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# Using the grey literature to better understand the potential health impacts of cabin air quality

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## Abstract

This paper presents an extensive database of 450 chemicals reported in the grey literature (technical reports and documents) in association with the aircraft cabin environment. 72% (325 chemicals) of these exhibited toxic properties. The most affected target organs were skin (302 chemicals), eyes (294 chemicals), respiratory system (234 chemicals), and central nervous system (94 chemicals). The database includes available occupational exposure limits for a wide range of these pollutants (118). Results from technical reports on pollutant levels in aircraft were compared against their threshold health-based screening values. When performing a human health risk assessment on a chemical-by-chemical basis, there were no exceedances of average concentrations against workplace exposure limits. However, there were exceedances in maximum reported concentrations for ozone and acrolein. When chemical exposure was assessed additively for chemicals affecting the same target organs, the average concentrations did not exceed workplace limits. However, there were exceedances for maximum concentrations for compounds that targeted the eyes, skin, cardiovascular system, blood, and respiratory system. When performing a conservative additive risk assessment of endocrine disruptors (and potential endocrine disruptors), exceedances were observed when compared with no observed adverse effect levels (NOAEL) and workplace exposure thresholds established for confirmed endocrine disruption. Our results indicate that no single chemical is responsible for the adverse health effects reported by aircrew and instead point towards a combination of chemicals and additional factors. This work stresses the need for more comprehensive assessments that are coupled with epidemiological studies and risk assessments that consider exposure to multiple pollutants and

specificities of the environment inside aircraft.

**Keywords:** Aerotoxic syndrome, air quality, indoor air quality, cabin air quality, aircraft, endocrine disruptor

## INTRODUCTION

Commercial aircraft are a workplace for the crew but also have to be a welcoming place for the public. This implies that different guidelines and regulatory limits on air quality must be taken into account in order to consider the great diversity of the people concerned. The public generally spends brief and occasional time periods on aircraft, whereas the crew has regular and repeated exposure to the cabin environment. There has been concern and understanding of the effects of indoor air quality on health for some time[1]. However, a lot of this research has focused on air quality in buildings and may not apply directly to the unique environment of an aircraft cabin.

For aircraft, there have been concerns raised about the use of current cabin air supply systems and the risk posed by the inhalation of toxic pollutants in cabin air[2-4].

Air breathed inside most aircraft comes from jet engine compressors and is not filtered. The studies of Winder and Balouet[5,6] identified possible issues with the toxicity of commercial jet oils leading to an increased focus on aircraft cabin air quality. Hayes *et al.* recently performed a systematic review of cabin air quality[7]. This concluded that the scientific literature was able to identify that aircrew appear to be adversely affected by cabin air quality; however, there was some uncertainty as to which pollutants were responsible for the reported symptoms. It concluded that more work was needed to link chemical exposure with reported symptoms so that researchers can appropriately address health and safety concerns of aircraft cabin air quality. Much of the debate on cabin air quality is focused on tricresyl phosphate in jet engine oil (although it is also present in flexible PVC and other vinyl products as a flame retardant). However, there are a wide number of different potentially toxic substances that are present in aircraft cabin air[7]. These can arise from fluids such as engine oil, hydraulic and de-icing products as well as leaching from fabrics and surfaces, and in some cases, the spraying of pesticides.

When assessing cabin air quality, two distinctive conditions for sampling and analysis have to be considered: (1) when aircraft systems are working properly (chronic exposure); and (2) when there is a fault leading to contamination of bleed air (acute exposure). This second condition is usually called a "fume event" or "cabin air contamination event". These acute events are noticed by the crew only when an odor is detected, or when contamination is strong enough that it becomes visible as a smoke/aerosol. The frequency of these events is debated but generally accepted to occur at a frequency of more than 0.02% (or 1 in 5,000) of flights[8,9]. The true frequency of these events is likely to be greater as contamination by odorless compounds cannot be detected, and are therefore likely to be underreported by aircrews (due to lack of awareness/training, consequences of reports, subjectivity of detection, transient contamination, *etc*). In 2002, U.S. National Research Council[10] estimated between 0.09 and 3.88 fume events per 1,000 flights. Most of the results on cabin air quality collated to date in the scientific literature come from baseline observations under normal conditions. To enable an accurate risk assessment to be conducted, both baseline conditions and fume events should be considered.

Investigations to understand cabin air quality has been performed for decades, with studies undertaken using different methods and protocols that include direct measurement of cabin air and simulating fume events. Many organic and inorganic products are present in aerosol form, liquid or solid, from ultrafine

particles[11,12], and gaseous phase, at concentrations ranging over several orders of magnitude. With such a range of conditions, assessment requires different sampling methods, as well as targeted and non-targeted analytical methods. The results of this testing that has been published in the scientific literature and have been summarized by Hayes *et al.*[7]. Regardless, there is still a vast amount of information that remains in the "grey literature". This comprises a range of documents not controlled by commercial publishing organizations, such as technical reports, sometimes held by airlines themselves. These resources contain valuable information on years of on-aircraft monitoring, controlled laboratory tests undertaken on aircraft products, and simulated fume events for different fluids on test aircraft and engines.

This manuscript aims to investigate if information from the "grey literature" can help inform future research directions on cabin air quality. All of the raw data collected as part of this manuscript has been compiled and presented in the Supplementary Materials. It is hoped that this information can be used by others to better understand the potential links between the chemical composition of cabin air with the adverse health effects reported by aircrew. Those who wish to use these values are advised to follow the references in the Supplementary Materials to assess the appropriateness of the data for their own applications.

Within this manuscript, we performed a preliminary assessment that includes identifying which pollutants may be present in aircraft cabin air, what the likely concentrations are, and what the reported toxic health effects for these compounds are. A detailed toxicological assessment is beyond the scope of this manuscript; however, we have performed a preliminary risk assessment by comparing average and maximum reported values against occupational exposure limits and performing an additive risk assessment based on endocrine disruption. When conducting this assessment, it was clear that current risk assessment approaches of assessing risk on a chemical-by-chemical basis are not appropriate. This manuscript therefore also highlights current limitations in exposure risk assessments of the aircraft cabin environment and suggests areas for further work.

## EXPERIMENTAL

There is a considerable amount of data on cabin air quality, but only a small fraction is published in the scientific literature. While there are obvious benefits to using peer-reviewed literature, there is still a large volume of useful data that is not published in this manner. To address this knowledge gap, we have been collecting data from technical reports identified as part of environmental forensic investigations on aircraft cabin air quality since 1989 (at this point, smoking was banned from short domestic flights in the U.S., Australia, and the Nordic Countries; an EU wide ban was only finally agreed in 1997). The review focused on gathering data from the "grey literature"; therefore, we were unable to follow standard data collection methods, e.g., PRISMA guidance for performing systematic reviews. Reports that were used within this manuscript have been identified through search engines and from reports that the authors were aware of or have been involved in. We accept that this is not the ideal method to gather data and will therefore inherently contain some bias, but it proved the most effective way to gather relevant data from the "grey literature" as search engines returned a large number of non-relevant hits, and a systematic review of the scientific literature has already been recently published[7].

Our search resulted in the collection of reports from 12 key sources [documented in the Supplementary Materials (Supplementary Table g)]. Each of these was reviewed to understand the aim of the investigation and assess if the analytical methods used were appropriate for our assessment. A major limitation of this approach is that all studies did not use the same sample collection and analytical procedure. This makes direct comparisons between the datasets challenging and therefore limits our ability to perform a detailed

toxicological assessment. The reports focused on using targeted analytical methods and so likely provide an underestimate of the total number of pollutants associated with cabin air. This manuscript uses data from a variety of different studies that sampled aircraft air, aircraft surfaces, and pyrolysis products from engine oil. All of these sources have been combined to produce a conservative assessment of the variety of pollutants that may be present. Others who wish to use the values reported in this manuscript are advised to follow the references in the Supplementary Materials to assess the appropriateness of the data collection methods for their own applications. A summary of the investigation rationale, sample collection methods, and analytical methods used is presented in the SI to help enable this. This manuscript is not intended to be a comprehensive review or detailed toxicological risk assessment but instead to investigate if information from the "grey literature" can help inform future research directions on cabin air quality.

Relevant toxicological databases have been used (e.g., Chemspider[13] / PubChem[14] / Institut National de Recherche et de Sécurité (INRS)[15] / Commission de la Santé et Sécurité au Travail (CNESST)[16]) to identify health effects reported with identified chemicals, as well as searching relevant resources (e.g. Health and Safety Executive (HSE)[17] / Institut für Arbeitsschutz (IFA)[18]) to identify appropriate occupational exposure thresholds. It should be noted that not all occupational exposure thresholds are health-based, some are political, technical, or economic-based, and all assume a healthy adult (i.e., no underlying health conditions which do not necessarily cover passengers)[19]. They also may not account for relevant environmental factors on aircraft, such as low humidity, and may assume sea level pressures. Furthermore, occupational exposure limits mainly focus on exposure by inhalation, neglecting other routes: skin pathway and ingestion (water used for hot drinks is pressurized by bleed air)[20]. Finally, workplace / occupational exposure limits are to be used only for workers and are not suitable for passengers. We do not consider these values to be wholly appropriate for assessing the human health risks on aircraft; they have instead been included for comparison and discussion.

## RESULTS AND DISCUSSION

### Pollutants identified and target organs

This review resulted in the identification of over 450 chemicals in aircraft cabin air, aircraft cabin surfaces, or turbine engine oil after pyrolysis [Supplementary Materials 1]. A large number of chemicals are likely to be found in any environment if enough measurements are collected and enough locations are examined. The identification of a large number of different chemicals, in and of itself, is not an indication of poor air quality or exposure concerns. Many assessments on cabin air quality use targeted approaches to only measure a handful of compounds. These results indicate the need for wider screening studies and can be used to help produce more informed targeted studies on exposure assessment for cabin air. To help prioritize chemicals of concern, the potential toxicity of these substances was assessed through comparison against relevant toxicological databases. This revealed that 72% of these chemicals were known to have toxic effects. The most commonly affected target organs were the eye, skin, respiratory system, and central nervous system [Table 1]. Symptoms related to these target organs have been reported in relation to "aerotoxic syndrome"[21-23].

### Limitations with the current risk assessment approaches

Just because a chemical has the potential to cause an adverse effect, this does not mean that it necessarily will. An adverse health effect is dependent on many factors, such as concentration, length of exposure, duration, and often the susceptibility or metabolism of the individual person. Occupational exposure limits have been proposed for a wide range of different compounds based on normal working days/conditions for a healthy adult. These are time-weighted average threshold exposure values for a wide range of pollutants on exposure intervals of 15 min and up to 10 hours a day. A summary of these is presented in Supplementary Materials 1 for chemicals identified in aircraft cabin air. These threshold values were

**Table 1. Summary of effects on target organs from compounds detected in aircraft cabin air**

| Reported target organ for toxicological effect | Eye | Skin | Cardiovascular system | Blood | Hematopoietic system | Respiratory system | CNS | Peripheral nervous. System | Liver | Gastrointestinal | Pancreas | Lymphoid system | DNA/RNA Synthesis inhibitor | AchE inhibitor | Reproductive system | Bone marrow | Teeth | Kidneys | Toxic effect noted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of chemicals | 294 | 302 | 19 | 18 | 1 | 234 | 94 | 13 | 44 | 13 | 1 | 1 | 1 | 7 | 8 | 1 | 1 | 40 | 325 |
| % of total | 65.3 | 67.1 | 4.2 | 4 | 0.2 | 52.0 | 20.9 | 2.9 | 9.8 | 2.9 | 0.2 | 0.2 | 0.2 | 1.6 | 1.8 | 0.2 | 0.2 | 8.9 | 72.2 |

compared against cabin air quality measurements. The average concentration of none of the individual chemicals exceeded French or UK workplace exposure limits (WELs). Similar results have been identified in studies[22,24,25] cited by Hayes *et al.*[7], and this rationale is often used as a reason why some interpret the findings to report that cabin air quality is not responsible for the adverse effects reported by aircrew. However, Watterson and Michaelis reported that these threshold values are not an appropriate way to establish risk for aircrew[26]. The UK EH40/2005 workplace exposure limits indicate that "WELs are approved only for use where the atmospheric pressure is between 900 and 1,100 millibars", which is not the case in aircraft cabin air. The importance of this parameter is confirmed for carbon monoxide by simulated high altitude experiments revealing that altitude increases toxicity[27]. More research is needed to establish the impact of atmospheric pressure on other pollutants.

Threshold values, as well as not necessarily being health based, do not consider differences in sensitivities or sensitization of workers, and importantly they were not derived for the cabin working environment (humidity, pressure, shift duration & crossing of time zones). Under the EU Working Time Directive (WTR) (2003/88/EC), the aviation industry and mobile workers in road and sea transport are currently exempt from the WTR, which enables variable and long shift patterns to be applied; Kecklund and Axelsson[28], amongst others, have identified a link between shift work and accidents, type 2 diabetes, weight gain/obesity, coronary heart disease, stroke, and cancer (breast, prostate and colorectal). The relations of shift work to physiological mechanisms, such as changes in regulatory hormones and cardiometabolic diseases, behavioral mechanisms, and psychosocial stress, all lead to poor health. A further limitation is that threshold values have not been established for the nanometer-sized contaminants, Ultra Fine Particles (UFP). The specificities of UFP imply a greater organism and cell penetration, increasing health risks. Risks from UFPs are gaining more attention[29], but more research is required to establish the risks from UFPs in aircraft cabin air.

Most risk assessments do not consider the potential for bioaccumulation and repeated exposure or the increase in inflammatory markers in those carrying out shift work to the chemicals in cabin air. All of these factors may make workers more susceptible to ill health. Another major failing of threshold values is that they only consider exposure to one individual chemical at a time and so do not take into account additive, antagonistic or synergistic effects[30].

### Risk assessment on chemical mixtures

Authoritative guidance on risk assessment of chemical mixtures is not available, although a number of authors and organizations have looked at this common problem. According to guidance from the European Food Safety Authority (EFSA)[31], cabin air would represent coincidental mixtures that originate from multiple sources and through multiple pathways. Such a mixture may potentially exhibit the characteristics of some or all of the chemicals present, and the level of interaction between components may change at different doses or potentially differ between different exposed individuals. EFSA[31] also noted that there does not have to be simultaneous exposure to chemicals for them to act in combination. In particular, chemicals that are persistent and bioaccumulate may gradually build up in the body over time until they affect the toxicological effects of other chemicals.

In the UK, guidance on the use of mixtures in risk assessment was published by the Inter-departmental Group on Health Risks from Chemicals[32]. The Steering Committee comprised the majority of government departments and organizations covering health, food, water, and occupational exposure. However, it did not consider combined exposures to chemicals and physical hazards such as shift patterns, radiation, or noise. A key conclusion by the Interdepartmental Group on Health Risks from Chemicals (IGHRC)[32] was that data was mostly unavailable, or generally absent, for the whole mixture. The IGHRC[32] noted that evidence from robust mixture studies suggested that interactions are not observed at dose levels below thresholds of effect. However, this does not necessarily relate to the Occupational Exposure Limits (OELs) that are nationally set, as OELs are not necessarily toxicology based, so do not always equate to thresholds of effect, but may equate to technical achievability, proportionality to other guidance, or outdated toxicology studies[32].

In the Supplementary Materials, we present Tables SI e) and f) that use dose addition ratios of OELs ($C_1/L_1 + C_2/L_2 + C_3/L_3 \ldots < 1$) for the same target organ, using UK WELs and French OELs. The method is described in EH40 and used by the MIXIE tool. This exercise was performed separately with data from the European Union Aviation Safety Agency (EASA) and Airliner Cabin Environment Research (ACER) cabin air quality (CAQ) studies. The concentrations of reported chemicals were found to vary by several orders of magnitude between different reports. This highlights the variability in conditions in the aircraft cabin. Several studies use mean concentrations over a relatively long period of time, or between different aircraft that can hide spikes of high concentrations of a chemical over shorter (more acute) time periods. When maximum concentrations were considered, ozone and acrolein were identified in concentrations exceeding workplace exposure limits. When chemical exposure was assessed additively (for chemicals affecting the same target organs), the average concentrations did not exceed occupational limits. However, there were exceedances for maximum concentrations for compounds that targeted the eyes, skin, cardiovascular system, blood, and the respiratory system.

While there is evidence that both synergistic and antagonistic interactions, as well as additive effects, can occur in mixtures, these are usually observed at high experimental exposure levels (higher than most real-life exposures). The type of combined action or interaction found at clearly toxic effect levels may not predict what will happen at lower (chronic) levels. The IGHRC[32] therefore recommended dividing

chemical mixtures into more discrete, precisely defined problems, such as endocrine disruption.

### Endocrine disruptors' current uncertainty in risk assessment approaches

Kortenkamp[33] reviewed 10 years of data to show that good evidence was available to confirm that the combined effects of endocrine disruptors (as long as they are in the same category, such as oestrogenic, antiandrogenic, or thyroid disrupting agents) can be predicted by using dose addition. We have therefore performed a preliminary endocrine risk assessment to attempt to better understand the risks from exposure to multiple chemicals. Combinations of endocrine disrupters are able to produce significant effects in the body, even when each chemical is present at low doses that individually do not induce observable effects, which is in contrast to EFSA's findings[31]. Kortenkamp[33] consideredmode of action approach as discussed by IGHRC[32], thus looking at the effect of the chemical; therefore, 'oestrogenicity' meant the affinity to the estrogen receptor (ER-α or ER-β), the ability to activate an expression of estrogen-dependent genes, or stimulation of cell proliferation of ER competent cells. Generally, the additive mechanism was suitable for each type of endocrine disrupter.

In contradiction to the IGHRC[32], Kortenkamp[33] concluded that every dose, even if low enough to not cause an effect, contributes to the overall combination effect. Thus, for cabin air and for specific groups of endocrine disrupters, combination effects could also result from chemicals present at or even below effect thresholds, provided sufficiently large numbers of chemicals sum to a sufficiently high total effect dose. This is of particular importance for endocrine disruptors that can mimic those hormones that can initiate cancers such as breast, prostate, and thyroid cancer.

Kortenkamp[34] also identified that the three important endocrine systems are the hypothalamus-pituitary-gonad (HPG) axis, the hypothalamic-pituitary-adrenal (HPA) axis, and the hypothalamic-pituitary-thyroid (HPT) axis. However, the report noted that scientific advances were blurring the borders between the nervous system, immune system, and endocrine system.

While thresholds and doses are regularly used in risk assessment, Demeneix *et al.*[35] noted that it may be inappropriate for endocrine disruptors as it will vary according to the various endpoints it reacts with. They noted that the efficacy of a 'natural' hormone on different endpoints in the body can vary by several orders of magnitude, and its effect can vary due to age or gender (e.g., fetus, young child, or adult/male or female). Thus, this variable hormone action concentration would also apply to endocrine-disrupting chemicals that interfere with hormones. The UNEP[36] reports that in in-vivo and in-vivo studies, it is usually assumed that there is a threshold for endocrine disruptor effects and that there will be no effects at low doses. However, they have also noted that there is no threshold for endocrine effects due to the presence of active hormone pathways, and their effects (dose-response curves) may not rise in proportion to the dose. Therefore, such chemicals are likely to have effects even at low doses.

When considering the 117 potential endocrine disruptors identified in this study, a range of different toxic effects could be identified. While tricresyl phosphate, diisobuthyl phthalate and dibutyl phthalate, amongst others, affect the seminiferous tubes (and thus reproductive functions), both naphthalene and phenol exhibit decreased antibody response (phenol) and cause decreased lymphocytes and neutrophils, thus decreasing antibody response (naphthalene), so weakening the immune system. Both chemicals can cause headaches, memory impairment, and confusion which are also symptoms of shift work. It should also be noted that the increase in Type 2 diabetes in shift work is mirrored by acetone (2-propanone) exposure which increases glucose levels[36,37]. Dimethylformamide affects the metabolic function of the liver by altering enzyme levels, and there is some evidence of the same effect from butylated hydroxytoluene (BHT). It is

important to note that in addition to contaminants, endocrine disruption has also been shown to be impacted by alcohol ingestion[38], cigarette smoking[39], and caffeine[40], as well as conditions associated with working patterns (shift work, working long hours, night work, artificial light, and trans-meridian air travel)[41,42].

Evidence is available to show that joint effects occur even when all mixture components are present at levels below doses that cause observable effects[33]. These can be further compounded by lifestyle choices and work expectations placed on flight crew[38-42]. In view of this evidence, we believe the traditional chemical-by-chemical approach to risk assessment of cabin air is hard to justify. By considering more holistic risk assessments that account for mixture effects and the wider environmental conditions, it is more understandable why many members of aircrew have reported adverse health effects.

### Risk assessment of endocrine disruptors

A total of 117 potential or known endocrine disruptors were identified in our review. A dose addition approach was therefore applied to perform a preliminary endocrine risk assessment. This approach can be applied to chemicals that affect the same target tissues and have the same molecular mechanism of toxicity as well as chemicals that produce functionally similar effects in a target tissue by different molecular mechanisms. This is especially important as our results show just how many of these contaminants can impact the same target organs [Table 1]. Concentrations in cabin air were reported for 41 chemicals by the European Union Aviation Safety Agency (EASA)[43] with a mean total concentration of 241 μg $m^{-3}$ and a maximum total concentration of 2327 μg $m^{-3}$ [Table 2 & Supplementary Materials 1C]. Using Airliner Cabin Environment Research (ACER) data[44], concentrations were reported for 53 of these, with a median total concentration of 1629 μg $m^{-3}$ and a maximum total concentration of 7,654 μg $m^{-3}$ [Table 2 & Supplementary Materials 1C]. There was a poor overlap in reported chemicals between these two studies; when the results were combined, it resulted in the detection of a total of 76 different chemicals and a total maximum concentration of 8,926 μg $m^{-3}$. The total concentrations reported in each study could be considered conservative estimates as values were only available for approximately 35% of identified endocrine disruptors in the EASA study[43] and 45% of identified endocrine disruptors in the ACEA study[44]. It is important to note that ethanol contributes from 26% to 88% of the total in each study. Ethanol is consumed recreationally (alcoholic drinks) and is used extensively as an active ingredient in many antimicrobial products, such as hand gels.

Tricresyl phosphate (TCP) has been a focus of many risk assessments on aerotoxic syndrome. Meta and para isomers were regularly detected; however, no triortho tricresyl phosphates were identified in the cabin environment in either the EASA[43] or ACER[44] study. Several other organophosphates were also detected within the cabin environment, including triphenyl phosphate (TPP), tris(2-chloroethyl) phosphate (TCEP), tris(chloro-isopropyl) phosphate (TCPP), tris(1,3-dichloro-isopropyl) phosphate (TDCPP), tris(2-ethylhexyl) phosphate (TEHP), and tris(2-butoxyethyl) phosphate (TBEP). This suggests that more comprehensive assessments of organophosphates are required rather than focusing solely on the presence of ortho-substituted tricresyl phosphates.

Data from Supplementary Materials 1 was obtained from a large range of different reports. Some reports were designed to monitor average conditions, whereas others specifically targeted fume events. To perform a preliminary risk assessment, we combined all available results to create an average reported concentration and also reported the highest concentrations observed. There will be inherent bias with this approach as not all reports measured the same pollutants or used the same analytical methods. The results should therefore be treated as a preliminary investigation and highlight the need for more comprehensive sampling

**Table 2. Mean and maximum reported concentrations for 41 chemicals recorded by EASA[43] and 53 chemicals reported by ACER[44]**

| CAS # | Chemical | EASA Mean reported concentration µg/m³ (*n* = 41) | EASA Max reported concentration µg/m³ (*n* = 41) | ACER Median reported concentration µg/m³ (*n* = 53) | ACER Max reported concentration µg/m³ (*n* = 53) | Max reported concentration in EASA & ACER |
|---|---|---|---|---|---|---|
| 100-41-4 | Ethylbenzene | 0.7 | 11 | 0.42 | 13 | 13 |
| 100-42-5 | Styrene | 0.5 | 3.8 | 0.42 | 12 | 12 |
| 100-44-7 | Benzyl chloride | | | 0 | 0.07 | 0.07 |
| 100-52-7 | Benzaldehyde | 2 | 15 | | | 15 |
| 104-76-7 | 2-Ethylhexan-1-ol | 4 | 15 | | | 15 |
| 106-93-4 | 1,2-dibromoethane | | | 0 | 0.02 | 0.02 |
| 106-99-0 | 1,3-Butadiene | | | 0.62 | 213 | 213 |
| 108-05-4 | Vinyl acetate | | | 0.29 | 0.76 | 0.8 |
| 108-88-3 | Toluene | 12 | 62 | 10 | 133 | 133 |
| 108-95-2 | Phenol | 1.2 | 5 | | | 5 |
| 109-99-9 | Tetrahydrofuran | | | 0 | 1.5 | 1.5 |
| 110-54-3 | Hexane | 0.5 | 4.8 | 68 | 1123 | 1123 |
| 111-84-2 | Nonane | 2 | 13 | | | 13 |
| 115-07-1 | Propylene | | | 1.1 | 72 | 72 |
| 115-86-6 | Triphenyl phosphate (TPP) | 0.009 | 0.12 | | | 0.12 |
| 115-96-8 | Tris(2-chloroethyl) phosphate (TCEP) | 0.01 | 0.041 | 0.008 | 0.2 | 0.20 |
| 118-56-9 | Homosalate | 0.7 | 4.1 | | | 4 |
| 118-60-5 | 2-Ethylhexyl salicylate | 2.3 | 19 | | | 19 |
| 120-12-7 | Anthracene | | | 0 | 0.008 | 0.008 |
| 123-38-6 | Propionaldehyde | 1.5 | 2.1 | 2.2 | 8.9 | 8.9 |
| 124-07-2 | Octanoic acid | 2.1 | 8.1 | | | 8.1 |
| 126-73-8 | Tributyl phosphate | 1.1 | 6.4 | | | 6.4 |
| 127-18-4 | Tetrachloroethene | 3.8 | 74 | 11 | 123 | 123 |
| 128-37-0 | Butylated hydroxytoluene | 0.6 | 12 | | | 12 |
| 129-00-0 | Pyrene | | | 0.001 | 0.01 | 0.01 |
| 1330-20-7 | Xylene mixture of isomers | 2.6 | 18 | 1.1 | 29 | 29 |
| 13674-84-5 | Tris(chloro-isopropyl) phosphate (TCPP) | 0.36 | 1.5 | | | 1 |
| 13674- | Tris(1,3-dichloro-isopropyl) | 0.005 | 0.011 | | | 0.01 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 87-8 | phosphate (TDCPP) | | | | | |
| 142-82-5 | Heptane | 0.9 | 25 | 0.061 | 0.58 | 25 |
| 1506-02-1 | Acetyl hexamethyl tetralin | | | 0.06 | 0.09 | 0.09 |
| 1634-04-4 | Methyl t-butyl ether | | | 0.035 | 16 | 16 |
| 192-97-2 | Benzo(e)pyrene | | | 0 | 0.007 | 0.007 |
| 193-39-5 | Indeno(1,2,3-cd)pyrene | | | 0 | 0.010 | 0.010 |
| 205-99-2 | Benzo(b)fluoranthene | | | 0 | 0.008 | 0.008 |
| 206-44-0 | Fluoranthene | | | 0.001 | 0.021 | 0.021 |
| 208-96-8 | Acenaphthylene | | | 0.004 | 0.008 | 0.008 |
| 207-08-9 | Benzo(k)fluoranthene | | | 0 | 0.006 | 0.006 |
| 218-01-9 | Chrysene | | | 0 | 0.007 | 0.007 |
| 26002-80-2 | Phenothrin | | | 0 | 0.006 | 0.006 |
| 334-48-5 | Decanoic acid | 0.8 | 5.4 | | | 5 |
| 35693-99-3 | PCB 52 | | | 0 | 0.005 | 0.005 |
| 4170-30-3 | Crotonaldehyde (cis/trans) | 0.1 | 0.2 | | | 0.20 |
| 50-00-0 | Formaldehyde | 8.9 | 14 | 2.7 | 12 | 14 |
| 50-32-8 | Benzo(a)pyrene | | | 0 | 0.016 | 0.02 |
| 541-73-1 | 1,3-dichlorobenzene | | | 0 | 0.22 | 0.22 |
| 556-67-2 | Octamethylcyclotetrasiloxane | 1.8 | 35 | | | 35 |
| 56-23-5 | Carbon tetrachloride | | | 0.65 | 2.8 | 2.8 |
| 56-55-3 | benzo[a]anthracene | | | 0.001 | 0.007 | 0.01 |
| 57-55-6 | Propylene glycol | 45 | 363 | | | 363 |
| 64-17-5 | Ethanol | 82 | 616 | 1434 | 4916 | 4916 |
| 65-85-0 | Benzoic acid | 5.2 | 73 | | | 73 |
| 66-25-1 | Hexanal | 4.4 | 14 | | | 14 |
| 67-64-1 | Acetone | 16 | 87 | 24 | 53 | 87 |
| 67-66-3 | Chloroform | | | 0.14 | 2.1 | 2.1 |
| 68-12-2 | Dimethylformamide | 7.7 | 541 | | | 541 |
| 71-43-2 | Benzene | 8.2 | 53 | 0.88 | 62 | 62 |
| 74-83-9 | Bromomethane | | | 0 | 3.2 | 3.2 |
| 75-07-0 | Acetaldehyde | 6.3 | 9.1 | 7.4 | 76 | 76 |
| 75-09-2 | Dichloromethane | 1.1 | 72 | 46 | 662 | 662 |
| 75-15-0 | Carbon disulfide | | | 0.57 | 0.8 | 0.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 78-42-2 | Tris(2-ethylhexyl) phosphate (TEHP) | 0.03 | 0.09 | | | 0.09 |
| 78-51-3 | Tris(2-butoxyethyl) phosphate (TBEP) | 0.05 | 0.11 | | | 0.11 |
| 78-79-5 | Isoprene | 9 | 47 | 14 | 50 | 50 |
| 78-93-3 | Butanone | 2.9 | 32 | 2.2 | 12 | 32 |
| 79-01-6 | Trichloroethene | | | 0.32 | 41 | 41 |
| 80-62-6 | Methylmethacrylate | | | 0.00 | 2.0 | 2.0 |
| 84-66-2 | Diethyl phthalate | 0.7 | 4.1 | 0.80 | 10 | 10 |
| 84-69-5 | Diisobutyl phthalate | 0.5 | 7.1 | | | 7.1 |
| 84-74-2 | Dibutyl phthalate | 0.3 | 5.3 | 0.30 | 1.2 | 5.3 |
| 85-01-8 | Phenanthrene | | | 0.012 | 0.026 | 0.026 |
| 85-68-7 | Butyl Benzyl Phthalate | | | 0.008 | 1.0 | 1.0 |
| 86-73-7 | Fluorene | | | 0.008 | 0.018 | 0.018 |
| 91-20-3 | Naphthalene | 1.4 | 49 | 0.09 | 0.40 | 49 |
| 92-52-4 | Biphenyl | | | 0.011 | 0.032 | 0.032 |
| 95-50-1 | 1,2-dichlorobenzene | | | 0 | 0.072 | 0.072 |
| 100-41-4 | Ethylbenzene | 0.7 | 11 | 0.42 | 13 | 13 |
| Totals | 75 chemicals | 241 | 2327 | 1629 | 7654 | 8926 |

campaigns that consider the wide range of different pollutants identified by this manuscript.

As no endocrine disruptor regulatory thresholds exist, we performed a risk assessment by considering the four chemicals in the ED List I (identified as endocrine disruptors), dibutyl phthalate, diisobutyl phthalate, diethylhexyl phthalate, and butyl benzyl phthalate. The French, US, and UK workplace values (VLEP, OSHA PEL, EH40 WELs, respectively) identify dibutyl phthalate and diethylhexyl phthalate as having an 8-hour exposure limit of 5 mg $m^{-3}$ (5,000 µg $m^{-3}$), which also applies to diisobutyl phthalate (the ED endpoint is reduced spermatocyte development) and butyl benzyl phthalate in the UK. By using the ECHA dossier[37], a threshold value of approximately 3 times lower can be calculated. This results in an occupational exposure threshold of 4.94 mg $m^{-3}$ (5 mg $m^{-3}$) and is based on a no observed adverse effects level (NOAEL) of 2 mg $kg^{-1}$ bw day; this is modified for the protection of the public to 1,740 µg $m^{-3}$. Figure 1 presents these threshold values against the mean and maximum total of potential or endocrine disruptor concentrations obtained from EASA[43] and ACER[44] [Supplementary Materials]. The results show that conservative average concentrations of potential or known endocrine disruptors in the ACER study are approaching NOAEL-based threshold values. Maximum concentrations from both studies exceeded NOAEL-based threshold values and maximum concentrations in the ACER study exceeded the 5,000 µg $m^{-3}$ 8 hr exposure threshold.

Exceedances of threshold values recorded in both the EASA[43] and ACER[44] studies are a cause of concern given the overly conservative nature of this risk assessment. Exposure thresholds used here for comparison are likely to be too high and not conservative for the cabin environment and work patterns of aircrew. The concentrations reported in these two studies are overly conservative and only report concentrations for approximately 40% of the endocrine disruptors identified in the SI. These studies only account for one

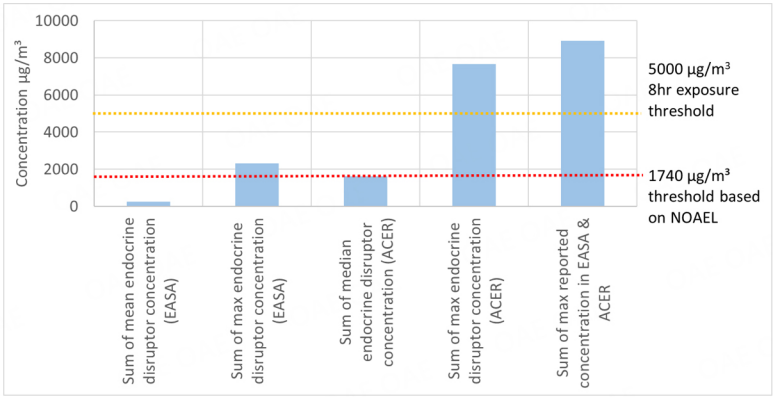


**Figure 1.** Concentration of the mean value of reported endocrine disruptors compared against threshold exposure values

exposure pathway (inhalation); exposure through dermal and ingestion routes should also be considered. More work is needed to comprehensively quantify the concentrations of endocrine-disrupting chemicals in the wider cabin environment. Specific health values should also be derived to assess the risk from these chemicals by taking into account the unique conditions under which aircrew operate. Further research could also include an assessment of the burden of disease to calculate DALYs (disability-adjusted life years) to investigate the impact of different pollutants and other factors.

### Considering the risks to passengers

Many passengers are healthy individuals who only fly occasionally. Therefore, the chronic risks from adverse cabin air quality to most people are understandably low. However, passengers can include a variety of vulnerable and sensitive individuals, including babies & young children, pregnant women (fetus), immunocompromised individuals, and frequent flyers. These individuals are not often considered in cabin air quality risk assessments, which instead focus on occupational exposure. On long-haul flights, many passengers suffer from "jet lag" and similar symptoms have been reported for chemical exposure, so it is a challenge to identify and distinguish these factors. Given the wide range of chemicals identified in this study, we would recommend future research to investigate the risks to vulnerable and frequent flyers.

### Potential impacts for legal proceedings

There have been over 100 legal cases filed worldwide that have concerned potential contamination events on aircraft and the perceived chemical exposure of aircrew to toxic compounds. Notable cases that have linked adverse air quality to health include the coroner's report on Capt. Richard Westgate stated that "Testing of samples taken both prior to and after death disclosed symptoms consistent with exposure to organophosphate compounds in aircraft cabin air"[45]. In a case in the Netherlands, a flight attendant was granted a sickness benefit. This was identified due to exposure to a "Medical Substrate" that caused her complaints, especially during her flights, that could be related to aerotoxic syndrome (case number 19/5376 WIA, 20/2 WIA). These instances show that the link between air quality on aircraft and reported adverse health effects is becoming more widely accepted, as is the term aerotoxic syndrome coined over 20 years ago.

One challenge in legal cases is establishing the time correlation between reported cabin air quality fume events and reported symptoms. This uncertainty is becoming more accepted by aviation accident/incident investigation boards and courtrooms, but there are still some uncertainties that need to be addressed. In these cases, samples were not able to be taken to measure the air quality at the times of the reported fume events (and many fume events may go unnoticed if odorless). We have to therefore rely on data from other

monitoring campaigns or simulated fume events (over 20 references cited within Hayes *et al.*[7]). These have included assessments on; polybrominated diphenyl ethers[46,47], volatile organic compounds,[48-55] carbon monoxide,[21,48,53,56,57] carbon dioxide[21-23,49-51,53,56,58-61], ozone[21,52,53,56,62], tricresyl phosphates[48,52-54,57,60,63], particulate matter[23,48,59,64], and cosmic radiation[65]. These investigations are often targeted and so only include the determination of a small fraction of all the chemicals that aircrew may be exposed to. When this is compared against threshold values that only consider one chemical in isolation, it makes it impossible to accurately identify the levels of risk. Furthermore, individual absorption, metabolism, and excretion will vary between staff, along with their susceptibility due to shift working. More specifically, the relationship of shift work to physiological changes in regulatory hormones is of specific importance for the additive effect of endocrine disrupter chemicals. It is hoped that the chemical data presented in the Supplementary Materials will be a useful addition to the existing information present in the scientific literature and will justify the need for broader chemical screening programs and more accurate human health risk assessments. It should be noted that this list is not expected to be complete or comprehensive; the aim of sharing this data is to raise awareness of the large number of toxic chemicals that are present in the cabin environment. Future investigations that incorporate a non-targeted analytical approach would be a welcome addition to the scientific literature.

## CONCLUSIONS

There have been a large number of reports and official documents on cabin air quality in the grey literature. These have been released by aviation authorities and aircraft manufacturers, several governmental enquiries, and national and international research projects. In this manuscript, we have attempted to collate relevant findings of this work so that it is more visible within the scientific literature and available for others to use. These findings are presented as a database in Supplementary Materials 1, which documents over 450 different chemicals that have been identified on aircraft. Of these, 325 (72%) have been shown to be toxic, with many affecting the same target organs skin (302), eyes (294), respiratory system (234), and central nervous system (94). When performing a human health risk assessment on a chemical-by-chemical basis, the results indicate there is no significant risk to worker health (as no individual chemical exceeds an exposure threshold value). Our preliminary risk assessment of the additive effects of endocrine disruptors indicated there may be a significant human health risk regardless of limit values. This is backed up by the wider scientific literature and medical records that clearly document a range of adverse health effects. Further research is needed that involves effective holistic risk assessments that consider; the additive effects of chemicals, nanoparticles, different exposure pathways, and the unique conditions inside aircraft.

The data provided in Supplementary Materials 1 and recommendations from this manuscript can be used to produce more informed investigations and risk assessments on cabin air quality. Existing occupational exposure limits and threshold values should not be applied on a chemical-by-chemical basis to assess risks in aircraft cabin air. Instead, the potential for a synergic effect of the multiple compounds present in aircraft air should be considered along with an appreciation for the additive effects of endocrine disruptors. This can be addressed by a more comprehensive analytical measurement of a wider range of pollutants. These need to be compared against exposure limits that consider the complexity of the aircraft cabin environment. This will facilitate more accurate and appropriate epidemiological studies and risk assessments that consider exposure to multiple pollutants and additional environmental factors unique to this work environment. The majority of research on cabin air quality has focused on risks to workers (pilots and cabin crew), but understanding the risks to passengers (especially vulnerable and frequent flyers) should not be ignored.

## DECLARATIONS

### Acknowledgments

This manuscript has been prepared in honor of Dr Jean Christophe Balouet, who sadly passed away in 2021. He dedicated his career to trying to increase our understanding of cabin air quality and help find answers for those who have suffered from aerotoxic syndrome. The database presented in the Supplementary Materials is a result of over 30 years of data collection that he has performed while investigating this issue. We hope that it will be of use to others to continue and build upon his worthwhile research.

### Authors' contributions

Made substantial contributions to the conception and design of the study, and performed data analysis and interpretation: Megson D, Delahaye JC, Dack S, Mulder MFA

Made substantial contributions to conception and data collection: Balouet JC

### Availability of data and materials

Supplementary Materials 1 Database of aircraft cabin contaminants.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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