and $\text{PM}_{2.5}$ ($420 \mu\text{g}/\text{m}^3$). Above these levels up to the “Critical” level, many personnel are expected to experience notable eye, nose, and throat irritation and some respiratory effects. Some lost duty days are expected. Significant aerobic activity will increase risk.
- Negligible at PM_{10} ($65 \mu\text{g}/\text{m}^3$) and $\text{PM}_{2.5}$ ($250 \mu\text{g}/\text{m}^3$). Above these levels up to the “Marginal” level, a few personnel may experience eye, nose, or throat irritation; most personnel will experience only mild effects.

The above recommendations do not necessarily account for nanoparticle exposures. Nanoparticles constitute those particles for which one dimension measures less than 100 nanometers. Research has shown that the defining properties of nanoparticles are their large surface area-to-volume ratio (Tran, 2000) and their unique biological reactivity due to their size (Borm and Donaldson, 2007). Critically, the same chemical which is inert in particle sizes in the microscale and larger (e.g. titanium dioxide), may become reactive in the nanoscale (Borm and Donaldson, 2007). At present, the ACGIH TLV for nanoscale titanium dioxide is the only TLV for nanoparticulate (ACGIH, 2022), but this TLV is not based on any effects on vision.

4.6 Aliphatics and Miscellaneous

A total of five miscellaneous chemicals and no aliphatics were identified that have ACGIH TLVs and documentation of short-term impacts on visual performance attributes (Table 11). ACGIH (2022) specifically cited irritancy to the eyes as a basis for the TLVs of sodium hydroxide, asphalt, and phenol. The TLV for naphthalene was derived to protect against cataract formation associated with human and animal naphthalene exposure, while the TLV for styrene was designed, in part, to protect against effects on color vision (ACGIH, 2022).

Table 11. Summary of ACGIH TLVs and Documentation for Aliphatics and Miscellaneous Chemicals with Short-Term Effects on Visual Performance Attributes

Chemical Name [CAS]	TLV	References	Notes
sodium hydroxide [1310-73-2]	2 mg/m ³ (ceiling)	<ul style="list-style-type: none"> • Patty, F.A.: Sodium Hydroxide. In: Industrial Hygiene and Toxicology, Vol II, pp. 560-561. F.A. Patty, Ed. Interscience, New York (1949). 	TLV from 1992. Patty (1949) reported that exposure to 2 mg/m ³ of aerosol sodium hydroxide was the threshold for upper respiratory and eye irritation, but not exceedingly irritating. The TLV uses this threshold as the ceiling value, meaning it is the maximum concentration ever to be encountered in a workplace.
asphalt (bitumen fumes as benzene-soluble aerosol) [8052-42-4]	0.5 mg/m ³ , inhalable fraction (TWA)	<ul style="list-style-type: none"> • Chase, R.M.; Liss, G.M.; Cole, D.C.; Heath, B.: Toxic Health Effects Including Reversible Macrothrombocytosis in Workers Exposed to Asphalt Fumes. Am. J. Ind. Med. 25: 279-289 (1994). • Gamble, J.F.; Nicolich, M.J.; Barone, N.J.; Vincent, W.J. Exposure response to asphalt fumes with changes in pulmonary function and symptoms. Scand J Work Environ Health. 23(3): 186-206 (1999). • Norseth, T; Waage, J.; Dale, I.: Acute Effects and Exposure to Organic Compounds in Road Maintenance Workers Exposed to Asphalt. Am. J. Ind. Med. 20: 737-744 (1991). 	TLV from 2000 with a basis meant to prevent eye and respiratory irritation. When asphalt was heated to >150°C, workers reported more irritation (Norseth <i>et al.</i> , 1991). When exposed to 0.5 – 1.3 mg/m ³ of asphalt aerosols, workers complained of mucous membrane irritation (Chase <i>et al.</i> , 1994). Gamble <i>et al.</i> (1999) wrote that workers did not report many symptoms when their asphalt aerosol exposure was below 0.5 mg/m ³ . The TLV recommends processes avoid heating asphalt above 150°C to minimize the change of irritation.
naphthalene [91-20-3]	10 ppm (TWA)	<ul style="list-style-type: none"> • Frasch HF; Barbero AM; Alachkar H; <i>et al.</i> 2007: Skin penetration and lag times for neat and aqueous diethylphthalate, 1,2-dichloroethane and naphthalene. Cutan Ocul Toxicol 26:147-160. 	TLV from 2014. Basis is for upper respiratory tract irritation, ocular effects and hemolytic anemia. Effects were very species-specific. The LC ₅₀ for rats exposed by inhalation for 8 hours

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> • Walker JD; Whittaker C; McDougal JN 1996: Role of the TSCA interagency testing committee in meeting the US government data needs: Designating chemicals for percutaneous absorption rate testing. In: <i>Dermatotoxicology</i>, 5th Ed. Taylor and Francis, Washington, DC. • US Agency for Toxic Substances and Disease Registry (US ATSDR 2005): Toxicological Profile for Naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene. US Department of Health and Human Services, ASTDR, Atlanta, GA. • US Environmental Protection Agency (US EPA) 1998: Toxicological Review of Naphthalene. US EPA, Washington, DC. • US Environmental Protection Agency (US EPA) 2004: Toxicological Review of Naphthalene: External Review Draft. (CAS No 91-20-3) NCEA-S-1707. US EPA, Washington, DC. • US National Toxicology Program (US NTP) 2000: Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene (CAS No 91-20-3) in F344/N Rats (Inhalation Studies). NTP TR-500. NIH Publication No 01-4434. US National Institute of Health, ResearchTriangle Park, NC. 	<p>was 500 mg/m³ (96 ppm) (U.S. NTP, 2000). Mice inhaling 10 ppm naphthalene for 4 hours showed swollen and vacuolated Clara cells in their airways, while slight reductions were attributed to 2 ppm (no quantitative or statistical analyses) in proximal airway Clara cell mass (West <i>et al.</i>, 2001). No such changes were seen in rats inhaling up to 110 ppm for 4 hours (West <i>et al.</i>, 2001). Hematological effects and cataracts are two other adverse effects associated with naphthalene exposure of humans and laboratory animals. It is generally believed that 1,2-naphthoquinone, a metabolic product of naphthalene is an important cause of each condition. Cataracts were associated with naphthalene exposure in 8 of 21 workers in an Italian dye plant (Ghetto and Mariani, 1956), however exposures of these employees who melted naphthalene in open vats were not determined. However, oral administration of high doses (e.g., 0.5 to 1.0 g/kg for 5 days to 6 weeks) has produced cataracts in several species of laboratory animals (as reviewed in U.S. ATSDR, 2005; U.S. EPA, 1998, 2004).</p> <p>A Skin notation is recommended, because powdered naphthalene has been shown to penetrate excised skin at a rapid rate that may result in moderate internal doses under extreme dermal exposure conditions (Frasch <i>et al.</i>, 2007; Walker <i>et al.</i>, 1996).</p>

Chemical Name [CAS]	TLV	References	Notes
		<ul style="list-style-type: none"> West JA; Pakehham G; Morin D; <i>et al.</i> 2001: Inhaled naphthalene causes dose dependent Clara cell cytotoxicity in mice but not in rats. <i>Toxicol Appl Pharmacol</i> 173:114-119. 	
phenol [108-95-2]	5 ppm (TWA)	<ul style="list-style-type: none"> Angel, A.; Rogers, K.J.: An Analysis of the Convulsant Activity of Substituted Benzene in the Mouse. <i>Toxicol. Appl. Pharmacol.</i> 21:214-229 (1972) Deichmann, W.B.; Keplinger, M.L.: Phenols and Phenolic Compounds. In: <i>Industrial Hygiene and Toxicology</i>, Vol. 2, pp. 1363-1408. D.W. Fassett and D.D. Irish, Eds. Interscience Publ., New York (1962) Deichmann, W.B.; Kitmiller, K.V.; Witherup, S.: Phenol Studies. VII. Chronic Phenol Poisoning with Special Reference to the Effects upon Experimental Animals of the Inhalation of Phenol Vapor. <i>Am. J. Clin. Pathol.</i> 14:273-277(1944) Pullin, T.G.; Pinkerton, M.N.; Johnston R.V.; Kilian, D.J.: Decontamination of the Skin of Swine Following Phenol Exposure: A Comparison of the Relative Efficiency of Water versus Polyethylene Glycol/Industrial Methylated Spirits. <i>Toxicol. Appl. Pharmacol.</i> 43:199-206 (1978) 	TLV from 1996. Basis for the TLV was to minimize the potential for eye and respiratory irritation, and cardiovascular, hepatic, renal, and neurologic toxicity. Has been found in automobile exhaust and in cigarette smoke. Acute oral LD ₅₀ (Lethal dose 50%) of phenol in rats, dogs, rabbits, and monkeys is about 530 mg/kg (Deichmann and Keplinger, 1962). Animals show an initial CNS stimulation, which can proceed to convulsions (Angel and Rogers, 1972). Absorption efficiency through the skin is approximately equal to that by inhalation (Pullin <i>et al.</i> , 1978 and Deichmann, Kitmiller, and Witherup, 1944).
styrene [100-42-5]	10 ppm (TWA)	<ul style="list-style-type: none"> Campagna D., Mergler D., Huel G., <i>et al.</i> Visual dysfunction among styrene-exposed 	TLV from 2020. TLV designed to minimize high frequency hearing loss due to synergistic effect of

Chemical Name [CAS]	TLV	References	Notes
	20 ppm (STEL) OTO*	<p>workers. Scand J Work Environ Health 21(5): 382-390 (1995).</p> <ul style="list-style-type: none"> • Campagna D., Gobba F., Mergler D., <i>et al.</i> Color vision loss among styrene-exposed workers neurotoxicological threshold assessment. Neurotoxicology 17(2): 367-373 (1996). • Eguchi T., Kishi R., Harabuchi I, e al. Impaired color vision among workers exposed to styrene: relevance of a urinary metabolite. Occup Environ Med 52: 534-538 (1995). • Gobba F., Galassi C., Imbriani M. <i>et al.</i> Acquired dyschromatopsia among styrene-exposed workers. J Occup Med 33: 761-765 (1991). • Gobba F., Cavalleri A. Kinetics of Urinary Excretion and Effects on Colour Vision after Exposure to Syrene. In: Butadiene and Styrene: Assessment of Health Hazards, pp 79-88. M. Sorsa, K Peltonen, H Vainio <i>et al.</i> (Eds). IARC Scientific Publications No 27. IARC, Lyon, France (1993). • Oltramare M., Desbaumes E., Imhoff C., <i>et al.</i> Toxicology of Monomeric Styrene—Experimental and Clinical Studies in Man. Editions Medicine et Hygiene, Geneva, Switzerland (1974). • Sisto R., Cerini L., Gatto MP., <i>et al.</i> Otoacoustic emission sensitivity to 	noise and styrene exposure, protect against upper respiratory irritation, avoid color vision effects, and mitigate central and peripheral nervous system effects.

Chemical Name [CAS]	TLV	References	Notes
		<p>exposure to styrene and noise. J Acoust Soc Am 134(5) 3739-3748 (2013).</p> <ul style="list-style-type: none"> • Triebig G., Bruckner T., Seeber A. Occupational styrene exposure and hearing loss: a cohort study with repeated measurements. Int Arch Occup Environ Health 82(4): 463-480 (2009). 	

5.0 DISCUSSION

5.1 Summary of Chemical Effects on Visual Attributes

A systematic review of the scientific literature was conducted on aldehydes, metals, and toxic gases and vapors found in AF occupational environments and their impacts on visual performance attributes of importance to AF occupations. To help link chemical exposure to the performance attributes, relevant toxicity search terms were also used in the literature search. The list of chemicals selected for review was 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. Additionally, for solvents, aerosols, aliphatics and miscellaneous chemicals on the list, ACGIH documentation was reviewed for any studies pertaining to short-term transient effects. Military exposure guidelines were also consulted, where applicable.

Across all classes of chemicals, eye irritation was the most commonly cited effect of exposure. Although not specifically associated with a single listed visual attribute of interest, irritation of the eyes could potentially impact multiple attributes through vision blurring and eye discomfort. Furthermore, severe or prolonged exposure to irritant chemicals could result in damage to the cornea (Fox and Boyes, 2019). Occupations that require prolonged visual focus may be most sensitive to productivity decrements brought on by eye irritation from chemical exposure. Neurotoxicity was the other major effect of exposure shared between multiple classes of chemicals, with specific solvents, metals, and miscellaneous chemicals associated with neurotoxic effects that impair certain aspects of the visual sensory system. Damage to neural structures including the retina and central visual pathway can impact color vision as well as contrast sensitivity (Fox and Boyes, 2019). A summary of effects by chemical class are listed in the remainder of this section.

Aldehydes

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 BF and lacrimation, were reported at 1.7 ppm (Arts *et al.*, 2006). These values are well above the ACGIH (2022) STEL and TLV for formaldehyde of 0.3 ppm and 0.1 ppm, respectively, suggesting that there were no pertinent studies found in the literature indicating that eye irritancy occurs at formaldehyde exposure concentrations at or lower than existing OELs.

One study on the effects of methacrolein exposure found increased BF among volunteers at an airborne concentration of 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 that the irritative effect may be a common feature of

exposure to this class of chemicals, in addition to indicating that certain aldehydes may be more irritative than formaldehyde. The commonality of eye irritant effects among aldehydes is further supported by acetaldehyde and valeraldehyde having TLVs that are based on eye irritancy (ACGIH, 2022).

Toxic Gases and Vapors

Occupational exposure to indoor concentrations of CO₂ greater than 800 ppm resulted in reported symptoms of eye irritation (Tsai, Lin, and Chan, 2012). Although 800 ppm is well below OELs for CO₂ that are based on its asphyxiant properties, with an ACGIH (2022) TLV of 5000 ppm and STEL of 30,000 ppm (3%), the study by Tsai, Lin, and Chan (2012) did not monitor for any other chemicals besides CO₂ and PM_{2.5}. Therefore, the association between increased CO₂ levels and eye irritation could have been a proxy for increased levels of other gases and vapors that were not monitored in the study rather than CO₂ being the causal agent. Increased eye irritation was also seen with increased CO₂ concentrations between 2% and 32% during a two-minute exposure. However, 2% is approaching the ACGIH STEL for asphyxiation, so irritancy at this level of exposure would be a secondary concern to oxygen deprivation. In summary, there is evidence for CO₂ as an eye irritant, but it is unclear if this occurs at a low enough level of exposure at which other more life-threatening toxicity is not a concern.

The exposure limits for sulfur dioxide vary between 0.25 ppm and 5 ppm. The ACGIH STEL is 0.25 ppm (ACGIH 2022). In the study by van Thriel *et al.* (2010), no sensory effects of acute sulfur dioxide exposures up to 2 ppm for 4 hours could be measured. The results of that study suggest that the ACGIH STEL would be protective against irritant effects on the eyes, however, it is unclear if irritancy would occur at higher exposure levels permissible by other agencies.

Chemical warfare studies indicated acrolein causes eye irritation and lacrimation in humans at 0.25 ppm (Prentiss, 1937). Humans experience intense irritation from acrolein exposure at 5.5 ppm and death after a short time at levels above 10 ppm (Henderson and Haggard, 1943). ACGIH suggests a ceiling OEL of 0.1 ppm to prevent eye and respiratory irritation. Although classified as a toxic vapor, acrolein is also an aldehyde and the relatively potent irritancy is consistent with formaldehyde and methacrolein as discussed previously.

Metals

Only one of the studies for metal exposures met the inclusion criteria that addressed visual attributes. In this study, MnO₂ nanoparticles translocated from the airways throughout the bodies of exposed rats, and were capable of crossing the blood-brain-barrier (Sárközi *et al.*, 2009). Through electrophysiology tests, Sárközi *et al.* (2009) determined that these particles delayed evoked potentials in visual cortex, which suggested an impact on visual attributes. Although the findings in this study occurred with a relatively high concentration (~5 mg/kg) daily exposure to MnO₂, it does highlight the neurotoxic potential of MnO₂ inhalation exposure with the visual cortex being a possible target. However, the functional consequences of these effects and a determination of their occurrence at more relevant occupational exposure levels remains to be investigated.

The Sárközi *et al.* (2009) study focused specifically on metal nanoparticle exposure. Nanoparticles possess unique features which impact their toxicity, including the ability to

translocate throughout the body and their high surface area to volume ratio. While it is clear that nanoparticles present a unique risk to human health, there is a dearth of information on the specific implications of metal nanoparticles on vision and a lack of nanoparticle exposure data in AF processes.

Other metals, including lead, are known to be neurotoxic to the visual system, but no studies were included in the final literature search results. One possible explanation for this absence is the exclusion criteria of “chronic” effects of exposure, and that many environmental and occupational lead exposure studies are concerned with lower-level, longer-term lead exposures. Investigation of visual effects may not exist for other metals of interest because of their well-characterized toxicity to other target organs even at very low exposure concentrations.

Solvents

Solvents represented the largest class of chemicals with documentation of short-term exposure impacts on visual performance attributes. There was evidence of eye irritation associated with exposure to all of the solvents with TLV documentation listed for visual effects, with many of these chemicals having ACGIH TLVs with a basis of eye irritation specifically cited. In addition to irritancy, exposure to methanol can also cause damage to the ganglion cells of the retina. This same effect also occurs with methyl acetate exposure because the chemical is rapidly metabolized to methanol in the body. Toluene exposure has been shown to impact color vision.

While the irritant effects and specific effects on peripheral nervous system of the eye were captured in the review, similar to the metals, many solvents are neurotoxic and could impact vision through additional effects on the central or peripheral nervous systems. Some of these effects may not be captured in the TLV documentation because either 1) these effects on vision occur at higher levels than toxic effects on other target organs or 2) specific testing has not been performed to determine if subtle effects on vision that are not captured in measures of overt visual impairment might occur at lower levels of exposure.

Aerosols

Eye irritation is associated with particle exposures above 250 $\mu\text{g}/\text{m}^3$ for PM_{10} and 420 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ according to MEGs developed by USAPHC (2014). These concentrations are well below ACGIH’s recommendations for exposure to non-soluble particles that don’t have existing TLVs (3 mg/m^3 for respirable particles and 10 mg/m^3 for inhalable particles), so there appears to be potential for irritancy even at concentrations below the OEL that were designed by ACGIH to be protective for other health effects.

No vision-specific TLVs currently exist for nanoparticle exposure. During a scoping literature review for select metals exposure and their impact on performance attributes, researchers noted that many recent articles studied metal nanoparticle exposure (Steele *et al.*, 2021), but only one was identified that focused on the effects of metal nanoparticle exposure on vision (Sárközi *et al.*, 2009). As engineered nanoparticles enter more sectors of the workplace, the number of nanoscale-specific TLVs is likely to grow.

Aliphatics and Miscellaneous

Consistent with the other classes of chemicals, a selection of the miscellaneous chemicals had TLV documentation that indicated an association with eye irritation. None of the aliphatics had any exposure-related association with effects on vision, however, similar to the solvent category, some of these effects may not have been captured in the TLV because they either occur at higher levels than other toxic effects, or those chemicals haven't been tested for vision-specific toxicity.

Naphthalene exposure was associated with formation of cataracts, although the evidence of this occurring is from a case study (Ghetti and Mariani, 1956) as well as animal studies occurring at relatively high concentrations (as reviewed in U.S. ATSDR, 2005; U.S. EPA, 1998, 2004). It is unclear whether the effects on vision occur at concentrations comparable, or lower to, effects on the respiratory system that have been demonstrated at the lower ppm levels (West *et al.*, 2001). Color vision changes among styrene-exposed workers have been documented in a number of studies (Campagna *et al.*, 1996; Campagna *et al.*, 1995; Eguchi *et al.*, 1995; Gobba *et al.*, 1991; Gobba and Cavalleri, 1993) and the styrene TLV is designed to protect against this effect.

5.2 Limitations

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 the questions covering multiple performance attributes/outcomes and how multiple different chemical exposures may affect them were used to form the protocol's inclusion and exclusion criteria. Furthermore, the review covered both human and animal literature. Similar systematic reviews on such a broad range of exposures and effects were not found in the literature. Because of the relatively large scope of the systematic review, AI capabilities were required to complete the analyses of thousands of articles within a reasonable timeframe. DistillerSR software was selected from an internal review of both open source and commercial systematic review software packages due to its AI feature, Daisy, which used the PRISMA format (Moher *et al.*, 2009). It is well known that the more specific the study question, the more precise 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 included as much published data/information as would be selected for inclusion if each chemical and attribute was reviewed separately. 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.

A risk of bias analysis was completed for the studies that were included from the literature review involving the DistillerSR software. The included studies had an average risk of bias of 29%, with a range from 16% to 54%. The wide range was unsurprising because many of the studies selected were not designed as randomized control trials. Several were *in vivo* animal studies or observational human studies, which were likely necessary to answer the respective research questions because of ethical limitations on controlled human exposures to potentially hazardous chemicals. While many of the included studies demonstrated a risk of bias near or below the average, a few of the studies of formaldehyde exposure and eye irritation had much higher bias risks in the 40-50% range (Arts *et al.*, 2006; Sekeryapan *et al.*, 2011; Kim *et al.*,

1999). Although the risk of bias values were elevated for these studies, their findings were still in line with the other formaldehyde exposure literature.

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 in the final literature review analysis. Short-term exposures can induce transient visual performance effects that are not well documented for many chemicals. The lack of understanding of the effects on visual performance could be due to the focus on more debilitating effects of these chemicals on other target organs, and research into more subtle effects on visual performance would be warranted for chemicals that plausibly could cause these effects. Chemicals with chronic effects on vision might also have underappreciated short-term effects on performance attributes that haven't been sufficiently investigated because of research interest in more overt effects on vision.

The TLV review utilized in this study for certain classes of chemicals also had limitations. The review of TLVs was intended to readily identify chemicals of interest to the AF that have well-established effects on visual performance attributes, but would not have captured chemicals that didn't have sufficient information for ACGIH to be able to derive a TLV. For example, emerging chemicals like nanoparticles, or niche chemicals that are only primarily of interest to specialized organizations like the AF are not necessarily going to have sufficient available information to derive a TLV, and therefore would not be included in the reviews based on ACGIH documentation. However, the TLV review may still have been more inclusive, because ACGIH's TLV determination includes comprehensive documentation of longer-term effects as well as the effects of short-term and acute exposures.

6.0 CONCLUSIONS AND RECOMMENDATIONS

There is a need for data about exposures to chemicals of interest to the AF and their impacts on visual performance attributes. The maintenance of the visual attributes described in Table 1 associated with optimal performance in many AF occupations may not necessarily be a focus for occupational health outside of the military, meaning that these endpoints may not be a priority for occupational exposure studies outside of the DoD. Occupational risk management in industry and academia has predominantly focused on identifying and mitigating chemical exposures that are either life-threatening or debilitating to a specific physiological function, rather than those that only impact performance while still allowing an individual to live an otherwise healthy, normal life. 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 could be negative impacts beginning at lower levels of exposure than those associated with traditional toxic effects. In a military environment, where small decrements to performance attributes can have disproportionate impacts on mission success, the AF may not be able to rely on industrial and academic partners to spearhead research in this area. In order to best serve Airmen and Guardians, the AF may need to conduct key studies in this area of interest.

In addition to performance attributes being unique to the AF interests, many of the 126 chemicals included in the AF priority list are exposures that are unique to the AF or aviation environments. Therefore, the knowledge base on the effects of exposure to these chemicals also may be limited because of a lack of broad interest in industry and academia due to exposure scenarios or exposure levels that only exist in AF occupations. In order to predict potential effects, identified as AF-relevant but lacking available data in published literature, *in silico* quantitative structure activity relationship models could be used for extrapolating effects based upon chemical structural similarities.

The bulk of the research cited in the aldehyde section of this report pertains to formaldehyde. The lack of studies on other aldehydes does not necessarily mean that these aldehydes do not have effects on the visual attributes of concern, only that these effects might not have been investigated in research studies. Because all of the chemicals within this class contain the same functional group, it is reasonable to hypothesize that the other chemicals of interest in this class share similar toxicity with formaldehyde. Additionally, acetaldehyde, valeraldehyde, and crotonaldehyde (listed with the toxic gases and vapors) have TLVs with a basis of eye irritation (ACGIH, 2022) even though no literature search results for these aldehydes were selected for inclusion in the review. Therefore, it is plausible that other aldehydes of interest to the AF could be eye irritants. Further research is needed to determine if indeed they cause this effect, and if they do, at what level of exposure.

Only one article was included in the metal class on potential visual effects of exposure to MnO₂, which were attributed to changes seen in neurological responses measured in the visual cortex of the brain. However, it is unclear what implications these changes would have on functional visual attributes. Furthermore, studies on the effects of neurotoxic metals such as lead were not

included in the final literature search results, which might be a result of the exclusion of “chronic” effects from the review. However, subtle functional changes in the detection or processing of visual images may result from acute or subchronic exposure to lead or other neurotoxic metals, and this has been proposed as a possible early marker for the toxic insult of metals to the visual system (Fox and Boyes, 2019). More research may be warranted to determine if there are early indicators of neurotoxicity that can be measured from effects of metal exposure on visual performance attributes.

As nanoparticles are an active area of research in human health and exposure, it is anticipated that additional AF-relevant health effects will come to light. Currently, the AF does not identify processes which could generate nanoparticles nor sample for them. The AF will not be able to capitalize on current and future nanoparticle research without the ability to understand how nanoparticles apply to AF occupational environments. As a first step, any processes which may generate nanoparticles (e.g. firing ammunition, welding) could be identified and prioritized for sampling, similar to currently conducted particle-size selective sampling (e.g. respirable, inhalable, thoracic).

In the absence of truly comprehensive data for the effects of all 126 chemicals of interest on visual performance attributes, this report can be a first step in the development of risk mitigation strategies the AF can undertake to reduce Airmen and Guardian exposure to chemicals of concern. Appendix A lists exposure locations for some chemicals, and with the identification in this report and recent exposure assessments, exposure scenarios can be more readily investigated and mitigation strategies developed to reduce effects where impacts on visual performance are anticipated.

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APPENDIX A: Exposure Limits for Aldehydes, Toxic Gases and Vapors and Metals

Appendix A1. Aldehydes of Interest to the Air Force based on Field Data and Chemical Inventory Usage

Chemical Abstract Service Number (CAS #)	Chemical Name	ACGIH TLV	Potential AF Exposure Source* (Shop - Actual Terminology)
50-00-0	formaldehyde	0.1 ppm	Measured in the field
75-07-0	acetaldehyde	25 ppm (ceiling)	Measured in the field
100-52-7	benzaldehyde		Measured in the field
123-72-8	butyraldehyde		Measured in the field
107-22-2	glyoxal	0.1 mg/m ³ IFV	Measured in the field
590-86-3	isovaleraldehyde		Measured in the field
123-38-6	propionaldehyde	20 ppm	Measured in the field
110-62-3	valeraldehyde	50 ppm	Measured in the field
104-87-0	p-tolualdehyde		Measured in the field
529-20-4	o-tolualdehyde		Measured in the field
620-23-5	m-tolualdehyde		Measured in the field
78-85-3	methacrolein		Measured in the field
78-98-8	methylglyoxal		Measured in the field

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; CAS = chemical abstract services; IFV = inhalable fraction and vapor; TLV = threshold limit value

*Process and locations where select metals are used in the AF based on EESOH-MIS

Appendix A2. Toxic Gases and Vapors of Interest to the Air Force based on Field Data and Chemical Inventory Usage

Chemical Abstract Service Number (CAS #)	Chemical Name	ACGIH TLV	Potential AF Exposure Source* (Shop - Actual Terminology)
124-38-9	carbon dioxide (CO ₂)	5000 ppm (TWA) 30,000 ppm (STEL)	Fixing bomb lift brakes, crane maintenance, cleaning and sealing aviation ground equipment (AGE), human respiration
74-98-6	propane	vacated	Engine repair and maintenance, thread & gasket sealing
7664-93-9	sulfuric acid (H ₂ SO ₄)	0.2 mg/m ³ (TWA) thoracic particulate mass	Testing for halogens in used oil, battery maintenance, AGE maintenance
74-86-2	acetylene	vacated	Welding

Chemical Abstract Service Number (CAS #)	Chemical Name	ACGIH TLV	Potential AF Exposure Source* (Shop - Actual Terminology)
7440-37-1	argon	vacated	In the onboard oxygen generating system (OBOGS), welding, soldering, and brazing, overhauling automatic cryogenic rectifier
630-08-0	carbon monoxide (CO)	25 ppm (TWA)	Air cart oxygen sensor, measured in the field
74-85-1	ethylene	200 ppm (TWA)	Measured in the field
115-07-1	propylene	500 ppm (TWA)	Carpentry, airfield construction, measured in the field
74-84-0	ethane	vacated	Measured in the field
10102-43-9	nitric oxide (NO)	35 ppm (TWA)	Measured in the field
107-02-8	acrolein	0.1 ppm (Ceiling)	Measured in the field
4170-30-3	crotonaldehyde	0.3 ppm (ceiling)	Measured in the field
10102-44-0	nitrogen dioxide (NO ₂)	0.2 ppm (TWA)	Measured in the field
7446-09-5	sulfur dioxide (SO ₂)	0.25 ppm (STEL)	Measured in the field

Abbreviations: TLV = threshold limit value; TWA = time weighted average; STEL = short-term exposure limit

*Process and locations where select metals are used in the AF based on EESOH-MIS

Appendix A3. Metals of Interest to the Air Force based on Field Data and Chemical Inventory Usage

Chemical Abstract Service Number (CAS #)	Chemical Name	ACGIH TLV	Potential AF Exposure Source (Process)	Potential AF Exposure Source (Shop - Actual Terminology)⁺
13463-67-7	titanium dioxide	NP: 0.2 mg/m ³ * Fine: 2.5 mg/m ³ *	Paint maintenance; building maintenance; F-16 wing change; fuel system maintenance; F-22 injection of non-curing sealant	Hospital maintenance contractor; threat training maintenance; fuels
7439-92-1	lead	0.05 mg/m ³	Fuel system maintenance; F-35 qrip installation; general aircraft maintenance uplock actuator; oil servicing; solder process for JT3 shops	Fuels; TES instrumentation; bolt AMU; lightning AMU; t-birds joint shop; JT4 LLC;
1313-13-9	manganese dioxide		F-16 wing change; fuel system maintenance; aircraft fuel cell cavity/tank repair; adhering, sealing; sealing F-16 strut assy.	Fuels; B252 sheet metal (F-22 a lo); phase-ar-wheel & tire-wash rack; pneudraulics
7727-43-7	barium sulfate	5 mg/m ³ (I)	Vehicle maintenance and repair; s/m painting operations; facility painting;	Outdoor recreation; maintenance flight-rescue; vertical shop; b256 corrosion control

Chemical Abstract Service Number (CAS #)	Chemical Name	ACGIH TLV	Potential AF Exposure Source (Process)	Potential AF Exposure Source (Shop - Actual Terminology) [†]
			carpentry; green primer; priming; full painting	
7439-89-6	iron		Oil servicing; F-22 panel gap filling/curing; F-22 brush/roll/spray coating; adhering; composites/related; ram; welding (metal inert-gas)	T-birds joint shop; B252 sheet metal (F-22 a lo); B252 lo; corrosion control; maintenance flight-rescue
7789-06-2	strontium chromate	0.0002 mg/m ³ (I)	Priming; s/m painting operations; s/m touch-up painting; priming; fiberglass repair; corrosion prevention	Sheet metal (F-22 a lo); maintenance flight-rescue; phase-ar-wheel & tire-wash rack
1309-60-0	lead dioxide		General wire repair; battery maintenance; radio maintenance and repair	Organizational maintenance; ccsd electronic systems center; transmissions sys (502 com); ccsd sigint systems radio
7440-43-9	cadmium	0.01 mg/m ³ 0.002 mg/m ³ (R)	OSHA expanded standards	
18540-29-9	chromium(VI)	0.0002 mg/m ³ (I)	OSHA expanded standards; found in corrosion control operations	
7440-41-7	beryllium	0.00005 mg/m ³ (I)	OSHA expanded standards	
1066-40-6	trimethylsilanol		Navy target chemical	

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; CAS = chemical abstract services; I= inhalable fraction; R = respiratory fraction; TLV = threshold limit value

*Notice of Intended Changes 2021

[†]Process and locations where select metals are used in the AF based on EESOH-MIS

APPENDIX B: Data Extraction Fields Used When Evaluating Included Studies

Extraction Question	Responses
What type of study is this?	<ul style="list-style-type: none"> -Human <ul style="list-style-type: none"> --Epidemiology --Exposure assessment --Medical case study -Animal <ul style="list-style-type: none"> --Mice --Rat --Primate --Chinchilla --Swine --Dog --Rabbit --Guinea Pig -In silico model -Other
What size was the study population per group?	<ul style="list-style-type: none"> *Group identification *Exposure chemical *N for group *Female N *Male N
Was this study qualitative or quantitative?	<ul style="list-style-type: none"> -Qualitative -Quantitative -Semi-quantitative
What performance attribute category was studied?	<ul style="list-style-type: none"> -Vision <ul style="list-style-type: none"> --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*)
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/Immediately Dangerous to Life & Health (IDLH)

Extraction Question	Responses
	<ul style="list-style-type: none"> --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 (OR) --Relative risk (RR) --Other *What is the OR or RR? *What is the confidence interval (CI)? *What is the percentile for the CI (e.g. 95th)?
Comments	Free text

- = check boxes; * = free text

ACGIH American Conference of Governmental Industrial Hygienists

APPENDIX C: Modified Downs & Black Risk of Bias Form

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 <0.05) for the main outcomes except 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 subjects/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

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

%	percent
ACGIH	formerly called American Conference of Governmental Industrial Hygienists
AETC	Air Education and Training Command
AF	Air Force
AI	artificial intelligence
Arcmin	arc minute
ATSDR	Agency for Toxic Substances and Disease Registry
BF	blink frequency
BPRs	Basic performance resources
CAS	chemical abstract services
CCT	Cambridge Colour Test
CHET	chemical hazard evaluation tool
CI	confidence interval
CNS	central nervous system
CO ₂	carbon dioxide
cpd	cycles per degree
DAISY	Distiller's AI capabilities
DNPH	dinitrophenylhydrazine
DoD	Department of Defense
EESOH-MIS	Enterprise Environmental, Safety, and Occupational Health Management Information System
EPA	Environmental Protection Agency
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
LD ₅₀	Lethal dose 50%
MAJCOM	Major Command
MEGs	Military Exposure Guidelines
mg/kg	milligrams per kilogram
mg/m ³	milligrams per cubic meter
Mn	Manganese
MnO ₂	manganese dioxide
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effects Level
NOEL	No Observed Effect Level
NTP	National Toxicology Program
OBVA	Operational Based Vision Assessment
OEL	Occupational Exposure Limit
OHC	Optimization of Human Capital
OSHA	Occupational Safety and Health Administration
OTO*	ACGIH ototoxicity designation
PBAO	Precision-based Airman Optimization

PECO	population, exposure(s), controls, and outcome
PICO	population, intervention(s), controls, outcome
PM	particulate matter
PM _{2.5}	particulate matter with ≤ 2.5 micrometer aerodynamic diameter
PM ₁₀	particulate matter with ≤ 10 micrometer aerodynamic diameter
ppb	parts per billion
ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RD ₅₀	Respiratory Depression 50%
RoB	risk of bias
SBS	sick building syndrome
SO ₂	sulfur dioxide
STEL	short-term exposure limit
TLV	threshold limit value
TWA	time weighted average
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter
μm	micrometers
USAPHC	United States Army Public Health Center