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Aerospace Toxicology: An Overview

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16. Abstract

The field of aerospace toxicology is composed of aerospace and toxicology. The term aerospace—that is, the environment extending above and beyond the surface of the Earth—is also used to represent the combined fields of aeronautics and astronautics. Aviation is another term frequently and interchangeably used with aerospace and aeronautics and is explained as the science and art of operating powered aircraft. Toxicology is the basic science of poisons. It deals with the adverse effects of substances on living organisms. Any substance could be poisonous, depending upon its exposure amount and frequency.

Although toxicology borrows knowledge from the fields of biology, chemistry, immunology, pathology, physiology, and public health, the most closely related field to toxicology is pharmacology. Economic toxicology, environmental toxicology, and forensic toxicology are 3 main branches of toxicology. Toxicology is a multidisciplinary field. Aerospace toxicology could be considered closely related to aerospace medicine.

In this overview, a literature search for the period of 1960–2007 was performed, covering aerospace toxicology-related subject matter. The article is divided into the sections of introduction, agricultural aviation (aerial application), aviation combustion toxicology, postmortem aviation forensic toxicology, cabin air contamination, and references. Further readings are also suggested. It is anticipated that this overview article would be a reference source for the topics related to aerospace toxicology.

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SYMBOLS, ABBREVIATIONS, AND ACRONYMS

λ ---------- (lambda) wavelength
2,4-D ---------- dichlorophenoxyacetic acid
5-HIAA ---------- 5-hydroxyindole-3-acetic acid
5-HTOL ---------- 5-hydroxytryptophol
AAFS ---------- American Academy of Forensic Sciences
AsMA ---------- Aerospace Medical Association
C ---------- concentration
CAA ---------- Civil Aviation Authority
C_{AEE} ---------- average effective exposure concentration
CAMI ---------- Civil Aerospace Medical Institute
CBI ---------- 1-cyano-2-benzoisoindole (1-cyano[*f*]benzoisoindole)
CFR ---------- Code of Federal Regulations
CN^- ---------- cyanide ion
CO ---------- carbon monoxide
CO_2 ---------- carbon dioxide
cyano-MetHb --------- cyanomethemoglobin
DDT ---------- dichlorodiphenyltrichloroethane
EUROCAE---------- European Organisation for Civil Aviation Equipment
FAA ---------- Federal Aviation Administration
FED ---------- Fractional Effective Dose
FTC ---------- Fractional Toxic Concentration
GAO ---------- General Accounting Office
HbA_{1c} ---------- hemoglobin A_{1c}
HCN ---------- hydrogen cyanide
HEPA: ---------- high efficiency particulate air
HHb ---------- deoxyhemoglobin
K ---------- constant
MetHb ---------- methemoglobin
NTSB ---------- National Transportation Safety Board
OxyHb ---------- oxyhemoglobin
PCR ---------- polymerase chain reaction
ppm ---------- parts per million
SOFT ---------- Society of Forensic Toxicologists, Inc.
SSRIs ---------- selective serotonin reuptake inhibitors
sulph-MetHb --------- sulphmethemoglobin
t ---------- gas exposure time
TCPs ---------- tricresyl phosphates
t_d ---------- time-to-death
tHb ---------- total hemoglobin
THC ---------- Δ^9- tetrahydrocannabinol
t_i ---------- time-to-incapacitation
TMPP ---------- trimethyl propane phosphate
TSB ---------- Transportation Safety Board of Canada

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AEROSPACE TOXICOLOGY: AN OVERVIEW

All substances are poisons; there is none which is not a poison.
The right dose differentiates a poison from a remedy.
—Paracelsus

1 INTRODUCTION

Aerospace toxicology is composed of 2 words, aerospace and toxicology. The former could be denoted as "the total environment extending above and beyond the surface of the planet Earth" (28). Aerospace is also used to represent the combined fields of aeronautics and astronautics. The field of aeronautics is the art and science of flight through the atmosphere (28), whereas astronautics is a relatively new field related to the art and science of space flight (26). Aviation is another term frequently and interchangeably used with aerospace and aeronautics and is explained as the science and art of operating powered aircraft (269).

Toxicology is the basic science of poisons. It deals with the adverse effects of substances on living organisms. Any substance could be poisonous, depending upon its exposure amount and frequency (106, 125, 182).

Toxicology borrows knowledge from the fields of biology, chemistry, immunology, pathology, physiology, and public health. The most closely related field to toxicology is pharmacology (182). The toxicology field can easily be branched into economic toxicology, environmental toxicology, and forensic toxicology. In view of the multidisciplinary nature of toxicology, one can deduce that aerospace toxicology is closely related to aerospace medicine, which is a specialty field of general medicine (27) and is concerned with the health and medical problems of man in aviation and space flights (199). Alternatively, aviation medicine could be considered as the branch of preventive medicine that deals with the special problems of flying, both within and outside the atmosphere (46).

In this overview, a literature search for the period of 1960–2007 was performed covering aerospace toxicology-related subject matter. In addition to the introduction, the article is divided into headings of agricultural aviation (aerial application), aviation combustion toxicology, postmortem aviation forensic toxicology, and cabin air contamination. At the end of the references section, further readings are also suggested. This article is anticipated to be an informative resource for subject matter associated with aerospace toxicology.

2 AGRICULTURAL AVIATION

2.1 Generality

Use of aerial application is increasing throughout the world to increase food production. The application process involves spraying of pesticides, herbicides, growth modifiers, fertilizers, and other agricultural chemicals on crops. Many of these chemicals are poisonous to human beings, causing serious signs/symptoms and possibly death (210). Incidents and accidents involving aerial applications and handling of commercial agricultural chemical preparations (formulations) do occur. Some examples are: (i) an experienced aerial applicator pilot, who accidentally spilled parathion on his clothes while pouring the concentrate from a 55-gallon drum 4 d earlier and who afterwards became irritable and introverted, was not feeling well and had a headache on the day he crashed his plane; (ii) a pilot, who was exposed to drifting parathion and required atropine therapy, flew into a tree during pull-up; (iii) an aircraft connector became loose after take-off and sprayed a mixture containing parathion in the pilot's face, saturating his body with the spray, causing him to lose control of the plane, which crashed; and (iv) a pilot was splashed with a defoliant during a flight, which caused a crash, almost resulting in the pilot's death (191). Such accidental exposures and the development of aerial dust allergies in pilots were topics of a group discussion on protecting agriculture pilots (191). In general, these agricultural chemicals are toxic (89, 109), and if occupational safety and precautionary measures are not properly taken, exposures of applicator personnel and agricultural aircraft accident investigators to such chemicals could lead to acute or chronic poisonings. Poisonings of agricultural pilots may, thus, contribute to aviation accidents, as well. These poisonings could be the result of exposures to a single chemical or to multiple chemicals (or chemical mixtures).

2.2 Pesticidal Toxicology

Toxicological aspects of organophosphorus and organochlorine insecticides have been elaborated in the literature (89, 168). Although not used anymore, dichlorodiphenyltrichloroethane (DDT) is the most

studied organochlorine insecticide and has also served as a prototype for the toxicological properties of other organochlorine insecticides (89, 168). Organophosphorus and organochlorine chemicals adversely affect the functions of the central nervous system. Behavioral difficulties have been implicated in aerial applicators following exposures to pesticides (100, 101, 171, 257, 299). Signs/symptoms of anxiety, uneasiness, depression with weeping, dizziness, emotional liability, frequent and severe disagreement with family and coworkers, and being unable to perform familiar tasks were reported during medical evaluations of 2 agricultural pilots actively engaged in the aerial application of organophosphorus/organochlorine insecticides, methyl parathion, DDT, toxaphene, endrin, and dieldrin (100, 101). Toxicological evaluation of postmortem samples from pilots killed while engaged in aerial application revealed that blood cholinesterase levels in 44 of 104 pilots (165) and 77 of 130 pilots (166) were below the normal range, suggesting a problem of acute and/or chronic toxicity from organophosphorus pesticides applied by agricultural aircraft. Reduced plasma cholinesterase levels were found in 2 agriculture pilots involved in non-fatal aviation accidents (98, 99). Accidents and poisonings in aerial applications have been documented (97-99). Aerial application-related precautions, signs and symptoms of pesticide poisonings, and their treatments are summarized for protecting the agricultural pilots (97, 191). These findings suggested that better educational efforts could reduce the accidents in this sector of the agricultural activity.

For an aerial spraying program to manage insect epidemics in large tracts of forest, extensive studies have been conducted of the toxicology of 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 (108). These studies culminated in improvements in pesticide application and the establishment of regulations on safety or buffer zones around human habitation for certain types of aircraft applying different formulations of the insecticides.

2.3 Multi-Agricultural Chemicals and Organic Solvents/Surfactants

There is a potential for aerial applicators, associated personnel, and aircraft accident investigators to be exposed to multiple agricultural chemicals and solvents/surfactants of their commercial preparations for sprays, if safety and precautionary measures were not properly taken. Such poisonings could be attributed to the resultant of, and/or interactive effects of, each of the chemicals and solvents/surfactants. Toxic effects of mixtures of parathion (5 $mg \cdot kg^{-1}$), toxaphene (50 $mg \cdot kg^{-1}$), and/or dichlorophenoxyacetic acid (2,4-D; 50 $mg \cdot kg^{-1}$) for up to 7- and 14-d treatments in mice were determined to be the resultant of the effects exhibited by their components individually (162). Metabolic aspects of these 3 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 the biotransformation of parathion, as well as of paraoxon, and the levels of aliesterase, thereby providing a pool of non-critical enzymes for the binding of paraoxon (61). Because of these properties of toxaphene, it is anticipated that the toxicity of the parathion plus toxaphene plus 2,4-D mixture would also be lower than that of parathion (61). Chronic studies on the mixtures of 3 herbicides—alachlor, atrazine, and/or picloram—in mice suggest that the mixtures may cause hepatotoxicity and stimulate the liver xenobiotic-metabolizing enzymes (51). A chronic toxicological evaluation of mixtures of 10 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 the pesticidal mixtures might cause deleterious effects in other species, including humans, by enhancing the metabolism of xenobiotics (52). In multi-chemical exposures, interactive effects among those chemicals play a contributory role towards associated poisonings. This type of poisoning could be exemplified in a multi-chemical death involving caffeine, nicotine, and malathion (62) and in a death attributed to ingestion of malathion insect spray (66). In the later case, in vitro inhibition of cholinesterases and presence of xylenes and other volatiles in certain postmortem samples were demonstrated (66). 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 used as solvents in agriculture insecticide sprays, has been found to increase incidences of renal tubule, alveolar/bronchiolar, and hepatocellular neoplasms and of testicular and renal tubule adenomas in rats (278). 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, may be formulated with surfactants (261). Such formulations increase the efficacy of the herbicide but, in some cases, are more toxic to aquatic organisms than the parent material. Some risks were observed for measured concentrations of glyphosate in surface waters resulting from aerial application of a formulation equivalent to Roundup to forestry areas in Canada.

2.4 Application Safety

Aviation authorities have been concerned about the toxic effects of agricultural chemicals on agriculture pilots. In the former Soviet Union, aerial applicators are required to maintain records of the chemicals used for crop spraying and its duration (89). In the United States, toxicological problems in aerial application were recognized in early 1960s, and a considerable amount of applied studies were conducted at the U.S. Department of Transportation Federal Aviation Administration's (FAA's) Civil Aerospace Medical Institute (CAMI) in Oklahoma City, OK, to enhance the safety of agricultural pilots and their support personnel. The studies conducted at CAMI are summarized in Table I.

2.5 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 cholinesterases, activities of these enzymes in red blood cells, plasma, or whole blood (30–50% inhibition) is measured for monitoring exposures to these insecticides (89, 128, 168). Examples of tentative maximum permissible concentrations of parent compounds and/or their metabolites are: (i) 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; (ii) 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; (iii) 30 μg of hexachlorobenzene per 100 mL of blood and/or presence of 2,4,5-trichlorophenol in urine; (iv) 0.05 mg of pentachlorophenol per 100 mL of plasma and/or 1 mg of pentachlorophenol per g of creatinine in urine; and (v) detection of 2,4-D and 2,3,5-trichlorophenoxyacetic acid in urine (168).

3 AVIATION COMBUSTION TOXICOLOGY

3.1 Combustion, Fire, and Smoke

Combustion is a rapid exothermic chemical chain reaction between a fuel and oxygen (air) (167, 189, 259, 264). Heat, fuel, oxygen, and chemical reaction are necessary components for the development of a fire. Fire is a complex, dynamic, and physicochemical process and is the result of a rapid chemical reaction generating smoke, heat, flame, and light. Smoke consists of particulate matters, as well as a variety of invisible combustion gases and vapors suspended in the fire atmosphere. In other words, smoke is a colloidal solution consisting of gases, volatiles, semi-volatiles, water vapors and droplets, solid particles, and irritants. The involvement of particles and irritants in obscuring vision and in causing eye irritation, including respiratory irritation, cannot be ignored. Thus, combustion of burnable materials generates various products in smoke and it may diminish light and obscure vision, and its gases could be toxic (53, 63, 64, 236).

Uncontrolled fires threaten residential and commercial structures and transportation systems, including aerospace travel. Modern aircraft benefit from fire retardants and fire extinguishing systems to such an extent that in-flight fires are rare. However, survivable crashes followed by fire do occur, primarily from fuel spills around the aircraft. Although the cabin occupants may survive the initial forces of such crashes, they are frequently unable to escape from the fire environment because of performance impairment from smoke-caused toxicity (236). Post-crash fire is considered to be the most important determinant of pilot fatalities in commuter aircraft/air taxi crashes (177). According to a study by the International Cabin Water Spray Research Management Group, there were 95 fire-related civil passenger aircraft accidents world-wide over a 26-yr period (32). Fire claimed approximately 2,400 lives in those accidents. A U.S. General Accounting Office publication reveals that 32 (approximately 16%) U.S. transport aircraft accidents between 1985 and 1991 involved fire, and 140 (22%) fatalities in these accidents resulted from the effects of fire and smoke (126). During 1991–1998, postmortem samples from 3,857 fatalities of 2,837 aviation accidents were received by CAMI for toxicological evaluation. Of these accidents, 1,012—encompassing 1,571 (41%) fatalities—were fire associated (67, 68). The deaths of the 3 Apollo 1 crewmembers in the 1967 fire accident was due to their exposure to toxic combustion products (276), and the involvement of fire has been documented in the 23 February 1997 accident on the Mir aerospace station (289). In this aerospace accident, the fire burned for approximately 90 s. The crew was exposed to heavy smoke for 5 to 7 min and donned their masks in response. Subsequent medical examination revealed that all crewmembers were in good health.

3.2 Smoke Gases and Toxicity

Depending upon the chemical characteristics of burning materials and environmental conditions, such as temperature and oxygen content, the amounts of smoke products, gases, and other volatiles generated varies from fire to fire (123, 212). Every fire is different. Smoke composition and its toxicity can change drastically when different materials are present in a combustion environment and can be further altered by the presence of fire retardants and pigments. A material burned under one condition could be nontoxic, but it could be toxic

Table I. Summarization of Aerial Application-Related Studies Conducted at CAMI

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. (93)
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 (254)
Cardiovascular effects of endrin	Causation of bradycardia, hypertension, salivation, hyper-excitability, 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. (111)
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. (94)
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 (100)
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 sympatho-adrenal action	Reins et al. (223)
	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.	
Pathological effects of endrin and dieldrin	More severe effects of dieldrin on the cold-adapted rats than on the room-temperature rats	Clark (72)
Effects of endrin and carbon tetrachloride	Reversible increase in hepatic fat contents of rats treated with endrin and carbon tetrachloride	Clark (71)
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. (144)
Exposure of parathion and development of allergy towards aerial dusts	Group discussion on protecting agriculture pilots	Mohler and Harper (191)
Human factors in general aviation accidents	Discussion on the role of medical conditions and pesticides in aviation accidents	Dille and Morris (98, 99)

Table I (continued)

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 (120)
Drug and toxic hazards in general aviation	Summary of aerial application related precautions, signs and symptoms of pesticide poisoning, and their treatments	Dillie and Mohler (97)
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. (211)
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 d at 4°C, and up to 6 wk at –20°C	Crane et al. (78)
	Note: Whole blood hemolysates and plasma may be stored for 6 d at room temperature and 6 wk, if refrigerated or frozen.	
Cholinesterase methods	Comparison of 3 cholinesterase methods	Crane et al. (77)
	Importance of cholinesterase tests in applicators prior to the aerial application season	
Effects of endrin on brain	Brain bioelectric phenomena caused by endrin at doses well below those causing seizures or other gross behavioral changes	Revzin (225)
	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	
Disulfoton	Adverse effects on the reproduction system in rats by disulfoton	Ryan et al. (231)
	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.	
Serum or plasma cholinesterase methods	Evaluation of 4 serum or plasma cholinesterase methods and relationships for inter-conversion among their respective units	Crane et al. (79)
	Emphasis on the importance of the cholinesterase test in applicators prior to the aerial application season	

Table I (continued)

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. (171)
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 $mg \cdot kg^{-1}$, with no peripheral signs of poisoning such as tremor and salivation	Revzin (226)
	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	
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 (227)
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. (165)
Chlordimeform	Little or no extra risk in aerial applicators (or others) should they be taking *p*-chlorophenylalanine, DL-*α*-methyl-*p*-tyrosine, phentolamine, methysergide, and phenylephrine during potential exposure to chlordimeform	Smith et al. (256)
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	Lacefield et al. (166)
	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	

when burned under a different condition (86, 123)—for example, cotton upon burning under low-oxygen smoldering conditions produces primarily carbon monoxide (CO) but the much less toxic carbon dioxide (CO_2) under flaming conditions. Nylons tend to break down into their relatively nontoxic monomers at low temperatures and produce toxic hydrogen cyanide (HCN) when flaming. Fire retardants decrease flammability, but they may also enhance smoke toxicity (123, 212). Smoke toxicity of a fire retardant-treated polymer was found to be considerably higher than that of the non-treated polymer, as it was determined that the smoke contained a very toxic bicyclic phosphate (212). Most cabin furnishings contain carbon and will produce CO when burned, but silk, wool, and many nitrogen-containing synthetics are common sources of HCN in fires (123). Carbon-containing materials generate CO, and nitrogen-containing materials also generate HCN (53, 64, 113, 123, 138, 244). Benzene vapors and aromaticity-associated black soot would be produced from the burning of phenyl group-containing polymers, whereas hydrogen chloride from chlorine-containing polymers (Table II). Irritants, hydrogen chloride and acrolein (CH_2CHCHO), can be produced from burning wiring insulation and some other cabin materials (76, 83, 123). Hydrogen fluoride, hydrogen sulfide, sulfur dioxide, and nitrogen dioxide gases have also been reported to be present in smoke (112, 113, 142). Formation of these gases is associated with aircraft material formulations containing halogens, cyanide, sulfur, and nitrogen moieties. Smoke inhalation can cause dizziness and confusion, can induce irritation, tears, pain, and disorientation, and can produce incapacitation and death. It can also cause delayed toxicological/pathological effects, which could be reversible or irreversible.

Oxygen, CO_2, and CO can easily be analyzed in a smoke environment sample by gas chromatography, but the acid gases, like hydrogen cyanide and hydrogen chloride, are not so easily analyzable. Their analyses require additional steps and precautions because of their high water solubility. Therefore, they are analyzed as their respective anions, for example, cyanide and chloride. Because of incomplete oxidation, organic compounds are also present in smoke. Those compounds can be analyzed by trapping the smoke in various solvents (water, acetonitrile, and chloroform) or in carbon traps. These trapped organic compounds can subsequently be analyzed by gas chromatography/mass spectrometry, by high performance liquid chromatography/mass spectrometry, and/or by gas chromatography with a Fourier transform infrared or atomic emission detector. Some of these compounds can be characterized and confirmed if they are common compounds or if their reference standards are commercially available. Otherwise, their chemical structures can only be elucidated by sophisticated, analytical techniques. Some of the smoke compounds cannot be characterized. This limitation is due to the very fact that free radical chemical reactions are involved in the combustion process; thus, it becomes difficult to predict the end products. This difficulty becomes more prevalent when burning conditions change—for example, between smoldering and complete burning—and when fire retardants, preservatives, and/or stabilizers are present in the material being evaluated. Phosphorus present in synthetic materials may add an extra variable. Because of the analytical limitations and the unknown toxicity of all the compounds in smoke, animal models have been used to determine its overall total toxicity. This approach integrates possible interactions among the smoke components and is able to demonstrate the net toxicity of all components. Otherwise,

Table II. Combustion Gases From Polymers[a]

Polymers	Chemical Unit Constituent	Combustion Gases
Polyethylene	$(–CH_2CH_2–)_n$	CO, CO_2
Nylon 6/6	$[–NH(CH_2)_6NHCO(CH_2)_4CO–]_n$	CO, HCN, CO_2
Polyamide	$[–NH(CH_2)_nNHCO(CH_2)_nCO–]_n$	CO, HCN, CO_2
Polystyrene	$[–CH_2CH(C_6H_5)–]_n$	CO, C_6H_6[b], CO_2
Chlorinated polyethylene	$(–CH_2CH_2–)_n$; (Cl = 40%)	CO, HCl[b], CO_2
Polysulfone	$[–C_6H_4–4–C(CH_3)_2C_6H_4–4–OC_6H_4–4–SO_2C_6H_4–4–O–]_n$	CO, SO_2[b], CO_2

[a]Sanders et al. (243, 244); Fenner (119); Harper (135).

[b]Benzene (C_6H_6); Hydrogen chloride (HCl); Sulphur dioxide (SO_2).

their contributions to the overall toxicity could not be evaluated. Although structures of compounds can currently be elucidated by modern sophisticated chemical and analytical techniques, an animal model is still an excellent and valid scientific approach to integrate the overall toxicity of smoke.

3.3 Aircraft Material Testing

The presence of cyanide in blood specimens of the victims of the 1970 Capitol International Airways DC-8 post-crash fire accident at Anchorage, AK, necessitated the research into the origin of cyanide in aircraft fires (204, 235). At that time, not much was known about the potential for aircraft interior materials to produce toxic combustion gases, even about the toxicity of individual combustion gases. Using a small-animal test system, 75 aircraft interior materials—panels, panel components, foams, fabrics, coated fabrics, floorings, thermoplastics, cargo liners, transparencies, insulations, and elastomers—were ranked for their toxicity based upon the relative time-to-incapacitation (t_i) and time-to-death (t_d) caused by the inhalation of thermal degradation of the interior materials in rats (88). The former is a realistic parameter for estimating escape time from fire environments, and the latter is a parameter for finding out delayed adverse effects after exposure to smoke. These 75 polymeric materials were thermally decomposed using an isothermal heating regimen at 600°C, though the decomposition method may not necessarily represent the actual processes occurring in a "true" fire. Toxic potentials of 14 insulating materials in rats with respect to response times were tested under 3 burning conditions (76). These conditions were low-temperature, non-flaming; low-temperature flaming with hot-wire ignition; and high-temperature, flaming at 750°C, with or without ignition. Naturally, there were differences in response times at different combustion conditions. Based upon the findings, it was proposed that materials should be tested at several conditions, and they should be ranked based upon the most toxic-response time observed.

Relative toxicity of 2 aircraft seat fire-blocking layer materials (Norfab and Vonar), designed to delay the involvement of thermally sensitive polyurethane foam seat cushions in an aircraft fire, was established for their gaseous combustion products (239). Each material was thermally decomposed under 5 thermal environments—2 contact temperatures (600°C and 750°C) in a horizontal hot tube furnace and 3 flux levels (2.5, 5.0, and 7.5 $W \cdot cm^{-2}$) in a radiant heat furnace. Rats were exposed to the produced combustion products in an animal exposure chamber with a cage, and the toxicological end point (t_i) was recorded when the rats could no longer perform the coordinated act of walking in the rotating cage (when sliding or tumbling began). In 3 of the 5 test environments, the gaseous products of Norfab (an aluminized synthetic fabric) produced shorter t_is than those by the products of Vonar (a neoprene foam product). HCN was detected in the combustion products of Norfab but not in the combustion products of Vonar. The greater apparent toxicity of Norfab was possibly because of HCN. Additional studies that ranked 9 flat panel materials based upon their combustion products in rats suggested that only the higher temperatures in both the combustion tube and radiant heat systems proved to be suitable for toxicological differentiation between the panels. The shortest t_is occurred at the highest temperature/heat flux condition for both chambers (86). A comparative toxicity study involving rankings of 6 polymeric aircraft cabin materials—polyamide (I), polystyrene (II), Nylon 6/6 (III), polysulfone (IV), polyethylene (V), and chlorinated polyethylene (VI)—was conducted in rats (243, 244). Animals were exposed to the pyrolysis products from selected weights of each polymer for 30 min in a 265-L combustion/exposure system. The LC_{50}s were determined following a 14-d observation period. The t_is were also measured at 16 g (60 $mg \cdot l^{-1}$) and at their respective LC_{50}s using the inability of rats to walk in rotating cages as a criterion for incapacitation. The LC_{50}s ($mg \cdot l^{-1}$) of the polymers had the order of I (45.7) < II (56.6) ≈ III (58.1) < IV (63.2) < V (75.5) < VI (87.5), while their t_is (min) at 16 g (60 $mg \cdot l^{-1}$) had the order of III (6.6) ≈ I (7.3) < V (11.7) ≈ II (12.0) < VI (18.4) < IV (21.1). Based on the t_is at LC_{50}s, the polymers were grouped into III and V (10.5, 11.0); I, II, and VI (14.1-15.0); and IV (19.5). These 2 endpoints did not exhibit the same relative toxic hazard rankings for these polymers. Also, t_is were not equal at the LC_{50} concentrations, a condition of equal lethality, demonstrating the possible involvement of different mechanisms of action for the combustion products of these polymers at the selected end points. In spite of experimental limitations, toxicity ranking of aircraft materials has applicability in minimizing the toxicity of smoke and the spreading of fires.

3.4 Gases and Their Interactive Effects

3.4.1 Gas Interactions

Since aircraft materials, upon combustion, have the potential for generating hydrogen halides (hydrogen fluoride and hydrogen chloride), HCN, and nitrogen dioxide (142), experiments were conducted with rats to determine toxic effects (lethality) of short-term exposures to these gases. These experiments were conducted both with single gases and in combination with CO. These studies show the toxicity rankings of the 4 products to be HCN > nitrogen dioxide > hydrogen fluoride > hydrogen chloride. CO concentrations, which alone are not hazard-

ous, do not enhance the toxic response to these gases. Effects of hydrogen chloride inhalation have been studied on t_i and t_d in rats (85). These 2 endpoints were equated to the atmospheric hydrogen chloride concentration by statistically derived regression equations, and the possible relationship was discussed between the effective toxic doses of this gas for rats and those reported for humans. Toxicological evaluation of another irritant acrolein—a combustion product of certain materials used in aircraft interiors—in rats indicated that concentrations required to produce incapacitation were 100 times greater than those suggested by the scientific literature; equations were derived to allow prediction of t_i and t_d for the laboratory rat (87). The possible relationship between the effective toxic doses of acrolein for rats, and those reported for humans, was also discussed.

Influence of elevated temperatures—ambient versus elevated temperatures from 40 to 60°C—on the effects of CO-induced t_is in rats were studied as a function of CO concentration and/or temperature in an exposure chamber (240-242). The combined CO plus elevated temperature exposures and exposures to CO and elevated temperatures (40–60°C) alone indicated that incapacitation occurred earlier when CO inhalation was combined with a whole-body, elevated temperature environment than that was observed for the same exposure parameters applied individually. An empirical equation was derived that allows calculating a predicted t_i for combinations of CO and temperature.

Further interactive studies on CO and acrolein by exposures of rats to experimental atmospheres of CO in air, acrolein in air, and mixtures of CO and acrolein in air and the measurement of t_i indicated no evidence of synergistic action, since the effect of the combination was never greater than that predicted by the sum of the 2 individual gas effects (81, 82). However, evidence did exist for an inhibitory or antagonistic effect of an undefined mechanism when acrolein was present in the mixture at concentrations of lesser toxic potency than that of CO. Equations were derived that allows the calculation of a predicted t_i for combinations of CO and acrolein concentrations.

Evaluation of the toxic potencies of CO, HCN, and their mixtures by the measurement of t_i in rats as a function of gas concentrations indicated that the 2 gases are fractionally additive (80), with no indication of synergism—wherein the effect of the combination would have been greater than that predicted from the sum of the 2 individual effects. Regression equations were derived that describe those relationships for exposure to CO or HCN alone. An empirical equation was derived that allows calculation of the predicted t_i for any combination of CO and HCN concentrations. A dose-response modeling, based upon the concept of "Fractional Effective Dose" (see next section), was used to devise a mathematical model for estimating t_i produced by defined mixtures of CO and HCN.

3.4.2 Fractional Effective Dose (FED)

The average concentration of a gas to which an animal was exposed is calculated from the area under the gas concentration (C)-exposure time (t) curve integrated from t = *0* to t = t_i, representing the $C{\cdot}t_i$ product (80). The $C{\cdot}t$ product for a gaseous toxicant is expressed in a volume fraction of $\mu l{\cdot}l^{-1}$ (parts per million; ppm) multiplied by minutes. Division of this product by t_i yields the average effective exposure concentration (C_{AEE}) of the gas to which the animal was exposed, causing incapacitation (Equation 1).

$$C_{AEE} = \frac{\int_{t=0}^{t=t_i} Cdt}{t_i} = \frac{C \times t_i}{t_i} \qquad (1)$$

FED is a ratio of the $C{\cdot}t$ product for a gas to that product of the gas expected to produce a given effect, such as t_i, on an exposed subject, such as a rat, of average susceptibility (65, 80, 139, 237, 263). When not used with reference to a specific gas, the term FED represents the summation of FEDs for all gases in a combustion atmosphere. As a concept, FED may refer to any toxicological effect, including incapacitation or lethality. The FED of each gas in a mixture is calculated by dividing the $C{\cdot}t$ value of the gas in the mixture by the corresponding $C{\cdot}t$ value for exposure to the same gas alone for any effect such as t_i or t_d. For an additive effect of 2 gases in their mixture, at time t, into exposure:

$$FED_{Gas1,t} + FED_{Gas2,t} = 1 \qquad (2)$$

FED is a function of time. The effect occurs when the FED reaches unity. Therefore, to be an additive effect, the reciprocal of the t_i value for the combined gases should be equal to the sum of the reciprocal t_i values observed with the individual gases, as

$$\frac{1}{t_{i(CO+HCN)}} = \frac{1}{t_{i(CO)}} + \frac{1}{t_{i(HCN)}} \qquad (3)$$

Such an FED-based model has been suggested to be applied to the evaluation of the toxicity of smoke in computer modeling of aircraft fire situations (263). To be used as a predictive tool to estimate human survivability in full-scale aircraft cabin fire tests, this model included literature data for CO_2, low oxygen, CO, HCN, hydrogen fluoride, hydrogen chloride, hydrogen bromide, nitrogen dioxide, sulphur dioxide, acrolein, and heat exposures and was based on exposures to single and mixed gases on humans, primates, rats, and mice at different physical activity levels. In this model, FEDs were obtained for

incapacitation and for lethality, and the exposure time required for either FED to reach unity represented the exposure time available to escape from the specified fire environment or to survive post-exposure. The effect of CO_2 in increasing the uptake of other gases was factored into the concentration term in the FED equation for all gases, with the exception of CO_2 and oxygen. In this regard, higher respiratory minute volumes, because of CO_2 exposure, were found to be an important factor in predicting the time available to escape. Computer modeling of human behavior in aircraft fire accidents, including toxicity sub-model through the FED calculations, has been elaborated (124).

3.4.3 Carboxyhemoglobin (COHb) and Blood Cyanide Ion (CN^-)

It is well-established that carbon-containing substances generate CO upon burning, whereas nitrogen-containing substances also produce HCN (53, 64, 113, 123, 138, 244). These chemical species are 2 primary toxic combustion gases and are present in relatively high concentrations in smoke. Both gases are present in the blood of fire victims (18, 68, 170, 183, 185, 253, 290). Since both gases have adverse effects on the central nervous system functions (129, 158, 258), excluding burn and physical injuries, the primary cause of incapacitation or death is attributed to exposures to these 2 gases. Other smoke constituents may also be toxic, but they are generally present at low concentrations, thus are unable to produce a considerable degree of the acute undesired effects. However, they may have the potential to produce delayed toxic effects, depending upon the duration and frequency of exposure to those products and their chemical structures. The hydrocarbon constituents of smoke have the capability of adversely affecting the central nervous system functions, as well.

Since aircraft materials do contain carbon and nitrogen, they generate CO and HCN upon burning, and air passengers could be exposed to these gases by inhaling smoke in the unfortunate event of in-flight or post-crash fires. The actual degree of toxicity produced by smoke can be established in the victims of fire by the analysis of their blood for CO as COHb and HCN as CN^-. Various analytical methods for the blood analysis of COHb and CN^- are summarized in Tables III and IV.

Although much research has been conducted in establishing the relationship between CO and/or HCN exposure doses and toxicological responses, there has been sparsity in examining the relationship between blood concentrations of COHb and/or CN^- and a toxicological response. In view of the suggestion that passenger protective breathing equipment protect aircraft passengers from smoke for 5 min during an evacuation phase and for 35 min during an in-flight-plus-evacuation phase (114), t_i was determined at 2 CO concentrations that produce 5- and 35-min t_is in rats (245). Also, blood COHb saturation was determined in rats exposed to these CO concentrations at intervals less than t_i. At the end of each exposure interval and at incapacitation, rats were quickly removed from the cage and killed for blood collection and COHb quantitation. The observed reaching of COHb to a maximal level before incapacitation suggests that blood COHb saturation levels may not necessarily be indicative of the onset of incapacitation. In similar experiments with HCN, t_i and blood CN^- at t_i for 2 HCN concentrations that produce 5- and 35 min t_is were determined in rats (60). Blood CN^- levels as a function of HCN exposure time were also measured. Blood CN^- levels increased as a function of HCN exposure time, but the blood CN^- level at the 5-min t_i was half of the 35-min blood CN^- level, and the HCN gas uptake rate at 184 ppm was about 3 times that at 64 ppm. Findings suggested that the blood CN^- level at incapacitation may vary substantially, depending upon the HCN exposure concentration. An equation was proposed for predicting blood CN^- levels in rats (Equation 4).

$$(C_{CN^-}) \div (C_{HCN} \times t) = K \qquad (4)$$

where

C_{CN^-} is blood CN^- concentration in $\mu g \cdot ml^{-1}$;
C_{HCN} is HCN exposure concentration in ppm;
t is exposure time in min; and
K is a constant with the value of 2.2×10^{-3}.

3.4.4 COHb and Blood CN^- Interactive Effects

Exposures to CO-HCN mixtures have demonstrated that these gases have additive effects, that is, shorter t_is (Equation 3), but the resulting concentrations of COHb and blood CN^- at incapacitation are not well defined. These undefined relationships between COHb and blood CN^- concentrations and the onset of incapacitation make the interpretation of postmortem levels difficult for medical accident investigators. Therefore, t_i was determined in laboratory rats exposed to 2 CO-HCN mixtures consisting of CO and HCN concentrations that produce 5- and 35-min t_is in individual gas exposures (65, 237). In the high concentration CO-HCN mixture, the resultant t_i was shortened from 5 min to 2.6 min; COHb dropped from 81% to 55% and CN^- from 2.3 $\mu g \cdot ml^{-1}$ to 1.1 $\mu g \cdot ml^{-1}$. At the lower concentration CO-HCN mixture, where the resultant t_i reduced from 35 min to 11.1 min, COHb dropped from 71% to 61%, and blood CN^- decreased from 4.2 $\mu g \cdot ml^{-1}$ to 1.1 $\mu g \cdot ml^{-1}$.

Both the $C \cdot t$-based FED model and t_i calculations from Equations 2 and 3 indicated that CO and HCN have additive effects on t_i at high concentrations and could

Table III. Analytical Methods for Determining COHb Concentrations in Blood

Method	Principle, Sensitivity, and Limitation	Reference
Whole-blood oximetry	Simultaneous automated differential visible spectrometry at various characteristic wavelengths. COHb as low as 10% in fresh blood from live victims (accuracy: 1−2%). Suitable for fresh heparinized blood and maybe unsuitable for putrid or clotted blood. Note: Ethylenediaminetetraacetate (EDTA) could be used with CO-Oximeter (74). Citrate, fluoride, oxalate, and EDTA cause errors with AVOXimeter (7).	Freireich et al. (121); CO-Oximeter (74); AVOXimeter (7)
Palladium chloride reduction	Release of CO from COHb by sulfuric acid added to blood in the outer rim of a Conway cell, reduction of palladium chloride in the centre well of the cell to palladium, and measurement of absorbance at 278 nm of the remaining unreacted palladium chloride solution in the centre well and of a new aliquot of the palladium chloride solution. Unable to measure COHb below 10% (coefficient of variation: ± 5.2%), could be used for analyzing fresh or uncoagulated antemortem or postmortem blood. Note: COHb saturation can be calculated by determining the concentration of total hemoglobin in blood (7, 74, 110, 115). Presence of a shiny black film of palladium on the palladium chloride solution may suggest presence of COHb > 30%. Putrid blood may not be suitable for analysis. Sulfides present in putrid blood in large concentrations interfere with analysis, but such interference can be rectified by using a saturated lead acetate-acetic acid solution in place of sulfuric acid as the CO releasing reagent.	Williams et al. (297); Williams (295, 296)
Visible spectrophotometry (calibration curve)	Hemolysis of red blood cells by ammonium hydroxide, treatment of the hemolysate by sodium dithionite to reduce methemoglobin (MetHb) and oxyhemoglobin (OxyHb) to deoxyhemoglobin (HHb), and measurement of the 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 (isobestic point). Note: A ratio of absorbance values at 540 nm and 579 nm is used to determine % COHb in the specimen from a calibration curve. Accurate estimation of COHb ≥ 10%, suitable for fresh or un-coagulated antemortem or postmortem blood, but unsuitable for putrid blood as resulting pigments can distort COHb and HHb spectra	Winek and Prex (298); Douglas (104); Tietz and Fiereck (272); Blanke (25);Sanderson et al. (246); Canfield et al. (43, 44)
Visible spectrophotometry (CO saturation)	Saturation of Part 1 of the 3 parts of blood hemolysate with CO and of Part 2 with oxygen (no treatment of Part 3 with any gas), addition of sodium dithionite to all the 3 parts to reduce MetHb and OxyHb to HHb, and determinations of ratios of the absorbance values of the solutions at 540 nm and 579 nm to find out % COHb in the specimen by using a mathematical relationship capable of accurately measuring ≥ 10% COHb in fresh and postmortem blood stored with sodium fluoride and potassium oxalate. Note: Clotted blood may be used after homogenization, but old or putrid blood may interfere with analysis.	Winek and Prex (298); Sanderson et al. (246); Canfield et al. (43, 44); Rodkey et al. (230); Widdop (293); Uges (279)

Table III. (continued)

Visible spectrophotometry (without CO saturation)	Hemolysis of red cells of blood specimens, reduction of MetHb and OxyHb to HHb, and calculation of ratios of the absorbance values of the specimens at 540 nm and 579 nm. Note: Absorbance ratios are used to determine % COHb in the specimen by using a mathematical equation in relation to a positive COHb control prepared in human blood by using CO. Capable of accurately measuring ≥ 10% COHb in fresh and postmortem blood samples stored with sodium fluoride and potassium oxalate. (Also, see previous method.)	Winek and Prex (298); Sanderson et al. (246); Canfield et al. (43, 44)
Headspace gas chromatography (nickel-hydrogen reduction)	Conversion of MetHb and OxyHb to HHb by sodium dithionite in 2 separate aliquots of blood samples; saturation of 1 aliquot with CO (no CO treatment of the second aliquot); release of CO from both blood aliquots by a ferricyanide or phosphoric acid solution; injection of headspace air samples of the CO-saturated and non-CO treated sample aliquots on a gas chromatograph equipped with a column, a methanation unit (nickel catalyst and hydrogen unit); flame ionization detection of methane; and calculation of % COHb level in a blood sample by comparing methane peaks of the CO-saturated original blood sample and of the non-CO treated blood sample. Capable of accurately determining COHb at the levels equal to or greater than 10% in fresh blood and postmortem blood samples. Note: Clotted blood can be homogenized prior to use. Putrid blood and both heparin and sodium fluoride-potassium oxalate treated blood can be used for analysis.	Griffin (130);Cardeal et al. (45)
Headspace gas chromatography (thermal conductivity detection)	Separation of the submitted sample into 2 parts; treatment of both parts with sodium dithionite to reduce MetHb and OxyHb to HHb saturation of 1 part with CO (other used without CO-treatment); release of CO from the both parts by sulfuric acid with saponin; injection of headspace air samples of the CO-saturated and the non-CO treated samples onto a micro-gas chromatograph; and comparison of gas chromatograph CO peaks of original blood sample (non-CO treated) and of the CO-saturated blood sample, thereby calculation of % COHb level in a blood sample. Note: For sensitivity and limitation, see previous methods.	Endecott et al. (113);Lewis et al. (174)

Table IV. Analytical Methods for Determining CN^- Concentrations in Blood

Method	Principle, Sensitivity, and Limitation[a]	Reference
Colorimetry (*p*-nitrobenzaldehyde and *o*-dinitrobenzene)	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, a quick qualitative method.	Rieders (229); Guilbault and Kramer (131); Dunn and Siek (105)
	Detectable minimum CN^- concentration by directly using the specimen: 0.3 $\mu g \cdot ml^{-1}$ and by diffusion: 0.05 $\mu g \cdot ml^{-1}$	
Visible spectrophotometry	Liberation of HCN from blood by acidification and microdiffusion, trapping of HCN in a dilute alkaline solution, and conversion of HCN to cyanogen chloride after reacting with chloramine-T.	Feldstein and Klendshoj (117); Rieders (228); Blanke (24)
	Subsequent reaction between 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, suggesting presence of CN^-.	
	Note: A CN^- concentration of as low as 0.25 $\mu g \cdot ml^{-1}$ can be easily detected by processing 0.5 ml of blood specimen. Blood or tissues containing formalin cannot be analyzed, as formaldehyde reacts with CN^- to form cyanohydrin, which is quickly converted into ammonia and glycolic acid.	
Headspace gas chromatography (nitrogen-phosphorous detection)	Equilibration of blood in the presence of acetonitrile as an internal standard in a vial at room temperature for 30 min and injection of the headspace of the vial onto a gas chromatograph equipped with a nitrogen phosphorus detector to detect HCN and acetonitrile.	Zamecnik and Tam (302); McAuley and Reive (186)
	Linearity: 0.25–15 $\mu g \cdot ml^{-1}$; sensitivity: 0.05 $\mu g \cdot ml^{-1}$	
Headspace gas chromatography (electron capture detection)	Liberation of HCN from blood, chlorination of HCN to cyanogen chloride by reaction with chloramine-T, and injection of headspace onto a gas chromatograph equipped with an electron capture detector.	Odoul et al. (206)
	Linearity: 0.005–1 $\mu g \cdot ml^{-1}$; suitable for clinical and toxicological purposes	
Spectrophotofluorimetry or high-performance liquid chromatography (fluorescence detection)	Transformation of CN^- by acidification from blood to HCN, reaction of CN^- in HCN with 2,3-naphthalenedialdehyde and taurine in a self contained system, and fluorimetric measurement ($\lambda_{excitation}$ = 418 nm; $\lambda_{emission}$ = 460 nm) of the reaction product, 1-cyano-2-benzoisoindole (1-cyano[*f*]benzoisoindole; CBI) derivative.	Felscher and Wulfmeyer (118)
	A specific method for CN^- with the detection limit of 0.002 $\mu g \cdot ml^{-1}$ CN^-; linearity: 0.002–1 $\mu g \cdot ml^{-1}$ by spectrophotometric determination and 0.002–5 $\mu g \cdot ml^{-1}$ by HPLC determination; suitable for clinical and toxicological purposes	

Table IV. (continued)

High-performance liquid chromatography (mass spectrometric detection)	Using isotopic potassium cyanide ($K^{13}C^{15}N$) as an internal standard, microdiffusion of CN^- and $^{13}C^{14}N^-$ from blood as HCN and $H^{13}C^{14}N$, reaction of CN^- and $^{13}C^{14}N^-$ in HCN and $H^{13}C^{14}N$ with 2,3-naphthalenedialdehyde and taurine in a self contained system to produce non-isotopic and isotopic analogs of CBI, and qualitative and quantitative determination of both CBI analogs by high performance liquid chromatography-mass spectrometric detection. Note: The molecular weight of the isotopic CBI–$^{13}C^{14}N$ derivative is more by 2 atomic mass units than that of non-isotopic CBI–CN derivative. This method should be suitable for clinical and toxicological purposes. A simple, rapid, and extremely specific method; detection limit: 0.005 $\mu g \cdot ml^{-1}$; linearity: 0.015–3 $\mu g \cdot ml^{-1}$	Tracqui et al. (273)

[a]Fresh and postmortem blood samples could be analyzed by the majority of methods included herein. Clotted blood may also be analyzed after homogenization. Other sample types that can be analyzed are plasma, serum, gastric content, cerebrospinal fluid, urine, and tissue homogenates. Only 33% of the unmeasurable CN^- could be attributed to the conversion of CN^- to thiocyanate (SCN^-). Sodium thiosulfate ($Na_2S_2O_3$), the antidote for treating CN^- poisoning, has been reported to interfere with colorimetric, fluorimetric, and potentiometric methods for CN^- measurement (192, 267, 288).

have other than additive effects at lower concentrations. The lower $t_{i(CO + HCN)}$ of 11.1 min in comparison to the calculated value 16.4 min from Equation 3 and less than unity value in Equation 2 could be associated with the limitations of the *C·t* theory and its related FED concept (80, 156, 207). When the FED model was employed using % COHb and μg·ml^{-1} CN^- levels at incapacitation, the FEDs—that is, $FED_{COHb} + FED_{HCN}$—were obtained for the high- and low-concentration mixtures of these 2 gases. The calculated values were correspondingly 1.16 and 1.12. In this regard, it should be realized that the COHb level was almost linear up to 5 min and started reaching a steady state before 11.1 min at the 35-min t_i CO concentration. Therefore, the FED model may have limitations for COHb and CN^- levels, except in the extremely short exposure periods when both CO and HCN uptakes are linear (65, 237). The evaluation of COHb and blood CN^- values with the values from the single gas exposure studies indicated that any alteration of the uptake of either gas in blood by the presence of the other gas was minimal. These findings suggested that changes in COHb and blood CN^- might not be directly correlated with the onset of incapacitation and that postmortem blood levels should be carefully evaluated, particularly when both gases are present in fire victims.

Interpretation of elevated levels of COHb and CN^- to the degree of toxicity caused by CO and HCN becomes challenging because both gases have interactive effects on the central nervous system (129, 138, 158, 258). When the FED concept (see Equation 2) is applicable, the $FED_{CO} + FED_{HCN}$ should equal unity for an additive effect of CO and HCN. By employing the FED model using blood % COHb and μg·ml^{-1} CN^- concentrations in place of CO and HCN effective exposure doses, Equation 5 could be used to account for the additive effects caused by these gases (38, 39). In this equation, "Fractional Toxic Concentration" in blood (FTC_{Blood}) is used in place of FED.

It is documented that CO at 70% COHb and HCN at 3.0 μg·ml^{-1} (μg/ml) CN^- would alone cause lethality (129, 137, 201). However, the FTC concept does not rule out other than additive effects of these gases. Therefore, the concentrations of COHb and CN^- in blood and interactive potentials of both species should be carefully considered when interpreting and correlating their blood concentrations with the toxicological effects. For example, the presence or absence of these species in blood would suggest whether the individual died after inhaling smoke or prior to the fire.

3.4.5 COHb and Blood CN^- in Fire-Involved Aircraft Accident Fatalities

As mentioned earlier, occurrences of in-flight smoke and fire are rare in modern aircraft. However, if and when that happens, the consequences are deadly (2, 73, 187, 213, 275). For instance, the involvement of an in-flight fire was deduced in the Swissair accident that occurred on 2 September 1998, near Peggy's Cove, Nova Scotia, Canada (275). Compared to in-flight fires, post-crash (ground) fires are generally more common, primarily originating from spilled fuel around the aircraft. In the crash of Galaxy Flight 203, on 21 January 1985, near Reno, Nevada, most victims survived the impact but succumbed to fire and toxic gases (234). Sixty-eight persons died at the scene, 2 died during hospitalization, and 1 survived. Fifty-four people died in the British Air Tours Boeing 737 accident at Manchester, United Kingdom, on 22 August 1985 (185). Fire was involved in the accident. Blood COHb and CN^- were elevated in most of the victims. Volatile substances were also detected in the blood of the victims and carbon particles in the trachea and bronchi.

In such post-crash fires, aircraft occupants are frequently unable to escape from the fire environment because of physical injuries and/or performance impairment from smoke-induced toxicity and visual obscuration. Such inability leads to incapacitation and death. Therefore, it is common to determine COHb and blood CN^- concentrations in fire-associated aircraft accident fatalities to establish the degree of toxicity (67, 68, 185, 204).

3.4.6 Analytical Results Interpretation

3.4.6.1 Analysis

Commonly used analytical procedures for measuring COHb and CN^- in blood are summarized in Tables III and IV. The blood quality could affect the accuracy of the concentrations of these species; therefore, it is an analytical and toxicological concern. From aviation accident fatalities, quality blood samples are frequently difficult to obtain. The quality of the blood is dependent upon the postmortem interval—that is, the time between death and blood collection. Old or putrid blood samples may interfere with the analysis. Clotted blood samples could be homogenized prior to analysis. Solid burned blood samples may not be suitable for analysis, though their aqueous homogenates could be analyzed. However, it would be difficult to interpret such analytical values. The blood collection technique and container, the types of anticoagulants and/or preservatives used, the sample storage conditions, the analysis time after sample collection, the ratio of surface area to volume of blood

$$FTC_{Blood} = FTC_{COHb} + FTC_{CN^-} = \frac{\%\ COHb_{Sample}}{70\%\ COHb} + \frac{CN^-_{\ Sample}\ (\mu g/mL)}{CN^-\ (3.0\,\mu g/mL)} = 1 \qquad (5)$$

exposed to the atmosphere, the storage condition and temperature, and the initial % COHb saturation (50) and blood CN^- concentration also adversely affect the outcome of such analyses.

3.4.6.2 COHb Concentrations

Although COHb below 5% is considered normal, healthy individuals may accumulate up to 10% COHb by inhaling CO-contaminated air (17, 296). COHb concentrations as high as 17% have been documented in heavy smokers (286). An approximately 20% decrease in COHb levels as a function of time has been reported in postmortem blood samples collected from fire victims (170). Therefore, COHb analytical values may not reflect the true levels of this species at the time of death, but they may represent approximate values at death. For a given % COHb concentration, effects may be more severe in physically active subjects or following prolonged exposures of several hours (190, 214, 215). Because of a considerable range of sensitivity to CO poisoning in the population, fatalities from CO exposures show a wide range of COHb concentrations, from approximately < 30% to 95% COHb (200). Toxicity of CO poisoning is associated with the central nervous and cardiovascular systems wherein the oxygen demand is high (129, 158, 258); COHb concentrations and associated signs and symptoms are given in Table V (129).

3.4.6.3 CN^- Concentrations

Blood CN^- concentrations are also strongly affected by the postmortem interval, decreasing by approximately 50% per day in a cadaver (10, 90). CN^- in blood can be in the HCN form. In its protonated form, CN^- as HCN could be easily diffused through the body and released into the surrounding atmosphere, thereby reducing CN^- levels. Release of HCN from cyanomethaemoglobin (cyano-MetHb) has been reported by heat denaturation, as well (252). The majority of the analytical methods measure total CN^- originating from both critical (cyanide-cytochrome oxidase complex) and non-critical (cyano-MetHb; erythrocytes) sites (65, 129, 158, 188, 284). Normal human blood concentrations range from 0.0 to 0.30 $\mu g \cdot ml^{-1}$ in nonsmokers and from 0.02 to 0.50 $\mu g \cdot ml^{-1}$ in smokers (12, 184, 268). Originating from cyanogenic glycosides or pyocyaneous organisms, CN^- concentrations up to 0.15 $\mu g \cdot ml^{-1}$ in blood could be found in adults without symptoms (16, 21, 24, 29, 91, 92, 129). A CN^- value of < 0.25 $\mu g \cdot ml^{-1}$ may not have toxicological relevance, as clinical manifestations are observed at CN^- concentrations of ≥ 0.5 $\mu g \cdot ml^{-1}$ (Table VI) (129), though toxic effects of CN^- on fire victims should not be solely based upon its blood concentration (193, 194).

CN^-, a rapidly acting toxic chemical entity, is capable of causing incapacitation quickly (129, 158, 258). As the CN^- concentration increases, unavailability of oxygen to the central nervous system may cause hypoxic convulsions, followed by death due to respiratory arrest. Inhalation of HCN rich smoke induces hyperventilation, thus increasing the rate of uptake until the victim collapses and becomes comatose. When the rate of uptake decreases, the victim may temporarily recover. Such recovery, however, may be short lived, leading into a gradual but fatal decline (214, 216). Although high blood CN^- concentrations probably result from the release of sequestered CN^- in the red blood cells (8, 11, 14, 15, 274, 284) and blood concentrations of CN^- could be correlated with its toxicity (13, 129, 188), the associated signs and symptoms may be more closely related to plasma CN^- concentrations than whole blood CN^-, as an unconscious victim may recover quickly of the cessation of exposure without any decline in whole blood CN^- (214, 216).

3.4.6.4 MetHb, Cyano-MetHb, and Sulfmethemoglobin (Sulf-MetHb)

Including CO and HCN, numerous species could be produced during combustion of substances (107, 113, 123, 136, 138, 244), and some of these may be very reactive, thus may convert HHb to MetHb. MetHb may also be produced by heat (116) and by postmortem oxidation of HHb (157, 203, 247). Smoke rich in HCN, hydrogen sulfide, or sulfur-containing substances may react with MetHb to form cyano-MetHb and sulf-MetHb (129). The latter could also be formed postmortem as hydrogen sulfide and sulfur species are produced during putrefaction.

Sulf-MetHb interferes with spectrophotometric analytical methods (74, 258), particularly when this species is present in high concentrations. Spectral absorbance of sulf-MetHb is similar to that of MetHb. Also, some analytical methods do not account for cyano- and sulf-MetHb in measuring total hemoglobin. Therefore, % COHb results could be erroneously high by using those methods.

During COHb measurements, sodium dithionite is used as a reducing agent to convert OxyHb and MetHb to HHb to maximize the CO binding capacity of the blood sample. However, it has not been clearly established whether such dithionite treatment would also reduce cyano- and sulf-MetHb to HHb, though polysulfides, thiosufate, and sulfate have been known to reduce sulf-MetHb to HHb (129). If these HHb-analogs, as well as OxyHb and MetHb, could not be completely converted to HHb by the dithionite treatment, then the binding capacity of the blood sample would not be maximum,

Table V. Percent COHb and Associated Sign and Symptoms (129)

% COHb	Signs and Symptoms
0–10	No symptoms
10–20	Tightness across forehead, possible slight headache, and dilation of cutaneous blood vessels
20–30	Headache and throbbing in temples, easily fatigued, and possibly dizziness
30–40	Severe headache, weakness, dizziness, confusion, vision dimness, nausea, vomiting, and collapse
40–50	Signs and symptoms same as above, but severity is higher; increased pulse and respiratory rate
50–60	Increased respiratory and pulse rate, coma, intermittent convulsions, and Cheyne-Stokes respiration
60–70	Coma, intermittent convulsions, depressed heart action and respiratory rate, and possible death
70–80	Weak pulse, slow respiration, respiratory failure, and death within a few hours
80–90	Death in less than an hour
> 90	Death in a few minutes

Table VI. Blood CN^- Concentrations and Associated Toxicity (129)

Degree of Toxicity (Blood CN^-)	Signs and Symptoms
Mild (0.5–1.0 $\mu g \cdot ml^{-1}$)	Flushed, rapid pulse, conscious, and headache
Moderate (1.0–2.5 $\mu g \cdot ml^{-1}$)	Stuporous but responsive to stimuli, tachycardia, and tachypnea
Severe ($\geq$ 2.5 $\mu g \cdot ml^{-1}$)	Comatose, unresponsive, hypotension, slow respirations, gasping, mydriasis, cyanosis at high concentration, and death

and thereby the observed % COHb values would be erroneously higher in comparison to the situation when these hemoglobin species would have been completely reduced to HHb. Therefore, cyano-MetHb and sulf-MetHb at high concentrations may potentially interfere with the COHb analyses, thus may provide inaccurate analytical results.

4 POSTMORTEM AVIATION FORENSIC TOXICOLOGY

4.1 Introductory Comments

The field of *Postmortem Aviation Forensic Toxicology* falls between the categories of *Postmortem Forensic Toxicology* and *Human-Performance Forensic Toxicology*. Per their definitions in the forensic toxicology laboratory guidelines (260), the former deals with the cause and manner of death, whereas the latter with human performance or behavior. The flying process involves the interaction between man and the machine, and it is not only the equipment failure, but also the performance impairment and/or abnormal behavior of aviators that might contribute to an accident. Such accident could be fatal. The performance/behavior-related changes in aviators may be because of the presence of foreign substances in their system and/or of health reasons. Therefore, during aviation toxicology evaluation, postmortem biological samples from aviators are analyzed for the presence of foreign substances—combustion gases, ethanol/volatiles, and drugs—to establish whether the foreign substance(s)-induced performance impairment/behavioral abnormality was the cause or a factor in a particular aviation accident (35, 41, 69, 262). Most of the drugs present in the pilot samples are in the subtherapeutic-to-therapeutic concentration range (6, 35, 41, 69, 250, 262), which is consistent with the nature of postmortem aviation toxicology and could basically be referred to as the human-performance associated postmortem forensic toxicology (260). The presence of drugs would also be suggestive of their underlying medical conditions for which they were treated.

During fatal aircraft accident investigations, postmortem samples are collected from pilot fatalities and toxicologically evaluated in a forensic toxicology facility. The facility could be associated with a local or state agency in some countries, while with a federal agency in others. In the United States, the toxicology facility is located at CAMI (1, 69, 103). The sample submission is coordinated through the FAA's Office of Accident Investigation by the National Transportation Safety Board. This Board is responsible for investigating all U.S. civilian aircraft accidents. In the majority of situations, the samples are from pilots and copilots. Samples from passengers and other crewmembers are also sometimes submitted, depending upon the nature of an accident—for example, an accident involving fire. Multiple types of postmortem specimens—blood, urine, vitreous fluid, spinal fluid, brain, lung, heart, liver, kidney, and/or other sample types—in sufficient amounts are needed for analysis (69), but this requirement frequently cannot be achieved in those accidents in which bodies are scattered, disintegrated, commingled, contaminated, and/or putrefied. Glucose concentrations in vitreous fluid and urine samples are determined, and in those situations wherein glucose levels are elevated, blood hemoglobin A_{1c} (HbA_{1c}; glycosylated hemoglobin) is also measured to monitor diabetic pilots, ensuring that the disease was in control at the time of accident, and to discover other pilots with undiagnosed or unreported diabetes (55). The postmortem forensic samples are submitted to CAMI in TOX-BOX evidence containers. The contents of a TOX-BOX kit and types, amounts, and analytical suitability of postmortem specimens are detailed in a previously published article (69).

4.2 Analytical Components

Evidence containers with samples should be received in a secured, specific area of the toxicology facility, and the samples should be accessioned following the standard operating procedure of the laboratory. Depending upon the types and amounts of submitted samples and the mission of the laboratory, the following analytical toxicology tests should be performed (69):

1) Blood CO as COHb by a spectrophotometric method and confirmation by gas chromatography
2) Blood CN^- by a colorimetric method and confirmation by another method, such by high-performance liquid chromatography
3) Ethanol/volatiles in vitreous fluid, urine, blood, brain, muscle, and/or other tissues by dual capillary column-flame ionization detection by headspace gas chromatography

   Note: The presence of ethanol in liquid samples—vitreous fluid, urine, and blood—should be confirmed by a second method such as radiative energy attenuation. In those cases wherein ethanol is positive in urine, urinary concentrations of serotonin metabolites—5-hydroxytryptophol (5-HTOL) and 5-hydroxyindole-3-acetic acid (5-HIAA)—should be measured by liquid chromatography-mass spectrometry and their ratio should be calculated to conclude whether ethanol found in the samples is from sources other than ingestion. A concentration ratio value of < 15 pmol/nmol is not consistent with ethanol ingestion; a value ≥ 15 pmol/nmol is suggestive of ethanol ingestion (153, 154).

4) Blood and other tissue samples should be screened for:
   a) Controlled substances—amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, methamphetamine, opiates, and phencyclidine—by radioimmunoassay
   b) Prescription and nonprescription drugs by high-performance liquid chromatography and gas chromatography-mass spectrometry
   c) Additional drugs in blood—acetaminophen, phenytoin, quinidine, salicylate, and theophylline—by fluorescence polarization immunoassay.
5) Urine should be screened for:
   a) Controlled substances—amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, methamphetamine, opiates, and phencyclidine—by fluorescence polarization immunoassay
   b) Prescription and nonprescription drugs by high-performance liquid chromatography and gas chromatography-mass spectrometry
   c) Additional drugs—acetaminophen, phenytoin, propoxyphene, quinidine, salicylate, and theophylline—by fluorescence polarization immunoassay.
6) Confirmatory/quantitative analysis should be performed in the samples wherein drug(s) was found during initial analyses (screening). In other words, confirmatory/quantitative analyses should be performed in the aliquots of the sample type, which was determined as presumptively positive for drug(s) during the initial analysis (screening), and of at least 1 additional sample type (if available) of the case. Preferred sample types are blood and urine, but other sample types could also be used. Depending upon the type of analyte, gas chromatography-mass spectrometry, liquid chromatography-mass spectrometry, or any other specific techniques could also be used for confirmatory/quantitative analyses.
7) Glucose in vitreous fluid and urine could be measured enzymatically and HbA_{1c} in blood by latex immunoagglutination inhibition methodology. Presence of glucose in vitreous and urine could be reconfirmed by color-sensitive reagent strips.
8) Sometimes, DNA profiling should also be performed on the samples of a case to ensure that the submitted samples originated from the same source. This approach becomes necessary when there is a reason to believe that the samples might have been commingled or mismatched with the samples of other victims during the sample collection (70).
9) Throughout the entire process of toxicological evaluation—that is, from receiving the samples to dispatching the analytical reports—a high level of quality assurance/quality control should be maintained (4, 260); this aspect could be easily exemplified by the previously described FAA's Postmortem Forensic Toxicology Proficiency-Testing Program (4, 54, 260).
10) The chain-of-custody of postmortem forensic samples and all records, including analytical data, should be securely maintained throughout the entire forensic evaluation process.

Since the presence of drugs in a pilot's system also suggests possible associated medical conditions for which they might have been taken, identification and quantification of parent drugs and their metabolites in multi-specimens are of relevance in the field of forensic science (56). Demonstrating the presence of drug metabolites such as Δ^9-tetrahydrocannabinol (THC) carboxylic acid of THC and benzoylecgonine of cocaine provides compelling evidence for use/abuse to the parent drug and facilitates interpretation of results and investigation of a case, particularly when the metabolites are pharmacologically active. Such analyses might not be as helpful if the metabolites are also marketed or available as drugs.

4.3 COHb and Blood CN^- Concentrations

Although in-flight fires in modern aircraft are rare, post-crash fires do occur (53, 64, 68, 177). Fire-involved civil passenger aircraft accidents claiming considerable number of fatalities have been documented (32, 126). In aviation accidents, COHb and blood CN^- analyses are performed to establish possible exposure of victims to smoke from in-flight/post-crash fires or to CO from faulty exhaust/heating systems. The elevated COHb, as well as CN^-, in blood would suggest that the victim was alive and inhaled smoke. If only COHb is elevated, the accident (or death) could be attributed to the contamination of the aircraft interior by CO.

The toxicological assessment of 485 fatal aircraft accidents that occurred in the United Kingdom between 1955 and 1979 found COHb concentrations ≥ 10% in 90 fatalities of the 439 evaluated (143). In another study for the 1967–1972 period, toxicology revealed elevated COHb of direct importance in 19% of the 113 accidents (23). Blood analysis of pilot fatalities of general aviation accidents (October 1968–September 1974) revealed COHb in excess of 10% in 79 of the 1,345 cases and elevated CN^- in 16 of the 1,345 cases (165). Elevated COHb was reported in 13 of the 2,449 pilots killed in general aviation operations (1973–1977) and was due to faulty heaters or exhaust systems (166). Three cases with

COHb > 10% have been reported in 202 general aviation accidents in a 1970 study (255). In an FAA study, analysis of samples from 377 aviation fatalities during October 1988–September 1989 concluded COHb at < 10% in 94% of the cases and cyanide at < 0.5 $\mu g \cdot ml^{-1}$ in 96% of the cases (161). Toxicological findings in military aircraft fatalities investigated by the Division of Forensic Toxicology at the U.S. Armed Forces Institute of Pathology from 1986 to 1990 suggested COHb concentrations > 10% in 4.3% of the 535 cases (159).

According to a 2001 study by Chaturvedi et al. (68), 1,571 (41%) fatalities (1,012 aviation accidents) out of the 3,857 fatalities (2,837 aviation accidents) occurring during 1991–1998 were fire-associated. There were 1,820 non fire-related accidents, and the fire status of 5 accidents was unknown. There were fewer fire-related fatalities and associated accidents in the category wherein COHb ≥ 10% and $CN^- \geq 0.25$ $\mu g \cdot ml^{-1}$ than that in the category of wherein COHb < 10% and $CN^- < 0.25$ $\mu g \cdot ml^{-1}$. No in-flight fire was documented in the former category; however, in-flight fires were reported in 14 accidents (18 fatalities) in the latter category. There were 15 non-fire accidents involving 17 fatalities. In these fatalities, only COHb (10–69%) was elevated. This study suggested that aviation fire accidents were fewer than non-fire accidents and confirms that aviation accidents related to in-flight fires and CO-contaminated interiors are rare occurrences. (Readers may also refer to the *Aviation Combustion Toxicology* section for additional details.)

4.4 Ethanol

Depending upon the nature of a fatal aviation accident, the bodies of victims are frequently scattered, disintegrated, and/or putrefied. It is well-established that the body is invaded by microbes after death, and these living micro-organisms are involved in putrefaction processes, leading to the postmortem production of ethanol in the body (22, 75, 160, 163). The extent of putrefaction is linked to the condition of the body, which is affected by the severity of injuries, the time between the death and the discovery of the body (postmortem interval), and the environmental factors. Indeed, the postmortem production of ethanol in aviation accidents has been an issue investigated for many years (89), but the production of ethanol after the postmortem collection of fluid samples can be minimized by collecting them in containers containing sodium fluoride and storing the collected samples in cold (69, 89, 172). Ethanol production by *Candida albicans* in postmortem human blood samples has been reported, and the necessity of immediately adding sodium fluoride to samples for ethanol analysis to prevent further ethanol production, if any, has been reemphasized (301). A polymerase chain reaction (PCR)-based method for detecting the presence of common ethanol producing microbial contaminants—*Escherichia coli, Proteus vulgaris, and Candida albicans*—in human blood has been published by using a set of DNA primers designed for use in PCR to amplify and detect the genomic DNA from humans and the 3 test microorganisms (163). This method is suitable for rapidly identifying microbial contaminants in postmortem blood, as well as solid tissue, samples (163, 287).

Because of the impact generally encountered during aircraft crashes, extensive abdominal damage and open wounds frequently occur in the fatalities. Such damage and wounds, thus, increase the potential for microbial invasion and for putrefaction; interpretation of ethanol concentrations in autopsied specimens from victims is highly arguable, and great caution is needed to reach valid conclusions of whether the deceased had consumed ethanol before death (160). In the past, the postmortem ethanol production was inferred from the presence of acetaldehyde, acetone, 2-butanol, and other volatiles, but this basis may not have always been correct (42). For example, in a study involving aviation accident fatalities, several cases with postmortem ethanol had no other volatiles, and volatile compounds were found in several cases where no ethanol was present (42). In addition, a case was found in which the relative ethanol concentrations in blood, bile, and vitreous humor were consistent with the ingestion of ethanol, but acetaldehyde, acetone, and 2-butanol were also found in blood. These observations indicate that the presence or absence of other volatiles does not necessarily establish postmortem ethanol production (42). Determination of ethanol concentrations in various sample types—vitreous humor, urine, brain, liver, kidney, and muscle—is helpful in establishing the distribution of ethanol. Based upon the distribution findings, it could be scientifically deduced whether ethanol was consumed before death or produced postmortem. The presence of ethanol in blood and its absence in vitreous fluid or brain would be indicative of postmortem formation of ethanol. Interpretation of postmortem production of ethanol and other associated factors has been covered in a critical review by O'Neal and Poklis (205).

Of the 485 U.K. fatal aircraft accidents (1955–1979), 28 were found to have medical cause (143). Seven of these 28 crashes were due to alcohol consumption. During 1967–1972 in the UK, aircraft accident toxicology revealed that the presence of ethanol was of importance in 7% of the 113 accidents (23). In the U.S., blood ethanol concentrations were found in excess of 0.05% in 117 of the 1,345 general aviation accident pilot fatalities (October 1968–September 1974) (165), in 226 of the 2,623 pilots killed during agricultural and general aviation operations (1973–1977) (166), and in 28 of the 202

pilots involved in fatal general aviation accidents (255). In an FAA study, the presence of ethanol at > 10 $mg \cdot dl^{-1}$ was found in 14.8% of the 377 aviation fatalities during October 1988 to September 1989, but only 4.5% were determined to be due to ethanol ingestion (161). Positive ethanol findings in military aircraft fatalities from 1986–1990 were suggestive of postmortem formation than antemortem consumption (159).

In a study by Canfield et al. (42), 79 (8%) of 975 victims of fatal aircraft accidents (1989–1990) had blood ethanol ≥ 0.04% (40 $mg \cdot dl^{-1}$), a legal blood alcohol concentration under the FAA regulation at which no person may operate or attempt to operate an aircraft (48, 233). Based on the distribution of ethanol in urine, vitreous humor, blood, and tissue (42), it was determined that 21 of the positive cases (27%) were from postmortem ethanol production. Postmortem ethanol production was > 0.15% (150 $mg \cdot dl^{-1}$) in 2 cases. Additionally, 22 (28%) of the positive cases were found to be from the ingestion of ethanol. The origin of the ethanol could not be established in 36 cases (45%). A study involving the postmortem toxicology analysis (1989–1993) of 1,845 aviation accident pilot fatalities revealed the presence of ethanol at or above the legal limit of 0.04% in 146 pilots (35, 48, 233). Similarly, ethanol at or above the legal limit was found in 124 out of 1,683 pilots during 1994–1998 (41) and in 101 out of 1,587 pilots during 1999–2003 (58, 59). The presence of ethanol with selective serotonin reuptake inhibitors (SSRIs) (6) and with first-generation H_1 antihistamines (250) has also been reported in aviation accident pilot fatalities.

The research on the production of ethanol has now been focused on developing various biochemical tests or markers of postmortem synthesis of ethanol (160). These tests/markers include the urinary metabolites of serotonin and non-oxidative metabolites of ethanol such as ethyl glucuronide (34, 133, 153, 154, 160, 195). Additionally, ethyl sulfate and the ratio between 5-hydroxytryptophol-glucuronide and 5-HIAA have further been emphasized as biomarkers for recent alcohol ingestion with longer detection times than measurement of ethanol itself (148). However, there has been debate about the total reliability of the biomarkers (140). The formation of ethyl glucuronide and ethyl sulfate has been reported even following inhalation of ethanol vapors (155). Disappearance of ethyl glucuronide during heavy putrefaction has also been implied (149). On the other hand, ratios of concentrations of serotonin metabolites, 5-HTOL and 5-HIAA, in urine have effectively been used for concluding whether ethanol found in the samples is from sources other than ingestion (34, 133, 153, 154). The use of the urinary 5-HTOL:5-HIAA concentration ratio as a marker of recent ethanol consumption stems from the fact that the oxidative deamination of serotonin to 5-HIAA is altered after ethanol consumption (89). Such alteration causes an increase in the concentration of 5-HTOL, which is normally < 1% of 5-HIAA. Recent consumption of ethanol increases this proportion of serotonin metabolites. Accordingly, a concentration ratio (5-HTOL:5-HIAA) value of < 15 pmol/nmol is not consistent with ethanol ingestion, while a value ≥ 15 pmol/nmol is suggestive of ethanol ingestion (34, 153, 154).

4.5 Drugs

4.5.1 Commonly Used and Abused Drugs

Although the topic of taking medications by aviators has been touched upon by Hill (143) in the 1986 study covering 485 U.K. fatal aircraft accidents (1955–1979), the U.K. aircraft accident toxicology experience (1967–1972) is elaborated in a study by Blackmore (23). This study involved 113 aircraft, encompassing 184 crew and 207 passengers. Cyclopenetamine, methaqualone, salicylate, and valium were detected in 4 pilots of the fatal accidents. In the U.S., a toxicological study with 202 pilot fatalities disclosed the presence of drugs—amitriptyline, barbiturate, chloroquine, chlorpromazine, morphine, perphenazine, pheniramine, and quinidine—in 7 pilots (255). A summary of toxicological findings of fatal general aviation accidents (October 1968–September 1974) suggested the presence of drugs in 16 of 1,345 fatalities (165). In another study (166), the use of drugs has been reported to be less in agricultural pilots (1.1% of 174) than in general aviation pilots (4.9% of 2,449) during the period of 1973–1977. Toxicological evaluations of samples from 377 aviation fatalities during October 1988 to September 1989 concluded that 12.6% of the cases were positive for 1 or more drugs (161). Cannabinoids were found in 1.3% of the cases and benzoylecgonine in 1.6%. Acetaminophen and salicylate were the most frequently encountered drugs. Including chloroquine and nicotine, over-the-counter analgesics, antihistaminics, and sympathomimetics have been identified in military aircraft fatality cases from 1986 to 1990 (159).

Between 1989 and 1993, postmortem samples from 1,845 pilots were toxicologically analyzed at CAMI (35). Controlled dangerous substances of Schedules I and II (amphetamine/methamphetamine, barbiturates, cocaine, codeine/morphine, marihuana, methaqualone, phencyclidine, and synthetic opiates) were found in 74 pilots and of Schedules III–V (benzodiazepines, phendimetrazine, and phentermine) in 28 [for the classification of Scheduled substances, see ref. (47)]. Prescription drugs were found in 110 pilots, over-the-counter drugs in 207, and ethanol in 146. Analyses of postmortem samples from 1,683 pilots during 1994 to 1998 disclosed the presence of controlled dangerous substances of Schedules I

and II (amphetamine/methamphetamine, barbiturates, cocaine, codeine/morphine, marihuana, methaqualone, phencyclidine, and synthetic opiates) in 89 pilots and of Schedules III–V (benzodiazepines, fenfluramine, pentazocine, phendimetrazine, phentermine, propoxyphene/norpropoxyphene) in 49 pilots (40, 41). Prescription drugs were detected in 240 pilots, over-the-counter medications in 301, and ethanol in 124. In continuation of these 2 preceding studies (35, 40, 41), an epidemiological assessment was made for an additional period of 5 years (1999–2003) (58, 59). Of 1,629 fatal aviation accidents from which CAMI received biosamples, there were 1,587 accidents wherein pilots were fatally injured. Drugs and/or ethanol were found in 830 of the 1,587 fatalities. Controlled substances of Schedules I and II (amphetamine/methamphetamine, barbiturates, cocaine and its metabolite(s), codeine/morphine, marihuana, 3,4-methylenedixoymethamphetamine, and synthetic opiates) and of Schedules III–V (benzodiazepines, phentermine, propoxyphene/norpropoxyphene, and zolpidem) were detected in 113 and 42 pilots, respectively. Prescription drugs were present in 315 pilots, nonprescription drugs in 259, and ethanol in 101. More than 1 drug was present in some fatalities, thus those fatalities were counted more than once—that is, for each drug or ethanol. Barbiturates included butalbital, pentobarbital, and/or phenobarbital; marihuana meant THC and/or THC carboxylic acid; synthetic opiates include hydrocodone, hydromorphone, meperidine, oxycodone, and/or their metabolites; and benzodiazepines entailed α-hydroxyalprazolam, alprazolam, diazepam, midazolam, nordiazepam, oxazepam, and/or temazepam. Prescription drugs found in the 3 studies (1989–1993, 1994–1998, and 1999–2003) are tabulated in Table VII (35, 40, 41, 58, 59). Commonly found non-prescription drugs were acetaminophen, chlorpheniramine, dextromethorphan, doxylamine, ephedrine, meclizine, (–)-methamphetamine, oxymetazoline, phenylpropanolamine, pseudoephedrine, quinine, salicylate, and triprolidine. These drugs were primarily associated with drug preparations and formulations used to alleviate allergy and cold symptoms.

Any increase seen in the prevalence of drugs during the 15-year period (1989–1993, 1994–1998, and 1999–2003) (35, 40, 41, 58, 59) could perhaps be attributed to the possibilities of scientific and technical advances in the sensitivity of analytical methods, genuine authorized medical use of such drugs, and/or their real abuse. Narcotic analgesics found in pilot fatalities could have been administered by emergency health care providers at accident scenes or at hospitals for pain reduction and/or surgical procedures. The presence of abused drugs—such as, amphetamine/methamphetamine, cocaine, marihuana, and 3,4-methylenedixoymethamphetamine—could have been associated with their unauthorized use. Atropine and lidocaine might have been administered by health care providers for resuscitation. The presence of prescription drugs found in the fatalities reflected the current trends in the popularly dispensed groups of medications—antihypertensives and antidepressants—in the U.S. (58, 59). Many of the prescription and nonprescription drugs, including the controlled substances, present in the pilot fatalities have the potential for impairing performance, thereby adversely affecting the ability of an individual to optimally pilot an aircraft. Findings from these studies support the FAA's programs, including the FAA's drug-testing program, aimed at identifying potentially incapacitating medical conditions and reducing the usage of performance-impairing drugs or ethanol (49, 102).

4.5.2 SSRIs

The prevalence of SSRIs was evaluated in pilot fatalities of civil aviation accidents that occurred during 1990–2001 (5, 6). Of 4,184 fatal civil aviation accidents, there were 61 accidents in which pilot fatalities had SSRIs. Blood concentrations of SSRIs were 11–1,121 $ng \cdot ml^{-1}$ for fluoxetine; 47–13,102 $ng \cdot ml^{-1}$ for sertraline; 68–1,441 $ng \cdot ml^{-1}$ for paroxetine; and 314–462 $ng \cdot ml^{-1}$ for citalopram. In 39 pilots, other drugs—such as, analgesics, antihistaminics, benzodiazepines, narcotic analgesics, and/or sympathomimetics—and/or ethanol were also present. Although blood SSRI concentrations ranged from subtherapeutic to toxic levels, the interactive effects of other drug(s) and ethanol in producing adverse effects in the pilots cannot be ruled out. To establish whether these pilots had disqualifying psychological conditions, including depression, and had properly reported the use of the antidepressants, the aeromedical history of these pilots was examined and reported by Sen et al. (248, 249).

Based upon the distribution of fluoxetine in 10 fatal aviation accident cases, its distribution coefficients, expressed as specimen type/blood ratios, were determined to be 0.9 ± 0.4 for urine, 0.10 ± 0.03 for vitreous humor, 9 ± 1 for bile, 38 ± 10 for liver, 60 ± 17 for lung, 9 ± 3 for kidney, 20 ± 5 for spleen, 2.2 ± 0.3 for muscle, 15 ± 3 for brain, and 10 ± 2 for heart (151, 175). Blood concentrations of this SSRI in these fatalities ranged from 21 to 1,480 $ng \cdot ml^{-1}$.

4.5.3 First-Generation H_1 Antihistaminics

Although first-generation H_1-receptor antagonists cause drowsiness and sedation leading to potential performance impairment, these antihistamines are popularly used for alleviating allergy and cold symptoms. The prevalence of these antagonists was evaluated in pilot fatalities of civil aircraft accidents that occurred during a 16-year (1990–2005) period (250, 251). Of 5,383 fatal

Table VII. Prescription Drugs Found in Pilot Fatalities

Drugs and Their Metabolites	
Aminophenazone	Labetalol
Amitriptyline/Nortriptyline	Lidocaine
Amlodipine	Maprotiline
Atenolol	Metoclopramide
Atropine	Metoprolol
Azacyclonol	Minoxidil
Benzocaine	Mirtazapine
Bisoprolol	Moricizine
Brompheniramine	Nadolol
Bupropion/Metabolite	Naproxen
Carbamazepine	Nizatidine
Cetirizine	Orphenadrine
Chloroquine	Pantoprazole
Cimetidine	Paroxetine
Citalopram/Metabolite(s)	Phenyltoloxamine
Cyclizine	Phenytoin
Cyclobenzaprine	Procainamide/*N*-Acetylprocainamide
Diltiazem	Promethazine
Diphenhydramine	Propoxyphene/Norpropoxyphene
Doxazosin	Propranolol
Doxepin/Nordoxepin	Quinidine
Etomidate	Ranitidine
Fenoprofen	Sertraline/Desmethylsertraline
Fluconazole	Sildenafil/Metabolite(s)
Fluoxetine/Norfluoxetine	Theophylline
Gemfibrozil	Thiopental
Griseofulvin	Tramadol
Hydrochlorothiazide	Trazodone
Hydroxyzine	Triamterene
Ibuprofen	Trimethoprim
Imipramine/Desipramine	Venlafaxine/Desmethylvenlafaxine
Ketamine	Verapamil/Norverapamil

aviation accidents, there were 338 accidents wherein pilot fatalities (cases) were found to contain brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine, and triprolidine. Antihistamines were detected alone in 103 fatalities, while other drug(s) and/or ethanol were also present in an additional 235 fatalities. More than 1 antihistamine was detected in 35 fatalities. Although blood was not available for analyses in all cases, blood concentrations ($ng \cdot ml^{-1}$) were: 5–200 (n = 8) for brompheniramine; 4–6,114 (n = 67) for chlorpheniramine; 9–3,800 (n = 125) for diphenhydramine; 10–1,309 (n = 33) for doxylamine; and 4 (n = 1) for phenyltoloxamine. These levels were in the sub-therapeutic to toxic range. In an earlier study (262), 47 (2.2%) accidents that occurred during 1991–1996 were associated with chlorpheniramine. Related to these accidents, 16 pilots had only chlorpheniramine at 109 $ng \cdot ml^{-1}$ (n = 4) in blood and 1,412 $ng \cdot g^{-1}$ (n = 12) in liver. Other drugs were also present in the remaining cases, wherein chlorpheniramine concentrations were 93 $ng \cdot ml^{-1}$ (n = 18) in blood and 747 $ng \cdot g^{-1}$ (n = 12) in liver. Ninety-five percent of all quantitated blood values were at or above the therapeutic level (10 $ng \cdot ml^{-1}$).

4.5.4 Other Drugs

4.5.4.1 Selegiline

Stereochemical determination of selegiline metabolites in postmortem biological specimens from an aviation accident pilot fatality was accomplished to deduce that the pilot was being treated for Parkinson's disease (164). Such analytical differentiation between dextrorotatory and levorotatory methamphetamine/amphetamine has been applied to establish the optical purity of methamphetamine found in toxic concentration in a fatally injured pilot of an aviation accident (57).

4.5.4.2 Sildenafil

Concentrations of sildenafil and its active metabolite have been reported in various biological samples from victims from 6 separate aviation fatalities (150, 173).

4.5.4.3 Vardenafil

The postmortem distribution of vardenafil, with an unusually high blood concentration, has been evaluated in an aviation accident victim (152).

4.5.4.4 Butalbital

In an attempt to estimate blood butalbital concentrations from the drug levels in available tissues, distribution of butalbital was studied in various postmortem tissues and fluids from aviation accident fatalities (176). The distribution coefficients for butalbital, expressed as specimen type/blood ratios, were (n = 2–4): 0.66 ± 0.09 for muscle, 0.98 ± 0.09 for kidney, 0.87 ± 0.06 for lung, 0.75 ± 0.03 for spleen, 0.96 ± 0.07 for brain, 2.22 ± 0.04 for liver, and 0.91 ± 0.17 for heart.

4.6 Elevated Glucose and HbA_{1c}

Vitreous fluid and urine samples from pilots fatally injured in aviation accidents are analyzed for glucose and blood for hemoglobin A_{1c} (HbA_{1c}) (19, 36, 37, 291). In an epidemiological study involving 1,335 pilots (1998–2005), 43 were found to have elevated glucose in vitreous fluid (> 125 $mg \cdot dl^{-1}$) and/or in urine (> 100 $mg \cdot dl^{-1}$). Of the 20 pilots whose blood samples were analyzed, 9 had > 6% HbA_{1c} (55). Four of the 9 pilots were known diabetics, while 5 were unknown diabetics. A considerable number of pilots (30 of 43) had elevated glucose and HbA_{1c} (5 of 20), suggesting undiagnosed/unreported diabetic conditions.

5 CABIN AIR CONTAMINATION

5.1 Introductory Aspects

Quality of air in cabins of aircraft 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 (210). These issues are in view of the facts that the crews must work, sleep, and live in the cabin environments of aircraft and space vehicles. Throughout the world, the possible adverse effects of cabin atmosphere contents on the health of air crews and travelers have been evaluated (30, 31, 122, 134, 217, 218, 220, 285, 300). Aircraft cabin air quality-related bills in the U.S. Congress and reports of the U.S. National Academy of Sciences have been in the limelight in the field of aerospace medicine (217, 218, 221). More than 30 years ago, the quality of cabin air was apparently not an issue in commercial aviation, and the incidence of disease through airborne vectors or toxic fumes was uncommon (3). However, modern jet airliners may have the threat of disease because their ventilator systems are designed for optimum efficiency, leaving them exposed to lapses in the recycling of clean air and blocking fumes from jet engine exhausts from entering the aircraft cabin areas. Aero-toxic fumes are most common in the cockpit, and the crew members are the most susceptible to the aero-toxic syndrome (3). In a comprehensive review of 21 studies examining the effect of the airliner cabin environment and other factors on the health and comfort of flight attendants, Nagda and Koontz (197) 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 "fatigue" symptoms with

factors such as disruption of circadian rhythm. Certain flight attendants complaints were consistent with possible exposure to air pollutants, but that relationship has not been established with a view that such complaints also were consistent with causes other than poor air quality. In spite of health issues associated with air travel, there are enormous benefits to travelers, to commerce, to international affairs, and to health (96).

Stresses, like airport tumult, barometric pressure changes, immobility, jet lag (238), noise, vibration, and radiation, imposed by commercial flights upon travelers and in-flight illness and medical care capability aboard U.S. air carriers have been addressed in a review article (219). Since the "cabin air quality" topic has been of concern and controversy, the Aerospace Medical Association (AsMA) has reviewed the scientifically accepted facts in the different elements (such as pressurization, ventilation, contamination, humidity, and temperature) associated with aircraft cabin atmospheres (270). AsMA recommended that regulators, airlines, and scientific associations work together on the issue of cabin air quality because no amount of technical data alone would solve the problem. Aircraft cabin CO_2 concentrations calculated from the published ventilation ratings were found to be intermediate to these sets of results obtained by actual measurement. These findings are used to arrive at recommendations for aircraft builders and operators to help improve aircraft cabin air quality at minimum cost (145). Based on the passenger aircraft cabin air quality covering trends, effects, societal costs, and proposals, suggestions for air quality improvement were made resulting in a net, multi-stakeholder savings and improved passenger comfort (146). Aviation industry and passenger perspectives in relation to cabin air quality have been evaluated by Hocking (147). Accordingly, recommendations and suggestions were made for aircraft builders, operators, and passengers. Those recommendations/suggestions would help improve aircraft cabin air quality and the partial pressure of oxygen that is available to passengers at minimal cost and enhance their comfort and decrease their risk of illness. In an overview by Rayman (221), recommendations have been made on how the cabin air quality issue may be resolved. Furthermore, a literature review demonstrated that airliner cabin air quality is adequate and does not compromise aircrew health (271), though the need for further studies was acknowledged.

5.2 Aircraft Cabin Air

Fatigue in aircrew members performing frequent and long-range flights has been linked to aircraft-related noise, temperature, cabin pressure, ventilation, atmosphere quality, humidity, jet lag, and flight characteristics (122, 285). Ventilation adequacy, cigarette fires, and pilot health issues have been addressed (122). Presence of less fresh air in cabin was acknowledged, but there was more than enough oxygen for human consumption (134). The concentration of microorganisms in airline cabin air was found to be much lower than their concentration in ordinary city locations (292), concluding that the small number of microorganisms found in the U.S. airliner cabin environments does not contribute to the risk of disease transmission among passengers. In a 1997 study of Airbus aircraft (95), the number of particles in cabin air was compared with fresh air and re-circulated air. Also, microbiological contamination and volatile organic compound concentrations in cabins were investigated. The particles were found to be mainly emitted by passengers, especially smokers, and the recirculation air contained a lower or equal amount of particles compared to the fresh air, whereas the amount of bacteria exceeded reported concentrations within other indoor spaces. The detected microbes were mainly non-pathogenic, and the concentrations of volatile organic compounds were well below threshold values. Modern high efficiency particulate air (HEPA)-filters minimize an accumulation of bacteria and viruses within the recirculation flow of the cabin air, thereby significantly reducing the overall risk of getting infectious diseases, compared with other means of transportation (20). The issue of the flying fitness of patients with infections has been discussed (132). Cargo, as well as passenger, aircrafts have proven to be vectors of disease because they transport humans, mosquitoes, other insects, and animals (96). The occurrence of transmission of tuberculosis and influenza to other travelers has been reported, and vectors for yellow fever, malaria, and dengue have been identified on aircraft. However, studies of ventilation systems and patient outcomes suggest that the spread of pathogens occurs rarely during flights (169).

A review of reported air concentrations of organic compounds in cabins indicated that contaminant levels in aircraft cabins are similar to those in residential and office buildings (198). However, there were 2 exceptions. First, levels of ethanol and acetone—indicators of bio-effluents and chemicals from consumer products—were higher in aircraft than in home or office environments and in other transportation modes; second, levels of certain chlorinated hydrocarbons and fuel-related contaminants were higher in residential/office buildings than in aircraft. The levels of chemicals such as *m*- and/or *p*-xylenes tend to be lower in aircraft. Although cabin air is filtered prior to recirculation to remove volatile organic compounds and odor by using adsorbers, such devices may not be installed in all aircraft and may not be capable of removing all pollutants. Therefore, the photo-catalytic air filtering approach was developed, and it seems promising to resolve odor

problems in aircraft (127). The overall efficiency of the photo-catalytic unit is the function of the characteristics of compounds (toluene, ethanol, and acetone) that challenge the unit. Toluene was apparently found to be the most difficult compound to be oxidized. The photo-catalytic technique used by the tested prototype unit is able to partially oxidize volatile organic compounds, but one has to be aware that some toxic intermediate chemical reaction products such as formaldehyde and acetaldehyde are also produced during the oxidation process.

High concentrations of ozone can lead to upper respiratory problems and of CO_2 may cause hyperventilation (20). Additionally, the mucous membranes of the respiratory tract are dried out due to the extremely low humidity of the cabin air. In a 2000 study by Backman and Haghighat (9), high CO_2 concentrations and low humidity levels were found in the Airbus 320. The highest humidity level was determined in the DC-9; the lowest CO_2 concentration in the Boeing 767. The authors concluded that poor air quality may cause intolerance to contact lenses, dry eyes, and may be a health hazard to both passengers and crew members. In the U.S. Air Force C-5 cabin air, CO and CO_2 concentrations were found to be well below health effect threshold, relative humidity a lowest level of 3%, and ozone at relatively low concentrations (141). The influence of ozone on self-evaluation of symptoms in a simulated aircraft cabin indicated that the air quality and 12 of the symptoms, including eye and nasal irritation, lip and skin dryness, headache, dizziness, mental tension, and claustrophobia, were established to be significantly worse ($p < 0.05$) for the "ozone" condition, compared to the "no ozone" condition (265).

During intercontinental flights (180), CO_2 levels were below 1,000 ppm in 97% of the cases and humidity was very low (5%). Low humidity might conceivably be a factor for mucosal irritation experienced by travelers and flight attendants in aircraft cabins (178, 196, 280), and tobacco-smoking onboard might contribute to significant pollution from respirable dust (178, 180, 294). An investigation on the influence of air humidification on intercontinental flights on the perception of cabin air quality among airline crew concluded that relative humidity can be slightly increased by using a ceramic evaporation humidifier, without any measurable increase of microorganisms (181). The evaluation of the optimum balance between fresh air supply and humidity from 7-h exposures in a simulated aircraft cabin exhibited that increasing the relative humidity in the cabin to 28% by reducing outside flow to 1.4 $l \cdot s^{-1}$ 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, due to the increased level of contaminants (266).

The assessment of the contribution of secondhand smoke to aircraft cabin air pollution and flight attendants has been made relative to the general population and was determined that ventilation systems massively failed to control secondhand smoke air pollution in cabins (224). However, smoking is now prohibited by most airlines and air pollution caused by smoking is no longer a relevant issue. Additional studies further emphasize that the relative air humidity was very low on intercontinental flights, and particle levels were high on flights with passive smoking (179). These findings suggested the need for improving cabin air quality by better control of cabin temperature, air humidification, air filtration (HEPA filters), and sufficient air exchange rate on all aircraft types.

5.3 Space Vehicle Cabin Air

Astronauts work, sleep, and live in space vehicles (210), and there is a strong potential for the slow and insidious buildup of toxic substances—such as refrigerants, CO, HCN, CO_2, ammonia, and other organic compounds—in the space vehicle cabin atmosphere. Toxic substances could also be released rapidly in high concentrations. The sources of these substances could be from off-gassing, human metabolism, payload chemicals, and thermal degradation of materials. Therefore, the protection of the astronauts' health and the prevention in their performance decrements are crucial. A major concern in the space cabin is the establishment of maximum allowable concentrations of potentially toxic substances. Such establishment should be based upon the facts that astronauts live in a closed environment of space vehicles 24 h a day, for weeks or even months, in comparison to an 8-h working shift on the Earth. Contracting microbes in the space cabin is of concern since crew members would release many bacteria into the environment, and their droplets in microgravity remain suspended in the atmosphere, thus making their exposures more likely. How microgravity affects the immune system of humans has not been well-established. Therefore, the monitoring of microorganisms and toxic substances is crucial in the space vehicle cabin atmosphere. Methods and means of qualitative and quantitative air monitoring on the International Space Station are sufficient for air control in emergency situations such as local fire and toxic leak. Also, the Station's air quality has suited to the adopted standards and crew safety requirements. However, there is a need to improve the space cabin air monitoring (208).

In the area of monitoring, the development of mass spectrometry instrumentation to support the goals of the U.S. space program (209) has taken place for studying the

composition of planetary atmospheres and monitoring air quality on manned space missions. The mass spectrometry instruments deployed on the Pioneer Venus and the Mars Viking Lander missions have been reviewed for illustrating the unique features of the sample introduction systems, mass analyzers, and vacuum systems, and for presenting their specifications. Various approaches for monitoring volatile organic compounds in cabin atmospheres were also reviewed. Previously, ground-based gas chromatography-mass spectrometry instruments have been used to identify and quantify volatile organic compounds in archival samples collected during the Mercury, Apollo, Skylab, Space Shuttle, and Mir missions. The development of direct sampling ion trap mass spectrometry and gas chromatography-ion mobility spectrometry has been discussed to illustrate their potential utility for future missions. A miniature electronic nose has been designed and built at the Jet Propulsion Laboratory (Pasadena, CA) to detect, identify, and quantify 10 common contaminants and relative humidity changes (232). The sensing array included 32 sensing films composed of polymer carbon-black composites. Event identification and quantification were done using the Levenberg-Marquart nonlinear least squares method. This electronic nose was used in a demonstration experiment aboard STS-95 (October-November, 1998) (277), in which the electronic nose was operated continuously for 6 d and recorded the responses of the sensors to the air in the mid-deck. Air samples were collected daily and analyzed independently after the flight. Changes in shuttle-cabin humidity were detected and quantified by the electronic nose. This device was found to be microgravity-insensitive.

5.4 Aircraft Engine Oils, Hydraulic Fluids, and Lubricants

Many incidents of smoke/fumes in aircraft cabins have been linked to contamination of cabin air with pyrolytic products of jet engine oils, hydraulic fluids, and/or lubricants by leaking into ventilation air (84, 235, 281, 283). These leaks can be subjected to 500°C or higher temperatures. If the origin of the smoke/fumes is of organic petroleum derivatives, then the smoke/fumes may cause a multitude of symptoms, including central nervous system dysfunction and mucous membrane irritation. There is a threat to safety posed by the many fluids and substances necessary for the operation of modern aircraft (222). Smoke/fume-related incidents could have been caused by broken seals in the engine and/or other associated systems, allowing these engine agents to enter the air compressor section and, then, contaminate the cabin air. To prevent such products from entering the cabin air, catalytic converters have been used to clean the air (282), but during an oil seal failure, the converters become overloaded, and smoke could be observed in the cabin. In some aircraft, the catalytic converters have been removed, with a claim that it improves cabin air quality. However, if the cabin air is contaminated, the flight crew is potentially exposed to the thermal breakdown products of the engine agents, causing the performance of the crew members to be impaired. Symptoms, like dizziness, nausea, disorientation, blurred vision, and tingling in legs and arms, have frequently been reported by flight crews. The reported symptoms are most consistent with exposures to CO and pyrolytic 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 (281). In this 1999 study (281), to rule out the possible exposure to toxic elements, like lead, mercury, and thallium, a multi-elemental analysis was performed on 2 hydraulic fluids and 3 lubricating oils that have been implicated in a number of air quality incidents. No significant concentrations of the toxic elements were found in any of the oils or hydraulic fluids.

In mid-1981, several accidents involving turboprop aircraft occurred. It was believed that those accidents resulted from pilot incapacitation from toxic fumes introduced through the cabin pressurization system (235). Therefore, the thermal (300–600°C) decomposition products from aircraft petroleum-based engine and synthetic lubricating oils were evaluated for their toxicity in rats (84). The animals were exposed to smoke from these products, and relative toxicity was evaluated in terms of t_i and t_d. The CO concentrations in smoke were measured. Based on this information, in conjunction with the animal response times, it was concluded that the decomposition of these oils did not produce any chemical species, other than CO, in quantities sufficient to contribute to the total toxicity.

Since bleed air is diverted from a location just prior to the engine combustion chamber at a temperature around 500°C and very little is known regarding the thermal breakdown products of jet engine lubrication oils, 2 commercially available oils were investigated under laboratory conditions at 525°C to measure the release of CO, CO_2, nitrogen dioxide, HCN, and volatiles (282). The volatiles were analyzed by gas chromatography-mass spectrometry to establish if the neurotoxic agents, tricresyl phosphates (TCPs) and trimethyl propane phosphate (TMPP), were present or formed in the release. Although some CO_2 was generated, along with CO (> 100 ppm), nitrogen dioxide and HCN were not detected under the analytical conditions. The presence of TCPs was confirmed in the bulk oils and in the volatiles, but TMPP was not found in these experiments. Localized condensation in the ventilation ducts and filters in the air conditioning

packs are likely the reasons for the absence of TCPs in cabin air. However, the possibility of the release of pyrolysis products cannot be ruled out from the localized condensates in the ducts at the time of high demand of cabin heat, leading to mid-flight incidents (283).

The United Kingdom's Civil Aviation Authority (33) conducted an extensive study on cabin air quality involving oils and fluids. This study examined and analyzed 2 contaminated cabin air supply ducts for the presence of chemical constituents and degradation products of engine oils, hydraulic fluids, and lubricants. These ducts were removed from 2 aircraft, wherein the inner surface of the ducts was found to be coated with black particulate material. Microscopic examination of this carbonaceous material determined that it was rich in various elements, such as aluminum, silicon, sulfur, and phosphorous. These black material deposits can be easily dislodged by gentle pressure. Thus, the material could potentially become part of the cabin and flight deck environment as solid aerosols. The gas chromatographic-mass spectrometric analyses of the airflow samples of the contaminated ducts suggested the presence of various short chain irritants, such as carboxylic acids, aldehydes, and ketones. Analyses of the solvent extracts of the carbonaceous material further indicated the presence of additional high molecular weight chemicals—for example, TCPs, TMPP, trimethylolpropane phosphates, and other associated esters—of relatively low volatility. It appeared that these molecules might have been tightly integrated to the carbonaceous material, suggesting that not all of the chemicals adsorbed onto the carbonaceous material could be desorbed by airflow.

It is true that the airflow samples did not contain all the chemicals present in the black solid coating of the ducts, but it does not necessarily mean that only those chemicals found in the airflow samples are responsible for the observed toxicological effects. Other chemical entities adsorbed onto the solid material could also contribute to the toxicity, if the solid material particles become part of the air. There is a strong potential for this type of situation, because the black particulate material present in the ducts can easily be dislodged by applying gentle pressure. The dislodging could also take place at times of high demand of cabin heat and/or by physical disturbances and/or stresses occurring during flights, particularly during taking off and landing. The ease of dislodging of particulate matter would also be dependent upon the amount of the solid matter coated inside the ducts—larger the size of the deposits, easier the dislodging of the deposits as the carbonaceous material particles would be loosely bound in the larger deposits. Hence, those solid particles could easily become part of the cabin and flight deck environment as solid aerosols.

In such scenarios, if the cabin and flight deck occupants inhale those particles, they would be exposed to all the chemicals and associated entities present in the airflow from the ducts, as well as in the solid deposits of the ducts. This exposure to the mixture of chemicals would cause a spectrum of adverse effects—for example, ocular and upper respiratory irritation, nausea, vomiting, dizziness, pulmonary toxicity, and even delayed adverse effects. In this way, the solid particles would actually be more effective in producing localized adverse effects. The nature and extent of such effects would, of course, be dependent upon the types and amounts of chemicals present in the air and the duration and frequency of such exposures, and these parameters would vary from flight to flight. Therefore, the whole episode is a complex set of events. Also, it is not so simple to adjudicate and predict the toxicity caused by the constituents and the pyrolytic products of engine oil, hydraulic fluids, and lubricants.

In the Civil Aviation Authority study (33), the smell of the airflow samples was subjectively characterized for the odor. This qualitative approach reconfirmed that the odor originated from the carbonaceous material. However, as discussed in the report, the interrelationship cannot be established between the odor and the toxicity of a chemical. For example, some chemicals produce odor at very low concentrations without causing toxicity, whereas some chemicals have no odor but are extremely toxic. Toxicity of the various substances found in the carbonaceous material is described and discussed in detail with sufficient relevant scientific references. However, it appears from the report that the described toxicity is the toxicity exhibited by individual chemical entities. The resultant of the toxicity of all of the chemicals present in the black solid material is not clearly evident. This aspect is of particular importance, as aircraft travelers would potentially be exposed to chemicals, not a single chemical, from the black material. It is well established that the toxicity of individual substances differ from their mixture(s). Such difference would be because of the interactive effects of chemicals present in the mixture(s). Thus, the overall toxicity would be the result of additive, potentiation, synergistic, and/or antagonistic type of interaction(s) among chemicals present in the mixtures in relation to the toxic effects exerted by the individual components of the chemical mixtures (106). In other words, the chemicals found in the carbonaceous material may not necessarily be individually toxic at the found concentrations, but if they are mixed together at those concentrations, the mixture might be highly toxic. Interaction of chemicals would also play a crucial role in exhibiting characteristic odor, which may not necessarily be consistent with the odor exhibited by an individual chemical itself. The issue of the interaction of chemicals in regard to the toxicity of

mixtures has apparently not been fully addressed or emphasized in the report. Because of the complexity, the best approach to resolve this toxicological and aviation safety issue would be preventive (33)—that is, to minimize oil leaks into bleed air and to monitor, clean, and/or replace air ducts. The toxicity of the oil additives that are used in aircraft engines should also be revisited (202).

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