Environment International 87 (2016) 74–84

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Pollutant exposures and health symptoms in aircrew and office workers: Is there a link?

Peder Wolkoff [a,*], Derrick R. Crump [b], Paul T.C. Harrison [b]

[a] National Research Centre for the Working Environment, Denmark
[b] Cranfield University, Bedfordshire, UK

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form 4 November 2015
Accepted 9 November 2015
Available online 28 November 2015

Keywords:
Commercial aircraft
Health effects
Offices
Ozone
Relative humidity
Tricresyl phosphates

ABSTRACT

Sensory effects in eyes and airways are common symptoms reported by aircraft crew and office workers. Neurological symptoms, such as headache, have also been reported. To assess the commonality and differences in exposures and health symptoms, a literature search of aircraft cabin and office air concentrations of non-reactive volatile organic compounds (VOCs) and ozone-initiated terpene reaction products were compiled and assessed. Data for tricresyl phosphates, in particular tri-ortho-cresyl phosphate (ToCP), were also compiled, as well as information on other risk factors such as low relative humidity.

A conservative health risk assessment for eye, airway and neurological effects was undertaken based on a "worst-case scenario" which assumed a simultaneous constant exposure for 8 h to identified maximum concentrations in aircraft and offices. This used guidelines and reference values for sensory irritation for eyes and upper airways and airflow limitation; a tolerable daily intake value was used for ToCP. The assessment involved the use of hazard quotients or indexes, defined as the summed ratio(s) (%) of compound concentration(s) divided by their guideline value(s).

The concentration data suggest that, under the assumption of a conservative "worst-case scenario", aircraft air and office concentrations of the compounds in question are not likely to be associated with sensory symptoms in eyes and airways. This is supported by the fact that maximum concentrations are, in general, associated with infrequent incidents and brief exposures. Sensory symptoms, in particular in eyes, appear to be exacerbated by environmental and occupational conditions that differ in aircraft and offices, e.g., ozone incidents, low relative humidity, low cabin pressure, and visual display unit work. The data do not support airflow limitation effects. For ToCP, in view of the conservative approach adopted here and the rareness of reported incidents, the health risk of exposure to this compound in aircraft is considered negligible.

1. Introduction

Epidemiological studies of aircraft crew members show a similar pattern of symptoms as those encountered in office workers within the umbrella of the so-called "sick-building syndrome" (for discussion, see Hodgson (2002)). As in offices (Wolkoff, 2013), eye related symptoms, e.g., dry or tired eyes and fatigue, are common symptoms in crew members (Nagda and Koontz, 2003) and also specifically pilots (McCarty and McCarty, 2000). Furthermore, central nervous system (CNS) related symptoms have been reported, including headache and tunnel vision — constituting the so-called "aerotoxic syndrome" (Winder et al., 2002) which has been postulated to be caused by exposure to tri-ortho-cresyl phosphate (ToCP), a known neurotoxin and an isomer of tricresyl phosphates (TCPs). Exposure to ToCP is suspected to occur as a result of bleed air contamination via the aircraft ventilation system; this includes "smoke-in cabin" or smell incidents, involving additives in jet engine oil and their possible oil pyrolysis products (e.g. Abou-Donia et al., 2013; de Boer et al., 2015, and references therein). It is suspected that bleed air contamination incidents from the aircraft ventilation system may contain TCP.

Historically, indoor pollutants, including volatile organic compounds (VOCs), have been measured in investigations of reported health effects in aircraft (Nagda and Rector, 2003; Nagda and Koontz, 2003; Wang et al., 2014) and in offices (Wolkoff, 2013); however, associations have not been established nor health risk assessment has not been carried out regarding the reported symptoms. Further, ventilation systems in aircraft with no or inadequate converters of high altitude ozone concentration may result in high cabin air ozone levels (e.g. Bhangar et al., 2008); this has prompted the 'reactive chemistry' hypothesis in which reported health outcomes are caused by ozone-initiated reaction products (Weschler et al., 2006; Wolkoff, 2013).

* Corresponding author at: National Research Centre for the Working Environment, Lersø Parkallé 105, DK-2100 Copenhagen, Denmark.
E-mail address: pwo@nrcwe.dk (P. Wolkoff).

http://dx.doi.org/10.1016/j.envint.2015.11.008

In public and commercial buildings, the advent of stricter energy efficiency measures has often resulted in a tighter building envelope and possibly lower air exchange rate; this elevates the concentration of reactive (unsaturated) VOCs like terpenes (common fragrances) in the gas-phase and may increase reactions with surface deposited reactants, e.g., squalene and other skin oils (Wisthaler and Weschler, 2010). A host of different oxygenated gas-phase products and ultrafine particles (secondary organic aerosols, SOAs) are formed (Walser et al., 2008; Nørgaard et al., 2013). This process has also been reported in aircraft cabin air (Coleman et al., 2008a; Weisel et al., 2013; Weschler et al., 2007). For instance, formaldehyde is one of the key oxidation products in the ozonolysis of limonene (Atkinson and Arey, 2003). Limonene is an abundant and common fragrance used in numerous consumer products (ter Burg et al., 2014), a major VOC emitted from meals and drink services in the aircraft cabin (Guan et al., 2014), and is present in deodorizers and disinfectants used by cabin cleaning staff (Nazaroff and Weschler, 2004). Thus, aircraft passengers and crew members are exposed not only to periodic high ozone levels, but also to a complex mixture of products from gas-phase and surface chemical reactions, while office workers may be exposed to mixtures caused by reaction of VOCs emitted into the indoor air with ozone and nitrogen dioxide from incoming ambient air.

Whether or not these terpene oxidation products cause adverse eye and respiratory effects in interior closed environments has been a long-standing research question (Carslaw et al., 2009; Rohr, 2013). For instance, a study in 100 public and commercial office buildings showed significant associations between late afternoon outdoor ozone and upper respiratory symptoms, with a trend also for irritated eyes; the authors speculated that ozone-initiated reactions could be associated with the observed symptoms (Apte et al., 2008).

The low relative humidity (RH) in aircraft cabins — usually under 10% — is another important risk factor (e.g. Backman and Haghighat, 2000; Wieslander et al., 2000) associated with the reported health effects in both aircraft and in offices (Nagda and Hodgson, 2001); however, this has never been substantiated with ophthalmologic findings.

It is generally recognized that the concentrations of non-reactive VOCs in public buildings are orders of magnitude below their threshold for sensory irritative symptoms (Wolkoff, 2013); this has never been assessed regarding aircraft cabin air, although non-reactive VOC levels, in general, are comparable with those reported for public buildings (Nagda and Rector, 2003). Thus, two possible causes for the sensory related symptoms seen in indoor environments such as aircraft cabins and offices have been proposed: reaction products from ozone-initiated chemistry and low RH. In addition, ToCP exposure of aircraft crew members has been postulated to cause the so-called aerotoxic syndrome.

Measurements in commercial aircraft cabins of non-reactive VOCs, carbonyls, TCP, and ozone-initiated reaction products have been compiled and their potential health effects on eyes and airways were assessed, together with CNS-related effects caused by ToCP in aircraft. For comparison, data on ozone-initiated reaction products in offices have also been compiled. This work integrates the information from the published aviation and indoor air literature, with the purpose of assessing whether (acute) sensory perception in eyes and airways and CNS-related symptoms are caused by reported concentrations of airborne pollutants.

2. Method

2.1. Literature search

Search in the indoor air and aviation literature was carried out for 'air quality' or 'ozone' or 'humidity' in combination with 'aircraft', 'cabin air', 'fragrance', 'limonene', 'volatile organic compounds', etc. In addition, on-line databases (including PubMed, GoogleScholar) were searched with the above keywords for papers published from 2000 until August 2015. Tricresyl phosphate was searched in combination with 'aircraft' and 'cabin air'. Data from four reports of studies were considered; Table 4 in Crump et al. (2011), Table B-3 in the BEAM and Teach studies (Spengler et al., 2012), (Houtzager et al., 2013), and Table 7 in Hecker et al. (2014). Bacteria, carbon dioxide, carbon monoxide, environmental tobacco smoke, brominated flame retardants, hypoxia, mental health, pesticides, radiation, viruses, and noise were excluded.

2.2. Health risk assessment

Health risk assessment of the non-reactive VOCs and the ozone-initiated terpene reaction products was based on a hypothetical "worst case scenario" that simulates continuous and simultaneous exposures to the maximum reported cabin (or office) air concentration of the compounds for 8 h – well-knowing that maximum or 95% percentile concentrations are episodic and brief. It is recognized that the quality and quantity of data have been limited by the general difficulties of sampling in these environments, the required sampling duration for obtaining analytical detectability, and available possibilities of sampling in view of costs. Some of the studies aimed to determine short-term peaks while others applied longer-term sampling to achieve detectability. Thus, the compiled concentration data are not homogenous. In addition, the difficulty of capturing fume/smell incidents is immense due to the requirement for sophisticated on-line analytical equipment (Bezold, 2012) and the low frequency of incidents (see below).

Risk assessment of the measured VOCs was based upon their hazard quotient (HQ) in %, defined as its concentration divided by the air quality (AQ) guideline value or estimated no-observed-adverse-effect (NOAEL) for sensory irritation, an acute effect, or respiratory airflow limitation. NOAELs for sensory irritation in eyes and upper airways were obtained from lowest-observed-adverse-effect levels (LOAELs) for sensory irritation (trigeminal stimulation) obtained from human exposure studies, divided by an assessment factor of five, as recommended by Nielsen et al. (2007); specific guidelines for limonene and acrolein were derived by Trantalidi et al. (2015). If not available, estimated NOAEL values for humans were derived from RD_{50} values obtained from mice head-alone inhalation studies (Wolkoff, 2013).

The NOAEL for benzaldehyde (2.2 mg/m^3) was based on a RD_{50} value of 1442 mg/m^3 (Steinhagen and Barrow, 1984) and use of the algorithm developed by Kuwabara et al. (2007) as described in Wolkoff (2013). Benzene was considered non-irritative (Nielsen and Alarie, 1982); further, the alkyl chlorides were considered anesthetics, not sensory irritants (RD_{50} values unavailable). Reference values and guidelines relate to acute exposure of the respective compounds (Wolkoff et al., 2013, 2014). For ozone, the WHO air quality guideline is applied (World Health Organization, 2006).

The hazard index (HI), in %, for the combined exposure of pollutants was calculated, where appropriate, as the sum of HQs assuming normal addition of the individual HQs for sensory irritation (Nielsen et al., 2007); a similar mode of action was assumed for airflow limitation in the airways. It should be noted that the guideline proposed by Wolkoff and Nielsen (2010) for sensory irritation by formaldehyde derived from the Lang et al. (2008) study may, according to the recent study by Mueller et al. (2013), be too low.

Tricresyl phosphates are not considered airway irritants. At sufficiently high concentrations, ToCP can cause respiratory failure (suppression of acetylcholinesterase) and a delayed (1–2 weeks) neurodegenerative condition (organophosphate-induced delayed neuropathy) (Craig and Barth, 1999). A tolerable daily intake (TDI) value of 50 ng/kg body weight per day (bwd) for neurotoxic effects (de Ree et al., 2014) was applied for the calculation of its HQ. This low TDI value takes into account very sensitive subjects by applying an assessment factor of 4000 * 5 to the identified ToCP NOAEL value of 1 mg/kg bwd; the factor combines the uncertainty for metabolism, clinical/neuropathological symptoms and neurobehavioral effects. Other researchers have applied a factor of only 100 or 1000, resulting in TDI values of 130,000 or 13,000 ng/kg bwd, respectively (de Boer et al., 2015; Ali et al., 2012). ECHA (2014) indicates long-term DNELs (derived no-effect levels) for the general population of 80 $\mu g/m^3$ for

inhalation and 50,000 ng/kg bwd for oral intake of TCP (systemic effects).

ToCP is considered the most toxic of the TCP isomers (de Ree et al., 2014; Weiss et al., 2015); more precisely, mono-*o*-cresyl-*m*/*p*-dicresyl phosphate (To-m/pCP) present in ToCP appears to have the greatest toxicity (de Boer et al., 2015; Denola et al., 2011). Along with the TDI value, the HQ was derived from the maximum estimated daily intake by inhalation (ng/kg bwd) following 8-h exposure to the maximum reported air concentration of ToCP, assuming an inhaled volume of 7 m^3 (20 $m^3 \times 8$ h/24 h), and 100% absorption and body weight of 70 kg.

3. Results

3.1. Reported symptoms and clinical tests

There is a strong overlap of symptom reporting among aircrew members and office workers regarding acute effects. Eye irritation, tiredness and headache are generally among the top-three reported symptoms in office workers (Wolkoff, 2013). Aircrew members also report eye-related and nasal symptoms, and tiredness (Backman and Haghighat, 2000; Fu et al., 2015; Hecker et al., 2014; Lindgren and Norbäck, 2005; Lindgren et al., 2006; Nagda and Koontz, 2003; Winder et al., 2002); similarly in passengers (Hinninghofen and Enck, 2006). However, a number of other symptoms have been reported in aircraft crew that are not common in office workers, e.g., dizziness and breathing problems (Hecker et al., 2014; Winder et al., 2002). Dry and itchy skin, ears, lips, mouth and hands have also been reported in aircraft, but less so in offices (Lindgren and Norbäck, 2005; Strøm-Tejsen et al., 2008). Stuffy and dry air and unpleasant odors (smell) are substantially more prevalent in aircraft than in offices (Lindgren and Norbäck, 2005); the prevalence of symptoms are generally higher on intercontinental than on domestic flights (Lindgren and Norbäck, 2005).

A neuropsychological assessment of a sample of 27 self-selected pilots indicated cognitive deficits, but the nature of the study did not allow for identification of a causal association with exposure to smelly fume incidents that was claimed by the pilots (Ross, 2008). Another study of 12 self-selected aircrew members used magnetic resonance imaging techniques to assess structural changes, with a focus on integrity of white matter (a component of the central nervous system and spinal cord) (Reneman et al., in press). Subtle differences in white matter were observed in comparison with 11 controls, but the sample size was small, the subjects were self-selected, and there was no information about exposures. Thus, the findings cannot be used for risk assessment purposes.

3.2. Frequency of oil and smoke related incidents in aircraft

The average incident frequency for all types of aircraft ($n = 33$), based on reported oil- and smoke-related incidents between 2007 and 2012 for US-based carriers for domestic flights and all international flights that either originated or terminated in the US, amounted to 2.1 per 10,000 flights; the highest frequency for a single aircraft type was 7.8 incidents per 10,000 flights (Shehadi et al., in press). The authors concluded that "tens of thousands of flights would have to be sampled to ensure the capture of a meaningful number of incidents", i.e., collection of hundreds of thousands of samples would be required. Other reported incident frequencies are 1/1000 flights (Hood, 2001), about 1 in 2000 flights, with those involving bleed air contamination constituting a minor proportion (UK Civil Aviation Authority, 2013), and 1 in 22,000 flights (Winder and Balouet, 2001). Thibeault (2002) concluded "The chance that it (experiencing an incident) always happens to the same crew is extremely remote".

3.3. Non-reactive VOCs and ToCP

3.3.1. Concentrations in air

Compilations of measured concentrations and health-related data for non-reactive VOCs in aircraft cabins are shown in Table 1. Table 2 shows measured and modeled concentrations of reactive VOCs and limonene in aircraft and offices; ethanol and three odorous VOCs (1,3-butadiene, styrene and menthol) are disregarded (Wang et al., 2014). All data entries are maximum or fourth quartile concentrations, generally based upon measurements from several flights and flight types (Table 1). The maximum concentrations may represent temporary and infrequent incidents, e.g., transient smells during start, take-off, pre-climb, cruise, and pre-landing conditions, as well as measurements made during the turning on of the ventilation system and "pack burns", when the ventilation system is heated to remove contaminants.

Major VOCs measured in the cabin air are aromatics (benzene, toluene, and xylenes), 2-propanol, C_2, C_8–C_{10} aldehydes, 2-butanone and benzaldehyde, methylene chloride and trichloroethylene. In general, toluene and limonene dominated with highest concentrations, together with 2-propanol and methylene chloride. The whole flight mean concentrations and those during the main cruise period usually show substantially lower concentrations than shorter-term measurements (Crump et al., 2011; de Ree et al., 2014). Furthermore, it is important to recognize that high maximum concentrations can be identified by use of short sampling durations, e.g., 5 min, in comparison with 2–10-h average concentrations (e.g. Solbu et al., 2011).

One study (100 flights) reported substantial maximum concentrations of ToCP and some isomers thereof; however, these compounds were only observed in 5% of the samples, i.e., 95% were below the limit of quantification (LOQ) of 0.12 μg/m^3 for these substances (Crump et al., 2011). The maximum reported concentration of 22.8 μg/m^3 ToCP represents a single reading out of approximately 1000 samples (Crump et al., 2011). Furthermore, the reported ToCP concentration could have been overestimated due to chromatographic overlap with other ortho-isomers (see De Nola et al., 2008). Samples from three other studies were below the LOQ of 75 ng/m^3 (Solbu et al., 2011), below the limit of detection (LOD) of 0.75–3 ng/m^3 (Houtzager et al., 2013), or were estimated as <1 μg/m^3 of ToCP and isomers (Denola et al., 2011). These three studies together represent more than 100 flights. In a further study of about 18 flights, TmCPs and TpCPs were detected at a level of a few ng/m^3, but not ToCP (Hecker et al., 2014). Furthermore, only 15% of 90 samples taken from two different aircraft types contained TCP in the range 2 to 67 ng/m^3 (close to LOD) during normal flight operation; To-m/pCPs and di-orthoTCP were undetected (Rosenberger et al., 2013). Van Netten (2009) reported TCP levels less than 0.1 μg/m^3. The content of ortho-TCP was <20 μg/kg (<0.0002%) in the jet oil. Hecker et al. (2014) measured the ToCP content as 0.01% or less in 11 out of 12 jet oils.

3.3.2. Biomonitoring of ToCP exposure

One study found that the metabolite of ToCP, *o*,*o*-dicresyl phosphate, was below the LOD in 332 urine samples that were collected from aircrew members after reports of smoke/fume incidents; only one sample showed the metabolite near its LOD (Schindler et al., 2013). Similarly, measurements of the covalent adduct between the metabolite cresyl saligenin phosphate and butyrylcholinesterase was below the LOD in 15 healthy F-16 pilots (Tacal and Schopfer, 2014).

3.3.3. Risk assessment of non-reactive VOCs

Except for ozone, the air cabin pollutant concentrations are in general comparable with reported concentrations of common VOCs in residences and offices, although the data are limited (Nagda and Rector, 2003). More recent measurements in public buildings indicate similar findings (e.g. Geiss et al., 2011; Wu et al., 2011). Thresholds for sensory irritation in the eyes and upper airways are one to three orders of magnitude higher than the reported cabin air concentrations; one exception is formaldehyde (see Table 2). Thus, the HQ for sensory irritation for

Table 1
Maximum concentrations (μg/m^3) of common non-reactive VOCs and carbonyls in aircraft cabins, NOAEL values, hazard quotients (HQ), and hazard index (HI).

Compound Study/number of flights/types Sampling duration	Acetaldehyde	Methylene chloride	2-propanol	2-butanone	Propanal	Hexanal	Heptanal	Octanal	Nonanal	Decanal	Benzaldehyde	Trichlorethylene	Tetrachlorethylene	TCP	TBP	ToCP	C_{11-12}	Benzene	Toluene	Ethylbenzene	Xylene[d]	HI %
Crump et al., 2011/100/5 5 min (Table 4)	nm											20	nm	38	22	23	87	nm	170	nm	52	
Denola et al., 2011 46/3 15 min to 10 hours	nm														nd		nm					
Houtzager et al., 2013 20/Boeing 737 ½–2 hours	nm													0.2[e]	nd		nm					
Rosenberger et al., 2013 26/2 ½–5 hours	nm													0.07	nd		nm					
Van Netten, 2009 2/1 55 min	nm													0.1	nm		nm					
Nagda and Rector, 2003[a]/71/18 No information	46	122	93	18	5	nm							13	nm			nm	7	87	nm	15	
Spengler et al., 2012[b]/86/6 No information	nm											41	10	nm			nm	62	133	13	61	
Solbu et al., 2011 40/6 2–10 hours	nm													nd	4	nd	nm					
Wang et al., 2014[c]/14/1 5 min	nm							17	36	57	32	nm	13	nm			39	145	237	45	74	
Weisel et al., 2013/52/4 2½–8½ hours	nm					8	4	5	14	12	nm	nm										
NOAEL value[f], mg/m^3 TDI, ng/kg bwd	7		17[g]	33	6	6	6	6	6	6	2					50	>1.4[h]		75	20	7.5	
Sensory effects: HQ % = $\frac{Max\ conc}{guideline}$	0.7	–[i]	0.6	0.05	0.1	0.1	0.1	0.3	0.6	1	2	–[i]	–[i]				0.6	–[i]	0.2[h]	0.2	0.1	7
Neurotoxic effects: HQ %= $\frac{daily\ intake\ (8\ hrs)}{TDI}$																4600						4600

nm = not measured. nd = below LOD.
[a]Averaged maximum values based on several studies (Table 4).
[b]Maximum concentration taken from Table B-3.
[c]Fourth quartiles (Table 2).
[d]Sum of ortho, meta and para isomers.
[e]Sum of four tricresyl phosphate isomers, but not ToCP.
[f]NOAEL values for sensory irritation (Wolkoff, 2013).
[g]Estimated as LOAEL/5 value (van Thriel et al., 2003).
[h]Estimated as LOAEL/5 for decane (Kjærgaard et al., 1989).
[i]Not considered a sensory irritant.

maximum cabin air concentrations of the non-reactive VOCs, limonene and carbonyls (except formaldehyde) was 1% or less, except for benzaldehyde (2%). The HI for the combined non-reactive VOCs, limonene and carbonyls amounted to about 8% (Tables 1 and 2). Hence the contribution of major aircraft cabin or office air VOCs are insufficient to cause eye and airway irritation symptoms. Although the aircraft studies have measured a selected number of VOCs or TCP, and reported concentrations averaged over some hours, they, where measured, are not considered to cause sensory irritation symptoms; a similar conclusion can be drawn from reported office VOC concentrations (Wolkoff, 2013). A review of studies of controlled human exposure to VOCs, generally at much higher concentrations than encountered in aircraft and offices, showed neither sensory symptoms nor CNS-related symptoms of any significance (Wolkoff, 2013).

Several of the VOCs, in particular the aldehydes, have low odor thresholds (Nagata, 2003) and may influence the perceived AQ and possibly the overall perception of sensory symptoms (Wolkoff, 2013). Thus, personality factors as expectations about the odor, anxiety or attitudes towards health risks, may lead subjects to increase reporting of symptoms (Dalton, 2003). Also, other temporary incidents affecting the aircraft, such as de-icing, may briefly alter the AQ by elevating concentrations of non-reactive, but smelly, VOCs such as glycol and glycol ethers (Rosenberger et al., 2014); the reported concentrations of these, however, would not give rise to sensory irritation (Wolkoff, 2013).

3.3.4. Risk assessment of ToCP

It is relevant to consider that ToCP has a high boiling point of 439 °C and a low vapor pressure at 1.8×10^{-7} mm Hg at 25 °C (van der Veen and de Boer, 2012); i.e., the compound will be partitioned between the gas and particle phase, but will be mostly in the particle phase according to De Nola et al. (2008). The particle size distribution of the samples is unknown and the deposition of ToCP in the airways is uncertain. Furthermore, ToCP is considered odorless (ToxNet). Due to its high boiling point, ToCP (or TCP) will deposit quickly onto interior surfaces of aircraft (ventilation ducts, filters and air conditioning packs) (Chaturvedi, 2011) and is not expected to re-emit; this is also the case in buildings. ToCP may slowly degrade by reaction with the OH radical generated by ozone-initiated reactions of terpenes (Atkinson and Arey, 2003)

ToCP has an estimated HQ of 4600% based on the maximum concentration recorded during measurements on 100 flights in the UK study (Crump et al., 2011). The HQ would be 58% if the 95th percentile value (0.29 μg/m^3) of the average concentration on each of the 100 flights were applied. Use of the higher TDI value of 130,000 ng/kg bwd would result in HQs of 1.8% and 0.02%, respectively. The maximum concentration is five-fold lower than the 8-h TLV/OEL of 100 μg/m^3 for ToCP (ACGIH, 2014; GESTIS, 2015). If an intended reduction of the TLV to 20 μg/m^3 occurs (ACGIH, 2014), the HQ for ToCP will increase to about 100%, now on the basis of concentration based TLV. Intended reductions of TLVs for TmCPs and TpCPs of 50 μg/m^3 have also been put forward by ACGIH (2014).

Table 2
Measured and modeled maximum concentrations (μg/m^3) in aircraft cabins (AC), offices (OF), and class rooms (CR) of limonene and terpene ozone-initiated reaction products, and the hazard quotient (HQ) for the maximum reported concentration, and hazard index (HI).

Study	Scenario	Limonene	Acetic acid	Formaldehyde	Acrolein	AMCH	IPOH	MHO	OPA	Ozone	HI %
Crump et al. (2011)	AC	540									
Dechow et al. (1997)	AC			26							
Nagda and Rector (2003)[a]	AC	62		10							
Pierce et al. (1999)	AC			<5	<1.5						
Rosenberger et al. (in press)	AC			44	6					300	
Wang et al. (2014)[b]	AC	660	23					21			
Weisel et al. (2013)	AC							13		~160	
Weschler et al. (2007)	AC, 4.4 h^{-1}		~25		1			~30	~25	128	
Carslaw (2013)[c]	OF, 0.5 h^{-1}	891		41		23	13			100	
Fischer et al. (2013)	CR							1	3	75	
Nørgaard et al. (2014a)	OF, 1–4 h^{-1}	52		24		1	14	8	21	37	
Salonen et al. (2009)	OF	240	610[e]	14				4			
Terry et al. (2014)[d]	OF, 1.5 h^{-1}	1110		23		50	22			57	
Wisthaler and Weschler (2010)	OF, 1 h^{-1}			9				12	8	66	
NOAEL or Guideline value		90,000[f]	5000[f]	100[f]	21[f]					100[h]	
Reference value						1130[g]	1100[f]	1550[f]	123[g]		
HQ % = $\frac{Max\ conc}{Value}$										100–300	100–300
AC		0.7	0.5	44	30			2			77
Sensory irritation											
OF/CR		1	(12[e])	41			2	0.5			45
AC									20		20
Airflow limitation											
OF/CR						4.4			17		21

[a] Averaged maximum concentration from several studies (Table 4).
[b] Fourth quartiles concentration.
[c] Gas-phase modeled peak concentrations after cleaning event.
[d] Modeled peak concentrations after a cleaning event (Table 5).
[e] Possibly, in part an analytical artifact.
[f] Sensory irritation (Trantalidi et al., 2015; Wolkoff and Nielsen, 2010; Wolkoff, 2013; Wolkoff et al., 2013).
[g] Airflow limitation (Wolkoff et al., 2013, 2014).
[h] Pulmonary irritant (WHO, 2006).

In five studies ToCP was not detected, leading to a HQ of 0.1%, assuming a LOD of 0.5 ng/m^3 (de Ree et al., 2014). In view of this and the conservative health risk assessment approach and short infrequent exposure durations (that are not necessarily associated with ToCP exposure), ToCP as a single isomer is considered to be of low risk; this is in agreement with Denola et al. (2011), de Ree et al. (2014), de Boer et al. (2015), and Schindler et al. (2013). Although ToCP is considered the most toxic of the isomers (or specifically To-m/pCP), it cannot be excluded that mixed ortho/meta/para isomers could add to the HQ. It should be noted that, because of its toxicity, the amount of ToCP in commercial TCP products is generally less than 0.2%, but To-m/pCP may be present (Denola et al., 2011; Brooke et al., 2009; de Ree et al., 2014). Denola et al. (2011) estimated that a 5 μg/m^3 TCP air concentration would contain ~0.2 ng/m^3 To-m/pCP; since these isomers are considered 10 times more toxic than ToCP, this level equates ~2 ng/m^3 ToCP. This would correspond to 0.2 ng/kg bwd, which is 0.4% of the TDI value suggested by de Ree et al. (2014).

Personal exposure to TCP at levels of 0.2 to 800 ng/m^3 have been measured in electronic dismantling facilities (Hartmann et al., 2004; Staaf and Östman, 2005; Mäkinen et al., 2009). Furthermore, indoor air concentrations of 2 and 0.4 ng/m^3 have been reported in a theater and an office, respectively (Hartmann et al., 2004). If the TCP contain 0.2% ToCP, this would amount to a maximum 1.6 ng/m^3 personal gas-phase exposure to ToCP, which is considerably lower than the 95th percentile value (0.29 μg/m^3) of the average concentration on each of the 100 flights in the UK study (Crump et al., 2011), but higher than in five other aircraft studies. Considerably higher levels of 24 to 280 μg/m^3 have been measured in a mechanical workshop (Solbu et al., 2007). TCPs have also been found in airborne office particles at a maximum concentration of 0.2 ng/m^3 (Yang et al., 2014). Thus, 20 m^3 inhalation would amount to 4 ng intake per day, corresponding to 0.06 ng/kg bwd, which is several orders of magnitude below the TDI value reported by de Ree et al. (2014). Electronic equipment in homes and cars appears to be a major source of both TCP and triphenyl phosphate found in surface sampled dust (Brandsma et al., 2014). Dust samples have shown maximum values of 8 ng/g and 47 ng/g in urban homes and near an electronic recycling facility, respectively (He et al., 2015). Brommer and Harrad (2015) showed average TCP values of 2, 0.3, 1, and 0.05 μg/g floor dust in living rooms, offices, cars, and classrooms, respectively; maximal exposure to TCP by ingestion was estimated to be 0.19 and 11 ng/kg bwd in adults and toddlers, respectively.

An in vitro study with mouse primary cortical neurons isolated from mouse embryos showed reduced glutamate signaling after 24-h treatment with TCP concentration for as low as 100 nM (Hausherr et al., 2014). This would correspond to a total acute uptake of 40 μg TCP. The daily intake over 8 h, based on the four aircraft studies, assuming a constant concentration and 100% uptake by inhalation, ranges from 3 μg (0.4 μg/m^3) to 266 μg (38 μg/m^3) of TCPs, which is thus above the lowest test concentration. One study investigated auto-antibodies in serum as biomarkers, but its clinical relevance is unclear and it cannot be used for risk assessment (Abou-Donia et al., 2013). Another study concerning induction of acetylcholinesterase and apoptosis in mouse lung cells by a high subcutaneous dose (1500 mg/kg) of ToCP (Jiang et al., 2012) is not relevant for risk assessment of cabin air levels. A third study showed human hepatic bioactivation of ToCP by involvement of different human P450s cytochromes (Reinen et al., 2015). Relevance for risk assessment, however, is doubtful and further hampered by the observed high LOAEL concentrations of ToCP.

3.4. Ozone and ozone-initiated reactions

3.4.1. Ozone concentrations

Ozone in cabin air may reach concentrations of up to 240–300 μg/m^3 (Bhangar et al., 2008; Rosenberger et al., in press; Spengler et al., 2004; Weschler et al., 2007; Weisel et al., 2013). In a study of 83 flights, 16% showed ozone concentrations greater than 60 ppb (120 μg/m^3) (Bekö et al., 2015), but cases of defective ozone converters may result in high ozone levels (Weisel et al., 2013). Ozone levels inside buildings

are considerably lower than outside; usually indoor/outdoor ratios are between 0.2 and 0.7 (Weschler, 2000). Mid-European offices had average 2-h concentrations ranging from below the LOD to 20 μg/m^3 (Nørgaard et al., 2014a), while one-week personal exposure medians during office work were 32–39 μg/m^3 in northern Swedish offices (range: < 16 to 165 μg/m^3) (Glas et al., 2015). Certain air cleaning devices, both portable or in-duct, and photocopiers may have substantial emission rates that add to the background ozone level (e.g. Britigan et al., 2006; Tuomi et al., 2000).

3.4.2. Risk assessment of ozone

Ozone, a pulmonary irritant (Nielsen et al., 1999), shows cabin air concentrations above the WHO guideline (2006); thus, with HQ > 1, airway effects such as coughing and chest pain may occur (Table 2). Effects on the pre-corneal tear film (PTF) are not expected at cabin air concentrations below 300 μg/m^3, based on a human exposure study (Mølhave et al., 2005). However, it may be speculated that prolonged exposure could alter the composition and thus the structure of the PTF by reaction with olefinic units in the outer oily layer. This would depend on the blink activity, which is substantially reduced during visual display unit (VDU) work, and on diet (Wolkoff, 2010). If ozone was to be associated with eye and dry lip symptoms in aircraft as suggested by Bekö et al. (2015), additional exacerbating factors should be present, e.g., reaction products such as formaldehyde, and low RH.

3.4.3. Ozone-initiated terpene reaction products

A number of studies have reported measured or modeled concentrations of ozone-initiated reaction products in aircraft cabins and offices (Table 2). These include inter alia formaldehyde, acrolein, 6-methyl-5-heptene-2-one (6-MHO), 4-oxopentanal (4-OPA), and acetic acid in aircraft, and additionally 4-acetyl-1-methylcyclohexene (4-AMCH) and 3-isopropenyl-6-oxo-heptanal (IPOH) in offices. Acetone (data not presented), nonanal, decanal, geranyl acetone, 6-MHO, and 4-OPA are usually simultaneously present as the result of ozone-initiated surface reactions of human debris (Weschler et al., 2007). One study reports an unusually high concentration of acetic acid in offices, although the authors state that this could have been an artifact (Salonen et al., 2009). It should also be noted that air sampling of acrolein and formaldehyde is hampered by instability (Ho et al., 2011) and degradation by ozone (Bates et al., 2000), respectively, that may result in underestimation. Furthermore, low RH as found in aircraft may also reduce the sampling efficiency of formaldehyde.

3.4.4. Risk assessment of ozone-initiated reaction products

The HQs show that apart from extremely high ozone concentrations in aircraft cabins, formaldehyde and acrolein appear to be the only VOCs of concern regarding sensory symptoms, having a HI of 74% and 41% in aircraft and offices, respectively (Table 2). Acrolein may be of concern, with a HQ of 30%; the NOAEL value, however, could be overestimated because a significant increase in blink frequency occurs at 0.26 ppm, indicating a LOAEL of between 0.17 and 0.26 ppm (390 and 600 μg/m^3) (Weber-Tschopp et al., 1977). This would result in an estimated NOAEL value between 78 and 120 μg/m^3 (applying a LOAEL to NOAEL correction factor of five). However, acute — but temporary and infrequent — activity-dependent exposures to ozone concentrations greater than 200 μg/m^3 and simultaneous high limonene levels that may result in sensory irritation cannot be excluded (Wolkoff et al., 2012a).

The HI for ozone-initiated reaction products, including formaldehyde and acrolein, are 77% and 45% in aircraft and offices, respectively (Table 2). This would increase to 84% and 52% by addition of the non-reactive VOCs (Table 1). Thus, the non-reactive VOCs and products of ozone-initiated chemistry are close to 100% HI for sensory reactions in aircraft. This, however, should be considered cautiously in view of the brief nature of incidents in aircraft and findings from the office environment (Glas et al., 2015; Nørgaard et al., 2014a) as well as the controlled human exposure studies by Fiedler et al. (2005) and Laumbach et al. (2005). Further, the threshold for reported sensory irritation by formaldehyde is 300–400 μg/m^3, with a NOAEL value of about 800–1000 μg/m^3 for objective changes (Mueller et al., 2013), which would result in a higher guideline than the WHO indoor AQ guideline (2010). Furthermore, the HI for formaldehyde and acrolein together would drop to a maximum of 10% if applying the average concentrations measured by Rosenberger et al. (in press) in A321 aircraft. The HI for airflow limitation by 4-AMCH and 4-OPA would amount to about 20% in aircraft and offices. It should be noted that both formaldehyde and 4-OPA may be generated by ozone-initiated reactions in ventilation systems (Destaillats et al., 2011).

Emission of VOCs from building products and furnishings (e.g. carpets) and their subsequent reaction with ozone can create more odor annoyance (Knudsen et al., 2003); likewise, the formation of new oxygenated species from ozone-initiated surface reactions, e.g., of skin oils (Coleman et al., 2008a; Wisthaler and Weschler, 2010), can produce a complex host of saturated and unsaturated species, e.g., aldehydes, with low odor thresholds (Nagata, 2003). These new odorous oxygenated VOCs may have a detrimental impact on the perceived AQ and increase odor-initiated symptoms (Strøm-Tejsen et al., 2008). This has been demonstrated, for instance, by intensive cleaning and removal of human debris and the associated observed reduction in the ozone-initiated surface reaction products (Nørgaard et al., 2014a).

3.5. Particles and combustion products

3.5.1. Particles

Respirable particle levels were less than 20 μg/m^3, and generally much lower, in non-smoking aircraft (Lee et al., 1999; Lindgren and Norbäck, 2002; Nagda and Rector, 2003; Lindgren et al., 2007; Pierce et al., 1999. Further, Lindgren et al. (2007) showed that humidification lowered particle levels. In general, respirable particles in aircraft are not considered to be of concern because of their relatively low concentrations.

Ultrafine particles (UFPs) have also been measured, with short term peaks of over 500,000 particles/cm^3, but with whole flight averages in the range of 1000 to 100,000 particles/cm^3 (Crump et al., 2011). Lindgren et al. (2007), in a study of 8 intercontinental flights, observed highest concentrations of UFPs (300,000 particles/cm^3) when an aircraft was flying behind another aircraft at cruise-level. UFPs have multiple sources: human activities (Géhin et al., 2008; Glytsos et al., 2010) (e.g. toasting bread in the cabin (Lindgren et al., 2007), ozone-initiated gas and surface reactions (e.g. Weschler and Shields, 1999; Coleman et al., 2008b), use of electrical appliances (Schripp et al., 2011)). Limonene-generated particles are not considered to cause sensory irritation (Nørgaard et al., 2014b; Wolkoff, 2013). Whether or not other indoor/aircraft-generated UFPs may be associated with adverse effects is uncertain, but they are considered minor in view of their low mass concentration.

A Nordic consensus group concluded that office particles are generally not associated with the reported health symptoms (Schneider et al., 2003), except for special cases as discussed in Wolkoff (2013). Lappalainen et al. (2013), however, showed that levels of airborne particles (>0.5 μm diameter) were significantly higher in offices with work-related eye and upper airway symptoms than in offices with no symptoms.

3.5.2. Combustion products

Exposure to combustion products, for example nitrogen dioxide (Bourcier et al., 2003; Novaes et al., 2007, 2010) and particulate matter (Torricelli et al., 2014), has been associated with alteration of the PTF. These pollutants may be considered proxies of traffic exhaust; smoke from wood fires has also been associated with alteration of the PTF (Berra et al., 2015). Exposure to these pollutants, either at home or during transport to work (e.g. Saxena et al., 2003), may further exacerbate the development of dry eye-related symptoms during office working hours. Time spent at airports and their vicinity can result in elevated

exposure to combustion products and fuel vapor including particles (and UFPs) and nitrogen oxides as well as VOCs (Hsu et al., 2013), and is thus a potential risk factor.

3.6. Low relative humidity

In the search for alternative explanations for the reported symptoms among aircrew, the impact of low RH in aircraft was reviewed by Nagda and Hodgson (2001). The authors concluded that a slightly elevated RH would have a beneficial effect on perceived AQ; however, it was unclear whether this would include typical sensory and CNS-related symptoms.

The stability of the PTF, that inter alia protects the eye against aqueous loss and pollution, is very sensitive to the impact of low RH. A number of controlled studies with both moderate dry eye patients and normal subjects in low RH conditions (desiccating stress) for a couple of hours have demonstrated adverse effects on the PTF such as increased aqueous loss (desiccation), reduced tear production and stability, and increased ocular discomfort (Abusharna and Pearce, 2013; Alex et al., 2013; Tesón et al., 2013, and references in Wolkoff et al., 2012b). Further, animal models have shown adverse effects on meibomian and lacrimal gland functions (Suhalim et al., 2014; Xiao et al., 2015). Desiccation increases the osmolarity of the PTF, which can result in a cascade of reactions including epithelial damage, e.g., Pelegrino et al. (2012).

3.6.1. Risk assessment of low relative humidity

There is substantial epidemiological and experimental evidence that low RH as encountered in aircraft and offices is associated with detrimental effects in eyes (Wolkoff et al., 2012b), manifested as perceived dryness and eye symptoms (dry, irritated and tired). For instance, in a blinded study, an increase from low RH to moderate RH showed beneficial effects through a more stabilized PTF, less eye dryness and less fatigue among crew members during long-distance flights (Norbäck et al., 2006) and improvement in perceived AQ (Lindgren et al., 2007); similar beneficial effects of air humidification have been demonstrated in offices (Hirayama et al., 2013; see also Wolkoff and Kjærgaard, 2007). Strong associations were observed between low RH and increase of perceived eye dryness in a large epidemiological study of office workers (Azuma et al., 2015) and with negative impacts on both the upper and lower airways (Lukcso et al., in press)

It is important to recognize that the reporting of dry eye-related symptoms is associated with three major risk factors, either singly or in combination: i) exposure to low RH causing desiccation of the PTF resulting in hyperosmolarity; ii) exposure to sensory irritants like formaldehyde; and iii) the presence of clinically diagnosed dry eye diseases. For instance, the reports of eye symptoms among young and middle-aged Japanese office workers were significantly higher among those with clinically diagnosed dry eyes (12%) than in those with probable (54%) or not diagnosed dry eyes (34%) (Yokoi et al., 2015). This implies that immanent dry eye diseases, affecting ≥20% of the population (Bron et al., 2014), will add to the overall complaint rate, in addition to possible exacerbation by occupational and environmental exposures (Wolkoff, 2010; Wolkoff et al., 2012b). It should be borne in mind, however, that adverse effects, especially in the eyes, depend upon a number of other risk factors, some of which are personal, for instance, age, gender, and use of medication (Wolkoff et al., 2012b), and also possibly psychological (Kawashima et al., 2015; Runeson et al., 2007), including increased work demand and limited control of the work environment (Fu et al., 2015).

Normal or slightly elevated RH at the ocular surface favors a thicker PTF, which retards aqueous loss by the presence of a thicker outer oily layer. For example, a significant increase in PTF thickness occurs within a 5-min exposure of the eyes to 100% RH, reaching a maximum thickness after 15 to 20 min, with simultaneous relief of eye symptoms (Korb et al., 1996). A cold season with low environmental (ambient) RH will thus also impact the PTF during transport prior to entering the workplace. Low RH, however, does not exacerbate the sensory effect of formaldehyde in the airways (Larsen et al., 2013). In general terms, low RH destabilizes the PTF, thus making it more susceptible (Wolkoff et al., 2012b), but does not impact the upper airways regarding sensory irritation (Larsen et al., 2013).

3.6.2. Other adverse effects related to low relative humidity

Exposure to low RH may result in additional effects that may adversely influence comfort and health. For instance, saccharin mucociliary clearance time has been found to increase significantly among elderly, but not among young, male subjects exposed for 90 min to 10% RH in comparison with 30% RH (Sunwoo et al., 2006). It was suggested that the increase was a result of decreased nasal mucociliary activity, and that mucous membranes of elderly men are more affected by low RH than of young men. The tympanic membrane is also affected at low RH by a decrease in pressure clearance; for instance, 22.7% RH during an aircraft cruise caused a 20% decrease (Morse, 2013).

In a study of the effects of RH and air pressure, 14 young healthy subjects were exposed for 6 h to 10% and 60% RH at different air pressures (sea level and 2000 m altitude), independently. Low cabin pressure increased body fluid loss, which was exacerbated by low RH; however, only low pressure — not low RH — increased the blood viscosity. It is acknowledged that more subjects would be needed to confirm this finding (Hashiguchi et al., 2013). Other effects potentially caused by low cabin pressure, including general discomfort and CNS-related nausea caused by gas expansion in the stomach, have been reviewed by Hinninghofen and Enck (2006).

4. Discussion and conclusion

Acute effects, including sensory irritative symptoms such as tired and irritated eyes, and CNS-symptoms such as headache, are commonly reported by aircraft crew members and office workers. Respiratory symptoms have also been reported, but with lower prevalence. Several studies have been carried out to identify risk factors and entangle the causalities. The so-called aerotoxic syndrome has not been accepted as a medical syndrome (Bagshaw, 2014), and although 'sick-building syndrome' continues to be widely used in the indoor air literature (despite the term being semantically incorrect) there is increasing agreement that it is obsolete (Brightman et al., 2008; Hodgson, 2002; Wolkoff, 2013). Thus, a distinction between "sick versus healthy buildings" is futile; as concluded by Brightman et al. (2008) "it is counterproductive to dichotomize buildings into healthy vs. unhealthy, instead the prevalence of health problems related to buildings span a continuum".

The influence on health and wellbeing of perceived AQ in aircraft cabin air is complex and depends on a number of exposure factors (Bezold, 2012); this is similarly the case in offices. These exposures might well be different for aircrew members and office workers due to the environmental and occupational conditions in the aircraft versus the office environment (Table 3). While, VOCs, especially ozone-initiated reaction products, and low RH have been the bases of the prevailing hypotheses in the indoor air community, some aircraft literature has focused upon exposure to ToCP (e.g. Winder et al., 2002). TCPs are odorless and, furthermore, elevated levels of ToCP samples have not been shown to coincide with smoke/smell incidents in aircraft (Denola et al., 2011; Schindler et al., 2013). On the other hand, a number of VOCs, especially the carbonyls, have low odor thresholds, and products from ozone-initiated gas-phase and surface reactions (e.g. on carpets) can also adversely affect perceived AQ in both aircraft and offices; however, the perception of (mal)odor from the combined exposure of odorous VOCs is unlikely to be medically significant (Greenberg et al., 2013). Turning on the ventilation system after an off period and "pack burns" may also result in temporary (mal)odor incidents. Perceived (mal)odors may create a number of reactions, some of which

Table 3
Selected environmental and occupational conditions in aircraft cabins and in offices, and exposure impact.

Condition	Aircraft cabin	Offices	Exposure impact
Contamination	Bleed air: tricresyl phosphates, deicing fluids, disinfectants, flame retardants, and plasticizers	Cleaning chemicals, material emissions, traffic pollutants, flame retardants, and plasticizers	Episodic events of temporary elevated exposure Possible thermal degradation Possible ozonolysis
Ozone, μg/m^3	High concentrations may occur (100–200 μg/m^3).	Certain regions have high outdoor concentrations, I/O ratios typically 0.2–0.7. Use of air cleaning devices and photocopiers may add substantially to the background level.	Higher concentrations initiate more gas- and surface reactions with unsaturated VOCs producing gas-phase and secondary organic aerosols (ultrafines). Dirty ventilation systems may emit ozone-initiated reaction products, e.g., 4-OPA.
Non-reactive VOCs	Variety of compounds		Likely to be similar patterns
Reactive VOCs (unsaturated)	High concentration of limonene from drink and meal services	High temporary concentration from use of consumer products, e.g., cleaning agents and orange peel; air fresheners may be constant sources.	Temporary high concentrations of oxygenated species may occur including, formaldehyde, 4-AMCH, IPOH, 6-MHO and 4-OPA, and other species can occur.
Reactive surfaces	Large surface area: high density of passengers, clothing, and textiles (seats and textile flooring)	Moderate surface area: moderate density of workers and textile flooring	The larger and the more soiled the surface the more ozone-initiated production of oxygenated species by surface reactions, e.g., 4-OPA.
Relative humidity (RH), %	<10	30–50	The lower the RH the more aqueous loss and decrease of tear production and PTF stability. Less stable PTF may become more susceptible to sensory irritants.
Temperature (T), °C	20–25	20–25	High T decreases tear production from the lacrimal gland, thus altering PFT stability.
Altitude, reduced pressure	Yes	No	Reduced pressure or high altitude enhances aqueous loss from the ocular surface and skin resulting in altered PTF.
Visual display unit (VDU) work Instrumental surveillance	Pilots	Yes, several hours.	VDU or surveillance work alters the PTF stability by a decrease of the eye blink frequency.
Combustion products, e.g., traffic	No	Infiltrated outdoor air, NO_2, particles	Combustion products may alter the PTF.

may result in a subjective perception of ill-health and other negative associations (see Glass et al., 2014; Wolkoff, 2013 and references therein).

We have applied a "worst-case scenario" assuming simultaneous and continuous exposure to maximum reported concentration of VOCs and ozone-initiated reaction products for 8 h obtained from different studies (though in practice these were infrequent and brief). This resulted in combined HI for sensory irritation of 84% and 52% in aircraft and offices, respectively, for irritative symptoms in eyes and upper airways. These values should be considered cautiously in view of the brief and infrequent incidents where maximum concentrations may occur. Furthermore, the applied thresholds, especially for formaldehyde and acrolein, may be too low, thus overestimating the HI. The main source of formaldehyde in aircraft is ozone-initiated reactions, in particular with limonene; this may also occur in offices (Nørgaard et al., 2014a). The HI for airflow limitation from ozone-initiated reaction products was about 20%. Taken together, our conservative approach does not indicate that non-reactive VOCs and ozone-initiated reaction products would be causative of sensory reactions or airflow limitation. However, an altered PTF by low RH may be more susceptible to irritants.

High-ozone incidents may cause pulmonary irritation, but are not expected to exacerbate eye symptoms directly. Particles have been a concern in aircraft and offices, but the generally low measured levels of respirable particles do not give rise to concern regarding sensory reactions; however, exposure to combustion-related particles may be relevant for eye effects (and inflammatory effects in the airways). Toxicological knowledge about ultrafine particles — indoors and in aircraft — that are derived from human activity (rather than ozone-limonene initiated) is insufficient for an assessment; however, their mass is considered negligible.

Other risk factors that could exacerbate sensory symptoms in the eyes are low RH, high temperature and (in aircraft) high altitude (i.e., low pressure); in offices, VDU work is another important factor. Personal risk factors for reported ocular symptoms, including immanent dry eye diseases, are also potentially important.

The main differences between aircraft cabin and office environments relate therefore to RH, high altitude and odor incidents in the former, and extended VDU work in the latter, with possibly a higher propensity for oxygenated species in aircraft cabins due to high ozone levels; the common key step for both environments would be a more susceptible PTF. Furthermore, reactive compounds from combustion, e.g., traffic pollutants and emissions at airfields, may alter the chemical composition and structure of PTF, thus exacerbating its instability.

Regarding the hypothesis that exposure to ToCP is the cause of the reported CNS effects in aircrew, one study reported a single exceptionally high (short-term) maximum concentration of ToCP, while levels were below the LOD in five other studies, leading to HQ < 0.5%. In view of the conservative approach adopted here and the infrequent short-term exposure that may be related to smoke/smell-incidents (though not necessarily to ToCP exposure), and the available evidence indicate that ToCP does not pose a health risk. However exposure data for smoke-in-cabin events would add reassurance that this conclusion is applicable to the infrequent incidents that are the subject of registered reports by aircrew. It has been speculated that dermal contact could be an alternative or additional important exposure route, but ToCP levels were shown to be below the LOD (0.1 ng/cm^2) in surface deposition wipe tests (Houtzager et al., 2013; Solbu et al., 2011). Lamb et al. (2012) found TCP surface levels to be similar in control vehicles and offices, but are slightly higher in aircraft cabins. Workers in electronic facilities may also be exposed to ToCP by skin contact, with dust levels of about 0.3 ng/cm^2 (Mäkinen et al., 2009). However, TCPs are expected to degrade by the reaction with OH radicals and this exposure route is therefore considered to be of low importance.

Conflict of interest

The authors declare no competing financial interest.

Acknowledgments

The work was in part (PW) supported by the Centre for Indoor Air and Health in Dwellings (CISBO) study, which was supported by the REALDANIA Foundation.

References

Abou-Donia, M.B., Abou-Donia, M.M., Elmasry, E.M., Monro, J.A., Mulder, M.F.A., 2013. Autoantibodies to nervous system-specific proteins are elevated in sera of flight crew members: biomarkers for nervous system injury. J. Toxicol. Environ. Health A 76, 363–380.

Abusharna, A.A., Pearce, E.I., 2013. The effect of low humidity on the tear film. Cornea 32, 429–434.

ACGIH, 2014. Threshold limit values (TLVs) for chemical substances and physical agents and biological exposure indices (BEIs): notice of intended change for tricresyl phosphate. Publications: #7NIC-274, #7NIC-275, #7NIC-276.

Alex, A., Edwards, A., Hays, J.D., Kerkstra, M., Shih, A., Paiva, C.S., Pflugfelder, S.C., 2013. Factors predicting the ocular surface response to desiccating environmental stress. Invest. Ophthalmol. Vis. Sci. 54, 3325–3332.

Ali, N., Dirtu, A.C., Van den Eede, N., Goosey, E., Harrad, S., Neels, H., 't Mannetje, A., Coakley, J., Douwes, J., Covaci, A., 2012. Occurrence of alternative flame retardants in indoor dust from New Zealand: indoor sources and human exposure assessment. Chemosphere 88, 1276–1282.

Apte, M.G., Buchanan, I.S.H., Mendell, M.J., 2008. Outdoor ozone and building-related symptoms in the BASE study. Indoor Air 18, 156–170.

Atkinson, R., Arey, J., 2003. Gas-phase tropospheric chemistry of biogenic volatile organic compounds: a review. Atmos. Environ. 37, S197–S219.

Azuma, K., Ikeda, K., Kagi, N., Yanagi, U., Osawa, H., 2015. Prevalence and risk factors associated with nonspecific building-related symptoms in office employees in Japan: relationships between work environment, indoor air quality, and occupational stress. Indoor Air 25, 499–511.

Backman, H., Haghighat, F., 2000. Air quality and ocular discomfort aboard commercial aircraft. Optometry 71, 653–656.

Bagshaw, J., 2014. Health effects of contaminants in aircraft cabin air. Summary Report v2.7, pp. 1–20 (http://www.asma.org/asma/media/asma/Travel-Publications/Health-Effects-of-Contaminants-in-Aircraft-Cabin-Air-Report-v2-5-Aug13.pdf).

Bates, M.S., Gonzalez-Flesca, N., Sokhi, R., Cocheo, V., 2000. Atmospheric volatile organic compound monitoring. Ozone induced artefact formation. Environ. Monit. Assess. 65, 89–97.

Bekö, G., Allen, J.G., Weschler, C.J., Vallarino, J., Spengler, J.D., 2015. Impact of cabin ozone concentrations on passenger reported symptoms in commercial aircraft. PLoS One 10, e0128454.

Berra, M., Galperín, G., Dawidowski, L., Tau, J., Márquez, I., Berra, A., 2015. Impact of wildfire smoke in Buenos Aires, Argentina, on ocular surface. Arq. Bras. Oftalmol. 78, 110–114.

Bezold, A., 2012. Cabin air quality — the key to a comfrotable flight. FAST Mag. 50, 22–29.

Bhangar, S., Cowlin, S.C., Sextro, R.G., Nazaroff, W.W., 2008. Ozone levels in passenger cabins of commercial aircraft on North American and transoceanic routes. Environ. Sci. Technol. 42, 3938-2943.

Bourcier, T., Viboud, C., Cohen, J.-C., Thomas, F., Bury, T., Cadiot, L., Mestre, O., Flahault, A., Borderie, V., Laroche, L., 2003. Effects of air pollution and climatic conditions on the frequency of ophthalmological emergency examinations. Br. J. Ophthalmol. 87, 809–811.

Brandsma, S.H., de Boer, J., van Velzen, M.J.M., Leonards, P.E.G., 2014. Organophosphorous flame retardants (PFRs) and plasticizers in house and car dust and the influence of electronic equipment. Chemosphere 116, 3–9.

Brightman, H.S., Milton, D.K., Wypij, D., Burge, H.A., Spengler, J.D., 2008. Evaluating building-related symptoms using the US EPA BASE study results. Indoor Air 18, 335–345.

Britigan, N., Alshawa, A., Nizkorodov, S.A., 2006. Quantification of ozone levels in indoor environments generated by ionization and ozonolysis air-purifiers. J. Air Waste Manage. Assoc. 56, 601–610.

Brommer, S., Harrad, S., 2015. Sources and human exposure implications of concentrations of organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices. Environ. Int. 83, 202–207.

Bron, A.J., Tomlinson, A., Foulks, G.N., Pepose, J.S., Baudoin, C., Geerling, G., Nichols, K.K., Lemp, M.A., 2014. Rethinking dry eye disease: a perspective on clinical implications. Ocul. Surf. 12, S1–S31.

Brooke, D.N., Crookes, M.J., Quaterman, P., Burns, J., 2009. Environmental Risk Evaluation Report: Tricresyl Phosphate (CAS No. 1330-78-5). Environment Agency, Aztec West, Almondsbury, Bristol, pp. 1–115.

Carslaw, N., 2013. A mechanistic study of limonene oxidation products and pathways following cleaning activities. Atmos. Environ. 80, 507–513.

Carslaw, N., Langer, S., Wolkoff, P., 2009. New direction: where is the link between reactive indoor air chemistry and health effects? Atmos. Environ. 43, 3808–3809.

Chaturvedi, A.K., 2011. Aerospace toxicology overview: aerial application and cabin air quality. Rev. Environ. Contam. Toxicol. 214, 15–40.

Coleman, B.K., Destaillats, H., Hodgson, A.T., Nazaroff, W.W., 2008a. Ozone consumption and volatile byproduct formation from surface reactions with aircraft cabin materials and clothing fabrics. Atmos. Environ. 42, 642–654.

Coleman, B.K., Lunden, M.M., Destaillats, H., Nazaroff, W.W., 2008b. Secondary organic aerosols from ozone-initiated reactions with terpene-rich household products. Atmos. Environ. 42, 8234–8251.

Craig, P.H., Barth, M.L., 1999. Evaluation of the hazards of industrial exposure to tricresyl phosphate: a review and interpretation of the literature. J. Toxicol. Environ. Health B 2, 281–300.

Crump, D., Harrison, P., Walton, C., 2011. Aircraft Cabin Air Sampling Study; Part 1 of the Final Report. YE29016V. Cranfield University, Institute of Environment and Health, pp. 1–110 (https://dspace.lib.cranfield.ac.uk/handle/1826/5305).

Dalton, P., 2003. Upper airway irritation, odor perception and health risk due to airborne chemicals. Toxicol. Lett. 140-141, 239–248.

de Boer, J., Antelo, A., van den Veen, I., Brandsma, S., Lammertse, N., 2015. Tricresyl phosphate and the aerotoxic syndrome of flight crew members — current gaps in knowledge. Chemosphere 119, 558–561.

De Nola, G., Kibby, J., Mazurek, W., 2008. Determination of ortho-cresyl phosphate isomers of tricresyl phosphate used in aircraft turbine engine oils by gas chromatography and mass spectrometry. J. Chromatogr. A 1200, 211–216.

de Ree, H., van den Berg, M., Brand, T., Mulder, G.J., Simons, R., van Zanten, B.V., Westerink, R.H.S., 2014. Health risk assessment of exposure to tricresyl phosphates (TCP) in aircraft: a commentary. Neurotoxicology 45, 209–215.

Dechow, M., Sohn, H., Steinhanses, J., 1997. Concentrations of selected contaminants in cabin air of airbus aircraft. Chemosphere 35, 21–31.

Denola, G., Hanhela, P.J., Mazurek, W., 2011. Determination of tricresyl phosphate air contamination in aircraft. Ann. Occup. Hyg. 55, 710–722.

Destaillats, H., Chen, W., Apte, M.G., Li, N., Spears, M., Almosni, J., Brunner, G., Zhang, J., Fisk, W.J., 2011. Secondary pollutants from ozone reactions with ventilation filters and degradation of filter media additives. Atmos. Environ. 45, 3561–3568.

ECHA (2014) http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7d1d44-36df-0195-e044-00144f67d249/AGGR-a9c789e8-25b2-4cc7-9371-db81b8e6d9df_DISS-9c7d1d44-36df-0195-e044-00144f67d249.html#AGGR-a9c789e8-25b2-4cc7-9371-db81b8e6d9df.

Fiedler, N., Laumbach, R., Kelly-McNeil, K., Lioy, P., Fan, Z.-H., Zhang, J., Ottenweller, J., Ohman-Strickland, P., Kipen, H., 2005. Health effects of a mixture of indoor air volatile organics, their ozone oxidation products, and stress. Environ. Health Perspect. 113, 1542–1548.

Fischer, A., Ljungström, E., Langer, S., 2013. Ozone removal by occupants in a classroom. Atmos. Environ. 81, 11–17.

Fu, X., Lindgren, T., Norbäck, D., 2015. Medical symptoms among pilots associated with work and home environments: a 3-year cohort study. Aerosp. Med. Hum. Perform. 86, 458–465.

Géhin, E., Ramalho, O., Kirchner, S., 2008. Size distribution and emission rate measurement of fine and ultrafine particle from indoor human activities. Atmos. Environ. 42, 8341–8352.

Geiss, O., Giannopoulos, G., Tirendi, S., Barrero-Moreno, J., Larsen, B.R., Kotzias, D., 2011. The AIRMEX study — VOC measurements in public buildings and schools/kindergartens in eleven European cities: statistical analysis of the data. Atmos. Environ. 45, 3676–3684.

GESTIS, 2015. GESTIS — international limit values for chemical agents (occupational exposure limits, OELs). http://www.dguv.de/ifa/Gefahrstoffdatenbanken/GESTIS-Internationale-Grenzwerte-f%C3%BCr-chemische-Substanzen-limit-values-for-chemical-agents/index-2.jsp.

Glas, B., Stenberg, B., Stenlund, H., Sunesson, A.-L., 2015. Exposure to formaldehyde, nitrogen dioxide, ozone, and terpenes among office workers and associations with reported symptoms. Int. Arch. Occup. Environ. Health 88, 613–622.

Glass, S.T., Lingg, E., Heuberger, E., 2014. Do ambient urban odors evoke basic emotions? Front. Psychol. 5, 1–11.

Glytsos, T., Ondrácek, J., Dzumbova, L., Kopanakis, I., Lazaridis, M., 2010. Characterization of particulate matter concentrations during controlled indoor activities. Atmos. Environ. 44, 1539–1549.

Greenberg, M.I., Curtis, J.A., Vearrier, D., 2013. The perception of odor is not a surrogate marker for chemical exposure: a review of factors influencing human odor perception. Clin. Toxicol. 51, 70–76.

Guan, J., Gao, K., Wang, C., Yang, X., Lin, C.-H., Lu, C., 2014. Measurements of volatile organic compounds in aircraft cabins. Part I: methodology and detected VOC species in 107 commercial flights. Build. Environ. 72, 154–161.

Hartmann, P.C., Bürgi, D., Giger, W., 2004. Organophosphate flame retardants and plasticizers in indoor air. Chemosphere 57, 781–787.

Hashiguchi, N., Takeda, A., Yasuyama, Y., Chishaki, A., Tochihara, Y., 2013. Effects of 6-h exposure to low relative humidity and low air pressure on body fluid loss and blood viscosity. Indoor Air 23, 430–436.

Hausherr, V., van Thriel, C., Krug, A., Leist, M., Schöbel, N., 2014. Impairment of glutamate signaling in mouse central nervous system neurons in vitro by tri-ortho-cresyl phosphate at noncytotoxic concentrations. Toxicol. Sci. 142, 274–284.

He, C.-T., Zheng, J., Qiao, L., Chen, S.-J., Yang, J.-Z., Yuan, J.-G., Yang, Z.-Y., Mai, B.-X., 2015. Occurrence of organophosphorous flame retardants in indoor dust in multiple microenvironments in Southern China and implications for human exposure. Chemosphere 133, 47–52.

Hecker, S., Kincl, L., McNeeley, E., Van Netten, C., Harrison, R., Murawski, J., Vallarino, J., Spengler, J.D., Milton, D., Tager, I., Gale, S., Bradley, J., 2014. Cabin Air Quality Incidents. Project Report. Final Report. Occupational Health Research Consortium in Aviation, pp. 1–66.

Hinninghofen, H., Enck, P., 2006. Passenger well-being in airplanes. Auton. Neurosci. 129, 80–85.

Hirayama, M., Murat, D., Liu, Y., Kojima, T., Kawakita, T., Tsubota, K., 2013. Efficacy of a novel moist cool air device in office workers with dry eye disease. Acta Ophthalmol. (Copenh) 91, 756–762.

Ho, S.S.H., Ho, K.F., Liu, W.D., Lee, S.C., Dai, W.T., Cao, J.J., Ip, H.S.S., 2011. Unsuitability of using the DNPH-coated solid sorbent cartridge for determination of airborne unsaturated carbonyls. Atmos. Environ. 45, 261–265.

Hodgson, M., 2002. Indoor environmental exposure and symptoms. Environ. Health Perspect. 110, 663–667.

Hood, E., 2001. Ops cause bad trips? Environ. Health Perspect. 109, A156.

Houtzager, M.M.G., Havermans, J.G.M.A., Bos, J.G.H., 2013. Onderzoek naar aanwezigheid en contratie van tricresylfosfaten in de cockpits van KLM Boeing 737 toestellen tijdens normale operationele condities (Research info and concentration of tricresylphosphates in cockpits of KLM Boeing 737 aircraft during normal operational conditions). pp. 1–56 TNO 2013 R11976.

Hsu, H.-H., Adamkiewicz, G., Houseman, E.A., Zarubiak, D., Spengler, J.D., Levy, J.I., 2013. Contribution of aircraft arrivals and departures to ultrafine particle counts near Los Angeles International Airport. Sci. Total Environ. 444, 347–355.
Jiang, W., Duysen, E.G., Lockridge, O., 2012. Induction of plasma acetylcholinesterase activity and apoptosis in mice treated with the organophosphorus toxicant, tri-o-cresyl phosphate. Toxicol. Res. 1, 55–61.
Kawashima, M., Uchino, M., Yokoi, N., Uchino, Y., Dogru, M., Komuro, A., Sonomura, Y., Kato, H., Kinoshita, S., Mimura, M., Tsubota, K., 2015. Associations Between Subjective Happiness and Dry Eye Disease: A New Perspective From the Osaka Study. PLoS ONE, e0123299.
Kjærgaard, S.K., Mølhave, L., Pedersen, O.F., 1989. Human reactions to indoor air pollutants: n-decane. Environ. Int. 15, 473–482.
Knudsen, H.N., Nielsen, P.A., Clausen, P.A., Wilkins, C.K., Wolkoff, P., 2003. Sensory evaluation of emissions from selected building products exposed to ozone. Indoor Air 13, 223–231.
Korb, D.R., Greiner, J.V., Glonek, T., Esbah, R., Finnemore, V.M., Whalen, A.C., 1996. Effect of periocular humidity on the tear film lipid layer. Cornea 15, 129–134.
Kuwabara, Y., Alexeeff, G.V., Broadwin, R., Salmon, A.G., 2007. Evaluation and application of the RD50 for determining acceptable exposure levels of airborne sensory irritants for the general public. Environ. Health Perspec. 115, 1609–1616.
Lamb, J., McGonagle, C., Cowie, H., Cherrie, J.W., 2012. Cabin Air — Surface Residue Study. TM/11/06. IOM, Edinburgh, pp. 1–83.
Lang, I., Bruckner, T., Triebig, G., 2008. Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regul. Toxicol. Pharmacol. 50, 23–36.
Lappalainen, S., Salonen, H., Salmi, K., Reijula, K., 2013. Indoor air particles in office buildings with suspected indoor air problems in the Helsinki Area. Int. J. Occup. Med. Environ. Health 26, 155–164.
Larsen, S.T., Wolkoff, P., Hammer, M., Kofoed-Sørensen, V., Clausen, P.A., Nielsen, G.D., 2013. Acute airway effects of airborne formaldehyde in sensitized and non-sensitized mice housed in dry or humid environment. Toxicol. Appl. Pharmacol. 268, 294–299.
Laumbach, R.J., Fiedler, N., Gardner, C.R., Laskin, D.L., Fan, Z.-H., Zhang, J., Weschler, C.J., Lioy, P., Devlin, R.B., Ohman-Strickland, P., Kelly-McNeil, K., Kipen, H., 2005. Nasal effects of a mixture of volatile organic compounds and their ozone oxidation products. J. Occup. Environ. Med. 47, 1182–1189.
Lee, S.-C., Poon, C.-S., Li, X.-D., Luk, F., 1999. Indoor air quality investigation on commercial aircraft. Indoor Air 9, 180–187.
Lindgren, T., Norbäck, D., 2002. Cabin air quality: indoor pollutants and climate during intercontinental flights with and without tobacco smoking. Indoor Air 12, 263–272.
Lindgren, T., Norbäck, D., 2005. Health and perception of cabin air quality among Swedish commercial airline crew. Indoor Air 15 (Suppl. 10), 65–72.
Lindgren, T., Andersson, K., Norbäck, D., 2006. Perception of cockpit environment among pilots on commercial aircraft. Aviat. Space Environ. Med. 77, 832–837.
Lindgren, T., Norbäck, D., Wieslander, G., 2007. Perception of cabin air quality in airline crew related to air humidification, on intercontinental flights. Indoor Air 17, 204–210.
Lukcso, D., Guidotti, T.L., Franklin, D.E., Burt, A., 2015. Indoor environmental and air quality characteristics, building-related health symptoms, and worker productivity in a federal government building complex. Arch. Environ. Occup. Health (in press).
Mäkinen, M.S.E., Mäkinen, M.R.A., Koistinen, J.T.B., Pasanen, A.-L., Pasanen, P., Kalliokoski, P., Korpi, A.M., 2009. Respiratory and dermal exposure to organophosphorus flame retardants and tetrabromobisphenol A at five work environments. Environ. Sci. Technol. 43, 941–947.
McCarty, D.J., McCarty, C.A., 2000. Survey of dry eye symptoms in Australian pilots. Clin. Exp. Ophthalmol. 28, 169–171.
Mølhave, L., Kjærgaard, S.K., Sigsgaard, T., Lebowitz, M.D., 2005. Interaction between ozone and airborne particulate matter in office air. Indoor Air 15, 383–392.
Morse, R.P., 2013. The effect of flying and low humidity on the admittance of the tympanic membrane and middle ear system. J. Assoc. Res. Otolaryngol. 14, 623–633.
Mueller, J.U., Bruckner, T., Triebig, G., 2013. Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int. Arch. Occup. Environ. Health 86, 107–117.
Nagata, Y., 2003. Odor intensity and odor threshold value. J. Jpn. Air Clean Assoc. 41, 17–25.
Nagda, N.L., Hodgson, M., 2001. Low relative humidity and air cabin air quality. Indoor Air 11, 200–214.
Nagda, N.L., Koontz, M.D., 2003. Review of studies on flight attendant health and comfort in airliner cabins. Aviat. Space Environ. Med. 74, 101–109.
Nagda, N.L., Rector, H.E., 2003. A critical review of reported air concentrations of organic compounds in aircraft cabins. Indoor Air 13, 292–301.
Nazaroff, W.W., Weschler, C.J., 2004. Cleaning products and air fresheners. Exposure to primary and secondary pollutants. Atmos. Environ. 38, 2841–2865.
Nielsen, G.D., Alarie, Y., 1982. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their termodynamic properties. Toxicol. Pharmacol. 65, 459–477.
Nielsen, G.D., Hougaard, K.S., Larsen, S.T., Wolkoff, P., Clausen, P.A., Wilkins, C.K., Alarie, Y., 1999. Acute airway effects of formaldehyde and ozone in BALB/c mice. Hum. Exp. Toxicol. 18, 400–409.
Nielsen, G.D., Wolkoff, P., Alarie, Y., 2007. Sensory irritation: risk assessment approaches. Regul. Toxicol. Pharmacol. 48, 6–18.
Norbäck, D., Lindgren, T., Wieslander, G., 2006. Changes in ocular and nasal signs and symptoms among air crew in relation to air humidification on intercontinental flights. Scand. J. Work Environ. Health 32, 138–144.
Nørgaard, A.W., Vibenholt, A., Benassi, M., Clausen, P.A., Wolkoff, P., 2013. Study of ozone-initiated limonene reaction products by low temperature plasma ionization mass spectrometry. J. Am. Soc. Mass Spectrom. 24, 1090–1096.
Nørgaard, A.W., Kofoed-Sørensen, V., Mandin, C., Ventura, G., Mabilia, R., Perreca, E., Cattaneo, A., Spinazze, A., Mihucz, V.G., Szigeti, T., de Kluizenaar, Y., Cornelissen, H.J.M., Trantallidi, M., Carrer, P., Sakellaris, I., Bartzis, J., Wolkoff, P., 2014a. Ozone-initiated terpene reaction products in five European offices: replacement of a floor cleaning agent. Environ. Sci. Technol. 48, 13331–13339.
Nørgaard, A.W., Kudal, J.D., Kofoed-Sørensen, V., Koponen, I.K., Wolkoff, P., 2014b. Ozone-initiated VOC and particle emissions from a cleaning agent and an air freshener: risk assessment of acute airway effects. Environ. Int. 68, 209–218.
Novaes, P., do Nascimento Saldiva, P.H., Kara-José, N., Macchione, M., Matsuda, M., Racca, L., Berra, A., 2007. Ambient levels of air pollution induce goblet-cell hyperplasia in human conjunctival epithelium. Environ. Health Perspect. 115, 1753–1756.
Novaes, P., do Nascimento Saldiva, P.H., Matsuda, M., Macchione, M., Rangel, M.P., Kara-José, N., Berra, A., 2010. The effects of chronic exposure to traffic derived air pollution on the ocular surface. Environ. Res. 110, 372–374.
Pelegrino, F.S.A., Pflugfelder, S.C., de Pavia, C.S., 2012. Low humidity environmental challenge causes barrier disruption and cornification of the mouse corneal epithelium via a C-Jun N-terminal kinase 2 (JNK2) pathway. Exp. Eye Res. 94, 150–156.
Pierce, W.M., Janczewski, J.N., Rowthlisber, B., Janczewski, M.G., 1999. Air quality on commercial aircraft. ASHRAE J. 41, 26–34.
Reinen, J., Nematollahi, L., Fidder, A., Vermeulen, N.P.E., Noort, D., Commandeur, J.N.M., 2015. Characterization of human cytochrome P450s involved in the bioactivation of tri-ortho-cresyl phosphate (ToCP). Chem. Res. Toxicol. 28, 711–721.
Reneman, L., Schagen, S.B., Mulder, M., Mutsaerts, H.J., Hageman, G., de Ruiter, M.B., 2015. Cognitive Impairement and associated loss in brain white microstructure in aircrew members exposed to engine oil fumes. Brain Imaging Behav. (in press).
Rohr, A.C., 2013. The health significance of gas- and particle-phase terpene oxidation products: a review. Environ. Int. 60, 145–162.
Rosenberger, W., Netz-Piepenbrink, S., Wrbitsky, R., 2013. Determination of mono- and diortho tricresyl phosphates in indoor air of aircraft. Gefahr Reinhalt Luft, pp. 138–143.
Rosenberger, W., Wrbitzky, R., Elend, M., Schuchardt, S., 2014. Determination of organic compounds in cabin air after aircraft de-icing of commercial aircraft. Gefahr Reinhalt Luft, pp. 467–475.
Rosenberger, W., Beckmann, B., Wrbitsky, R., 2015. Airborne aldehydes in cabin-air of commercial aircraft: measurement by HPLC with UV absorbance detection of 2,4-dinitrophenylhydrazones. J. Chromatogr. B (in press).
Ross, S.M., 2008. Cognitive function following exposure to contaminated air on commercial aircraft: a case series of 27 pilots seen for clinical purposes. J. Nutr. Environ. Med. 17, 111–126.
Runeson, R., Wahlstedt, K., Wieslander, G., Norbäck, D., 2007. Personal and psychological factors and symptoms compatible with sick building syndrome in the Swedish workforce. Indoor Air 16, 445–453.
Salonen, H.J., Pasanen, A.-L., Lappalainen, S.K., Riuttala, H.M., Tuomi, T.M., Pasanen, P.O., Bäck, B., Reijula, K.E., 2009. Airborne concentrations of volatile organic compounds, formaldehyde and ammonia in Finnish office buildings with suspected indoor air problems. J. Occup. Environ. Hyg. 6, 200–209.
Saxena, R., Srivastava, S., Trivedi, D., Anand, E., Joshi, S., Gupta, S.K., 2003. Impact of environmental pollution on the eye. Acta Ophthalmol. Scand. 81, 491–494.
Schindler, B.K., Weiss, T., Schütze, A., Koslitz, S., Broding, H.C., Bünger, J., Brüning, T., 2013. Occupational exposure of air crews to tricresyl phosphate isomers and organophosphate flame retardants after fume events. Arch. Toxicol. 87, 645–648.
Schneider, T., Sundell, J., Bischof, W., Bohgard, M., Cherrie, J.W., Clausen, P.A., Dreborg, S., Kildesø, J., Kjærgaard, S.K., Løvik, M., Pasanen, P., Skyberg, K., 2003. EUROPART. Airborne particles in the indoor environment. A European interdisplinary review of scientific evidence on associations between exposure to particles in buildings and health effects. Indoor Air 13, 38–48.
Schripp, T., Kirsch, I., Salthammer, T., 2011. Characterization of particle emission from household electrical appliances. Sci. Total Environ. 409, 2534–2540.
Shehadi, M., Jones, B., Hosni, M., 2015. Characterization of the frequency and nature of bleed air contamination events in commercial aircraft. Indoor Air (in press).
Solbu, K., Thorud, S., Hersson, M., Øvrebø, S., Ellingsen, D.G., Lundanes, E., Molander, P., 2007. Determination of airborne tri alkyl and triaryl organophosphates originating from hydralic fluids by gas chromatography–mass spectrometry. Development of Methodology for Combined Aerosol and Vapour Sampling. J. Chromatogr. A 1161, 275–283.
Solbu, K., Daae, H.L., Olsen, R., Thorud, S., Ellingsen, D.G., Lindgren, T., Bakke, B., Lundanes, E., Molander, P., 2011. Organophosphates in aircraft cabin air and cockpit air — method development and measurements of contaminants. J. Environ. Monit. 13, 1393–1403.
Spengler, J.D., Ludwig, S., Weker, R.A., 2004. Ozone exposures during trans-continental and trans-Pacific flights. Indoor Air 14 (Suppl. 7), 67–73.
Spengler, J.D., Vallarino, J., McNeely, E., Estephan, H., 2012. In-flight/Onboard Monitoring: ACER's Component for ASHRAE 1262, Part 2. RITE-ACER-CoE-2012-6. National Air Transportation Center of Excellence for Research in the Intermodal Transport Environment (RITE), pp. 1–50.
Staaf, T., Östman, C., 2005. Organophosphate triesters in indoor environments. J. Environ. Monit. 7, 883–887.
Steinhagen, W.H., Barrow, C.S., 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. Toxicol. Appl. Pharmacol. 72, 495–503.
Strøm-Tejsen, P., Weschler, C., Wargocki, P., My'sków, D., Zarzycka, J., 2008. The influence of ozone on self-evaluation of symptoms in a simulated aircraft cabin. J. Expo. Anal. Environ. Epidemiol. 18, 272–281.
Suhalim, J.L., Parfitt, G.J., Xie, Y., de Pavia, C.S., Pflugfelder, S.C., Shah, T.N., Potma, E.O., Brown, D.J., Jester, J.V., 2014. Effect of dessiccating stress on mouse meibomian gland function. Ocul. Surf. 12, 59–68.

Sunwoo, Y., Chou, C., Takeshita, J., Murakami, M., Tochihara, Y., 2006. Physiological and subjective responses to low relative humidity in young and elderly men. J. Physiol. Anthropol. 25, 229–238.
Tacal, O., Schopfer, L.M., 2014. Healthy F-16 pilots show no evidence of exposure to tri-ortho-cresyl phosphate through the on-board generating system. Chem. Biol. Interact. 215, 69–74.
ter Burg, W., Bouma, K., Schakel, D.J., Wijnhoven, S.W.P., van Engelen, J., van Lovern, H., Ezendam, J., 2014. Assessment of the risk of respiratory sensitization from fragrance allergens released by air fresheners. Inhal. Toxicol. 26, 310–318.
Terry, A.C., Carslaw, N., Ashmore, M., Dimitroulopoulou, S., Carslaw, D., 2014. Occupant exposure to indoor air pollutants in modern European offices: an integrated modelling approach. Atmos. Environ. 82, 9–160.
Tesón, M., González-Garcia, M.J., López-Miguel, A., Enriquez-de-Salamanca, A., Martin-Montañez, V., Benito, M.J., Mateo, M.E., Stern, M.E., Calonge, M., 2013. Influence of a controlled environment simulating an in-flight airplane cabin on dry eye disease. Invest. Ophthalmol. Vis. Sci. 54, 2093–2099.
Thibeault, C., 2002. Airliner cabin air quality. Occup. Med. State Art. Rev. 17, 279–292.
Torricelli, A.A.M., Matsuda, M., Novaes, P., Braga, A.L.F., Saldiva, P.H.N., Alves, M.R., Monteiro, M.L.R., 2014. Effects of ambient levels of traffic-derived air pollution on the ocular surface. Analysis of symptoms, conjunctival goblet cell count and mucin 5 AC gene expression. Environ. Res. 131, 59–63.
Trantalidi, M., Dimitroulopoulou, C., Wolkoff, P., Kephalopoulos, S., Carrer, P., 2015. EPHECT III: health risk assessment of exposure to household consumer products. Sci. Total Environ. 536, 903–913.
Tuomi, T., Engström, B., Niemelä, R., Svinhufvud, J., 2000. Emission of ozone and organic volatiles from a selection of laser printers and photocopiers. Appl. Occup. Environ. Hyg. 15, 629–634.
UK Civil Aviation Authority, 2013. Evidence given to Department of Health Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeets2013/cotmeeting29oct13.
van der Veen, I., de Boer, J., 2012. Phosphorous flame retardants: properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88, 1119–1153.
Van Netten, C., 2009. Design of a small personal air monitor and its application in aircraft. Sci. Total Environ. 407, 1206–1210.
van Thriel, C., Kiesswetter, E., Blaszkewicz, M., Golka, K., Seeber, A., 2003. Neurobehavioral effects during experimental exposure to 1-octanol and isopropanol. Scand. J. Work Environ. Health 29, 143–151.
Walser, M.L., Desyaterik, Y., Laskin, J., Laskin, A., Nizkorodov, S.A., 2008. High-resolution mass spectrometric analysis of secondary organic aerosol produced by ozonation of limonene. Phys. Chem. Chem. Phys. 10, 1009–1022.
Wang, C., Yang, X., Guan, J., Li, Z., Gao, K., 2014. Source apportionment of volatile organic compounds (VOCs) in aircraft cabins. Build. Environ. 81, 1–6.
Weber-Tschopp, A., Fischer, T., Gierer, R., Grandjean, E., 1977. Experimentelle reizwirkungen Von akrolein Auf den mensch. Int. Arch. Occup. Environ. Health 40, 117–130.
Weisel, C., Weschler, C.J., Mohan, K., Vallarino, J., Spengler, J.D., 2013. Ozone and ozone byproducts in the cabins of commercial of aircraf. Environ. Sci. Technol. 47, 4711–4717.
Weiss, T., Schindler, B.K., Schütze, A., Koslitz, S., Broding, H.C., Bünger, J., Brüning, T., 2015. Reply to the Letter of Anderson J Entitled "Comment of Schindler, BK; Weiss, T; Schütze, A; et al. Occupational exposure of air crews to tricresyl phosphate isomers and organophosphate flame retardants after fume events, Arch Toxicol (2013) 87: 645–648". Arch. Toxicol. 89, 263–264.
Weschler, C.J., 2000. Ozone in indoor environments: concentrations and chemistry. Indoor Air 10, 269–288.
Weschler, C.J., Shields, H.C., 1999. Indoor ozone/terpene reactions as a source of indoor particles. Atmos. Environ. 33, 2301–2312.
Weschler, C.J., Wells, J.R., Poppendieck, D., Hubbard, H., Pearce, T.A., 2006. Workgroup report: indoor chemistry and health. Environ. Health Perspect. 114, 442–446.
Weschler, C.J., Wisthaler, A., Cowlin, S., Tamás, G., Strøm-Tejsen, P., Hodgson, A.T., Destaillats, H., Herrington, J., Zhang, J., Nazaroff, W.W., 2007. Ozone-initiated chemistry in an occupied simulated aircraft cabin. Environ. Sci. Technol. 41, 6177–6184.
Wieslander, G., Lindgren, T., Norbäck, D., Venge, P., 2000. Changes in the ocular and nasal signs and symptoms of aircrew in relation to the ban on smoking on intercontinental flights. Scand. J. Work Environ. Health 26, 514–522.
Winder, C., Balouet, J., 2001. Symptoms of irritation and toxicity in aircrew as a result of exposure to airborne chemicals in aircraft. J. Occup. Health Saf. — Aust. N. Z. 17, 471–483.
Winder, C., Fonteyn, P., Balquet, J.-C., 2002. Aerotoxic syndrome: a descriptive epidemiological survey of aircrew exposed to in-cabin airborne contaminants. J. Occup. Health Saf. - Aust. N. Z. 18, 321–338.
Wisthaler, A., Weschler, C.J., 2010. Reactions of ozone with human skin lipids: sources of carbonyls, dicarbonyls, and hydroxycarbonyls in indoor air. Proc. Natl. Acad. Sci. 107, 6568–6575.
Wolkoff, P., 2010. Ocular discomfort by environmental and personal risk factors altering the precorneal tear film. Toxicol. Lett. 199, 203–212.
Wolkoff, P., 2013. Indoor air pollutants in office environments: assessment of comfort, health, and performance. Int. J. Hyg. Environ. Health 216, 371–394.
Wolkoff, P., Kjærgaard, S.K., 2007. The dichotomy of relative humidity on indoor air quality. Environ. Int. 33, 850–857.
Wolkoff, P., Nielsen, G.D., 2010. Non-cancer effects of formaldehyde and relevance for setting an indoor air guideline. Environ. Int. 36, 788–799.
Wolkoff, P., Clausen, P.A., Larsen, S.T., Hammer, M., Nielsen, G.D., 2012a. Airway effects of repeated exposures to ozone-initiated limonene oxidation products as model of indoor air mixtures. Toxicol. Lett. 209, 166–172.
Wolkoff, P., Kärcher, T., Mayer, H., 2012b. Problems of the "outer eyes" in the office environment: an ophthalmologic approach. J. Occup. Environ. Med. 54, 621–631.
Wolkoff, P., Larsen, S.T., Hammer, M., Kofoed-Sørensen, V., Clausen, P.A., Nielsen, G.D., 2013. Human reference values for acute airway effects of five common ozone-initiated terpene reaction products in indoor air. Toxicol. Lett. 216, 54–64.
Wolkoff, P., Larsen, S.T., Hammer, M., Kofoed-Sørensen, V., Clausen, P.A., Nielsen, G.D., 2014. Corrigendum to "Human Reference Values for Acute Airway Effects of Five Common Ozone-initiated Terpene Reaction Products in Indoor Air" [Toxicol. Lett. 216 (2013) 54–64]. Toxicol. Lett. 225, 498.
World Health Organization, 2006. WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Oxide — Global Update 2005. WHO Press, Geneva.
World Health Organization, 2010. Selected Pollutants. WHO Indoor Air Quality Guidelines. WHO Regional Office for Europe, Copenhagen.
Wu, X.M., Apte, M.G., Maddalena, R., Bennett, D.H., 2011. Volatile organic compounds in small- and medium-sized commercial buildings in California. Environ. Sci. Technol. 45, 9075–9083.
Xiao, B., Wang, Y., Reinach, P.S., Ren, Y., Li, J., Hua, S., Lu, H., Chen, W., 2015. Dynamic ocular surface and lacrimal gland changes induced in experimental murine dry eye. PLoS One 10, e0115333.
Yang, F., Ding, J., Huang, W., Xie, W., Liu, W., 2014. Particle size-specific distribution and preliminary exposure assessments of organophosphate flame retardants in office air particulate matter. Environ. Sci. Technol. 48, 63–70.
Yokoi, N., Uchino, M., Uchino, Y., Dogru, M., Kawashima, M., Komuro, A., Sonomura, Y., Kato, H., Tsubota, K., Kinoshita, S., 2015. Importance of tear film instability in dry eye disease in office workers using visual display terminals: the Osaka study. Am J. Ophthalmol. 159, 748–754.