Occupational risk of chemical exposure in aviation: A systematic review

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Highlights

- A systematic review of literature of 138 manuscripts was conducted.
- On aircraft sampling demonstrates limited chemical exposure risk.
- Toxicology studies indicate apparent exposure and risk.
- Occupational risk is evident, with a need to correlate symptoms & exposure.

Abbreviations: ToCP- Tri-ortho-cresyl phosphate **TmCP**-Tri-meta-cresyl phosphate **TpCP**-Tri-para-cresyl phosphate *Other isomers noted by mmp etc. **TnaP**- Tri amyl phosphate **TnBP**-Tributyl phosphate DBPP-Dibutyl phenyl phosphate **CBDP**- Cresyl saligenin phosphate **TMPP**- tris(methyl-phenyl) phosphate **TCEP**-tris(2-chloroethyl) phosphate **TCIPP**- tris(2-chloroisopropyl) phosphate **TBOEP**- tris(2-butoxyethyl) phosphate **TPHP**- triphenyl phosphate **EHDPP**- 2-ethylhexyl-diphenyl phosphate **OP**- Organophosphate **OPIDN**-Organophosphate-induced delayed neuropathy **6-MHO**- 6-Methyl-5-hepten-2-one **AChE**- Acetylcholinesterase **BChE**- Butyrylcholinesterase **(C)AQ**- (Cabin) Air Quality **UFP**- Ultrafine particles **PBDEs**-Polybrominated diphenyl ethers **ECS**- Environmental control system **ASHRAE**-American Society of Heating, Refrigerating, and Air-Conditioning Engineers **FAA**-Federal Aviation Administration **EASA**-European Union Aviation Safety Agency **HEPA**- High-Efficiency Particulate Air

Graphical Abstract

Abstract

Occupational exposure to oil fumes, organophosphates, halogenated flame retardants, and other volatile and semi-volatile contaminants is a concern within the aviation industry. Regulation of this exposure is limited and difficult to enforce. Contaminant concentrations rarely exceed conventional air quality guidelines, but concerns have been raised about these guidelines' applicability within the aircraft environment. The Science Direct, Scopus, and Web of Science databases were queried with five search terms within this review, generating 575 results. Manuscripts that met acceptance criteria and screening (138) were subdivided into categories: On aircraft sampling, biomonitoring, survey and cohort studies, laboratory and modeling experiments, and review / informative manuscripts. Each category is analyzed, compared, and distilled within the review. Several potential areas requiring future examination were identified: Potable water on aircraft should be examined as a potential source of pollutant exposure, as should air conditioning expansion turbines. Historical exposure should also be more fully explored, and non-targeted analysis could provide valuable information to comprehend the aircraft cabin exposome. Occupational risk under typical flight scenarios appears to be limited for most healthy individuals, but questions remain regarding those that are more vulnerable. Additionally, establishing the effects of chronic low dose exposure and exposure to contaminant mixtures has not been satisfied. Finally, the risk of acute exposure in mitigable fume events is substantial, and technological solutions or the replacement of compounds of concern for safer alternatives should be a priority.

Key Words:

"Aircraft," "Organophosphate," "Air Quality," "Flight crew," "Aerotoxic"

1.0 Introduction

The International Labour Organization, a specialized agency under the United Nations umbrella, estimates that a worker dies directly, or resultant from, toxic chemical exposure every twenty seconds (United Nations, 2018). Globally, occupational health and safety legislation provide workers and employers with rights and responsibilities for safe work. For example, the Canadian Occupational Health and Safety Act (S.N.B. 1983, c. O-0.2) legislates three rights that workers have regarding their employment; the right to refuse what is perceived to be unsafe, the right to participate in safety-related decision making, and the right to be informed regarding potential or actual dangers present in the workplace (Government of Canada, 2021). In the United States of America, the 1970 Occupational Safety and Health Act (91-596) asserts that employers must provide "… employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees" (Occupational Safety and Health Administration, 2004). Occupational hazards associated with flight include increased dosage of cosmic radiation, circadian rhythm disruption, mild hypoxia, low humidity, increased ozone concentration with associated reaction products, and potential exposure to a host of volatile organic compounds (VOCs) (Wilson et al., 2003; Waters et al., 2009; Harrison and Mackenzie Ross, 2015; Wolkoff et al., 2015). Many of these risks are innately coupled with flying at altitude, such as increased exposure to cosmic radiation. Others are similar to working in other indoor environments, such as exposure to a quantity of VOCs. However, it is theorized that the method of pressurization of most aircraft cabins, bleed air systems, may add occupational risk not innately linked to flight or work in other environments.

The majority of modern jet aircraft utilize air bled from the engines to perform several tasks essential for high altitude flight. Cabin and hydraulic system pressurization, engine cowl and wing deicing, windshield rain and ice protection, engine thrust reversers, and pressurizing the potable water and waste systems on the aircraft are all completed in this manner (Moir and Seabridge, 2008). On most modern commercial aircraft, the air is drawn into the engine, entering several compression stages before adding fuel and the mixture's combustion. Pressures and temperatures within the compression sections are highly variable, depending on the location and engine operating conditions (Moir and Seabridge, 2008). In conjunction with the environmental control system (ECS), the bleed air system provides relatively consistent pressure and quantity of fresh air that can be supplied to the aircraft at any engine speed. The ease, efficiency, and availability of this pressurized gas make it invaluable for the numerous functions. Even so, the interaction between the air and the engines before entering the cabin has been identified as a possible source of contamination (Michaelis et al., 2017).

Bleed air contamination may occur when seals, bearings, and hydraulic components fail, allowing intact and pyrolyzed oil and additives to enter the cabin (Michaelis, 2018). Additionally, these components are typically designed to "leak" at low levels (Michaelis, 2018). The air's pathway to the aircraft's cabin and cockpit is typically not filtered and is not generally monitored for contamination (Hunt et al., 1995; Harrison and Mackenzie Ross, 2015). Commercial aircraft engine oil often contains isomers of tricresyl phosphate (TCP), used as an anti-wear agent and flame retardant at approximately 3% by volume (Winder and Balouet, 2002). TCP, particularly the ortho-substituted isomers, are known to be neurotoxic (Petroianu, 2016). It is the suspected exposure of pilots and flight attendants to this compound, as well as an unknown aggregation of other contaminants found within the engine oil, deicing fluid, hydraulic fluids, and flame-retardant materials, followed by potentially resultant symptomology, that has led to the coining of the term “Aerotoxic Syndrome” to describe occupational illness on aircraft (Winder and Balouet, 2000). In response to the concern about the neurotoxicity of Tri-ortho-Cresyl Phosphate (ToCP), concentrations have been reduced in oil formulations resulting in the absence of detectable levels of ortho isomers of TCP in new or used aircraft oil (Winder and Balouet, 2002; Megson et al., 2016; 2019). ToCP, other TCP isomers, other organophosphates (OPs), and VOC concentrations on monitored flights have been reported at concentrations well below traditional safety guidelines, often falling below limits of detection; this has led to the belief by some that “Aerotoxic Syndrome” may not be an occupational illness (Wolkoff et al., 2015; de Ree et al., 2014).

At issue with this determination is the limited and conflicting data regarding air contamination during fume, smoke, and smell events and the impacts of chronic low dose exposure. The majority of studies to date have not been able to sample fume events, although the concentrations of many contaminants have been estimated (Wolkoff, 2015; de Ree et al., 2014; Harrison and Mackenzie Ross, 2015). Fume events are expected to produce the highest concentrations of contaminants in the cabin (Solbu et al., 2011), but such events' random occurrence makes practical sampling very difficult. Shehadi et al. (2016) calculated the average frequency of fume events as 2.1 incidences per 10,000 flights, and the maximum reported incidence, by aircraft type, per flight was 7.8 per 10,000. This creates a significant temporal and financial challenge in collecting a statistically relevant number of fume event samples. However, contamination of the cabin and cockpit may occur without a detectable fume event occurring. Several studies imply that low-level contamination of cabin air occurs in the absence of noted fume events. There may be additional TCP sources on aircraft, the impacts of which are still in question (de Ree et al., 2014; Crump et al., 2011).

This review aims to use a balanced and systematic approach to examine, summarize, and critique the available literature to determine if a significant occupational risk from chemical exposure exists in this environment. A holistic approach is taken including characterization of the contaminants present on aircraft by direct measurement (Section 3.1), and modeling and laboratory experimentation (Section 3.2). Also assessed are the potential health consequences of exposure in animal and biomonitoring studies (Section 3.3), and the reported health effects reported by aviation employees on an occupational scale (Section 3.4). The review is completed to identify discrete knowledge gaps within this research area and provide a comprehensive understanding of occupational risk as it applies to work within the aircraft cabin.

2.0 Methods

2.1 Search Parameters and Resource Identification

The present systematic review follows the 2009 PRISMA guidelines (Moher et al., 2009) to identify research articles on occupational risk in aircraft (Figure 1.). The systematic review employed five search terms:

1. *(("aerotoxic" AND aircraft) AND (organophosphate OR occupational OR exposure OR neurotoxic OR psychosomatic OR symptoms)).*
2. *(("cabin air quality" AND aircraft) AND (fumes OR smoke OR oil OR mist OR particles OR sulfur OR metals OR flame retardant OR pesticide)).*
3. *(("aircraft engine oil") AND (tricresyl phosphate OR tcp OR tocp OR tmcp OR tpcp OR bleed air OR hydraulic OR potable OR pyrolyzed OR tnap))*.
4. *(("flight crew" AND chemical exposure NOT "Space") AND (inhalation OR absorption OR ingestion OR illness OR complaint OR death OR flight hours OR cohort)).*
5. *("sample collection" AND "aircraft cabin" NOT tobacco).*

Each search term reflects themes within the literature, briefly stated as occupational exposure and symptoms, contamination events, source delineation and contaminants of concern, exposure pathway and duration, and sample collection. The words "tobacco" and "space" were excluded due to large numbers of irrelevant results generated. Each term was searched for within three databases: Science Direct, Scopus, and Web of Science, generating 285, 212, and 78 results, respectively, for a total of n = 575 manuscripts (Fig 1.). Searches were conducted up to January 15, 2021.

2.2 Acceptance Criteria and Screening

Three acceptance criteria were applied; 1) Papers must be in the English language due to author fluency, 2) Full-text availability and 3) Duplicate Removal. Initial screening involved a title review (removing n = 102), abstract review (removing n = 76), and finally, a full-text review (removing n = 23). Each of these removals was at the author's discretion (KH, following consultation with DM & GoS), based principally on relevance to this manuscript. Following the screening, commonly cited manuscripts from within the systematic review and the general field were included for completeness (n = 22) (SI-Table 1). Results included a total of 138 manuscripts that are analyzed. Finally, these manuscripts were subdivided into two categories: *Experimental* and *Review*. Experimental manuscripts were further classified into four subgroups (Fig 1.). Resources that fit more than one category were placed in each to which they belonged for meta-analysis.

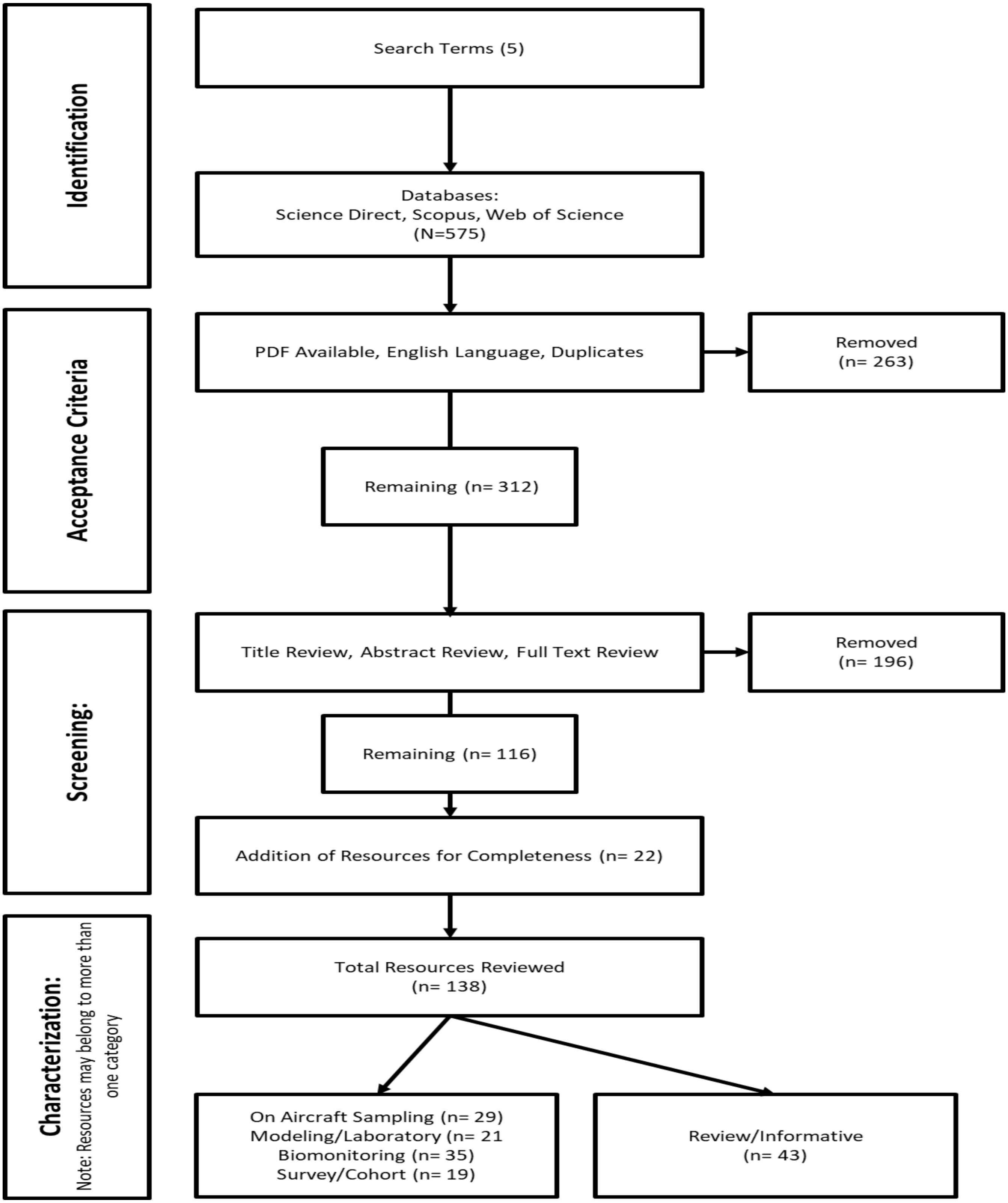

Figure 1. Abbreviated methods describing the acquisition and screening of identified manuscripts.

3.0 Results and Discussion

One hundred thirty-eight manuscripts were reviewed in this study, spanning slightly over three decades of research. Grouping the manuscripts by decade, 1990-1999 (n=8), 2000-2009 (n=26), 2010-2019 (n=88), and 2020-2021 (n=17), the progression of the field may be observed. The research in the 1990s was principally related to tobacco smoke or radiative dose. The first manuscript considering bleed air as a potential source of contamination on BAe-146 aircraft was van Netten (1998). In the 2000s, research turned towards symptoms of aircrew and passengers and cabin air quality. The impact on circadian rhythm crossing time zones and ozone in the cabin were also prominent in this period. The first biomonitoring experiment on chromosome aberrations and translocations linked to cosmic radiation exposure was also reported (Heimers, 2000; Yong et al., 2008). This period also included early discussions on jet oils' potential toxicity and the term Aerotoxic Syndrome's coining (Winder and Balouet, 2000;2002). The 2010-2019 decade saw increases in airplane cabin sampling experiments, biomonitoring studies related to chemical exposure on aircraft, and increased focus on TCP isomers. The most recent research (2020-2021) is largely focused on demonstrating susceptibility to OP exposure via genetic mutation, impacts of exposure, and possibly potential treatments for chronic effects. This review will examine the field's evolution through aircraft cabin sampling, biomonitoring, cohort/ survey studies, and laboratory experiments in upcoming subsections.

3.1 Chemical Characterization of the On Aircraft Cabin Environment

Concern has been raised that research has not adequately confirmed that health impacts result from chemical contamination of the aircraft cabin, primarily based upon the intermittency and lack of severity of exposure (Bagshaw and Illig, 2019). In support of this claim are several studies: Wolkoff et al. (2015); Lindgren et al., (2002); Schuchardt et al., 2019; and de Ree et al., 2015; that suggest there is a limited, if any, chemical contribution occupational risk for aircrew. This is based mainly upon conventional threshold values. Some of the manuscript results are described as conclusive or not meeting the definition of occupationally related disease in the study's respective country. However, the prescribed threshold limits cited in these studies are not explicitly designed for, and may not be adequately suited to, the aircraft environment. Watterson & Michaelis (2017) discuss some of the established threshold limits' failings: They do not consider differences in sensitivities or sensitization of workers, atmospheric pressures, and time of exposure. Additionally, the authors state that threshold limit values (TLVs) are for individual compounds and are not suited for application in complex mixtures' incidences. Multiple sources within this manuscript are quoted as stating that TLVs or occupational exposure standards are not well suited to the aircraft environment, including the Aerospace Medical Association, ASHRAE, EASA, aircraft manufacturers, and other industry sources.

A wide range of contaminants of concern have been investigated within aircraft cabins, including tobacco, particulate matter, flame retardants, tricresyl phosphates, and other OPs, smoke, fume and smell events, and volatile organics. Table 1 summarizes the measurement of center values, max concentration, and an abbreviated list of citations for the manuscripts reviewed in this study. More detailed information is available in SI-Table 2. In the following sections, we will explore the literature around each of these contaminants of concern.

Table 1. An abbreviated description of on aircraft sampling manuscripts from within the systematic review. Mean and Median (denoted by *) composed of the measurement range of all relevant manuscripts. Max value is the maximum value individually within all relevant manuscripts. Unit Changes (denoted by **) used temperature

=25°C, Pressure= 760hPa (8000ft equivalent).

Contaminent of Concern	Range of Measure of Center	Max Value	Literature
PBDEs (air sampling)	<0.4 - 1.3ng/m3 *	2100ng/m3	Allen et al, 2013
PBDEs (dust sampling)	20 - 495000ng/g*	2600000ng/g	Allen and Stapleton et al, 2013
TVOCs	7ug/m3 - 4ppm*	>10ppm	Crump et al, 2011; Guan et al, 2015; Rosenberger, 2018; Rosenberger et al, 2016; Solbu et al, 2011; Wang et al, 2014
Carbon Monoxide	<LOD - 3ppm	>5ppm	Crump et al, 2011; Lee et al, 2000; Nagda et al, 1992; Rosenberger, 2018; van Netten, 1998
Carbon Dioxide	520 - 2700ppm	5177ppm	Giaconia et al, 2013; Guan et al, 2019; Guan et al, 2015; Lindgren and Norback, 1991; Lee et al, 2000; Li et al, 2014; Lindgren et al, 2007; Nagda et al, 1992; Rosenberger, 2018; van Netten, 1998; Wieslander et al, 2000
Ozone	<LOD - 117ug/m3**	302ug/m3**	Lindgren and Norback, 1991; Lee et al, 2000; Nagda et al, 1992; Rosenberger, 2018; Rosenberger et al, 2016; Spengler et al, 2004
TCPs (air sampling)	<LOD - 2.9ug/m3	51.3ug/m3	Crump et al, 2011; Denola et al, 2011; de Ree et al, 2014; Rosenberger, 2018; Rosenberger et al, 2016, Solbu et al, 2011; van Netten, 2009; van Netten, 1998
TCPs (wipe sampling)	<LOD - 1.15 ng/dm/day	8.3ng/dm/day	de Ree et al, 2014; Solbu et al, 2011
ToCP	<LOD - 0.07ug/m3	22.8ug/m3	Crump et al, 2011; Denola et al, 2011; de Ree et al, 2014; Rosenberger et al, 2016; Solbu et al, 2011
Particulate (UFP) & <1.0um	417 - 100000 counts/cm3	>500000counts/cm3	Crump et al, 2011; Guan et al, 2019; Li et al, 2014; Lindgren et al, 2007; Zhai et al, 2014
Cosmic Radiation	1 - 4 mSv annual	4.69 mSv annual	Lewis et al, 1999; Verhaegen and Poffijn, 2000

3.1.1 Tobacco

In some of the earliest manuscripts on cabin air quality (CAQ), tobacco smoking and the resulting particulate matter was the principal agent of concern (Lee et al., 2000; Lindgren and Norback, 1991; Nagda et al., 1992; Wieslander et al., 2000). The manuscripts found in this review included information on the sampling of 138 flights and are summarized in SI-Table 2. Following the smoking ban on aircraft, all studies demonstrated a significantly lower respirable particle count and improved CAQ.

3.1.2 Particulate Matter

Particulates exposure risk on modern flights, post-ban on smoking, are described in 5 manuscripts sampling 148 flights (Table 1; SI- Table 2). The manuscripts related increased particle counts to several factors, including particle size, age of the aircraft, flight phase, weather, human emissions, following aircraft in flight, and unknown causes. The mean range of PM by flight varied dramatically (Table 1), indicating that some of these factors must play an important role. Particle size played a predictable role in particle count, increasing by volume with decreasing diameter. Flight through clouds or trailing aircraft, presumably drawing engine emissions and water vapor through the bleed air system, demonstrated large particle count increases. Cruising appears to demonstrate low particle counts, while taxiing causes higher counts. Turbulence also increases particle count, possibly shaking loose particulate that otherwise would remain entrained within the ECS of the aircraft. Particulates that remain airborne within the cabin are likely to be brought through the aircraft's recirculation system, including HEPA filtration, decreasing counts by volume. This, coupled with deposition, is likely responsible for the temporal spike nature of the measurements. Sustained high counts have been demonstrated to exist when a steady source of particulates enters the cabin via the bleed air system. This issue will likely not be resolved on bleed-less aircraft, pending filtration of the pathway, as outside air is still required to pressurize the cabin. For a complete description of the measurement of center values and particle size breakdown, see SI-Table 2.

Chemical qualification of the particulate matter was lacking in most cases within the reviewed manuscripts. The sample collection primarily involved continuous monitoring, determining counts by volume but neglecting to determine particle composition (SI-Table 2). Dust and wipe sampling (sections 3.1.3 & 3.1.4) have demonstrated that OPs and brominated flame retardants are present as PM, emphasizing the need for qualification (Table 1; SI-Table 2). Chaturvedi (2009) refers to a 2004 U.K. study in which black carbon-like deposits were found in cabin air supply ducts. This carbon-like material contained many VOCs and semi-volatiles (SVOCs) such as TCP isomers and tris(methyl-phenyl) phosphate (TMPP). It was determined that this substance was easily dislodged; however, the semi-volatiles only became available following solvent extraction. Fouling of the palladium catalyst to remove ozone from the air was also noted (Farrauto & Armor, 2016). Early designs of the catalyst were fouled by elements not expected to exist in the high-altitude air. These included sulfur, phosphorus, silicon, chlorine, sodium, and calcium, positively correlated with increasing flight time (Farrauto & Armor, 2016). Silicon was determined to have originated from o-rings within the engine; sodium and chlorine may be explained by saltwater mist; phosphorus and traces of zinc result from traces of oil vapor used to lubricate equipment. The sulfur collected on the catalyst may be due to the emission from other aircraft or deicing procedures (Farrauto & Armor, 2016). Deicing before takeoff can contribute to elevated contamination within the cabin (Rosenberger, 2018).

3.1.3 Flame Retardants

Manuscripts by Allen et al. (2013), Allen and Stapleton et al. (2013), and He et al. (2018) explore the presence of flame-retardant compounds through the sampling of 83 flights or aircraft (SI-Table 2). Dust sampling demonstrated a much greater median loading and detection percentage of most PBDE congeners compared to air monitoring (Table 1: SI-Table 2). In general, PBDEs and OP flame retardants' loadings were higher on aircraft than in offices or homes, emphasizing PBDE 209, tributyl phosphate (TnBP), and TMPP (He et al., 2018; SI- Table 2). While air sampling demonstrated median and max values significantly lower than exposure thresholds described in Allen et al. (2013), the much larger loadings in dust and potentially related exposure routes need to be further investigated to determine potential harm.

3.1.4 Tricresyl Phosphates and other OPs

TCP isomers have been considered important when describing occupational risk on aircraft and were the principal contaminants of concern in eight manuscripts found in this review, summarizing the sampling of 400 flights (Table 1). When conducting active air monitoring, TCP is found rarely within aircraft, and when found, it is within the low µg m^{-3} range (Table 1; SI-Table 2). Other OPs such as TnBP and dibutyl phenyl phosphate (DBPP), typically linked to hydraulic oil, are more common, found in 100% and 92% of relevant samples in Solbu et al. (2011; SI- Table 2). The tri-ortho cresyl phosphate isomer (ToCP) has been the focus of several studies but is rarely reported in the aircraft environment. This may be because it was largely removed from jet oil formulations, and it is unlikely that engine conditions or catalysis will result in trans-isomerization (Megson et al., 2018). ToCP was reported in only one of the found manuscripts, with a max concentration of 22.8 µg m^{-3} (Crump et al., 2011). TCPs, excluding ToCP, are more commonly found when sampling passively, via wipe sampling, or sampling filters onboard aircraft (SI-Table 2). This is a testament to the isomers' low vapor pressure and a tendency to not remain in the air phase within the environment, raising suggestions from de Ree et al. (2014) that the compounds may become fixed within the ducting of the ECS and released sporadically in particulate form (see 3.1.2). Another exposure route that is yet to be explored fully is ingestion. Moir & Seabridge (2008) describe that the water systems, including potable onboard aircraft, are pressurized by the bleed air system. Cleaning of the water system is infrequent and may be a reservoir for contaminants. It is likely a minor issue for most workers, but hot beverages, sometimes drinking water, and cleaning procedures use this reservoir.

3.1.5 Smoke, Fume, and Smell Events

Smoke and smell events indicate increased contaminants but may not be a strong indicator of TCP entering the aircraft. Smoke was seen in several cases within Denola et al. (2011). While an incidence of smoke did lead to maximum TCP loadings of all studies included (Table 1), several other noted smoke events did not generate high loadings; for example, the second-highest TCP loading completed within Denola et al. did not have a smoke event. Smell events are likewise not consistent indicators of TCP contamination. Within Schuchardt et al. (2019), all high TCP loadings' incidences did not correlate to 17 recorded smell events. However, this does not imply that TCP concentrations are not a good indicator of potential oil leaks. In Solbu et al. (2011), an aircraft with a known oil leak was sampled, and TCP concentrations increased a hundred-fold over other TCP loadings within the study.

Chaturvedi, (2009) describes 15 non-fire aviation incidents with 17 fatalities from 1991-98. Some of these are linked to CO poisoning/ incapacitation citing exhaust malfunction as the significant cause; this review also cites a manuscript that describes many of the deaths associated with accidents in 1981 that were suspected of having been caused by contamination of the ECS (turboprop aircraft).

Additionally, TCP found in de Ree et al. (2014) shared a similar signature to the aircraft engine oil, and Schuchardt et al. (2019) also acknowledge that the compounds may be useful in providing evidence of oil leaks on bleed aircraft. Schuchardt et al. (2019) raise questions in that TCP was also found on the bleed-free Boeing 787; the authors tentatively source the contaminants in these cases to the compound's background levels within the aircraft environment. However, nondelineated sources may provide clarity to this claim. Likely the most prominent potential source that has been somewhat overlooked thus far are the air conditioning packs. Wright et al. (2018) describe that air conditioning systems are expected to be removed from aircraft at 18-month intervals for maintenance but require servicing following 3-9 months of use. This is "directly attributed to a fouling buildup on the pack PFHE," indicating that bleed air containing contaminants enters the system where the contaminants are deposited on the plate-fin heat exchangers. This deposition is not the principal issue of concern as it indicates that many of the contaminants will not reach the cabin. The air conditioning system on large commercial aircraft involves air passing through heat exchangers, a compression section, and a turbine used for expansion cooling within the air conditioning pack. Turbines require lubrication; Aviation Structural Mechanic E 1 & C by Arthur R. Paulsen Identifies this oil as meeting Mil-L-23699 specifications. This location is directly before air being sent to the mixing unit and entering the cabin. All air that passes through this section is destined to the aircraft's interior, as opposed to the vast majority of air that passes through the engines without being bled to the pneumatic system. This may imply that a small leak on a malfunctioning air conditioner pack turbine could be significantly more impactful in contamination loading than a similar leak within the engines.

The concern of fume and smoke events has not lessened; while the EASA and FAA generally consider cabin air safe for most people, they have acknowledged that risk may be present. The FAA issued an alert for operators in

2018 that calls for enhanced procedures to ensure the safety of flight crew and passengers in the event of fumes or smoke entering the cabin (Michaelis, 2017).

3.1.6 VOCs

Twelve manuscripts focus on VOC qualification and/ or quantification (Crump et al, 2011; Guan et al, 2014; Guan & Wang et al, 2014; Guan et al, 2015; Lindgren & Norback, 1991; Lindgren et al, 2007; Rosenberger, 2018; Rosenberger et al, 2016; Schuchardt et al, 2019; van Netten, 1998; and Wang et al, 2014). The sampling of 524 flights is represented within this data (SI- Table 2). In general, VOC concentrations were lower inside the aircraft cabin as compared to other indoor locations. Guan & Wang et al. (2014) found only four compounds that exceeded airport terminal concentrations onboard aircraft, namely limonene, nonanal, acetone, tetrachloroethene, and octanal. The low values are emphasized by Schuchardt et al. (2019), who reported that higher VOC and aldehyde concentrations are found in kindergartens. Unlike a typical kindergarten, however, bleed air contamination events provide an intermittent source that may increase VOC concentrations significantly over short periods. Van Netten (1998) noted several VOCs present in an aircraft (BAe-146) grounded due to fume issues that were not present in blanks; Rosenberger et al. (2018) noted VOC concentrations that briefly exceeded German indoor air quality thresholds following a wing deicing procedure. This variability is described in (Table 1) where Total VOCs (TVOCs) measurement of center values range significantly. Unlike particulates, VOC concentrations tend to peak during the cruising phase of the flight; this has been attributed to the passengers on board or food service; Guan et al. (2015) describe that the VOC concentrations within the cabin are only minimally sourced to bleed air during flight (10%). This is contradicted in Wang et al. (2014), in which a source apportionment of the VOCs found indicated that 34% of the compounds were resultant from fuels, non-fuel oil, and combustion products. Additionally, the authors note a significant (15%) contribution from ozone reaction products. VOC reduction appears to be possible. Both Rosenberger (2018) and Schuchardt et al. (2019) noted that activated carbon filters in the recirculation air pathway decrease VOC concentrations on aircraft. For a more complete list of individual VOC loading, see SI-Table 2.

3.1.7 Other Concerns

Studies also took place to principally determine the humidity (Giaconia et al., 2013),) ozone (Spengler et al., 2004), the presence of magnetic fields (Nicholas et al., 1998), or cosmic radiation on aircraft (Lewis et al., 1999; Verhaegen & Poffijn, 2000). Relative humidity (RH) on aircraft is generally lower than other indoor environments and is consistently one factor that does not conform to guidelines. It is not uncommon for RH to drop below the 20% recommended by ASHRAE during the cruising phase of flight (Giaconia et al., 2013; Lee et al., 2000). Symptoms such as eye and throat discomfort may be due to this dryness and often improve when humidification is present (Lee et al., 2000; Lindgren et al., 2007). Humidification is not always possible on aircraft as increased weight, and corrosion issues make the prospect prohibitive. The concentration of the reactive gas ozone is enhanced at altitude; to mitigate this, many aircraft are equipped with catalytic converters to degrade the gas phase molecule (Megson et al., 2018; Farrauto & Armor, 2016). The catalysts may not always function as intended, as demonstrated by Spengler et al. (2004). Approximately one-third of the samples on transcontinental and trans-Pacific flight routes exceeded the EPA 8-hour recommended concentrations for ozone. Cosmic radiation exposure to flight crews appears to fall within traditional safety guidelines for occupationally exposed workers, with a maximum annualized dose lower than 5mSV (Table 1). Though magnetic fields were found to be elevated in the cockpit of aircraft, the impacts may be inconsequential as Nicholas et al. (2008) describe that the health effects, if any exist, are unknown.

3.1.8 Summary and Future Work

Gaps identified by de Boer et al. (2014) included limited sampling during fume events, lack of mono-ortho substituted TCP analysis, exploration of other compounds which may be pyrolyzed or otherwise, altitude effects of the compounds, and the possible introduction of contaminants via the APU. While some of these gaps have begun to be filled, it is evident that the understanding of the bleed air contamination on aircraft is very much incomplete. The concentrations of compounds of concern on aircraft are described within most reviewed manuscripts as low; however, the full exposome onboard aircraft is undescribed. The bulk of manuscripts have focused on certain organophosphates and VOCs, often due to the availability of suitable standards (SI- Table 2). However, these substances make up only a portion of what one is potentially exposed to onboard the aircraft (Winder and Balouet, 2002). High-Resolution Mass Spectrometry now allows for non-targeted analysis (Kauffman, 2014; Cavanna et al., 2016; Megson et al., 2016). This technique allows for the tentative identification of detectable compounds within the exposome without prior knowledge of the compound's existence (Cavanna, 2016). This technique could allow researchers to more fully understand what contaminants exist within the aircraft, such as the multitude of potential pyrolyzed compounds present during a fume event, allowing practitioners the ability to identify contaminants capable of entirely or synergistically contributing to the symptoms of the flight crews that have been unidentified to date.

3.2 Laboratory Experimentation and Modeling Contaminant Concentrations on Aircraft

The following describes the examination of laboratory and modeling experimentation detailed within the identified manuscripts. For a completed citation list as well as abbreviated findings, see Table 2.

Table 2. An abbreviated description of modeling and laboratory experimentation manuscripts from within the systematic review.

Author	Concern	Experiment Type	Result
Cao et al, 2014	Cabin air movement	Aircraft Mockup	Air more turbulent when cooling vents closed.
Coleman et al , 2007	Ozone Interaction with surfaces +VOCs	Laboratory Analysis	Ozone decreases with reactions on surfaces; Surface reactions form volatile products.
Isukapalli et al, 2013	Pesticide deposition	Aircraft Mockup	Aisle and center seat areas of the aircraft demonstrated elevated conc.
Ke et al, 2014	Airworthiness guidelines and compliance	Mathematical Modeling	Potentially useful model requiring experimental validation
Lushchekina et al, 2013	Reaction Kinetics- CBDP-BChE	Molecular Modeling	Describes bonding mechanisms and energy requirements for enantiomers
Megson et al, 2016	Chemical changes- new and used aircraft oil	Laboratory Analysis	No ortho-TCP was detected, xylenyl cresyl phosphates present in used oil
Megson et al, 2018	Transisomerisation via catalysis	Laboratory Analysis	TCP is probably not being altered by the palladium catalyst found onboard aircraft
Nicholas et al, 1998	Estimation of radiation dose	Mathematical Modeling	Estimated annual dose between 0.2 and 5.3 mSv
Pan et al, 2019	Particle deposition- Multislot diffuser	Laboratory Analysis	Lagrangian model suitable for prediction of particle deposition velocity.
Pan et al, 2020	Particle deposition- Multislot diffuser improvement	Aircraft Mockup	Surface roughness impacts deposition, nozzles currently fairly smooth, inconclusive
Pan...Dong et al, 2020	Particle deposition- Multislot diffuser improvement	Aircraft Mockup	New nozzle design lessens proximal particle deposition
Rai and Chen, 2009	Ozone Interactions with surfaces	Aircraft Mockup	Increase in surface area/reactive surfaces increases ozone removal efficiency
Sun et al, 2008	Photocatalytic air treatment	Aircraft Mockup	Complete decomposition of some VOCs (Toluene, Ethanol, Isoprene); Intermediate products of other compounds increase significantly
Tamas et al, 2006	Ozone Interactions with surfaces	Aircraft Mockup	Humans responsible for the majority of ozone removal; Used HEPA filters remove more ozone than new
Wu and Ahmed, 2012	Aircraft ventilation method	Mathematical Modeling	Periodic as opposed to constant fresh air supply may improve mean cabin air age. Potentially useful model requiring experimental validation
Zhou et al, 2020	Catalysis of TCP	Laboratory Analysis	Iron (II) Hydroxide or Ruthenium (II) Hydroxide catalysts effective in solution
Zhu et al, 2016	Engine oil toxicity improvement	Laboratory Analysis	Bisphenol AF bis(diphenyl phosphate) (BAFDP) may be an effective replacement for TCP

Modeling airflow and efficiency throughout the cabin and the soiling of air nozzles (multi-slot diffusers) and contaminant deposition and reactions were common themes within this category (Table 2). The soiling of air nozzles discussed by Pan et al. (2019; 2020) and Pan, Dong et al. (2020) were more concerned with the appearance of contamination as compared to concentration, in that preventing deposition on air nozzles will result in suspension or deposition of the contaminants elsewhere in the cabin. Therefore, the problem they are attempting to solve demonstrates CAQ issues. Ozone reactions and removal experimentation were also common (Coleman et al., 2007; Rai and Chen, 2009; Tamas et al., 2006). In general, the findings indicate that increased surface area, especially the presence of passengers, increases ozone removal from the air and contributes to volatile ozone reaction products within the cabin. Catalysis of contaminants within the cabin was also explored; Sun et al. (2008) installed photocatalysts in a mock aircraft cabin. Results indicate that ethanol, isoprene, and toluene were fully photo-catalytically decomposed, but intermediate products of photocatalytic ethanol oxidation such as formaldehyde and acetaldehyde were elevated. Zhou et al. (2020) attempted to develop a catalyst for the degradation of TCP. Iron (II) hydroxide or ruthenium (II) hydroxide catalysts in solution were determined to be capable of limited degradation of the compounds over a relatively short time, perhaps leading to a future in pathway catalyst for bleed air. Additionally, research is seeking to find alternatives to the use of TCP in engine oil. Zhu et al. (2016) sought to determine the effectiveness of bisphenol AF bis(diphenyl phosphate) (BAFDP) as an anti-wear additive. The thermal decomposition of BAFDP begins at approximately 359.8 °C. The total decomposition occurs at over 800C. TCP begins to decompose at 273.5 °C. The authors determined that a 2% by weight inclusion of BAFDP created the best lubrication properties in pentaerythritol oleate (PETO) as the lubricant mixture. It surpassed TCP in the same concentration in reducing wear experienced during testing. For a summary of other Laboratory/Aircraft Mockup resources included within this review, see Table 2.

3.2.1 Summary and Future Work

Although there has been more of a focus on direct characterization of the aircraft cabin environment (Section 3.1), laboratory experimentation and modeling have yielded promising methods for improving safety within the aircraft cabin. While many potential mitigating factors are early in their development, continued work should allow for their implementation on aircraft. Catalysis, filtration, and the exchange of compounds for less harmful alternatives all seem to be promising avenues for reducing occupational risk.

3.3 Biological Sampling: Evidence of Chemical Exposure

The following subsections examine the potential health consequences to the individual worker should they be exposed to identified onboard contaminants or contaminant mixtures. For a complete timeline outlining progress and the gradual change of experimental focus of biomonitoring manuscripts found within this review, see Fig. 2. For more detailed information, see SI- Table 3.

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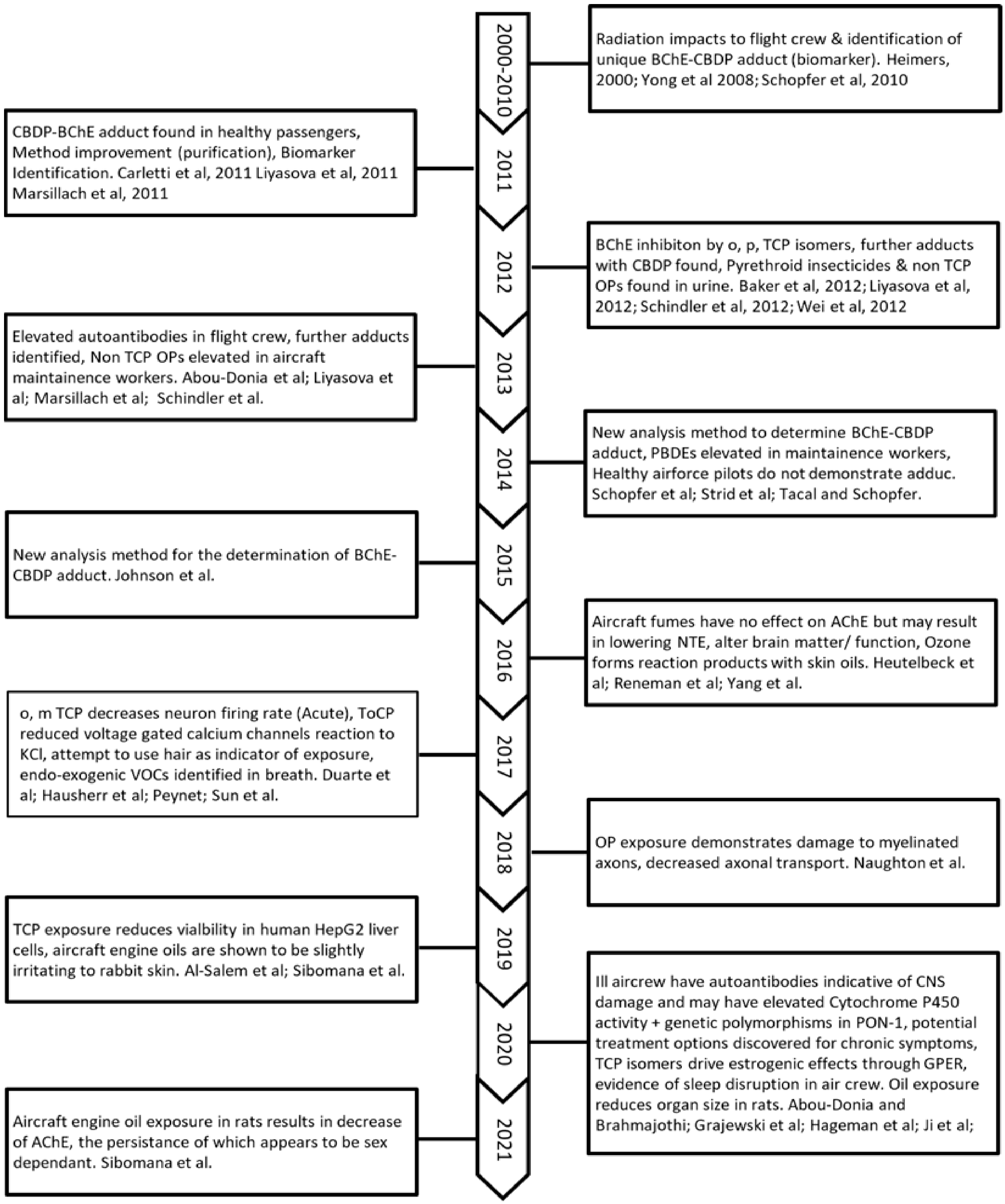

407 **Figure 2.** Timeline of biomonitoring manuscripts and principal conclusions within the systematic review.

3.3.1 Animal Exposure Studies

Eight studies were identified as animal studies, implying the use of whole animals or tissues; mice or rats or rabbits were the subjects of all studies (Baker et al. 2012; Hausherr et al., 2017; Duarte et al., 2017; Naughton et al., 2018; Naughton et al., 2020; Sibomana et al., 2019; and Sibomana & Mattie, 2020; Sibomana et al., 2021). Multiple manuscripts sought to determine the impacts of ToCP exposure (SI- Table 3). ToCP forms the metabolite cresyl saligen phosphate (CBDP) within the body through activation of the Cytochrome P450 enzyme superfamily. CBDP is a potent neurotoxicant demonstrated by resources in this review to be capable of inhibiting BChE, Neuropathy Target Esterase (NTE), impacting the microstructure of neurons, and reducing voltage-gated calcium channels reaction to KCl, on a dose-dependent basis. This is not altogether surprising as ToCP has been known to cause neurological damage for over 100 years (Petroianu, 2016). However, ToCP has mostly been removed from aircraft engine oils and is rarely detected within the aircraft cabin (Table 1; SI- Table 2). Examining the more commonly identified tri-meta isomer has led to the conclusion that while not as potent as the ortho isomers, it also possesses the capability to cause neurological illness despite differing chemical pathways in the animal subjects (Fig. 2; SI- Table 3).

In general, the literature suggests that it is not BChE inhibition by ToCP or the other TCP isomers responsible for the complaints/symptoms associated with "Aerotoxic Syndrome" and that another action is more likely responsible. Damage to myelinated axons and decreased axonal transport, which persisted at least 30 days following exposure, was determined in rats following DFP exposure (Naughton et al., 2018; Fig. 2). Organ mass has also been demonstrated to be impacted in rats following dermal exposure to engine oil (Sibomana and Mattie, 2020). AChE inhibition arising from dermal exposure of whole oil products on rats has also been demonstrated with a possible sex-linked correlation (Sibomana et al., 2021; SI- Table 3).

3.3.2 Human Exposure-Organophosphates

Several manuscripts employed human tissues/fluids, either unaltered or with contaminant additions, to identify exposure incidences or health consequences (Fig. 2; SI- Table 3). Biological sampling, especially in those cases where the participants have been subject to aircraft environments, provides further context into the potential effects of exposure and reveals possible genetic precursors that may relate to the more seriously impacted. Polilmanti et al. (2012) describe genetic variation in the cytochrome P450 superfamily. Hageman et al. (2020) acknowledged this variability, as well as genetic differences in paraoxonase enzyme (PON-1); when tested, those believed to be symptomatic as a result of exposure were found to possess mutations on one or both. Hageman et al. (2020) suggest that if an individual were to have a low PON 1 activity and high cytochrome P450 action, they might be up to 4000x more susceptible to OP exposure. Additionally, elevated autoantibodies indicative of CNS damage have been identified in the blood of ill flight crew by Abou Donia et al. (2013) and Abou Donia and Brahmajothi. (2020). Healthy participants may also display indications of exposure; Carletti et al. (2011) describe an adduct of CBDP and BChE, which may be unique to ToCP exposure; this adduct was identified in half of a group of airline passengers who displayed no health effects (Liyasova et al., 2011). Tacal and Schopfer (2014), searching for the same adduct in healthy Airforce pilots, could not find it. Schindler et al. (2012; 2013) sought TCP and other OP metabolites in healthy aircrew and maintenance workers' urine, finding no ortho TCP and very little evidence of other TCP isomer exposure. This claim is disputed by Schopfer et al. (2014) as they argue Schindler et al. (2012; 2013) were not looking for the expected human urinary metabolites. Additionally, blood, tissue, and imaging experiments in those exposed have reported damage to liver cells, identification of other CBDP adducts, and changes to brain blood flow and white matter (Al-Salem et al., 2019; Liyasova et al., 2012; 2013; Reneman et al., 2016). Treatment options to mitigate exposure risk were also sought; Baker et al. (2012) note that a compound in grapefruit (naringenin) may be an effective treatment post OP dose. It inhibits the breakdown of triaryl phosphates to their more toxic metabolites. Naughton et al. (2020) describe that previously approved drugs, when used outside their current purpose, may prevent axonal damage and long-term neurological problems arising from OP exposure, namely lithium chloride and methylene blue.

3.3.3 Other Biological Studies

ToCP and other TCP compounds provide the simplest explanation for the neurological symptoms expressed by a small percentage of aircrew. However, they do not wholly describe what could be considered an occupational risk. The measurement of melatonin levels as an indicator of sleep disruption found that flight attendants have a significant disruption in circadian rhythm (Grajewski et al., 2020). Chromosomal abnormalities were noted in Heimers (2000) and related to cosmic radiation exposure; the abnormalities were eight times higher in Concord pilots than the control group but insignificantly increased compared to subsonic pilots. Yang et al. (2016) attempted to identify which compounds found in skin oils form reaction products with ozone. Reaction products of ozone included acetone, 6-MHO, nonanal, and decanal, each with several potential precursors in the skin oil extract. Both pyrethroid pesticides and certain PBDEs were found to be elevated in exposed flight crew and, in the cases of PBDEs, maintenance workers (Wei et al., 2012; Strid et al., 2014). Pesticides and insecticides may be related to health concerns, but they also serve critical purposes. In these and all incidences of exposure, it is essential to weigh the pros of the compound's presence with the health risks associated with their absence. Pang et al. (2020) described chemical exposure and symptoms in flight crew via pyrethroid insecticides but described the effects as limited due to very high exposure and low symptomatic response. Wei et al. (2012) also found evidence of this exposure. This must be weighed against the potential transmission of insect vectored diseases. Increasingly, the field has become more focused on low-dose chronic exposure. To quote Nicholson (2009)," Sub-clinical long-term effects cannot be completely ruled out, and whether contaminants in the air supply could be a factor in the malaise experienced by passengers remains uncertain.” Howard (2017) describes axonal transport damage caused by repeated low-dose exposure to OPs. Axonal damage is also noted in Naughton et al. (2018) and Naughton & Terry (2018). Howard (2017) suggests that multiple proteins may be "irreversibly modified by

OPs" based on the findings that adducts have been found with tyrosine and lysine and suggests that the axonal damage and protein damage may be the potential cause of the symptoms experienced in flight crews. The sensitivity of individuals is also a significant concern. Variations in cytochrome p450 superfamily, PON-1, or BChE enzyme reactivity could play an important role in some passengers' sensitivity (Carletti et al., 2011; Chen et al., 2017; Hageman et al., 2020).

3.3.4 Summery and Future Work

The examination of animal models and workers occupationally exposed to identified contaminants demonstrate undesirable effects and therefore occupational risk. Evidence is mounting; however, efforts should be made to ensure that exposure is related completely or synergistically with the aircraft environment. Additionally, if sensitivity to compounds of concern can form from exposure, as theorized by Watterson & Michaelis (2017), historical exposure to the contaminants must be considered. Schopfer et al. (2010) describe TCP as being a lead scavenger from leaded gasoline. The product is still used in the leaded fuel for piston-engine aircraft (AVGAS) and is sanctioned by the FAA (Alcor, 2012). This implies that commercial pilots in training, or any flight crew that fly recreationally and are exposed to fuels, may interact with significant TCP concentrations before/outside of occupational exposure.

3.4 Health Effects: Survey, Cohort, and Records Studies.

The following subsections describe the examination of the aggregated health consequences of occupational exposure of aviation workers. For a completed citation list of manuscripts as well as abbreviated findings, see Table 3.

Table 3. An abbreviated description of the survey, cohort, and record study manuscripts.

Author	Concern	Experiment Type	Participants	Result
Burdon et al, 2017	Health concerns- Aircraft fumes	Survey	Part A- Pilots- 274 Part B- Flights with oil leaks- 15	Part A- 142 reported symptoms and diagnosis, 30 AHE, 77 healthy; Part B- 14 impairment of flight crew, 11 AHE, 4 passenger AHE
Weislander et al, 2000	Subjective cabin air quality	Survey	Flight Crew- 51	Noted improvement in CAQ following smoking cessation on aircraft
dos Santos Silva et al, 2013	Cancer Prevalence	Cohort	Flight Crew- 16329 Air Traffic Controllers- 3165	Lower than average risk as compared to the general UK population, less skin cancer. Lower than average risk as compared to the general UK population, not inclusive skin cancer
Grajewski et al, 2011	Circadian rhythm disruption; Cosmic radiation exposure	Records Review	Pilots (male)- 83	Potential for chronic sleep disturbance; Est. 1.92mSv annual. Additional risk due to solar storms, avg exposure rate 1 : 3.7 years
Lee et al, 2000	Subjective cabin air quality; Health concerns- Cabin environment	Survey	Flight Crew- 185	37% Reported CAQ as acceptable. 21% considered it to be poor. Humidity was a concern; Health symptoms ranging from none-severe. Majority not related to dryness low on scale.
Lindgren et al, 2007	Subjective cabin air quality	Survey	Flight attendants-58 Pilots-22	CAQ reported as improved when humidification present.
Lindgren et al, 2002	Subjective cabin air quality; Health concerns- Cabin environment	Survey	Flight Crew- 19	Improvement in all categories save facial rash following smoking cessation on aircraft; CAQ reported as improved after smoking ban
McLain and Jarrell, 2007	Perception of Safety VS obligation	Survey	Hazardous Job Workers- 239	Did not significantly demonstrate a relationship between working safely and production pressure
McMurtrie and Molesworth, 2017	Risk Perception	Survey	Pilots- 270	Pilots over estimated risk across age and experience categories. More experienced/older pilots tend to identify the risks in lower categories.
McNeely et al, 2018	Health concerns- Cabin environment	Cohort	Flight Attendants-5366	Increased risk of reproductive cancer, all cancers, fatigue, sleep disorders, mental health concerns; Reduced risk of respiratory and cardiovascular disease
Nicholas...Dosemeci et al, 1998	Health concerns- Cabin environment	Cohort- Mortality	Pilots & Navigators- 1538	Cancer of the prostate, colon, mouth, throat, lips, and brain increased Lungs, trachea, stomach reduced. Significant increase in motor neuron disease; suggested increase in nervous system and sense organs disease; Reduced heart, respiratory, and digestive system diseases
Pinkerton et al, 2016	Health concerns- Cabin environment	Cohort- Mortality	Flight attendants- 11311	Possible increased risk of ALS, not clearly linked to exposure (Employment duration not correlated).
Polimanti et al, 2012	Genetic variation- Cytochrome P450	Records Review	Individuals- 1694	Significant genetic differences in P450 super family observed in terms of ethnicity (Single nucleotide polymorphisms)
Sagiraju et al, 2020	Health Concerns- Military Service	Cohort	Service People- 1149620	Significant increase in ALS within the Airforce as compared to other disciplines. Significant increase in ALS people who routinely fly/ work with aircraft (Quantified tactical operations officers)
Schubauer-Berigan et al, 2015	Health concerns- Cabin environment	Cohort	Flight Attendants- 11324 (total)	Breast cancer rate 37% higher than general US population, could not be linked to workplace exposure, Link may reflect differing reproductive habits of flight attendants VS the US general population
Stravola et al, 2012	Health concerns- Cabin environment	Cohort	Flight Crew- 16327 Air Traffic Controllers-3162	Mortality (all cause) of flight crew was about 1/3 of the general population (largely male study group); Only category that exceeded the UK general population or the control group was death due to aircraft accidents
van Drongelen et al, 2015	Health concerns- Flight duration	Records Review	Flight Crew- 8228	Short haul flights linked to reduced sickness absenteeism.

3.4.1 Comparative Health & Cohorts

In general, pilots and flight attendants are considered to be more physically fit as compared to the general populations within their respective countries of residence, typically demonstrating reduced risk of cardiovascular and respiratory disease (De Stravola et al., 2012; dos Santos et al., 2013; McNeely et al., 2018). They do seem to have an elevated risk of certain cancers (sex-dependent), mental health, and neurological issues, with tenuous links to the workplace (Table 2). Of particular concern is the potential risk of working with/around aircraft and the incidence of amyotrophic lateral sclerosis (ALS). Two studies identified a potential link between this disease and work in the field; Pinkerton et al. (2016) conducted a mortality study of flight attendants collected from airline records (PAN AM) that indicated ALS occurrence in the cohort is 2.21x that of the general population. This finding was based on a small number (nine) of deaths and could not be correlated to flight hours. More significantly, a second study including more than a million post 9-11 servicemen and women in the United States demonstrated a significant increase in the disease within the Airforce branch of the armed forces and elevated within tactical operations officers (pilots, aircraft crews, and missile combat operations staff officers) as compared to other officers within this service (Sagiraju et al., 2020). The authors suggest that due to the difference between the people who routinely work with aircraft and other officers, environmental concerns should be explored.

3.4.2 Self-Reported Symptoms and Air Quality

Generally, cabin humidity and the cessation of smoking on flights weigh heavily on perceived CAQ (Table 3). Lee et al. (2000) and Lindgren et al. (2002; 2007) describe many symptoms noted by aircrew, the majority of which can be explained by cabin dryness with only a minority that could be neurologically related. Burdon et al. (2017) conducted surveys more directly related to chemical exposure (Table 2). More than half of the pilots surveyed reported specific symptoms and diagnoses. Approximately 10% reported adverse health effects (AHE), with 28% reporting no health effects. The majority of participants were aware of the risk of exposure. In a second study, 15 CAQ incidents on various aircraft were examined, in which leaking oil could be detected in 13 of the cases. Degrees of incapacitation/impairment of flight crew were reported in 14 of these cases, and adverse health effects were experienced in 11 cases. Adverse effects in passengers (four) were also noted. The authors use Bradford Hill causation criteria, and according to their interpretation, eight of nine factors were in agreement with only dose-response not met.

3.4.3 Safety and Risk

McLain and Jarrell (2007) issued questionnaires to workers in hazardous positions, weighing safety versus production, to better understand how safety is treated when several conflicting demands are made upon the worker. The survey result failed to "find a significant relationship between pressure to produce and safe work behavior." McMurtrie and Molesworth (2017) questioned how different pilots experience risk and assessment of said risk. They attempted to determine if the accuracy of risk assessment changes with many factors, including experience (i.e., rank, flight hours, license type, recency) and age. In general, the pilots overestimated risk across age and experience categories. However, more experienced/older pilots did trend to identify the risks in lower categories.

3.4.4 Summary and Future Work

The nature of these studies results in data that may lag years or decades behind changes made within the workplace. Continued cohort studies should be conducted to determine if any modifications, such as the introduction of bleed-free aircraft, have the desired effect on occupational risk. Additionally, surveys should be conducted, including those who fly recreationally or for training purposes and use products which contain TCP or similar products as lead scavengers for their fuel. This may help with the determination of historical exposure and sensitization. Finally, further work is needed to clear conflicting information that is provided by these manuscripts. Health effects range from several types of cancers and neurological concerns elevated in aircrew, to the only cause of elevated mortality in the group relating to aircraft accidents (Table 2; Nicholas et al., 1998; De Stravola et al., 2012). A clearer picture, addressing confounding variables, would be very beneficial for the determination of occupational risk.

4.0 State of the Science: Knowledge Gaps and Future Recommendations

Numerous recognized incidences of illness, at least tangentially, are related to chemical exposure onboard aircraft, likely due to technological /design flaws. It is in everyone's best interest to ensure aircraft safety, yet the changes in technology/design are difficult to make due to financial, logistical, and technological reasons. Pilots, other aircrew, airline management, and manufacturers are aware, or should be made aware, of the potential for contaminated air to enter the aircraft (Burdon et al., 2017; Michaelis, 2017)) and yet a potential hazard remains. Even if this applies only to severe fume events and not the low dose chronic exposure theorized by many, a mitigable concern is not resolved; this is bound to create dissonance. Occupational risk reduction may be beneficial for all stakeholders involved. There may be financial benefits to freeing or limiting contaminant intrusion into the cabin. Shehadi et al. (2015) estimated the overall losses in 2012 by airlines in the USA due to fume events between $4.5M to $7M, with each incident ranging from S32K - $47K.

It is evident within the literature that there are opposing viewpoints in determining occupational exposure risk to flight crew. Of the experimental manuscripts reviewed, 38% made declarative statements in favor of, or opposed to, the occupational risk of chemical exposure within the cabin and 62% did not. Within the declarative subset, those papers which were determined to be in favor of occupational risk acknowledged stakeholders in 33% of the manuscripts. Those manuscripts which were opposed to occupational risk acknowledged stakeholders in 67% of the cases. Stakeholders included pilot and flight attendant unions, advocacy groups, aircraft manufacturers, and operation firms. When pilot and flight attendant unions or advocacy groups were acknowledged, 80% found in favor of occupational risk, none were opposed, and the remaining 20% undeclared. When airline manufactures and operator stakeholders were acknowledged, 5% were in favor of occupational risk, 42% were opposed, and 53% were undeclared.

4.1. Summary of Identified Gaps Requiring Further Research

This systematic review identified two key areas where there were significant knowledge gaps and need for further research. These included a better characterization of the on aircraft environment and understanding the cause of adverse health effects. There is also an imperative to combine these two approaches as research appeared to be aimed at achieving one of these two objectives, however they should be considered in unison.

Characterization of the on-aircraft environment

From reviewing manuscripts that have measured the on-aircraft environment it is clear that the full exposome onboard aircraft has not been fully characterized. Modeling and laboratory-based experiments have provided useful incites to help develop mitigation technologies, however many of these are still in the proof of concept stage. To help address these knowledge gaps the following research would prove useful;

- A determination of the contamination contribution of the expansion turbines within the air conditioning systems on aircraft needs to be completed. These turbines use similar oil to that found in aircraft engines and contain the same principal contaminants of concern. This may apply not only to bleed-air equipped aircraft but also to bleed-free designs should they use this cooling method.
- The potable water on aircraft should be explored as it is currently an undefined potential source of exposure.
- Non-targeted screening of active air and passive samples taken on aircraft should be conducted to supplement targeted studies to identify potential contaminants that have not yet been described.
- Scaling up of proof of concept laboratory studies to involve more on flight testing of technologies to reduce contaminant levels in the cabin environment

Understanding the cause of adverse health effects

- Historical exposure to TCP and other OPs should be examined, especially in the cases of those who fly/flew recreationally or in training in piston engine aircraft using lead scavenging products in the fuel.
- Further evidence of genetic mutations responsible for OP exposure susceptibility is required as the claim is currently supported by small sample sizes.
- Continued monitoring of health, especially of those who work on bleed-free aircraft should be conducted. This will allow more complete source delineation should the symptoms of exposure remain or decrease on this type of aircraft.

5.0 Conclusions

Flying, in general, is safer than it has ever been. Improvements to technology and ruggedness of aircraft components and improved pilot training have led to fewer accidents (Oster et al., 2013). However, the manuscripts identified within this systematic review provide evidence of occupational risk. To qualify, many of the individual manuscripts reviewed suffer due to small sample sizes, experimental design flaws, or perceived potential bias. However, when examining the totality of manuscripts, the potential for occupational risk cannot be ruled out. Biological sampling and cohort studies indicate that neurological concerns are elevated in those that work on and with aircraft. However, the sampling of aircraft has not yet identified a contaminant or mixture of contaminants in sufficient concentration proven to be capable of the symptomology. Further research is required to determine this contaminant or mixture should it exist, and further evidence of the impacts of chronic low dose exposure and susceptibility studies are required for the known contaminants. Additionally, fume events continue to create a significant risk for those flying. Despite the relatively low incidence of occurrence, in a return to normal flight frequency, several of these events would be estimated to occur daily.

7.0 Declaration of Competing Interest

The authors declare that they have no known competing financial interests that could have influenced this paper's writing.

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