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METAL EXPOSURE AND ITS IMPACT TO PHYSIOLOGICAL ATTRIBUTES: A SCOPING LITERATURE REVIEW USING SOFTWARE WITH ARTIFICIAL INTELLIGENCE

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14. ABSTRACT
The Air Force (AF) needs information detailing AF chemicals, performance attributes impacted, and dose-response relationships between chemicals and level of impact on performance attributes for vision, audiology, physiology, and psychology. A list of relevant AF chemicals in occupational environments was developed to conduct literature reviews to determine impact on performance attributes of concern. The second chemical class reviewed was metals. The commercial software, DistillerSR, with artificial intelligence capabilities was used to help screen 54,824 publications identified in the literature search down to 550 for the scoping review and provided the structure for the steps leading to summaries of key studies found to impact attributes. The primary metal for which research was found was lead. Other metals were manganese oxide, titanium dioxide, cadmium and mercury. Primary performance attributes negatively impacted by metals are cardiopulmonary effects, including respiratory irritation and obstruction (physiology), and a number of cognitive functions, such as learning, memory and fatigue (psychology). The literature search found only one reference for a metal affecting auditory and visual attributes. Due to limited dose-response data available for most attributes, additional research and model development is recommended. Non-occupational and short-term exposures can potentially induce transient impacts on performance attributes.

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Metals, performance attributes, scoping systematic literature review, artificial intelligence, auditory, physiological, psychological/cognition, vision

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1.0 SUMMARY

The Air Force (AF) needs information detailing the potential for chemical exposure in an AF environment, the performance attributes impacted, and the dose-response relationship between the amount of chemical and level of impact. A program sponsored by the Air Education and Training Command (AETC) Surgeon General developed performance attributes for vision, audiology, physiology, and psychology. A list of relevant AF chemicals in occupational environments was developed in order to conduct systematic literature reviews to determine their impact on performance attributes of concern. The second class of chemicals reviewed were metals which are a large class of metallic and organic compounds. The organic metal compounds can contain one or more metal to carbon or metal to nitrogen bonds.

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

The primary metal for which articles and research was found was lead. Lead exposure can be through repair of parts or materials containing lead, construction using materials with lead, paints/painting/paint removal using both old and new paints, firing ranges and lead bullets, welding, lead in plumbing (pipes and solder), electronic components and lead batteries. Lead is more of a chronic toxicant so it has less impact on performance attributes during acute or initial exposure (Bolla *et al*., 1995). The literature search only found one reference for manganese effecting the auditory and visual pathways and potentially attributes associated with both. A number of references were for titanium dioxide particles of various sizes including the nanoscale. However, there is a lack of nanoparticle exposure data for AF processes. The major attributes affected by metals were respiratory, irritation, cardiovascular and cognitive effects. Lead, cadmium, manganese dioxide, titanium oxide and zinc oxide were the metals found to impact attributes. Additional research and model development is recommended due to the limited dose-response data available for most attribute. Non-occupational and short-term exposures can potentially induce transient impacts on performance attributes.

2.0 INTRODUCTION

2.1 Performance Attributes of Concern

The AF has a vested interest in understanding the impact of chemical exposure on the performance attributes that Airmen need to successfully complete their mission. Performance attributes were selected by the Precision-based Airman Optimization group in the Optimization of Human capital program through a series of questions that highlighted what skills an Airmen needed to possess to succeed in their occupational specialty.

Subject matter experts were solicited to give input on basic performance resources (BPRs) and individual attributes (e.g. cognition, balance) that could be quantitatively assessed and used for performance benchmarking in a career field (Scheiman *et al.*, 2020). The basis for the BPR development came from General Systems Performance Theory and the Elemental Resource Model (ERM; Kondraske *et al.*, 2011). After a comprehensive analysis which included information from the U.S. Department of Labor's Occupational Information Network (O*NET; U.S. Department of Labor, 2019), literature sources, and working groups from two AF Specialty Codes, four general performance resources were identified: vision, audiology, physiology, and psychology. In total, 101 performance attributes were identified with 11 in vision, 9 in audiology, 37 in physiology, and 44 for psychology. A complete list of the attributes can be found in Steele *et al.* (2021a).

2.2 Potential Sources in the Air Force

To understand potential exposures across the AF, a subject matter expert recommended a representative base from each Major Command (MAJCOM) (Table 1). The 2020 chemical usage report was obtained from Enterprise Environmental, Safety, and Occupational Health Management Information System (EESOH-MIS).

Table 1. List of representative bases from each MAJCOM

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

In reviewing EESOH-MIS data for these 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 (Table 2). 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 Occupational Safety and Health Administration (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.

Table 2. Process and locations where select metals are used in the Air Force based on EESOH-MIS

CAS #	**Chemical Name**	**Process**	**Shop (Actual Terminology)**
13463-67-7	titanium dioxide	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	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	Vehicle maintenance and repair; s/m painting operations; facility painting; carpentry; green primer; priming; full painting	Outdoor recreation; maintenance flight-rescue; vertical shop; b256 corrosion control
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	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	OSHA expanded standards	
18540-29-9	chromium(VI)	OSHA expanded standards; found in corrosion control operations	
7440-41-7	beryllium	OSHA expanded standards	
1066-40-6	trimethylsilonal	Navy target chemical	

3.0 METHODS

3.1 Systematic Review

A thorough description of the systematic review as it pertains to the review of chemical exposures and their impact to performance attributes is available in Steele *et al.* (2021a). Briefly, a systematic review follows a rigorous structure which begins by identifying an exposed population and determining if a theorized impact exists. Once the hypothesis is formed, the research group determines the inclusion/exclusion criteria for a study and codifies their decisions in a review template. Once inclusion criteria are established, peer-reviewed literature, grey literature, and conference publications are collected. Each potential source is evaluated by two independent reviewers using the same criteria to determine if the study meets the inclusion criteria. If a study does meet the criteria, data are extracted using a pre-determined form. Finally, the study is reviewed for potential biases using a standardized questionnaire, such as Downs and Black. Each stage of the review is documented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) figure for transparency.

3.1.1. Search Terms

The selection process for identifying 125 chemicals to study is documented in Steele *et al.* (2021a). Primary sources for chemical identification included chemical inventories pulled from the AF's EESOH-MIS, chemicals identified through AF field studies and subject matter expert suggestions.

Over 800 chemicals were first identified. Using a chemical hazard evaluation tool (CHET) developed by the bioenvironmental engineering (BE) consulting branch, any chemical for which no significant health hazards were expected was removed from the list. Chemicals which were only used at two bases were also removed. Any chemical found in the McKinley *et al.* (2016) hardened aircraft shelter study was included as these chemicals represented potential exposures not found on Safety Data Sheets. After winnowing down the list of 800, 125 chemicals were selected to go forward. Of those 125 chemicals, 11 were categorized as metals.

Search terms were generated for the auditory, physiological, psychological, and visual attributes. The full list of search terms used by the research librarian is available in Steele *et al.* (2021b).

3.1.2. Study Selection

Even with keyword refinement and the assistance of a research librarian, over 54,000 titles and abstracts were identified for metals. Once these articles were uploaded into DistillerSR, the AI software was used to identify those articles which might be suitable for inclusion. Researchers individually reviewed the 550 titles and abstracts identified by the AI and selected the most promising for a full text review. For a full list of disqualifying conditions, see Steele *et al.* (2021b). In general, a study was only included if it was original research specifically focused on short term impacts to the physiological attributes. Any outcome associated with organ toxicity, cancer, or mutagenicity was excluded from the review.

3.1.3. Data Extraction

For studies with quantitative results, data were extracted by the researchers using standardized forms created in DistillerSR. A complete listing of questions is available in Steele *et al.* (2021b).

Typical data extracted included study population characteristics, exposure characteristics, information on the attributes studied, and the final result of the exposure on the study population. Data were exported as an Excel table and grouped based on general physiological attribute.

3.1.4. Risk of Bias (RoB)

Every quantitative study selected for this review underwent a RoB analysis, a process designed to objectively evaluate the potential biases existing in the study design. A full description of the modified Downs and Black (1998) RoB form is available in a prior technical report (Steele *et al.*, 2021b). Briefly, studies were evaluated for 1) reporting bias, 2) external validity (suitability of the study population), 3) internal bias and 4) selection bias. If a question was answered “Yes”, it was assigned a score of 1 and if “No”, assigned a score of 2. The higher the final RoB number, the higher the likelihood of bias in the study. A perfect score in a human study was 29/29 and for animal studies a score of 25/25. Numerical scores were turned into percentages to allow comparison between human and animal studies.

4.0 RESULTS

The study began with the same study population as described in Steele *et al*. (2021b), but the chemicals of interest were 11 metals. Less than 0.5 percent (%) of the initial records were included for final analysis (Figure 1). Many of the studies evaluated focused on long-term health effects that did not fall within the scope of performance attributes. Some of the 22 studies included more than one general performance attribute, so a description is provided more than once but with a different emphasis each time based on the attributes involved.

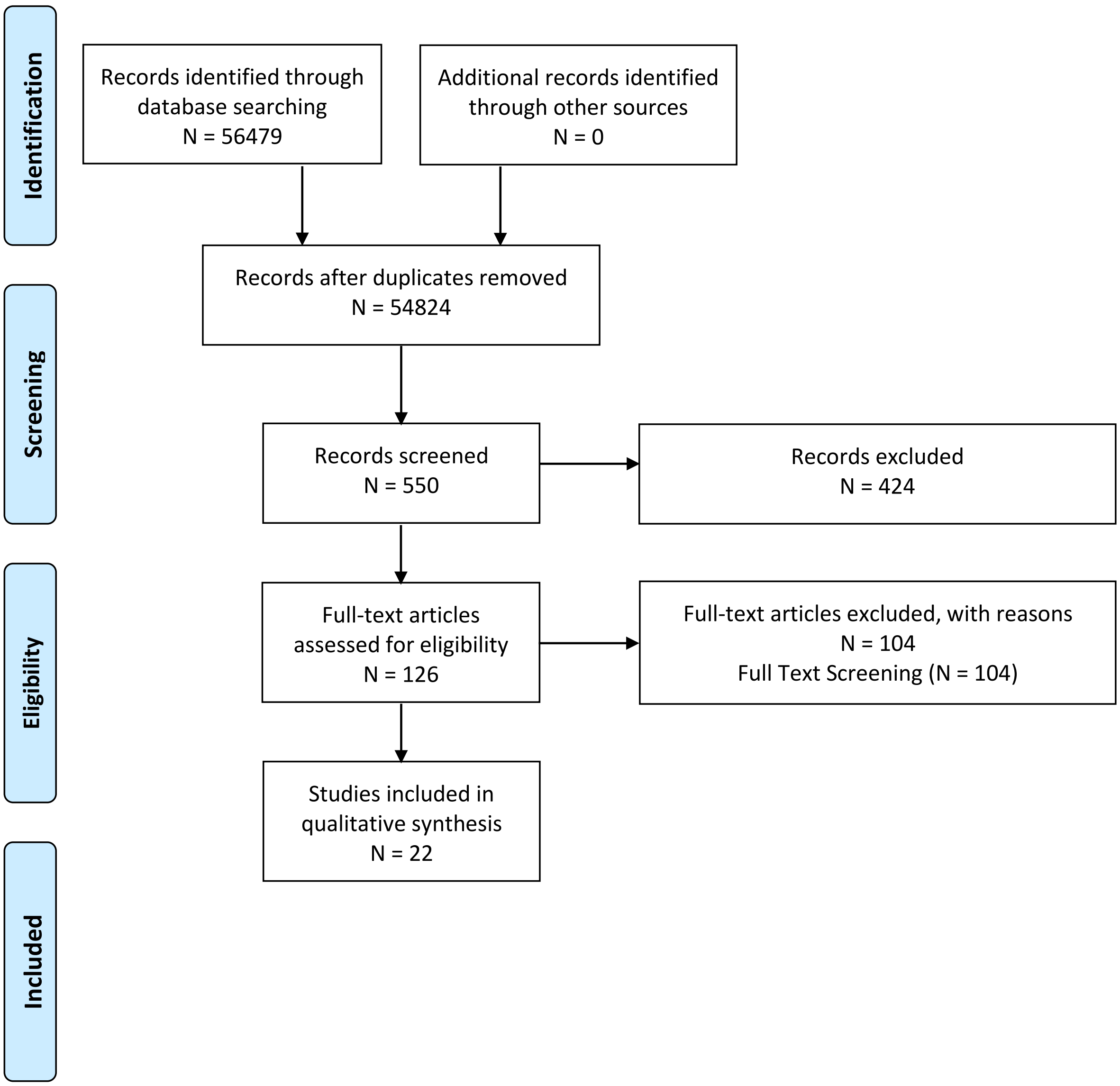

Figure 1. PRISMA format describing the systematic screening and selection of studies for analysis

4.1 Visual Attributes

Sárközi et al. (2009)

Sárközi *et al*. (2009) instilled nanosuspension of manganese dioxide (MnO_2) into the trachea of adult male Wistar rats for 3, 6, and 9 weeks. The doses of the MnO_2 particles with an approximate 23 nanometers (nm) 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 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. 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 (NPs) had access from the airways to the brain, and the resulting effects on behavioral and neurophysiology endpoints could impact multiple visual and psychological attributes.

4.2 Auditory Attributes

Sárközi et al. (2009)

Sárközi *et al*. (2009) instilled nanosuspension of MnO_2 into the trachea of adult male Wistar rats for 3, 6, and 9 weeks. The doses of the MnO_2 particles with an approximate 23 nm nominal diameter were 2.63 and 5.26 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 primary auditory 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. 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 NPs had access from the airways to the brain, and the resulting effects on behavioral and neurophysiology endpoints could impact multiple auditory and psychological attributes.

4.3 Physiological Attributes

Gan et al. (1988)

Workers from two manganese ore milling plants and three dry-cell battery manufacturing plants in Singapore were studied by Gan *et al*. (1988) to determine the extent of absorption and exposure of workers to manganese dioxide. An attempt was also made to determine the usefulness of blood and urine manganese estimations as biological indicators of exposure. The highest manganese exposures were in the manganese ore mills. Fifteen of the twenty-eight samples collected exceeded the Threshold Limit Value (TLV). The battery factories had significantly lower exposure levels. No cases of chronic manganese poisoning or manganism were detected. However, four workers from the manganese ore mills had urine manganese concentrations exceeding the biological TLV of 50 micrograms (µg)/liter. The blood manganese concentration of all the workers were below the biological TLV of 300 µg/liter with an average of 22.59 picograms (pg)/liter. Manganese concentrations in air correlated significantly with manganese concentrations in urine (r = 0.77) and blood (r = 0.69). At the time of this study the inhalation TLV of 5 milligrams per cubic meter (mg/m^3) corresponded with blood and urine manganese concentrations of about 30 µg/liter. However the TLV for manganese is now 0.02 mg/m^3 (20 $\mu g/m^3$). Worker complaints were tiredness, drowsiness and muscular cramps which could impact performance attributes. Although no attributes were studied, this article shows the potential for effects on attributes as well as the feasibility of measuring manganese in urine, which is noninvasive, as well as in blood. It also shows the decrease in TLV over the last 3 decades.

Harfoush et al. (2020)

Based on the evidence, workers exposed to inhaled nanosized titanium dioxide (TiO_2) powder are more susceptible to the risks of developing respiratory diseases. Harfoush *et al*. (2020) conducted a study to analyze the local effects of TiO_2 NPs on allergic airway inflammation and their uptake in a mouse model of ovalbumin (OVA)-induced allergic airway inflammation. Female BALB/c mice with or without asthma were intranasally administered 25 microliters (µl) TiO_2 NPs suspension (50 milligrams per milliliter (mg/mL)) 1 hour after OVA exposure on days 17 and 20. Lung function testing by specific airway resistance and uptake of NPs were conducted. Exposure to TiO_2 NPs increased airway responsiveness to methacholine and percentages of specific airway resistance in the TiO_2 exposed mice as well as in the OVA-induced asthmatic mice. The TiO_2 NPs were taken up by alveolar macrophages at different time points and were present in most of the organs in both asthmatic and non-asthmatic mice. Based on the findings of the current study, intranasal or inhalation exposure to high-dose nanosized TiO_2 particles appears to cause airway inflammation and exacerbate allergic airway inflammation and lead to systemic uptake in extrapulmonary organs.

Zhao et al. (2018)

Data collected from humans are currently limited although toxicological studies have reported that exposure to titanium dioxide nanoparticles (nano-TiO_2) may have adverse cardiopulmonary effects. Zhao *et al*. (2018) explored cardiopulmonary effects among workers exposed to nano-TiO_2. A cross-sectional study was conducted in a nano-TiO_2 manufacturing plant in eastern China. Exposure assessment and characterization of TiO_2 particles were performed in a packaging workshop. Physical examination and biomarkers for cardiopulmonary effects were examined for 83 exposed workers and 85 controls from management positions at the same plant. In the packaging workshop the total mass concentration of particles was 3.17 mg/m^3. The mass concentration of NPs was 1.22 mg/m^3 which was 39% of the total mass. For lung damage markers, one pulmonary disease marker (SP-D) was significantly lower than controls and the other 3 were the same which may have been due to cell injury and/or that they were being used more to block the inflammatory cytokines. Pulmonary function was significantly decreased based on forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0), and peak expiratory flow (PEF). Although there were no differences for blood pressure or heart rat, the concentration of cardiovascular disease markers creatinine, triglyceride, and total cholesterol were significantly lower while low density lipoproteins (LDLs) were significantly higher than controls. Oxidative stress marker malondialdehyde was significantly increased while superoxide dismutase was significantly decreased. Three of six inflammatory markers tested (interleukin (IL)-8, IL-6, tumor necrosis factor alpha (TNF-α)) were significantly elevated due to occupational exposure to nano-TiO_2. Two serum cardiovascular disease markers (intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)) that are activated by inflammatory cytokines were significantly increased. The data strongly suggest that nano-TiO_2 can contribute to the cardiopulmonary effects observed in workers. The studied markers and pulmonary function tests may be useful in health surveillance for workers exposed to nanomaterials.

Leppänen et al. (2015a)
Since the knowledge of the health effects of different engineered nanomaterials (ENMs) is lacking, Leppänen *et al*. (2015a) studied the irritation and inflammation potential of a commercially available silica-coated TiO_2 ENMs (10x40 nm, rutile). Single 30 minute exposures at mass concentrations 5, 10, 20 and 30 mg/m^3 induced the first phase of pulmonary irritation which was seen as rapid, shallow breathing. Sensory irritation was observed only at the beginning of the single exposure periods. Silica-coated TiO_2 ENMs induced pulmonary and a brief sensory irritation during a single exposure.

Leppänen et al. (2015b)
Used widely as a pigment in various applications, TiO_2 is manufactured in millions of tons yearly, and was considered to not have adverse health effects. Leppänen *et al*. (2015) studied respiratory irritation and inflammation potencies of commercially available pigmentary TiO_2 particles (<5 µm, rutile). Male Crl:OF1 mice received single 30 minute head-only exposures of TiO_2 particles at mass concentrations 6, 11, 21, and 37 mg/m^3. Minor but statistically significant sensory irritation was observed during acute exposures at 11, 21, and 37 mg/m^3. There was elongation of the break after the inhalation, which is typical in sensory irritation, and caused by closure of the glottis inhibiting airflow from the lungs after inspiration. Breaths per minute were only statistically decreased at 37 mg/m^3. No pulmonary irritation, airflow limitation, nasal or pulmonary inflammation was observed. In conclusion, respiratory effects were limited to minor sensory irritation in mice.

Kan et al. (2014)
The inhalation of nanosized air pollutant particles is a recognized risk factor for cardiovascular disease. The link between occupational exposure to engineered nanoparticles and adverse cardiovascular events still need additional studies to elucidate. Although pulmonary inhalation of ultrafine titanium dioxide ($UFTiO_2$) did not change the basal heart rate and blood pressure compared with the control group (exposed to filtered air) at 24 hour post-exposure, Kan *et al.* (2014) demonstrated that pulmonary exposure of rats to 21 nm, 6 mg/m^3 $UFTiO_2$ for 4 hours significantly increased heart rate, depressed the diastolic function of the heart in response to isoproterenol and elevated mean and diastolic blood pressure in response to norepinephrine. The exposure scheme produced an actual pulmonary deposition of 10 mg $UFTiO_2$ in rats, which is equivalent to workers exposed to 0.1 mg/m^3 for 27 workdays in a typical occupational environment.

Leppänen et al. (2011)
Leppänen *et al*. (2011) used the ASTM mouse bioassay to study sensory and pulmonary irritation, airflow limitation, and inflammation potency of nanosized TiO_2. Single exposures for 0.5 hours to generated TiO_2 (primary particle size 20 nm; geometric mean diameters of 91, 113, and 130 nm at mass concentrations of 8, 20, and 30 mg/m^3, respectively; crystal phase anatase + brookite (3:1)) caused airflow limitation in the conducting airways of outbred Crl:OF1 male mice at each studied exposure concentration. This was shown as a reduction in expiratory flow, being at the lowest 73% of baseline. The response was not dose dependent. Repeated exposures (altogether 16 hours, 1 hour/day, 4 days/week for 4 weeks) to TiO_2 at mass concentration of 30 mg/m^3 caused an airflow limitation effect as intense as the single exposures, and the extent of the responses stayed about the same during repeated exposures. Sensory irritation was minor. Pulmonary irritation was more pronounced during the latter part of the repeated exposures compared to the single exposures. Sensory and pulmonary irritation were also observed in the control group. TiO_2 NPs did not cause nasal or pulmonary inflammation. Irritation and inflammation potencies of these TiO_2 nanoparticles were low.

Perry et al. (1983)
Perry *et al*., (1983) examined the effect of other metals upon cadmium induced hypertension in rats. Rats exposed to one percent sodium, 1 parts per million (ppm) cadmium, or 1 ppm cadmium plus 1 ppm lead in drinking water all caused similar mild hypertension in rats. The hypertensive effect of sodium, given for 4 months beginning at weaning, disappeared when the salt was withdrawn but subsequently returned without further exposure. Rats continuously given 1 ppm cadmium during and after salt exposure were continuously hypertensive, but salt did not increase their hypertension. Rats continuously exposed to cadmium or cadmium plus lead without extra sodium remained hypertensive for 20 months. Rats exposed to cadmium or cadmium plus lead for months 4 through 8 remained hypertensive after metal exposure was discontinued; addition of 0.35 ppm selenium corrected the hypertension in cadmium-fed rats but had little effect in the cadmium plus lead exposed rats.

Fischbein et al. (1982)
Fischbein *et al.* (1982) performed clinical examinations on 45 cable-manufacturing workers in a cross-sectional study to identify effects from low level lead exposures. Thirteen workers (blenders) were in direct contact with lead-containing stabilizers, while 31 were only indirectly exposed. Exposure levels measured where the blenders worked ranged from 130.0-384 ug/m^3 with a mean and standard deviation of 259.9 ± 99.1 µg/m^3. These workers directly exposed to the stabilizers reported a higher prevalence of gastrointestinal and respiratory irritation symptoms than those with low or insignificant lead exposure. None of the directly exposed had blood lead levels exceeding 60 micrograms per 100 milliliters (ml). The clinical symptoms correlated with blood lead and zinc protoporphyrin. However, when the data were subjected to hierarchical log-linear modeling, a partial association was found between zinc protoporphyrin and symptoms, but not between blood lead and symptoms. The data suggest that non-specific gastrointestinal symptoms may occur at relatively low blood lead and zinc protoporphyrin levels, and that measurement of zinc protoporphyrin and exploration of clinical symptoms are valuable components in lead screening programs.

Li et al. (2020)

Li *et al*. (2020) investigated the effects of low cadmium burden on the respiratory symptoms and pulmonary function in occupational workers. The study population consisted of 98 nickel-cadmium battery workers. Levels of urinary cadmium and creatinine, and data for adverse respiratory symptoms and pulmonary function of exposed workers were measured. The urinary cadmium level in cadmium-exposed workers (n = 53) was within the normal range but greater than 2.4 times than those of the control group (n = 45). Compared with the control group, the cadmium-exposed workers had higher prevalence of all subjective respiratory symptoms noted. The prevalence of cough (30%), phlegm (23%), and upper respiratory tract infection (79%) in the exposure group was significantly ($p < 0.05$) higher than the prevalence of cough (11%), phlegm (7%), and upper respiratory tract infection (31%) in the control group, respectively. There was no significant difference between the cadmium-exposed workers and control group for the pulmonary function test. Adverse subjective respiratory symptoms were increased, and pulmonary function was unchanged in low cadmium exposed workers. Unchanged pulmonary function may have been related to age, exposure duration, and distribution of cadmium in the body.

Mameli et al. (2001)

The effects of lead exposure at low concentrations were evaluated by studying the post-rotatory nystagmus (PRN), which assesses the perception of the vestibular system, in two groups of 40 rats each (20 males and 20 females) exposed for 3 months to 50 ppm of sodium acetate and 50 ppm of lead acetate, respectively, in the drinking water. Only animals treated with lead acetate showed changes in the PRN parameters which were significantly related to the concentration of lead in the blood and in brain structures. No alterations of the PRN parameters were observed in the animals treated with sodium acetate, but exposure to lead, even at low concentrations, impairs both sensory and motor functions. After 90 days of exposure to lead acetate, a significant increase of lead concentration was observed both in the blood ($p < 0.01$) and nervous tissue ($p < 0.001$) samples in respect to the basal conditions. Furthermore, the comparison of lead concentration in the telencephalon, brainstem and cerebellum did not show significant differences 80–90 days after sodium acetate administration, whereas, in the same structures, significant differences (1%) were observed 90 days after lead acetate administration in comparison to basal conditions. The findings also point out that the vestibular system and brain stem structures which generate and control the PRN represent targets for the action of this heavy metal. Finally, the results indicate that the evaluation of the vestibulo-ocular-reflex can provide a test suited for the screening of the neurotoxic effects of lead even in the absence of clinical signs typical of lead intoxication.

Moitra et al. (2013)

A cross-sectional study of 133 workers in jewelry workshops using cadmium under poor hygienic conditions and 54 controls (jewelry sales staff) was performed, assessing symptoms, spirometry, urinary cadmium levels and quantified airborne total oxidant contents for 35 job areas. Control work areas had a mean airborne oxidants concentration of 85.3 ppm (68.1–92.4 ppm). The mean concentration in exposed work areas was 270.3 ppm (138.3 - 510.0 ppm). Exposed workers had 10 times higher urinary cadmium values than controls (geometric mean 5.8 vs 0.41 µg/dl; $p < 0.01$). Of the exposed subjects, 75% reported respiratory tract symptoms compared with 33% of the controls (Odds Ratio = 3.1, 95% Confidence Interval 1.4 to 7.3).

FVC) and FEV_1 were also lower among the exposed workers than the controls (> 600 ml decrement for each, $p < 0.001$). For every 1 µg increase in urinary cadmium there was a 34 ml decrement in FVC and a 39 ml decrement in FEV_1 ($p < 0.01$), taking into account other covariates including workplace airborne oxidant concentrations. Overall, this cohort of heavily exposed jewelry workers experienced frequent respiratory symptoms and manifested a marked deficit in lung function, demonstrating a strong response to cadmium exposure.

Mehrifar et al., 2018
Industrial welders are exposed to noxious fumes and metals, creating a hazardous environment. Mehrifar *et al.* (2018) conducted a cross-sectional study of Iranian shipbuilders with 60 welders and 45 non-exposed administrative staff. Participants were given a questionnaire about their respiratory health and breathing zone samples were collected from workers to estimate exposure levels. Respiratory symptom reporting was significantly higher in welders than in administrative staff ($p < 0.05$) and spirometry indicated obstructive breathing. The FVC, FEV_1 and FEV_1/FVC values for exposed workers were lower than those measured for unexposed workers. Welders were exposed to a mixture of chromium, manganese, zinc, copper, iron, and aluminum in addition to light gases such as carbon dioxide, nitrogen oxides, ozone, and carbon dioxide. This complex environment made it difficult to determine a single culprit for decreases in lung function.

4.4 Psychological Attributes

Sárközi et al. (2009)
Sárközi *et al*. (2009) instilled nanosuspension of MnO_2 into the trachea of adult male Wistar rats for 3, 6, and 9 weeks. The doses of the MnO_2 particles with an approximate 23 nm nominal diameter were 2.63 and 5.26 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. Action potentials in the tail nerve were recorded under urethane anesthesia. 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 conduction velocity of the tail nerve decreased. These results indicate that the Mn content of instilled NPs had access from the airways to the brain, and the resulting effects on behavioral and neurophysiology endpoints could impact multiple psychological attributes.

Gan et al. (1988)
Workers from two manganese ore milling plants and three dry-cell battery manufacturing plants in Singapore were studied by Gan *et al*. (1988) to determine the extent of absorption and exposure of workers to manganese dioxide. An attempt was also made to determine the usefulness of blood and urine manganese estimations as biological indicators of exposure. The highest manganese exposures were in the manganese ore mills. Fifteen of the twenty-eight samples collected exceeded the TLV. The battery factories had significantly lower exposure levels. No cases of chronic manganese poisoning or manganism were detected. However, four workers from the manganese ore mills had urine manganese concentrations exceeding the biological TLV of 50 µg/liter. The blood manganese concentration of all the workers were below the biological TLV of 300 µg/liter with an average of 22.59 pg/liter. Manganese concentrations

in air correlated significantly with manganese concentrations in urine (r = 0.77) and blood (r = 0.69). At the time of this study the inhalation TLV of 5mg/m^3 corresponded with blood and urine manganese concentrations of about 30µg/liter. However the TLV for manganese is now 0.02 mg/m^3 (20 µg/m^3). Worker complaints were irritability which could impact performance attributes. Although no attributes were studied, this article shows the potential for effects on attributes as well as the feasibility of measuring manganese in urine, which is noninvasive, as well as in blood. It also shows the decrease in TLV over the last 3 decades.

Aijie et al. (2017)

To explore whether NPs can be transported into the central nervous system (CNS) via the taste nerve pathway, Aijie *et al*. (2017) instilled zinc oxide (ZnO) and TiO_2 NPs on the tongue of male Wistar rats. Toxicity was assessed by Zn/Ti biodistribution, histopathological examination, oxidative stress assay, quantitative reverse-transcriptase polymerase chain reaction analysis, learning and memory capabilities. ZnO NPs and TiO_2 NPs were significantly deposited in the nerves and brain, respectively. The histopathological examination indicated a slight injury in the cerebral cortex and hippocampus. The Morris water maze results showed that learning and memory of the rats were impaired. ZnO NPs on training days 1, 2, 3 and 5 had significantly longer escape latencies finding the platform and had significantly longer escape latency on the second day of reacquisition (day 8). TiO_2 NPs on training days 2, 3, 4 and 5 had significant longer escape latencies finding the platform and had significantly longer escape latency on the second day of reacquisition (day 8). During the probe test (day 6), rats in the ZnO NPs and TiO_2 NPs groups remained in the target quadrant for a shorter time. Also on day 6, rats in the TiO_2 NPs group travelled less distance in the target quadrant than controls. The results show that NPs can enter the CNS via the taste nerve translocation pathway and cause adverse effects.

Vázquez and de Ortiz (2004)

Long-term memory (LTM) in the brain depends on a variety of intracellular signaling cascades utilizing calcium (Ca^{2+}) and cyclic adenosine monophosphate as second messengers. The activity of the Ca^{+2}/phospholipid-dependent protein kinase C (PKC) has been proposed to be necessary for the transition from short-term memory to LTM. Because the neurobehavioral toxicity of lead has been associated with its interference with normal Ca^{+2} signaling in neurons, Vázquez and de Ortiz (2004) studied its effects on spatial learning and memory using a hippocampal-dependent discrimination task. Adult male hooded Long Evans rats received microinfusions of either sodium or lead acetate (0, 0.3, 0.7, 1.0, 3.0 nMol) in the CA1 hippocampal subregion before each one of four training sessions. A retention test was given 7 days later to examine LTM. Results suggested that intrahippocampal lead did not affect learning of the task, but significantly impaired retention. The effects of lead selectively impaired reference memory measured in the retention test, but had no effect on the general performance because it did not affect the latency to complete the task during the test. Examining the effects of lead on the induction of hippocampal Ca^{+2}/phospholipid-dependent PKC activity during acquisition training showed that lead interfered with the learning-induced activation of Ca^{+2}/phospholipid-dependent PKC on day 3 of acquisition. Overall, results indicate that lead causes cognitive impairments in adult rats and that these effects might be caused by interference with Ca^{+2}-related signaling mechanisms required for normal LTM.

Bolla et al. (1995)

Bolla *et al*. (1995) compared the neurobehavioral effects of lead (organic and inorganic) and organic solvents in 386 U.S. workers (52 controls, 190 lead, and 144 solvent workers). The weighted average blood lead level for the lead workers was 24.0 ± 9.4 µg/dl. The paint manufacturing workers were exposed to a mixture of solvents consisting of toluene, xylene, other aliphatic and aromatic hydrocarbons, methyl ethyl ketone and other ketones, butanol, propanol, and esters. The association between neurobehavioral test performance and duration of exposure to lead or solvents was also examined and compared. The neurobehavioral test battery (30 total tests) consisted of examiner and computer-administered neurobehavioral tests, a test of olfactory function, and questionnaires that assessed neuropsychiatric symptoms. Adjusted mean differences on the neurobehavioral test scores were estimated by comparing the exposed group to the control group using linear regression and adjusting for premorbid intellectual ability, age, and race. Both lead and solvents were associated with diminished neurobehavioral performance in all neurobehavioral areas tested. While lead and solvent exposure had roughly the same magnitude of adverse effects on manual dexterity tests, lead exposure was associated with greater adverse effects on memory and learning tests, but with less adverse effects on executive/motor tests than solvent exposure. Olfactory function was adversely affected by solvent exposure but unaffected by lead exposure. An elevated number of neuropsychiatric symptoms was reported by 7% of the control group, 43% of the lead group, and 15% of the solvent group. For exposure duration of less than or equal to 10 years, more neurobehavioral decrements were found in the solvent group relative to the lead group. However, for exposure duration of greater than or equal to 18 years, the lead group showed more decrements than the solvent group. Thus, lead is more of a chronic contaminant. Overall, these data suggest differences in neurobehavioral functioning between the lead (organic and inorganic) and solvent exposed workers examined in this study.

Papp et al. (2005)

Heavy metals, due to their numerous applications in industrial processes, agrochemicals and household articles, have caused widespread contamination. One of their target organs is the central nervous system. The toxic effects of heavy metals can be modified by lifestyle-originated factors such as consumption of alcohol. Papp *et al*. (2005) investigated the changes in spontaneous cortical activity (ECoG), cortical sensory evoked potentials (EPs) and peripheral nerve action potentials recorded in rats pre-treated with alcohol and acutely treated with lead, mercury and manganese by intraperitoneal injection. In the ECoG, mercury caused a massive shift to lower frequencies while the effect of manganese and lead was slight. Alcohol pretreatment minimally altered the effect of the metals. The amplitude of EPs increased upon the application of heavy metals, and the peak latency lengthened. The effect of mercury was the strongest and that of lead the weakest. These effects were potentiated by alcohol. Exposure to heavy metals, together with alcohol consumption, can aggravate known neurotoxic effects.

Nehru and Sidhu (2001)

Long-term exposure to lead has been shown to produce behavioral disturbances in human and animal models. These disturbances are shown to be associated with alterations in cholinergic and dopaminergic neurotransmission in the central nervous system. The experiment by Nehru and Sidhu (2001) was designed to study the effect of lead exposure on neurotransmitters such as dopamine, serotonin, norepinephrine, and activity of acetyl cholinesterase as well as alterations in memory and locomotor functions. Lead acetate (50 mg/kg) was administrated orally to ten

Sprague-Dawley rats for 8 weeks on alternate days. Ten additional rats served as controls. A study was done at the end of exposure and also after 8 weeks of recovery. Lead exposure significantly reduced the brain (17.4%) and body weights (7.3%), which did not improve after 8 weeks of recovery. Significant decreases in brain norepinephrine, serotonin, and acetylcholinesterase remain unchanged at the end of recovery. Dopamine was significantly decreased at the end of recovery. Lead exposure for 8 weeks affected the locomotor and cognitive functions as assessed by the rota rod treadmill and active avoidance test. Following the recovery period, improvement but not total recovery, was seen in locomotor as well as cognitive behavior. The short-term memory as assessed by the passive avoidance test appeared to be affected but was not statistically altered after exposure. At the end of recovery period, treated and control rats responded the same showing complete recovery.

Fischbein et al. (1982)
Fischbein *et al.* (1982) performed clinical examinations on 45 cable-manufacturing workers in a cross-sectional study to identify effects from low level lead exposures. Thirteen workers (blenders) were in direct contact with lead-containing stabilizers, while 31 were only indirectly exposed. Exposure levels measured where the blenders worked ranged from 130.0-384 ug/m^3 with a mean and standard deviation of 259.9 ± 99.1 μg/m^3. These workers directly exposed to the stabilizers reported a higher prevalence of neurological, gastrointestinal and respiratory irritation symptoms than those with low or insignificant lead exposure. None of the directly exposed had blood lead levels exceeding 60 micrograms per 100 ml. The clinical symptoms correlated with blood lead and zinc protoporphyrin. However, when the data were subjected to hierarchical log-linear modeling, a partial association was found between zinc protoporphyrin and symptoms, but not between blood lead and symptoms. The data suggest that non-specific neurological symptoms may occur at relatively low blood lead and zinc protoporphyrin levels, and that measurement of zinc protoporphyrin and exploration of clinical symptoms are valuable components in lead screening programs.

Stollery et al. (1991)
In a short-term prospective study 70 male lead workers performed a series of cognitive tasks on three occasions during an eight-month period (Stollery *et al*., 1991). Concurrently with the cognitive testing, the concentrations of blood lead were measured. Indicators of lead absorption were stable during the study and each subject was allocated to either a low (below 20 ug/dl), medium (21-40 ug/dl), or high (41-80 ug/dl) group on the basis of their average blood lead concentrations. Performance deficits tended to be restricted to the high lead group and, in general, neither practice nor continued exposure during the study altered the magnitude of these deficits. The main deficit was a slowing of sensory motor reaction time, which was seen most clearly when the cognitive demands of the task were low. In the cognitively simple five choice task, blood lead concentration correlated with impaired decision making, response execution, and "lapses in concentration." In the other cognitive tasks the high blood lead group tended also to be slower by a factor of about 1.08 but the dominance of cognitive over sensory motor demands attenuated the exposure-performance correlations. The high lead group also had difficulty in recalling nouns poorly related to the focus of an earlier semantic classification task. This difficulty increased over time and was one of the few findings that correlated with all measures of lead absorption. It is concluded that the primary psychological profile of lead impairment is one of sensory motor slowing coupled with difficulties in remembering incidental information.

Haider et al. (2015)
There is evidence that prolonged exposure to cadmium results in neurobehavioral deficits due to central nervous system toxicity, but few comparable acute studies exist. In this study, Haider *et al*. (2015) randomly assigned 24 Albino Wistar rats to either a control group where rats were administered a saline injection or to an exposure group where rats were administered 1, 2, or 3 mg/kg of cadmium via intraperitoneal injection. One hour after injection, rats were monitored for changes in locomotor activity via the Open Field Test, depression-like symptoms in the Forced Swimming Test, anxiety via the Light-dark Transition test, and memory via the Morris Water Maze test. Cadmium exposed rats had increased anxiety and depression, likely due to decreased superoxide dismutase activity with increased brain lipid peroxidation. Learning and memory were impaired in exposed rats when compared to the controls. These effects were observed in a dose-response manner, suggesting that level of impairment correlates with increasing exposure.

Engstrom and Xia (2017)
Lead is a known neurotoxicant though most studies have evaluated its impact on the cognitive development of children or life-long impacts of chronic exposure. Engstrom and Xia (2017) exposed adult male C577BL/6 mice to lead acetate in their drinking water for 12 weeks. Exposed mice did not show impact to their locomotion or anxiety during open field tests but they did display deficits in spatial short-term memory. Even after exposure ceased these memory deficits were still evident two months later. In euthanized mice, Engstrom and Xia (2017) found fewer adult-born neurons in the hippocampus of exposed mice when compared to controls, suggesting that even short-term lead exposure as an adult can impact neuronal differentiation.

4.5 Analysis of Risk of Bias

The range of percent values for the RoB scores was 13 to 81% (Table 3). There were no studies that had a perfect RoB score but there was one study with a score of only 13%, which indicates low bias for this study. The most biased study was at 81%. The average RoB was 34%.

Table 3. RoB Scores in the Studies reviewed

Reference [RefID]	**Performance Category**	**RoB Score**
Sárközi *et al.* 2009 [285]	Vision, Auditory, Psychology	33%
Gan *et al.* 1988 [353]	Physiology	38%
Harfoush *et al.* 2020 [662]	Physiology	81%
Zhao *et al.* 2018 [1508]	Physiology	13%
Aijie *et al.* 2017 [1593]	Psychology	17%

Reference [RefID]	Performance Category	RoB Score
Leppänen *et al.* 2015a [2346]	Physiology	67%
Leppänen *et al.* 2015b [2769]	Physiology	37%
Kan *et al.* 2014 [3112]	Physiology	28%
Leppänen *et al.* 2011 [3769]	Physiology	29%
Papp *et al.* 2005 [10370]	Vision, Auditory, Psychology	30%
Vázquez *et al.* 2004 [10680]	Psychology	37%
Nehru *et al.* 2001 [11372]	Psychology, Physiology	35%
Mameli *et al.* 2001 [11502]	Vision, Physiology	38%
Bolla *et al.* 1995 [12848]	Psychology, Physiology	28%
Stollery *et al.* 1991 [13525]	Psychology	N/A
Perry *et al.* 1983 [14695]	Physiology	25%
Fischbein *et al.* 1982 [14746]	Psychology, Physiology	62%
Moitra *et al.* 2013 [23467606]	Physiology	15%
Li *et al.* 2020 [31123925]	Physiology	21%
Haider *et al.* 2015 [34231831]	Psychology	29%
Mehrifar *et al.* 2019 [34249936]	Physiology	25%
Engstrom *et al.* 2017 [34249953]	Psychology	38%

5.0 DISCUSSION

5.1 Vision and Auditory

Only one of the 22 included studies addressed visual and/or auditory attributes. MnO_2 NPs translocated from the airways throughout the exposed bodies of rats, and is capable of crossing the blood-brain-barrier. Through a battery of behavioral and electrophysiology tests, Sárközi *et al*. (2009) determined that these particles delayed evoked potentials in visual and auditory brain regions which suggest impacts on visual and auditory attributes. No studies on other metals or other sized particles were identified in this literature review. While it is clear that NPs 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.

5.2 Physiology

Thirteen studies met the selection criteria and demonstrated potential physiological performance impacts from acute and subchronic exposures to metals. The majority of these studies focused on inhalation exposures to nanosized TiO_2, lead or cadmium. Only one study examined manganese dioxide exposure and absorption among workers at ore milling and dry-cell battery manufacturing plants. The subjects reported tiredness, irritability, drowsiness and muscular cramps (Gan *et al*., 1988). Air manganese concentrations significantly correlated with concentrations in urine and blood and the symptoms reported by the workers. The average blood level was 22.59 ug/liter.

Powdered TiO_2 is used as a pigment and the military uses it in smoke grenades to block detection of light waves in the visible portion of the electromagnetic spectrum. During training with smoke grenades, military personnel are likely to be exposed to airborne TiO_2 particles (NRC, 1999). It was long considered to be harmless, but both human and animals studies about the inhalation of nanosized TiO_2 indicate increased risks of respiratory and cardiovascular diseases. In mice, nanosized TiO_2 administered intranasally or through inhalation, caused airway inflammation and resistance and was taken up by alveolar macrophages and systemically circulated (Harfoush *et al*., 2020). Leppänen *et al.* (2011, 2015a, 2015b) performed a number of mice studies for sensory and pulmonary irritation, airflow limitation, and inflammation potency of nanosized TiO_2 from both acute and repeated exposures. Overall sensory irritation was minor and pulmonary irritation was more pronounced during the latter part of the repeated exposures compared to the single exposures, in their studies. In addition cardiovascular effects in rats was reported by Kan *et al*. (2014) from a 4 hour exposure to 21 nm, 6 mg/m^3 UFTiO_2 marked by increased heart rate and depressed diastolic function. This is below the American Conference of Governmental Industrial Hygienists (ACGIH) TLV of 10 mg/m^3. Data for human exposures to TiO_2 NPs were limited, but cardiopulmonary effects have been shown. Pulmonary function, based on FVC, FEC1.0 and PEF, were decreased in exposed vs non-exposed workers in a manufacturing plant (Zhao *et al*., 2018). There were no differences in blood pressure or heart rate, but the concentration of cardiovascular disease markers: creatinine, triglyceride, and total cholesterol were significantly lower while LDLs were significantly higher than controls. Oxidative stress may be a key mechanism as malondialdehyde was significantly increased and superoxide dismutase was significantly decreased. Significant increases in several inflammatory markers (IL-8, IL-6, TNF-α, ICAM-1 and VCAM-1) may also contribute to oxidative stress.

Three studies were found which examined the effects of cadmium, and cardiopulmonary types of effects were dominant. Rats that consumed one percent sodium, 1 ppm cadmium, or 1 ppm cadmium plus 1 ppm lead in drinking water and all developed mild hypertension in rats (Perry *et al.*, 1983). Human occupational studies on cadmium inhalation were focused on respiratory effects. Exposed nickel-cadmium battery workers had a significantly higher prevalence of subjective respiratory symptoms including cough, phlegm, and upper respiratory tract infections, but no difference was noted for the pulmonary function test (Li *et al*., 2020). Cadmium in urine may be a good biomarker for assessing pulmonary risk. In the cross-sectional study of jewelry workers by Moitra *et al.* (2013), urinary cadmium was 10 times higher in exposed vs. exposed workers and for every 1 µg increase in urinary cadmium there was a 34 ml decrement in FVC and a 39 ml decrement in FEV1 ($p < 0.01$).

Two studies were selected for lead exposures. Mameli *et al*., (2001) exposed rats for 3 months to either 50 ppm of sodium acetate or 50 ppm of lead acetate in the drinking water had effects on PRN, which assesses the perception of the vestibular system. Lead acetate exposed animals had increases in the blood lead ($p < 0.01$) and nervous tissue lead ($p < 0.001$). This exemplifies how readily lead is taken up into the brain, particularly the vestibular system and brain stem, making the vestibulo-ocular-reflex a meaningful non-invasive screening tool for neurotoxic effects of lead even in the absence of overt signs. In addition to neurological effects, Fischbein *et al.* (1982) reported gastrointestinal and respiratory irritation in cable-manufacturing workers who were directly exposed to lead-containing stabilizers with air concentrations of 130.0-384 $\mu g/m^3$ with a mean and standard deviation of 259.9 ± 99.1 $\mu g/m^3$. None of the worker's blood lead levels exceeded 60 micrograms per 100 ml, but their symptoms correlated with blood lead and even better with zinc protoporpyrin, which could be used as a biomarker of lead toxicity.

Lastly, one study measured respiratory symptoms resulting from industrial welding fumes which included a mixture of chromium, manganese, zinc, copper, iron, and aluminum in addition to light gases such as carbon dioxide, nitrogen oxides, ozone, and carbon dioxide (Mehrifar *et al*., 2018). As expected, respiratory symptoms were significantly higher in welders than in administrative staff ($p < 0.05$) and spirometry indicated obstructive breathing. While it is difficult to attribute the effect to a certain material in the mixture, the effect is consistent with other studies reported here.

5.3 Psychology

The majority of articles selected, based upon psychological or cognitive attributes impacted by metals, were in reference to lead exposures (Vazquez and de Ortiz, 2004; Nehru and Sidhu, 2001; Bolla *et al*., 1995; Fischbein *et al*., 1982; Stollery *et al*., 1991; Haider *et al*., 2015; Engstrom and Xia, 2017). Other metal studies about the broad topic of cognitive impacts included nanosized manganese oxide, TiO2, ZnO_2, mercury and cadmium. Both animal and human (occupational) exposures were included in these studies. Heavy metals, particularly lead, are well known neurotoxins and many of the animal studies demonstrated rapid metal uptake into the brain following exposures through various exposure routes, primarily inhalation or microinfusion into airways. However, one study administered ZnO_2 or TiO_2 on the tongues of rats and demonstration rapid deposition in nerves and brain for both metals. Histopathology revealed damage to the cerebral cortex and hippocampus, impacting learning and memory (Aijie *et al*., 2017). Following infusions of manganese oxide nanosuspensions into the trachea of rats, manganese was detected in the lungs and brain (Sarkozi *et al*., 2009). Electrophysiology of primary auditory and vision areas of the brain revealed that the latency of evoked potentials was lengthened in these brain regions, and could impact hearing and vision. In open field activity tests the rats' motor activity was decreased. Similar results have been seen with acute cadmium exposures in rats (Haider *et al*., 2015). Haider and colleagues did not measure cadmium in the brain, however one hour after intraperitoneal injection, rats were monitored for changes in several behavioral tests and exhibited increased anxiety and depression, demonstrating rapid uptake in the brain. Effects were observed in a dose-response manner suggesting that the level of impairment correlates with increasing exposure. The use of alcohol potentiates neurotoxic effects of metals which was shown with mercury (Popp *et al*., 2005). On a molecular level, animal studies for lead demonstrated prolonged disruption of neurotransmitters and acetylcholinesterase levels (Nehru and Sidhu, 2001) and interference in neuronal calcium signaling (Vazquez and Ortiz, 2004), which was supported with detriments in locomotor and cognitive capabilities.

Central nervous system toxicity makes metal exposures a major concern to the AF. As such, exposures are common in fabrication and maintenance of equipment, handling of spent fuels and munitions operations, to name a few. The human occupational studies selected in this review support the animal findings. Symptoms like tiredness, irritability, drowsiness and muscular cramps from nanosized MnO_2 exposures were reported by Gan *et al*., (1988). The primary psychological profile of lead impairment is one of sensory motor slowing coupled with difficulties in remembering incidental information (Stollery *et al*., 1991). Other researchers reported an elevated number of neuropsychiatric symptoms among lead workers (Bolla *et al*., 1995; Fischbein *et al*., 1982). Such profound impacts on psychological and cognitive attributes emphasize the importance of good engineering controls and industrial hygiene to limit exposures to metal workers, and close biomonitoring such as measuring zinc protoporphyrin as an indicator of lead exposure as suggested by Fischbein *et al*., (1982). In addition, there is a lack of nanoparticle exposure data for AF processes.

5.4 Gaps and Recommendations

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

The AI capabilities were required to complete the analyses of over 54,000 articles, collected from multiple literature databases within a reasonable time frame. DistillerSR was selected from an internal review of both open source and commercial systematic review software packages, due to its AI feature, which uses the PRISMA format (Figure 1). Unlike typical systematic reviews of a unique pharmaceutical or therapy intervention, which cover a set of standard study questions, this review was unique in that questions covering multiple different performance attributes or outcomes and how multiple different chemical exposures may affect them, in humans and animals were used to form the protocol's inclusion and exclusion criteria. Similar systematic reviews on such a broad range of exposures and effects were not found in the literature. It is well known that the more specific the study question, the better the search process and results will be. Therefore, this review represents a novel approach of using AI for "scoping" multiple related topics simultaneously, which may not have identified as much published data/information as would be collected, if each chemical and attribute was reviewed separately. In addition, due to the AF's interest in performance impacts resulting from only short-term exposures, it should be noted that effects from chronic exposures were not included. Short term exposures can induce transient effects that are not well documented for many performance attributes. Future research may be warranted in this area.

There is a need for human dose-response data for exposures to metals of interest to the AF and their impacts on attributes. The performance attributes of interest to the military means they are not commonly studied endpoints in general research especially related to acute exposures. In order to best serve Airmen and Guardians, the AF may need to conduct key studies.

In the metal class, literature meeting the selection criteria was found predominantly on lead, cadmium, manganese dioxide, titanium oxide. Exposures were mainly via inhalation of either nanosized particles or metal fumes. Data was found supporting potential impacts upon all four categories of attributes (vision, auditory, psychology/cognition, and physiology). Among these performance attributes, pulmonary function and cardiopulmonary effects, including respiratory irritation and obstruction (physiology), and a number of cognitive functions, such as learning, memory and fatigue (psychology) were most common. Only one article was found on potential vision and auditory effects, which were suggested from changes seen in neuroplasticity seen in visual and auditory brain regions. In addition, non-occupational exposure of metals (such as from hobbies) can impact performance attributes at work. In order to extrapolate potential effects of other metals from the data available in literature about metals, in silico quantitative structure-activity relationship models incorporating nearest neighbor analysis could be used. Interestingly, no studies on hexavalent chromium, which is a chemical of concern to the AF and is a known sensitizer and carcinogen, made full text review. This is likely because dermal sensitization and carcinogenicity were not included in the search terms for performance attributes of concern to the AF.

Analysis of the RoB showed that many studies have a degree of bias and that it is hard to design and conduct a perfect study. The average RoB score of the articles selected for data extraction and qualitative assessment was 34%, ranging from 13 to 81%. In general these score were higher than those of studies selected in the aldehyde review (Steele *et al*., 2021). However, due to time constraints, abstracts and articles for this report were each reviewed by one person and the DistillerSR AI, rather than two people and DistillerSR. This may have reduced the number of studies selected for full text extraction. Bias assessments are important in systematic reviews, however, it is not a replacement for scientific judgement. Most of the studies selected were not designed as randomized control trials (RCTs). Several were in vivo observational studies, as most environmental and occupational exposures are not possible, as one cannot ethically randomize people to potentially harmful exposures with no perceived benefit. Meta-analysis could not be conducted from the extracted data, as it pertained to multiple different chemicals (exposures) and multiple different performance attributes (outcomes), which are not comparable and therefore, this review was limited to scoping for relevant data.

A third of the studies included in this review (8/22) 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. 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) should be identified and prioritized for sampling, similar to currently conducted particle-size selective sampling (e.g. respirable, inhalable, thoracic).

In the absence of human dose-response data, there are risk mitigation strategies the AF can undertake to reduce Airmen and Guardian exposure to metals. For situations where nanoparticles may be generated, robust ventilation systems should be installed and their efficacy verified through real-time monitoring. For all heavy metal exposures, periodic post-decontamination hand wipes can help verify the decontamination process is effective and being followed. Many of the metals included in this study pose skin sensitization risks, so the dermal route of exposure cannot be overlooked.

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

6.0 CONCLUSIONS

Non-occupational exposure of metals (gun enthusiast, fishing weights, doing your own plumbing, stained glass artwork, soldering, hobby electronics, cosmetics and painting) can potentially impact attributes at work.

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

Bias is an issue in study design and conduction of a high quality study.

The major attributes affected by metals were respiratory, irritation, cardiovascular and cognitive effects.

Lead, cadmium, manganese dioxide, titanium oxide and zinc oxide were the metals found to impact attributes.

36% of the articles focused on nanoparticles, but the full impact of the research cannot be applied until the AF identifies processes which may generate metal nanoparticles as there is a lack of nanoparticle exposure data in AF processes.

Although not an attribute, dermal sensitization is an issue with many metals.

The AF may not be able to rely on their industrial and academic partners to spearhead research in levels of metals causing decrements to performance attributes.

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APPENDIX: Metal Occupational Exposure Limits

CAS #	Chemical Name	ACGIH TLV	NIOSH REL	OSHA PEL
13463-67-7	titanium dioxide	NP: 0.2 mg/m^{3*} Fine: 2.5 mg/m^{3*}		15 mg/m^3 (TD)
7439-92-1	lead	0.05 mg/m^3	0.05 mg/m^3	0.05 mg/m^3
1313-13-9	manganese dioxide			
7727-43-7	barium sulfate	5 mg/m^3 (I)	10 mg/m^3 (TD) 5 mg/m^3 (R)	15 mg/m^3 (TD) 5 mg/m^3 (R)
7439-89-6	iron			
7789-06-2	strontium chromate	0.0002 mg/m^3 (I)	0.0002 mg/m^3	0.005 mg/m^3
1309-60-0	lead dioxide			
7440-43-9	cadmium	0.01 mg/m^3 0.002 mg/m^3 (R)		0.05 mg/m^3
18540-29-9	chromium(VI)	0.0002 mg/m^3 (I)	0.0002 mg/m^3	0.005 mg/m^3
7440-41-7	beryllium	0.00005 mg/m^3 (I)	0.002 mg/m^3	0.005 mg/m^3 (C)
1066-40-6	trimethylsilonal			

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; CAS = chemical abstract services; I= inhalable fraction; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; R = respiratory; REL = recommended exposure limit; TD = total dust; TLV = threshold limit value; * Notice of Intended Changes 2021

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

%	percent
ACGIH	American Conference of Governmental Industrial Hygienists
AF	Air Force
AETC	Air Education and Training Command
AI	artificial intelligence
BE	Bioenvironmental Engineering
BPRs	basic performance resources
Ca^{2+}	calcium
CAS	chemical abstract services
CHET	chemical hazard evaluation tool
CNS	central nervous system
ECoG	spontaneous cortical activity
EESOH-MIS	Enterprise Environmental, Safety, and Occupational Health Management Information System
ENMs	engineered nanomaterials
EP	evoked potentials
FEV_1	Force Expiratory Volume in one second
FVC	forced vital capacity
HER	Health Effects Ratings
I	inhalable fraction
ICAM-1	intercellular cell adhesion molecule-1
IL	Interleukin
LDLs	low density lipoproteins
LTM	long-term memory
MAJCOM	Major Command
MnO_2	manganese dioxide
mg/m^3	milligrams per cubic meter
mg Mn/kg	milligrams manganese per kilogram
mg/mL	milligrams per milliliter
ml	milliliters
nano-TiO_2	titanium dioxide nanoparticles
nm	nanometers
NPs	nanoparticles
NIOSH	National Institute of Occupational Safety and Health
O*NET	Occupational Information Network (U.S. Department of Labor)
OSHA	Occupational Safety and Health Administration
OVA	ovalbumin
PKC	protein kinase C
PEF	peak expiratory flow
PEL	permissible exposure limit
pg	picograms
ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRN	post-rotatory nystagmus

REL	recommended exposure limit
RoB	risk of bias
R	respiratory
TiO_2	titanium dioxide
TLV	threshold limit value
TNF-α	tumor necrosis factor alpha
µg	micrograms
µl	microliter
$UFTiO_2$	ultrafine titanium dioxide
VCAM-1	vascular cell adhesion molecule-1
ZnO	zinc oxide