

Aerospace Toxicology Overview: Aerial Application and Cabin Air Quality*

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1 Introduction

The environment extending above and beyond the surface of the planet Earth is referred to as aerospace (Blashfield and Johnson 1969). This word also symbolizes the joint fields of aeronautics and astronautics. The former is the art and science of flight through the atmosphere (Blashfield and Johnson 1969) and the latter is the art and science of space flight (Blashfield and Johnson 1968a). Another term frequently and interchangeably used with aerospace and aeronautics is aviation, which is defined as the art and science of operating powered aircraft (Chaturvedi 2010a, b; The Encyclopedia Americana 1989).

Toxicology is defined as being “the basic science of poisons” and deals with the adverse effects of substances on living organisms; any chemical substance is recognized as potentially being poisonous, although the induction of toxicity is exposure-, amount-, and frequency-dependent (Eaton and Klaassen 1996; Gallo 1996; Loomis 1978). Toxicology is a multidisciplinary subject and acquires and integrates knowledge from biology, chemistry, immunology, pathology, physiology, and public health. The field most closely related to toxicology is pharmacology (Loomis 1978). Toxicology can be divided into subareas referred to as economic, environmental, or forensic toxicology, among others. Thus, aerospace toxicology can be considered to be closely related to aerospace medicine. This medical field is newly emerged and is a specialty area of general medicine (Blashfield and Johnson 1968b). Aerospace toxicology is concerned with the health and medical issues of man in aviation and during space flights (National Library of Medicine 2008). Aerospace medicine can be viewed as the branch of preventive medicine that addresses the special problems of flying, both within and outside the atmosphere (Case University 2008).

To prepare this review, I performed a literature search for the period from 1960 to 2007; the scope of the search covered aerospace toxicology-related subspecialties, agricultural aviation (aerial application) and aircraft cabin air quality. Overviews of other subspecialties – aviation combustion toxicology and postmortem aviation forensic toxicology – have been included in separate scientific articles (Chaturvedi 2010a, b). In the present article, I address the safety of aerially applied chemicals, cabin air quality in aviation, and the harmful effects of fumes and smoke, including the toxicants that may exist in space vehicle cabin air. During the course of the review, I also address chemical exposure monitoring, exposure monitoring methods, aspects of agricultural aviation, in general, and the application of potentially toxic agricultural chemical active ingredients in combinations and with component chemicals (organic solvents and surfactants), in the context of agricultural aviation. Furthermore, in this review I emphasize the potential for the presence of chemical constituents and pyrolysis products of engine oils, hydraulic fluids, and lubricants in aircraft cabin air, and suggest the need for a thorough evaluation of oil additives used in aircraft.

2 Agricultural Aviation

2.1 Application of Chemicals in Agriculture

The use of aerial application is increasing throughout the world to help address increasing food production needs. Many types of agricultural chemicals are applied to crops, crop land, pastures, rangeland, or forests by hand, or by ground or aerial equipment; such agents include insecticides, herbicides, growth modifiers, fertilizers, and others. Many of the chemicals used can be toxic to human beings and may cause serious symptoms and possibly death (Patterson and Rayman 1996). Handling of commercial agricultural chemical preparations (formulations) is involved during aerial application programs, and application incidents and accidents do occur. Some actual examples of such incidents are (1) an experienced aerial applicator pilot, who accidentally spilled parathion on his clothes while pouring the concentrate from a 55-gallon drum four days earlier, and who afterward became irritable and introverted, was not feeling well, and had a headache on the day he crashed his plane, (2) a pilot, who was exposed to drifting parathion and required atropine therapy, flew into a tree during pull-up, (3) an aircraft connector loosened after takeoff and resulted in the spraying of a mixture containing parathion in the pilot's face, saturating his body, and causing him to lose control of the plane, which crashed, and (4) a pilot was splashed with a defoliant during a flight, which caused a crash, almost resulting in the pilot's death (Mohler and Harper 1966). Such accidental exposures and the development of aerial dust allergies in pilots were topics of a group discussion on protecting agriculture pilots 45 years ago (Mohler and Harper 1966); therefore, this problem is a long existing one. In general, agricultural chemicals are toxic (Cullen and Hill 2006; Ecobichon 1996), and if occupational safety and precautionary measures are not properly taken, exposures of applicator personnel (i.e., aircraft loaders, mixers, and agricultural aircraft accident investigators) to such chemicals could lead to acute or chronic poisonings. In addition, poisonings of working agricultural pilots may contribute to aviation accidents. Such poisoning incidents, when they occur, may result from exposures to a single or multiple chemicals (or chemical mixtures).

2.2 Pesticidal Toxicology and Agricultural Aviation

The toxicology of organophosphorus and organochlorine insecticides has been well covered in the literature (Cullen and Hill 2006; Lauwerys 1996). Although no longer used except for malarial programs in Africa, dichlorodiphenyltrichloroethane (DDT) is the most studied organochlorine insecticide, and has also served

as a prototype for the types of toxicological properties that may exist for many other organochlorine insecticides (Cullen and Hill 2006; Lauwerys 1996). Organophosphorus and organochlorine chemicals adversely affect the functions of the central nervous system, though they do so by different mechanisms. Behavioral difficulties have been experienced by aerial applicators following their exposures to certain pesticides (Dille and Smith 1963, 1964; Lewis et al. 1972; Smith et al. 1968; Wood et al. 1971). Symptoms of such exposures have included anxiety, uneasiness, depression with weeping, dizziness, emotional lability, frequent and severe disagreement with family members and coworkers, and being unable to perform familiar tasks. These effects were reported during medical evaluations of two agricultural pilots actively engaged in the aerial application of organophosphorus (methyl parathion) or organochlorine insecticides (DDT, toxaphene, endrin, and dieldrin) (Dille and Smith 1963, 1964).

Toxicological evaluation of postmortem samples from pilots killed while engaged in aerial application revealed that blood cholinesterase levels in 44 of 104 pilots (Lacefield et al. 1975) and 77 of 130 pilots (Lacefield et al. 1978) were below the normal range. This suggests a problem of acute and/or chronic toxicity from exposure to the organophosphorus pesticides these pilots were applying. Reduced plasma cholinesterase levels were found in two agriculture pilots who were involved in nonfatal aviation accidents (Dille and Morris 1966, 1967). The types of accidents and poisonings that have occurred as a result of aerial applications have been documented (Dille and Mohler 1968; Dille and Morris 1966, 1967). Aerial application-related precautions, signs, and symptoms of pesticide poisonings, and their treatments have also been summarized in the literature to help protect agricultural pilots (Dille and Mohler 1968; Mohler and Harper 1966). Among the precautions suggested is a key one that points out the need for better educational efforts designed to reduce accidents in this sector of agricultural activity.

Aerial spraying programs are also used to help manage insect infestations of large tracts of forest. In this area, extensive studies have been conducted on the toxicity of forest insecticides (fenitrothion and aminocarb), the technology of aerial spraying, the development of less hazardous formulations, and the quantitation of off-target drift of aerosolized insecticides (Ecobichon 1990). These studies resulted in improved pesticide application techniques, and they have fostered the establishment of regulations to implement buffer zones around human habitation for certain types of aircraft that apply different formulations of forest insecticides.

2.3 *Exposure to Multiagricultural Chemicals and Organic Solvents/Surfactants*

If proper safety and precautionary measures are not observed, there is a clear potential for aerial applicators, associated personnel, and aircraft accident investigators to be exposed to multiple agricultural chemicals and the solvents/surfactants in their commercial spray preparations. Such exposure may result in poisonings and could

be produced by any one ingredient, or interactive effects among several active ingredients, or other components of a formulation to which exposure occurs.

During the course of 7- and 14-day treatments, the toxic effects in mice of mixtures of parathion (5 mg/kg), toxaphene (50 mg/kg), and/or dichlorophenoxyacetic acid (2,4-D; 50 mg/kg) were observed to emulate the effects exhibited by the individual components (Kuntz et al. 1990). Metabolic aspects of these three chemicals suggest that the toxicity of the parathion plus toxaphene mixture would be lower than that of parathion, as toxaphene has the ability to increase aliesterases and the biotransformation of parathion to paraoxon, thereby providing a pool of noncritical enzymes for the binding of paraoxon (Chaturvedi et al. 1991). Because of these properties of toxaphene, it is anticipated that the toxicity of a mixture of parathion plus toxaphene plus 2,4-D would also be lower than that of parathion alone (Chaturvedi et al. 1991). Chronic studies in mice on the mixtures of three commonly used herbicides – alachlor, atrazine, and/or picloram – suggest that the mixtures may cause hepatotoxicity and stimulate the liver xenobiotic-metabolizing enzymes (Chaturvedi 1993a). A chronic toxicological evaluation of mixtures of ten widely used pesticides – alachlor, aldrin, atrazine, 2,4-D, DDT, dieldrin, endosulfan, lindane, parathion, and toxaphene – in mice revealed that these mixtures induce the xenobiotic-metabolizing enzymes in liver. Therefore, exposures to such pesticidal mixtures may cause deleterious effects in other species, including humans, by enhancing the metabolism of xenobiotics (Chaturvedi 1993b).

In multichemical exposures, interactive effects among chemicals to which exposure occurs may play a contributory role toward the associated poisonings. This type of poisoning could be exemplified by citing two actual examples: first, a multichemical death that involved caffeine, nicotine, and malathion (Chaturvedi et al. 1983), and another death attributed to ingestion of malathion insect spray (Chaturvedi et al. 1989). In the later case, *in vitro* inhibition of cholinesterases and the presence of xylenes and other volatiles, in certain postmortem samples, were demonstrated (Chaturvedi et al. 1989). Therefore, these organic solvents may not only interact with other mixture-chemicals, but may also exhibit their own toxic effects.

Ethylbenzene, a major component of mixed xylenes, is used as solvents in agriculture insecticide sprays and has been found to increase the incidences of renal tubule, alveolar/bronchiolar, and hepatocellular neoplasms, and of testicular and renal tubule adenomas, in rats (US National Toxicology Program 1999). Increased incidences of renal tubule hyperplasia of alveolar epithelial metaplasia, and of severe nephropathy have been reported in rats exposed to ethylbenzene. The herbicide glyphosate, though it does not bioaccumulate, biomagnify, or persist in a biologically available form in the environment, and is nontoxic to animals, is formulated with surfactants (Solomon and Thompson 2003). Such formulations increase the efficacy of the herbicide but, in some cases, are more toxic to aquatic organisms than is the parent material. Some risks were observed for measured concentrations of glyphosate in surface waters that resulted from aerial application to forests of a formulation equivalent to Roundup® in Canada.

2.4 Aerial Application Safety

Aviation authorities have long been concerned about the toxic effects of agricultural chemicals on agriculture pilots. In the former Soviet Union, aerial applicators were required to maintain records of the chemicals used for crop spraying and the duration of spraying (Cullen and Hill 2006). In the USA, toxicological problems associated with aerial applications were recognized in the early 1960s, and a considerable number of applied studies were conducted at the US Department of Transportation Federal Aviation Administration's (FAA's) Civil Aerospace Medical Institute in Oklahoma City, OK, to enhance the safety of agricultural pilots and their support personnel. The cogent studies conducted at the FAA's Civil Aerospace Medical Institute are summarized in Table 1.

2.5 Agricultural Chemical Exposure Monitoring

The health risk of aerial spraying is well known for pilots and ground maintenance workers. Therefore, such agricultural workers in the aerial spraying industry must be placed on occupational surveillance programs designed to detect the earliest toxic exposures to these chemicals. Since organophosphorus compounds and carbamates inhibit acetylcholinesterase and other cholinesterases, activities of these enzymes in red blood cells, plasma, or whole blood (30–50% inhibition) are routinely measured for monitoring exposures to these insecticides (Cullen and Hill 2006; Gossel and Bricker 1994a; Lauwerys 1996). In addition, residues of pesticides or their metabolites in body fluids may be measured directly. Examples of tentative maximum permissible concentrations for parent pesticides and/or their metabolites are (1) 0.5 mg of *p*-nitrophenol per g of creatinine in urine for parathion and 10 mg of naphthol per g of creatinine in urine for carbaryl, (2) 15 µg of dieldrin per 100 mL of blood, 2 µg of lindane per 100 mL of blood, and 5 µg of endrin per 100 mL of blood, (3) 30 µg of hexachlorobenzene per 100 mL of blood and/or presence of 2,4,5-trichlorophenol in urine. (4) 0.05 mg of pentachlorophenol per 100 mL of plasma and/or 1 mg of pentachlorophenol per g of creatinine in urine, and (5) detection of 2,4-D and 2,3,5-trichlorophenoxyacetic acid in urine (Lauwerys 1996).

3 Cabin Air Contamination

3.1 Aviation Cabin Air Quality

The quality of air in aircraft cabins has been a topic of debate and discussion since at least the 1970s. Aerospace air pollution issues – that is, cabin air quality of aircraft and space vehicles – have been succinctly addressed in an article by Patterson and Rayman (1996). These issues are viewed in the context of the fact that crews

Table 1 A summary of aerial application-related studies conducted at the Civil Aerospace Medical Institute

Agent(s) or topic	Summary	Reference
Lindane and dieldrin	Alterations in several biochemical values of rat tissues by chronic exposures to lindane and changes in the uptake of L-methionine by chick heart and liver cells by chronic exposure to dieldrin	Daugherty et al. (1962)
Analysis of hazards in the aerial application	Discussion on the nature of the chemicals, the symptoms of toxicity, recommended treatment, and suggestions for safe handling of toxic pest-control chemicals	Smith (1962)
Cardiovascular effects of endrin	Causation of bradycardia, hypertension, salivation, hyperexcitability, tonic-clonic convulsions, increased body temperature, leukocytosis, and decreased blood pH by endrin, appeared to be caused by direct action on the central nervous system	Emerson et al. (1963)
Dieldrin, lindane, heptachlor, isodrin, and endrin	Reduction in the esterification of inorganic phosphate by 50%, without affecting lactic acid production in chickens and rats exposed to dieldrin, but no such reduction in esterification by other chlorinated pesticides lindane, heptachlor, isodrin, and endrin	Daugherty et al. (1963)
Cases involving aerial application of organophosphorus insecticides	Signs/symptoms of anxiety, uneasiness, depression, weeping, dizziness, emotional liability, disagreement with family/coworkers, and unable to perform familiar tasks	Dille and Smith (1963)
Chronic and acute effects of endrin on renal function	Systemic hypertension and increased renal vascular resistance in dogs by acute exposure to endrin, attributed to a sympathoadrenal action Development of progressive systemic hypotension with variable changes in renal function and terminal renal vasodilatation in dogs chronically exposed to endrin Note: These findings were related to hemodynamic alterations in the peripheral vasculature. No evidence of renal failure was observed due to chronic insecticide poisoning.	Reins et al. (1963)
Effects of endrin and carbon tetrachloride	Reversible increase in hepatic fat contents of rats treated with endrin and carbon tetrachloride	Clark (1966a)
Pathological effects of endrin and dieldrin	More severe effects of dieldrin on the cold-adapted rats than on the room-temperature rats	Clark (1966b)
Effects of endrin on renal function and hemodynamics, peripheral vascular system, venous return and catecholamine release, and the cardiovascular system	Exploration of the effects of endrin in dogs on renal function and hemodynamics, peripheral vascular system, venous return and catecholamine release, and the cardiovascular system; and elucidation of the mechanisms of endrin-induced hemoconcentration	Hinshaw et al. (1966)

(continued)

Table 1 (continued)

Agent(s) or topic	Summary	Reference
Exposure of parathion and development of allergy toward aerial dusts	Group discussion on protecting agriculture pilots	Mohler and Harper (1966)
Human factors in general aviation accidents	Discussion on the role of medical conditions and pesticides in aviation accidents	Dille and Morris (1966, 1967)
Cholinesterase measurement	Development of an automated method for measuring cholinesterase activity in blood and tissues of animals poisoned with organophosphates and carbamates	Fowler and McKenzie (1967)
Drug and toxic hazards in general aviation	Summary of aerial application related precautions, signs and symptoms of pesticide poisoning, and their treatments	Dille and Mohler (1968)
Effects of disulfoton	Increase in performance in rats given disulfoton at 10, 25, and 50 ppm in diet and water ad libitum and inhibition of brain acetylcholinesterase by more than 75% of normal in the most severely exposed group	Pearson et al. (1969)
Cholinesterase methods	Comparison of three cholinesterase methods Importance of cholinesterase tests in applicators prior to the aerial application season	Crane et al. (1970a)
Human blood cholinesterase	Decrease of only 10% of the original cholinesterase activity upon storage of red cell hemolysates for less than 12 h at room temperature, up to 3 days at 4°C, and up to 6 weeks at -20°C Note: Whole-blood hemolysates and plasma may be stored for 6 days at room temperature and 6 weeks, if refrigerated or frozen.	Crane et al. (1970b)
Effects of endrin on brain	Brain bioelectric phenomena caused by endrin at doses well below those causing seizures or other gross behavioral changes Seizures in squirrel monkeys by chronic administration of this pesticide Reoccurrence of seizures some months after the termination of endrin administration, under stressful conditions, suggesting that this phenomenon may have been caused by a stress-induced release of endrin from adipose tissue storage sites Discussion on some implications of these findings for aerial applicators	Revzin (1970)
Disulfoton	Adverse effects on the reproduction system in rats by disulfoton Note: The number of pregnancies was decreased in the animals receiving this pesticide. Such decrease could have been attributed to such factors as alteration in the estrus cycles, the receptivity of the female animals, and decrease in sperm concentration or viability.	Ryan et al. (1970)

(continued)

Table 1 (continued)

Agent(s) or topic	Summary	Reference
Serum or plasma cholinesterase methods	Evaluation of four serum or plasma cholinesterase methods and relationships for interconversion among their respective units Emphasis on the importance of the cholinesterase test in applicators prior to the aerial application season	Crane et al. (1972)
Effects on performance of pigeons and monkeys of phosdrin (mevinphos), a cholinesterase inhibitor	A dose related decrease in response rate with the animals and decrements in behavior at doses below which external symptoms of phosdrin poisoning occurred	Lewis et al. (1972)
Mevinphos (phosdrin)	Inhibition of the amplitude of hippocampal-evoked potentials in squirrel monkeys by mevinphos (phosdrin) in the dose range of 0.05–0.2 mg/kg, with no peripheral signs of poisoning such as tremor and salivation Emphasis that mevinphos produces changes in brain function in the absence of the peripheral symptomatology usually taken as indicators of poisoning by aerial applicator personnel Conclusion that exposure to mevinphos may be unexpectedly hazardous since the aerial applicators may be unaware that they have been poisoned	Revzin (1973a)
Mevinphos poisoning with atropine	Based upon squirrel monkey experiments, potentially hazardous dysfunctions of visual perception in aerial applicator personnel being treated for mevinphos poisoning with atropine	Revzin (1973b)
Toxicological findings in fatal civil aviation accidents (1968–1974)	Blood cholinesterase activity below the lower limit of the normal range in 44 of the 104 aerial applicator pilots	Lacefield et al. (1975)
Chlordimeform	Little or no extra risk in aerial applicators (or others) should they be taking <i>p</i> -chlorophenylalanine, DL- α -methyl- <i>p</i> -tyrosine, phen-tolamine, methysergide, and phenylephrine during potential exposure to chlordimeform	Smith et al. (1977)
Toxicological evaluation of postmortem samples from 174 pilots killed in aerial application accidents	Incidence of alcohol in specimens similar for agriculture pilots and other general aviation pilots, but the alcohol blood levels tended to be lower in the former category of pilots Evidence of the use of drugs or medications less in agriculture pilots than in other general aviation pilots Cholinesterase levels below normal in the agriculture pilots, suggesting a continuing problem of acute and/or chronic toxicity from pesticides applied by agricultural aircraft	Lacefield et al. (1978)

must work, sleep, and often live in the cabin environments of aircraft and space vehicles. Throughout the world, the possible adverse effects of cabin atmosphere content on the health of air crews and travelers have been evaluated (Brown et al. 2001; Brundrett 2001; Fulton 1985; Harding 1994; Rayman 2001, 2002; Rayman, RB 2001; Vieillefond et al. 1977; Wyss et al. 2001). Congressional bills that relate to aircraft cabin air quality, and a report on the same topic by the US National Academy of Sciences, have addressed the topic of aerospace medicine (Rayman 2001, 2002; Rayman, RB 2002). Before 30 years ago, the quality of cabin air was apparently not an issue in commercial aviation, and the reporting of disease resulting from airborne vectors or toxic fumes was uncommon (Abeyratne 2002).

Modern jetliners may pose a greater threat of disease because their ventilator systems are designed for optimum efficiency, and may lapse in the recycling of clean air, and/or in the effective blocking of engine exhaust fumes that may enter cabin areas. Aerotoxic fumes are most common in the cockpit, and therefore, crew members are the most susceptible to the aerotoxic syndrome (Abeyratne 2002). In a comprehensive review of 21 studies, in which authors examined the effect of the airliner cabin environment and other factors on the health and comfort of flight attendants, Nagda and Koontz (2003) found that various complaints and symptoms reported by the attendants appeared to be associated with their job duties and with the cabin environment. The “dryness” symptoms were attributable to low humidity, and the “fatigue” symptoms to the disruption of circadian rhythm. Certain flight attendant complaints were consistent with possible exposure to air pollutants, but that relationship has not been established because such complaints also were consistent with other causes. Despite health issues associated with air travel, there are enormous benefits of this mode of travel to travelers, to commerce, to international affairs, and to health (DeHart 2003).

Stresses (e.g., airport tumult, barometric pressure changes, immobility, jet lag (Sanders et al. 1999), noise, vibration, and radiation) imposed on travelers by commercial flights, and the capability of US air carriers to deal with in-flight illness and medical care have been addressed in an earlier review article (Rayman 1997). The “cabin air quality” topic has been controversial and of concern to the Aerospace Medical Association (AsMA). As a result, the AsMA has reviewed the scientifically accepted facts associated with the different elements (e.g., pressurization, ventilation, contamination, humidity, and temperature) of aircraft cabin atmospheres (Thibeault 1997). The AsMA recommended that regulators, airlines, and scientific associations work together on the issue of cabin air quality, since technical data alone is inadequate to solve the problem.

Aircraft cabin carbon dioxide (CO_2) concentrations, calculated from the published ventilation ratings, were found to be intermediate to those obtained by actual measurement. These findings were used to arrive at recommendations for aircraft builders and operators to help improve aircraft cabin air quality at minimum cost (Hocking 1998). Several factors were considered that pertained to cabin air quality before proposals were made. These factors included the trends, effects, and societal costs of cabin air quality on passengers and crew. Improvement was successfully made in cabin air quality that has resulted in a net, multistakeholder savings and improved passenger comfort (Hocking 2000). Aviation-industry and

passenger perspectives on cabin air quality have been evaluated by Hocking (2002). Accordingly, recommendations and suggestions were made for aircraft builders, operators, and passengers. These recommendations were designed to help improve aircraft cabin air quality, to improve the partial pressure of oxygen that is available to passengers at minimal cost, and to enhance passenger comfort and decrease risk of illness. Rayman, RB (2002) made recommendations on how the cabin air quality issue may be resolved, whereas Thibeault (2002) argued in a review that airliner cabin air quality was adequate and did not compromise the health of aircrews, though this author acknowledged the need for further studies.

3.2 Harmful Effects of Aircraft Cabin Air

Air crew fatigue for those performing frequent and long flights has been linked to effects from aircraft-related noise, temperature, cabin pressure, ventilation, atmosphere quality, humidity, and jet lag, among other flight characteristics (Fulton 1985; Vieillefond et al. 1977). Fulton (1985) addressed the effects of ventilation adequacy, cigarette fires, and pilot health issues in aircraft cabins. Harding (1994) acknowledged that the amounts of fresh air in aircraft cabins may be marginal, but there was nonetheless sufficient oxygen for human consumption. The concentration of microorganisms in airline cabin air was found to be much lower than concentrations in ordinary city locations (Wick and Irvine 1995). Hence, it was concluded that the small number of microorganisms found in US airliner cabin environments does not contribute to the risk of disease transmission among passengers.

In a 1997 study of Airbus aircraft (Dechow et al. 1997), the number of particles in cabin air was compared with those found in fresh air and recirculated air. In addition, levels of microbiological contamination and volatile organic compounds were investigated in cabin air. Results indicated that particles were mainly emitted by passengers, especially smokers, and particle counts in recirculated air were lower or equal to those occurring in fresh air. By contrast, bacterial counts in the aircraft cabin exceeded those in fresh air. The detected microbes were mainly nonpathogenic and the concentrations of volatile organic compounds were well below threshold values. Modern high-efficiency particulate air (HEPA)-filters are used in aircraft and minimize the accumulation of bacteria and viruses in recirculated cabin air. Such HEPA filtration in aircraft significantly reduces the overall risk of acquiring infectious diseases, compared with other means of transportation (Bergau 1999).

The issue of the flying fitness of patients, who have infections, has also been addressed (Haditsch 2002). Aircraft that carry both cargo and passengers have been implicated in disease transmission, since they may transport humans, along with mosquitoes or other insect disease vectors, and animals (DeHart 2003). Events of tuberculosis and influenza transmission to other travelers have been reported, and the vectors of yellow fever, malaria, and dengue have been identified on aircraft. However, studies of the ventilation systems and patient outcomes suggest that the spread of pathogens rarely occurs during flights (Leder and Newman 2005).

A review of the concentrations of organic compounds in cabin air has indicated that contaminant levels are similar to those that exist in residential and office buildings (Nagda and Rector 2003). However, there were two exceptions. First, levels of ethanol and acetone – indicators of bioeffluents and chemicals from consumer products – were higher in aircraft air than in home or office environments, or in other transportation modes; second, levels of certain chlorinated hydrocarbons and fuel-related contaminants were higher in residential/office buildings than in aircraft air. The levels of the *m*- and/or *p*-xylenes tend to be lower in aircraft. Although cabin air is filtered through adsorbents, prior to recirculation, to remove volatile organic compounds and odor, such devices are not installed in all aircraft and may not be capable of removing all pollutants. Therefore, the photocatalytic air filtering approach was developed and this approach seems to be a promising method to resolve odor problems in aircraft (Ginestet et al. 2005). This photocatalytic unit consists of four UV lamps sandwiched between two interchangeable titanium dioxide-coated panels and is designed to oxidize volatile organic compounds. The overall efficiency of the catalytic unit was dependent upon the chemical characteristics of the compounds that were used to challenge the unit. The compounds used were toluene, ethanol, and acetone. The tested unit did not fully remove toluene, since the unit relies on oxidation to remove substances, and toluene is the most difficult compound to be oxidized. Moreover, although the tested prototype unit is able to partially oxidize volatile organic compounds, partial oxidation of some toxic intermediate chemical reaction products may result in the production of intermediates such as formaldehyde and acetaldehyde.

High concentrations of ozone in cabin air can lead to upper respiratory problems, and inhaling the high levels of CO₂ that may occur in cabin air may produce hyperventilation (Bergau 1999). Breathing cabin air may also cause the mucous membranes of the respiratory tract to dry out because of the extremely low humidity of cabin air. In a 2000 study by Backman and Haghighat (2000), air quality in 15 different aircraft was measured at different times and altitudes. High CO₂ concentrations and low humidity levels were found in the Airbus 320 aircraft. The highest humidity level was found in the DC-9 aircraft and the lowest CO₂ concentration was analyzed in the Boeing 767 aircraft. The authors concluded that poor air quality may cause intolerance to contact lenses, and dry eyes, and may be a health hazard to both passengers and crew members. In the US Air Force C-5 aircraft cabin air, carbon monoxide (CO) and CO₂ concentrations were found to be well below health effect thresholds, whereas the lowest level of relative humidity found was 3%, and ozone existed at relatively low concentrations (Hetrick et al. 2000). The influence of ozone on self-evaluation of symptoms in a simulated aircraft cabin indicated that air quality, as measured by the presence or absence of 12 symptoms (e.g., eye and nasal irritation, lip and skin dryness, headache, dizziness, mental tension, and claustrophobia), was established to be significantly worse ($p < 0.05$) for the 60–80 ppb ozone atmosphere (“ozone” condition), compared to the <2 ppb ozone atmosphere (“no ozone” condition) (Strom-Tejsen et al. 2008).

During intercontinental flights, CO₂ levels were below 1,000 ppm in 97% of the cases and humidity was very low (mean 5%) (Lindgren et al. 2000). Low humidity

in aircraft cabins is further demonstrated to be a factor for the mucosal irritation experienced by travelers and flight attendants (Lindgren and Norback 2002; Nagda and Hodgson 2001; Uva Ade 2002), and tobacco-smoking onboard may contribute to significant pollution from respirable dust (Lindgren and Norback 2002; Lindgren et al. 2000; Wieslander et al. 2000). Lindgren et al. (2007) investigated the influence of air humidification during intercontinental flights on the perception of cabin air quality among airline crew. These authors concluded that relative humidity can be slightly increased by using a ceramic evaporation humidifier, without showing any measurable increase of microorganisms (Lindgren et al. 2007). Their evaluation of the optimum balance between fresh air supply and humidity, involving 7-h exposures in a simulated aircraft cabin, indicated that increasing the relative humidity to 28% by reducing outside flow to 1.4 L/s per person did not reduce the intensity of the symptoms that are typical of the aircraft cabin environment. However, this adjustment intensified complaints of headache, dizziness, and claustrophobia that resulted from the increased level of contaminants (Strom-Tejsen et al. 2007).

The contribution of secondhand tobacco smoke to aircraft cabin air pollution was assessed for flight attendants, and compared to results from the general population; results indicated that ventilation systems massively failed to control secondhand smoke air pollution in cabins (Repace 2004). However, smoking is now prohibited by most airlines, and the pollution caused by smoking is no longer a relevant issue. The authors of another study emphasized that the relative air humidity of cabin air was very low on intercontinental flights, and particle levels were high on flights with passive smoking (Lindgren and Norback 2005). These findings suggested the need for improving cabin air quality by better controlling cabin temperature, air humidification, and air filtration (HEPA filters), and having a sufficient air exchange rate on all aircraft types.

3.3 Possible Toxicants in Space Vehicle Cabin Air

Astronauts work, sleep, and live in space vehicles (Patterson and Rayman 1996), and there is a strong potential for a slow and insidious buildup of toxic substances – such as refrigerants, CO, hydrogen cyanide (HCN), CO₂, ammonia, and other organic compounds – in the space-vehicle cabin atmosphere. Also, high concentrations of toxic substances may be rapidly released from onboard fires. The deaths of the three Apollo 1 crew members in the 1967 fire accident resulted from their exposure to toxic combustion products (US National Aeronautics and Space Administration 1967). Moreover, the involvement of fire has been acknowledged in the 23 February 1997 accident on the Mir aerospace station (Welch and Navias 1997), wherein the fire burned for approximately 90 s and the crew was exposed to heavy smoke for 5–7 min.

In addition to the combustion gases (e.g., CO and HCN) originating from fire (Chaturvedi 1995; Chaturvedi and Sanders 1995, 1996; Sanders and Chaturvedi 1994), sources of toxic substances in cabin air can result from off-gassing of space

vehicle material, crew metabolism (CO_2 in particular), payload chemicals, and thermal degradation of materials present in the aircraft (Patterson and Rayman 1996). Therefore, the protection of the astronauts' health and preventing their performance decrements are crucial. A major need in the space cabin is to establish maximum allowable concentrations of potentially toxic substances. Such an effort should be based on the fact that astronauts live in the closed environment of their space vehicles 24 h a day, for weeks or even months, in comparison to the standard 8-h shift worked by most terrestrial workers. Exposure to microbes in the space cabin is also of concern because crew members release many bacteria into the environment, and exudation of aerosols in a microgravity environment results in droplets being suspended in the atmosphere. Both factors render exposures more likely. How microgravity affects the immune system of humans has not been well established. Therefore, monitoring for microorganisms and toxic substances in the space vehicle cabin atmosphere is essential. Surveys have shown that the methods and means of qualitative and quantitative air monitoring on the International Space Station are currently sufficient for air control in emergency situations such as local fire and toxic leak; moreover, the Station's air quality is regarded to be suited to the existing standards and crew safety requirements (Pakhomova et al. 2006).

3.4 Fumes/Smoke in Aircraft Cabins: Analysis and Effects

Pyrolytic products of jet engine oils, hydraulic fluids, and/or lubricants may enter aircraft air by leaking in through ventilation systems (Crane et al. 1983; Sanders 2007; van Netten 1999; van Netten and Leung 2001). When this occurs, exposures to them may impose a threat to the operating aircraft and to their occupants (Rayman and McNaughton 1983). Smoke/fumes-related incidents are usually caused by broken engine seals or associated systems that allow smoke and fumes to enter the air compressor section from where they can contaminate the interior of the aircraft. Catalytic converters have been used to clean the air (van Netten and Leung 2000), but when an oil seal fails, such systems can easily become overloaded, allowing smoke to enter the cabin. The potential for exposure to thermal breakdown products, including smoke or other toxic gases, may cause performance impairment of the crew members. Dizziness, nausea, disorientation, blurred vision, tingling in legs and arms, central nervous system dysfunction, and mucous membrane irritation have frequently been reported by flight crews. Such symptoms are consistent with exposures to CO and some pyrolysis products, including volatile organic compounds and the organophosphate constituents of the oils and fluids, but the involvement of these liquids has not been clearly demonstrated (van Netten 1999).

Smoke consists of particulate matter and a variety of invisible combustion gases and vapors that are suspended in the fire environment, resulting from a rapid exothermic chemical chain reaction between a fuel and oxygen (Landrock 1983; Meyer 1977; Smyth et al. 1992; Strahle 1993). The types of combustion gases produced depend upon the nature of the chemical constituents of the material being burned.

For example, polymers, such as polyethylene produces CO and CO₂; Nylon 6/6 produces CO, HCN, and CO₂; polyamide produces CO, HCN, and CO₂; polystyrene produces CO, CO₂, and benzene; chlorinated polyethylene produces CO, CO₂, and hydrogen chloride; and polysulfone produces CO, CO₂, and sulfur dioxide (Fenner 1975; Harper 1975; Sanders et al. 1991, 1992). Of these, CO and HCN are two primary toxic gases present in smoke (Chaturvedi 1995; Chaturvedi and Sanders 1995, 1996; Sanders and Chaturvedi 1994).

Carbonaceous compounds produce CO and CO₂ upon burning, and nitrogenous compounds also produce HCN (Chaturvedi 1995; Sanders et al. 1991, 1992; Chaturvedi and Sanders 1995, 1996). Because the aircraft structure is composed of a variety of carbon- and nitrogen-containing polymeric materials, there is strong potential for the generated smoke to be rich in CO and HCN. In the absence of fire, the presence of CO in the interior of the aircraft would suggest a malfunctioning of the heating/exhaust systems. Since aviation fuel is primarily a mixture of non-nitrogen-containing hydrocarbons, aircraft engine exhaust would contain a negligible amount of HCN (Chaturvedi et al. 2001).

Exposure of aircraft occupants to CO and HCN can be monitored by analyzing for these gases in the blood as carboxyhemoglobin (COHb) or the cyanide ion (CN⁻). Analytical methods for measuring COHb and CN⁻ are mentioned in an overview (Chaturvedi 2009, 2010a) and in an international standard (ISO International Standard 2008). Those analytical methods are summarized herein.

For COHb:

1. Whole-blood oximetry by simultaneous differential visible spectrometry at various characteristic wavelengths (AVOXimeter 2001; CO-Oximeter 1978; Freireich et al. 1975).
2. Reduction of palladium chloride to palladium by releasing CO from COHb in blood by sulfuric acid and measuring absorbance at 278 nm of the remaining unreacted palladium chloride solution (Williams 1970, 1975; Williams et al. 1960).
3. Visible spectrophotometry by hemolyzing red blood cells by ammonium hydroxide, treating the hemolysate with sodium dithionite to reduce methemoglobin (MetHb) and oxyhemoglobin (OxyHb) to deoxyhemoglobin (HHb), and measuring absorbance at 540 nm, a wavelength of maximum absorbance for COHb, and at 579 nm, a wavelength at which the spectra of various species of HHb have the same absorbance (Blanke 1976a; Canfield et al. 1998, 1999; Douglas 1962; Sanderson et al. 1978; Tietz and Fiereck 1973; Winek and Prex 1981). A ratio of absorbance values at 540 nm and 579 nm is used to determine %COHb in the specimen, with the help of a calibration curve.
4. Visible spectrophotometry by saturating Part 1 of three equal parts of blood hemolysate with CO, and of Part 2 with oxygen (Part 3 was not treated with any gas), adding sodium dithionite to all the three parts to reduce MetHb and OxyHb to HHb, and determining ratios of the absorbance values of the solutions at 540 and 579 nm to find out %COHb in the specimen by using a mathematical relationship (Canfield et al. 1998, 1999; Rodkey et al. 1979; Sanderson et al. 1978; Uges 2004; Widdop 2002; Winek and Prex 1981).

5. Visible spectrophotometry by hemolyzing red cells of blood specimens, reducing MetHb and OxyHb to HHb, and calculating ratios of the absorbance values of the specimens at 540 and 579 nm (Canfield et al. 1998, 1999; Sanderson et al. 1978; Winek and Prex 1981).
6. Headspace gas chromatography by (1) converting MetHb and OxyHb to HHb by using sodium dithionite in two separate aliquots of blood samples, (2) saturating one aliquot with CO (the second aliquot is not treated with CO), (3) getting the release of CO from both aliquots by a ferricyanide or phosphoric acid solution, (4) injecting headspace air samples of the CO-saturated and non-CO treated aliquots into a gas chromatograph, equipped with a column and a methanation unit (nickel catalyst and hydrogen unit), (5) detecting methane by flame ionization, and (6) calculating %COHb level in a blood sample by comparing methane peaks of the CO-saturated blood sample and of the non-CO treated (original) blood sample (Cardeal et al. 1993; Griffin 1979).
7. Headspace gas chromatography by dividing the sample into two parts, saturating one part with CO (other used without CO-treatment), treating both parts with sodium dithionite to reduce MetHb and OxyHb to HHb, releasing CO from the both parts by sulfuric acid with saponin, injecting headspace air samples of the CO-saturated and the non-CO treated samples into a micro-gas chromatograph, and comparing gas chromatographic CO peaks of the original (non-CO treated) blood sample and of the CO-saturated blood sample, and calculating %COHb in a blood sample (Endecott et al. 1996; Lewis et al. 2004).

For CN^- :

1. Colorimetry by the reaction of CN^- present in blood with *p*-nitrobenzaldehyde and *o*-dinitrobenzene under an alkaline condition and production of a violet color, suggesting the presence of a potentially toxic CN^- concentration (Dunn and Siek 1990; Guilbault and Kramer 1966; Rieders 1975a).
2. Visible spectrophotometry by the liberation of HCN from blood by acidification and microdiffusion, trapping of HCN in a dilute alkaline solution, conversion of HCN to cyanogen chloride after reacting with chloramine-T, and then reacting cyanogen chloride and pyridine to form *N*-cyanopyridinium chloride, followed by a cleavage reaction to form an anil of glutaconic aldehydes and then coupling with barbituric acid to generate a red-pinkish, highly resonant product indicating the presence of CN^- (Blanke 1976b; Feldstein and Klendshoj 1957; Rieders 1975b).
3. Headspace gas chromatography (nitrogen-phosphorus detection) by equilibration of blood in the presence of an internal standard (acetonitrile) in a vial and injection of the headspace of the vial onto a gas chromatograph to detect HCN and acetonitrile (McAuley and Reive 1983; Zamecnik and Tam 1987).
4. Headspace gas chromatography (electron capture detection) by the liberation of HCN from blood, conversion of HCN to cyanogen chloride by reaction with chloramine-T, and injection of headspace onto a gas chromatograph (Odoul et al. 1994).
5. Spectrophotofluorimetry or high-performance liquid chromatography (fluorescence detection) by transformation of CN^- by acidification from blood to

HCN, reaction of CN^- in HCN with 2,3-naphthalenedialdehyde and taurine, and fluorimetric measurement ($\lambda_{\text{excitation}}=418\text{ nm}$; $\lambda_{\text{emission}}=460\text{ nm}$) of the reaction product, 1-cyano-2-benzoisoindole (1-cyano[*f*]benzoisoindole; CBI) derivative (Felscher and Wulfmeyer 1998).

6. High-performance liquid chromatography by using isotopic potassium cyanide ($\text{K}^{13}\text{C}^{15}\text{N}$) as an internal standard, microdiffusion of CN^- and $^{13}\text{C}^{14}\text{N}^-$ from blood as HCN and $\text{H}^{13}\text{C}^{14}\text{N}$, reaction of CN^- and $^{13}\text{C}^{14}\text{N}^-$ in HCN and $\text{H}^{13}\text{C}^{14}\text{N}$ with 2,3-naphthalenedialdehyde and taurine to produce nonisotopic and isotopic analogs of CBI, and qualitative and quantitative determination of both CBI analogs by high performance liquid chromatography-mass spectrometric detection (Tracqui et al. 2002).

Signs and symptoms for exposures to CO and HCN, in relation to their respective concentrations as %COHb and blood CN^- , are tabulated in previous publications (Chaturvedi 2009, 2010a; Gossel and Bricker 1994b; ISO International Standard 2008).

Fifteen nonfire aviation accidents, involving 17 fatalities (15 pilots and 2 passengers), were reported during 1991–1998 (Chaturvedi et al. 2001). The levels of COHb in these fatalities ranged from 10 to 69%; CN^- was not detected. The selective presence of COHb in the absence of CN^- and fire in these accidents was hypothesized to result from the inhalation of CO present in the interior, because of the faulty exhaust/heating systems. The source of such CO is incomplete oxidation of aviation fuel. The factors that contributed to these 15 accidents were heating/exhaust system malfunctions, pilot error, and/or CO-induced incapacitation. Of these factors, three accidents, accounting for five fatalities (COHb levels of the five: 12, 24, 41, 43, and 69%), were attributed to CO-induced incapacitation or a defective exhaust system. Of the total fatal accidents (2,837) that occurred during the 8-year period, nonfire, CO-related accidents amounted to only 0.53%.

Elevated COHb levels were reported in 13 of the 2,449 pilots killed in general aviation operations between 1973 and 1977, possibly from faulty heaters or exhaust systems (Lacefield et al. 1978). Many accidents reported in 1981 that involved turboprop aircraft potentially resulted from incapacitation of pilots who had inhaled toxic fumes introduced through the cabin pressurization system (Sanders 2007). In response to these accidents, the thermal (300–600°C) decomposition products from aircraft petroleum-based engine and synthetic lubricating oils were evaluated for time-to-incapacitation and time-to-death in rats; the animals were exposed to smoke from these products (Crane et al. 1983). The decomposition of these oils produced CO in sufficient quantities to produce the toxic responses noted.

The bleed air that is diverted from a location just forward of the jet engine combustion chamber has a temperature of approximately 500°C. Thermal breakdown products of jet engine lubrication oils have not been fully characterized at this temperature. Thus, the temperature stability of two commercially available jet oils was investigated by van Netten and Leung (2000), who analyzed for the release of various volatiles and gases by gas chromatography-mass spectrometry. The results show that >100 ppm CO and some CO_2 were generated after exposing the oils to a temperature of 525°C. Nitrogen dioxide and HCN were not detected. The presence of

the neurotoxic tricresyl phosphates (TCPs) was confirmed in the bulk oils and in the volatiles, but trimethyl propane phosphate (TMPP) was not found in these experiments. The absence of TCPs in cabin air possibly resulted from localized condensation in the ventilation ducts and filters, and in the air-conditioning packs. The possibility of the release of pyrolysis products from localized condensates could not be ruled out, particularly when cabin heat demand is high (van Netten and Leung 2001).

The quality of cabin air associated with a contamination of cabin air supply contaminated with the degradation products of oils and fluids was addressed in a UK study (CAA 2004). In this study, two contaminated cabin air supply ducts were examined and analyzed for the presence of chemical constituents and degradation products of engine oils, hydraulic fluids, and lubricants. The inner surface of the ducts was found to be coated with black carbonaceous particulate material, which could be easily dislodged by gentle pressure. Therefore, the material could potentially have become airborne and emitted as solid aerosols in the cabin and flight deck environment. The material was found to contain aluminum, silicon, sulfur, and phosphorus. Gas chromatographic-mass spectrometric analyses of air samples from the contaminated ducts disclosed the presence of short-chain irritants (carboxylic acids, aldehydes, and ketones). Analyses of the solvent extracts of the black duct material further indicated the presence of high molecular weight compounds such as TCPs, TMPP, trimethylolpropane phosphates, and associated esters, suggesting that these compounds may have been tightly bound to the black material. These findings suggest that not all of the chemicals adsorbed onto the material could be desorbed by airflow (for further discussion of this event also see: Chaturvedi 2009, 2010a).

The absence of the solvent extractable chemicals in duct airflow does not mean that those chemicals present in the airflow are the only chemicals responsible for toxicological effects, because other compounds adsorbed onto the duct's material may be released as particulates and may contribute to the toxicity. Since the particles can easily be dislodged, they could easily enter the aircraft interior when the temperature in the cabin is high, and/or when physical disturbances occur during flights (e.g., takeoffs and landings). If the cabin and flight deck occupants inhale those particles, they would be exposed to any chemical present in the duct airflow, including airborne particulates emitted from solid deposits. Such exposure is likely to cause adverse effects, including ocular and upper respiratory irritation, nausea, vomiting, dizziness, and pulmonary toxicity. Because some of the neurotoxins involved have delayed effects, some toxic symptoms may not appear in exposed individuals for some time.

Although the toxicity of the substances in the black carbonaceous particulate material found in the ducts is described and discussed with sufficient relevant scientific references in the UK study (CAA 2004), the toxicity of this solid carbonaceous material, as a whole entity, is not given in detail. The chemicals comprising the carbonaceous material may not necessarily be individually toxic at the concentrations found, but if they are mixed together at those concentrations, the mixture may be highly toxic (Eaton and Klaassen 1996). Because of the difficulty of dealing with complex chemical mixtures, including pyrolysis products, the best approach to

resolve this toxicological and aviation safety issue would be to minimize risks by preventing oil leaks into bleed air, and monitoring, cleaning, and/or replacing air ducts on a regular schedule. In addition, a more thorough evaluation of the toxic nature of the oil additives used in aircraft engines would be useful (Nicholson et al. 2003).

4 Summary

Aerospace toxicology is a rather recent development and is closely related to aerospace medicine. Aerospace toxicology can be defined as a field of study designed to address the adverse effects of medications, chemicals, and contaminants on humans who fly within or outside the atmosphere in aviation or on space flights. The environment extending above and beyond the surface of the Earth is referred to as aerospace. The term aviation is frequently used interchangeably with aerospace.

The focus of the literature review performed to prepare this paper was on aerospace toxicology-related subject matters, aerial application and aircraft cabin air quality. Among the important topics addressed are the following:

- Aerial applications of agricultural chemicals, pesticidal toxicity, and exposures to aerially applied mixtures of chemicals and their associated formulating solvents/surfactants
- The safety of aerially encountered chemicals and the bioanalytical methods used to monitor exposures to some of them
- The presence of fumes and smoke, as well as other contaminants that may generally be present in aircraft/space vehicle cabin air
- And importantly, the toxic effects of aerially encountered contaminants, with emphasis on the degradation products of oils, fluids, and lubricants used in aircraft, and finally
- Analytical methods used for monitoring human exposure to CO and HCN are addressed in the review, as are the signs and symptoms associated with exposures to these combustion gases

Although many agricultural chemical monitoring studies have been published, few have dealt with the occurrence of such chemicals in aircraft cabin air. However, agricultural chemicals do appear in cabin air; indeed, attempts have been made to establish maximum allowable concentrations for several of the more potentially toxic ones that are found in aircraft cabin air. In this article, I emphasize the need for precautionary measures to be taken to minimize exposures to aerially encountered chemicals, or aircraft cabin air contaminants and point out the need for future research to better address toxicological evaluation of aircraft-engine oil additives.

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