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Airliner Cabin Ozone: An Updated Review

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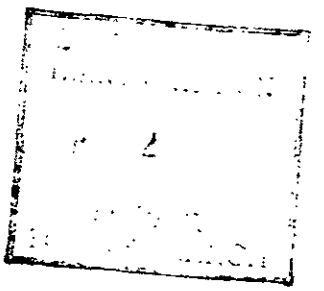

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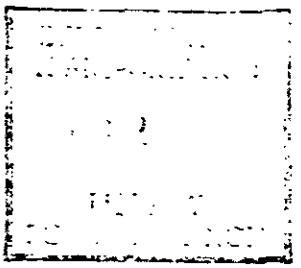

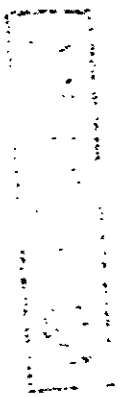

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16. Abstract

The recent literature pertaining to ozone contamination of airliner cabins is reviewed. Measurements in airliner cabins without filters showed that ozone levels were about 50 percent of atmospheric ozone. Filters were about 90 percent effective in destroying ozone.

Ozone (0.12 to 0.14 ppmv) caused mild subjective respiratory irritation in exercising men, but 0.20 to 0.30 ppmv did not have adverse effects on patients with chronic heart or lung disease. Ozone (1.0 to 2.0 ppmv) decreased survival time of influenza-infected rats and mice and suppressed the capacity of lung macrophages to destroy Listeria. Airway responses to ozone are divided into an early parasympathetically mediated bronchoconstrictive phase and a later histamine-mediated congestive phase.

Evidence indicates that intracellular free radicals are responsible for ozone damage and that the damage may be spread to other cells by toxic intermediate products: Antioxidants provide some protection to cells *in vitro* from ozone but dietary intake of antioxidant vitamins by humans has only a weak effect, if any.

This review indicates that earlier findings regarding ozone toxicity do not need to be corrected. Compliance with existing FAA ozone standards appears to provide adequate protection to aircrews and passengers.

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INTRODUCTION

Prior to 1980, there was a great deal of concern about the adverse effects of ozone on the health and well-being of crewmembers and passengers in high altitude jet aircraft. These concerns had their origin in complaints, primarily from flight attendants, consisting of a constellation of symptoms including sore throat, cough, substernal pain on exertion, headache, fatigue and eye irritation. Subsequent investigations by the FAA and others led to the conclusion that ambient air ozone, compressed into the cabin air, caused physical discomfort (1). Laboratory investigations confirmed and extended conclusions already in the literature that sea level concentrations of ozone below 0.3 parts per million by volume (ppmv) were innocuous for normal people in that significant effects of such exposures did not outlast the exposure period (2,3). A later review of the literature led to the conclusion that a short-term innocuous dose of ozone (concentration x time of exposure) was also innocuous over the long term (4). It was further concluded that concentration is more important than is duration of exposure in determining the toxicity of a dose of ozone.

RESULTS AND DISCUSSION

The Federal Aviation Administration responded to these findings with rulemaking that required cabin ozone levels during flight above 18,000 feet mean sea level be maintained at or below 0.25 ppmv (sea level equivalent) at all times and that the time-weighted average not exceed 0.1 ppmv during any 3 hour (h) interval (5,6). Aircraft manufacturers and airline operators responded to the rule with various strategies for mitigating cabin ozone contamination, among which were the installation of catalytic filters to destroy ozone in the cabin air delivery system and by flight planning to avoid known areas of high atmospheric ozone concentration.

Since the final rule was published in 1980, few reports have appeared in the literature specifically related to airliner cabin ozone contamination. However, reports abound on the health effects of ozone and on anthropogenic factors in the depletion of stratospheric ozone. Most of these reports respond to concerns about urban air pollution from combustion of hydrocarbon fuels and from fears of excessive solar radiation at the earth's surface consequent to depletion of the stratospheric ozone layer. The data in these reports are, nonetheless, somewhat relevant to airliner cabin ozone contamination as the effects of ozone on the health of people are the same, regardless of its source.

While the rule may have stilled most expressions of concern about cabin ozone, not much research has been reported as yet to tell how effective ozone scrubbing in airliner cabin air really is. The National Research Council's Committee on Airliner Cabin Air Quality has recommended that the FAA establish policies for periodic removal and testing of ozone-scrubbing catalytic filters to establish the effective life of these units (7). The committee further recommended that a program of on-board, in-flight monitoring be established so that compliance with the rule could be assured. The FAA has responded by contracting with a private research organization to carry out extensive monitoring of cabin ozone concentrations during commercial airline flights.

To review briefly for perspective, upper air ozone is one product in a complex cycle of photochemical reactions (8). Ozone is formed from biatomic oxygen acted upon by solar ultraviolet radiation with a wavelength of less than 242 nm, thus:

1. $O_2 + hv \text{ ------> } 0 + 0$

In the high atmosphere:

2. $0 + O_2 + M \text{ ------> } O_3 + M$

Where M is any body, most commonly nitrogen.

3. $O_3 + hv \text{ ------> } O_2 + 0^*$

Where 0* is an electronically excited oxygen atom that can enter into a destructive reaction with ozone, thus:

4. $O_3 + 0^* \text{ ------> } 2\ O_2$

This latter reaction destroys about 20 percent of the ozone continuously formed in reaction 2. The "hydrogen system" destroys another 10 percent of the ozone formed in 2, thus:

5. $H_20 + 0^* \text{ ------> } 2\ HO$

The following reactions are more important at altitudes above 40,000 meters (>130,000 feet) than at lower altitudes:

6. $HO + O_3 \text{ ------> } HO_2 + O_2$

$HO_2 + 0$ ------> $OH + O_2$

Thus, converting one ozone molecule and one atom of oxygen into two molecules of biatomic oxygen. The catalyst, OH, is renewed to re-enter the reaction with O_3 formed in 2. OH radicals can also appear in the stratosphere from upwardly-diffusing methane formed by ground generators such as marshes and swamps and react thus:

7. $CH_4 + 0^*$ ------> $CH_3 + OH$

The perhydroxyl radical (HO_2) formed in 6, above, reacts with OH to produce water, which can drift down into the lower atmosphere.

8. $OH + HO_2$ ------> $H_20 + O_2$

The "Nitrogen System" is principally responsible for maintaining ozone balance in the stratosphere and consists mainly of N_20 released at the earth's surface by micro-organisms in the oceans and soil, which diffuse into the stratosphere where reactions with UV and O occur, thus:

9. $N_20 + 0^*$ ------> 2 NO

$NO_2 + hv$ ------> $NO + 0$

Nitric oxide, NO, breaks down ozone, thus:

10. $NO + O_3$ ------> $NO_2 + O_2$

$H02 + O_2$ ------> $NO + 2\ O_2$

transforming ozone into biatomic oxygen. Finally, NO_2 is removed:

11. $OH + NO_2 + M$ ------> $HNO_3 + M$

Nitric acid is washed out of the upper atmosphere and is the major sink of the cyclic system. Almost 60 percent of the ozone formed is destroyed in this way. NO_2 in the upper atmosphere is increased by the use of nitrogen fertilizers and acid rain, which enhance release of NO_2 at the earth's surface. NO is formed at temperatures above 2000 degrees Centigrade in nuclear explosions and in jet engines.

12. $O_2 + M \text{ ------> } O + O + M$

$O + N_2 \text{ ------> } N + NO$

The remainder of the ozone formed from O_2 is destroyed by other systems, such as chlorine, sulfur, and man-made products--mainly chlorofluoromethanes and carbon tetrachloride (natural and man-made). The consensus is that the sum of destructive reactions presently exceeds synthetic ones so that stratospheric ozone levels are falling. Of course, all other constituents of the ozone cycle are also compressed into airliner cabin air, though their contributions as contaminants have apparently not been reported and are probably negligible.

Ozone levels naturally vary with latitude, altitude, and season of the year. Ozone concentration seems to be maximal in the atmosphere between 20,000 and 90,000 feet, the so-called ozone layer; present-day airliners normally operate in the lower to middle part of this layer (9).

Ozone levels have been measured in cabin air in a few instances. Brabets (10) reported that many (unspecified number) passengers on commercial jet airliners stated that the odor of ozone was detectable at flight altitudes of 30,000 to 40,000 feet. Ozone measurements were made during 285 flights covering the 48 contiguous states and Alaska and five flights from California to Hawaii. Concentrations ranging from 0.01 to 0.40 ppmv were found on half of the flights with the highest level occurring on a flight from Anchorage to New York. No differences were found, on the average, between cabin and cockpit ozone levels, although cabin values fluctuated less than the cockpit values because of the larger cabin volume.

Briehl and Perkins (11) simultaneously measured outside air and cabin air ozone in a Gates Learjet at altitudes up to 42,500 feet on six flights in February 1978. Peak concentration was 0.41 ppmv and cabin ozone decreased in proportion to the number of passengers, amount of luggage, etc. in the cabin. Ozone concentration near the cabin air vents was only slightly reduced from the outside air ozone concentration. Cabin air levels followed but lagged behind atmospheric ozone by about 54 seconds; therefore, it was difficult to know the cabin ozone retention value when atmospheric ozone was changing rapidly. Generally, cabin ozone levels were about 50 percent (47 to 60 percent) of atmospheric levels. The maximum atmospheric ozone level encountered was 0.89 ppmv.

Holdeman and Nastrom (12) and Perkins Holdeman and Nastrom (13) have reported results from the Global Air Sampling Program (GASP) of

simultaneous cabin and ambient ozone concentrations in two Boeing 747 aircraft in commercial service. Ambient levels were measured by an outside probe located near the nose of the aircraft; the cabin probe was located in the forward compartment on the outside wall of the circular staircase. The GASP system was completely automated and data were recorded on magnetic tape every 5 minutes. When the cabin air of the B-747 SP had not been passed through an activated charcoal filter, the retention ratio was 82.5 percent, whereas passage of the air through a charcoal filter resulted in about a ten-fold reduction in the cabin ozone level.

Rogers (1) has reported the results of an on-board ozone monitoring program on commercial airline flights. On 16 of 98 flights at latitudes greater than 37.5 degrees north and at flight levels at or above 35,000 feet, cabin ozone levels and time-weighted averages later established by the rule were exceeded.

The U. S. Air Force uses the C-9 (DC-9) aircraft for aeromedical transport. On four flights of less than 4 hours' duration, cabin ozone levels were monitored. Only once did the level (0.344 ppmv) exceed allowable amounts of ozone established by the rule (14).

With regard to "ozone sickness," there is such a plethora of papers published in the last few years reconfirming that ozone causes lung and airway damage, that one is left to wonder why it is necessary to do, or publish, further work in this area.

Exposure to high levels (unspecified) of ozone in an electric motor factory was claimed to have caused eye and respiratory tract irritation, headache, fever, chills, dizziness, nausea, vomiting, general malaise and weakness, radiographic abnormalities of the lung, reduction of ventilatory function, and blood gas abnormalities (15). In aluminum arc welders exposed to more than 1.05 ppmv ozone, Ohmori et al. (16) described alterations in ventilatory function consisting of reductions in maximum expiratory flow at 25 percent of vital capacity. Those who had worked four years or more were more compromised than were workers who had been in the trade for shorter lengths of time. Rats exposed to 0.95 ppmv ozone, 8 hours per day (h/d) for 90 d, exhibited lung damage consisting of reduced intermediate bronchiolar diameter (17). Impedance of lungs of rats exposed to 0.64 ppmv ozone for 7 d reportedly changed toward decreased reactance at higher frequencies, which was interpreted to mean increased peripheral resistance of the lung (18).

Several papers deal with the exacerbating effects of exercise on the pulmonary response to ozone exposure (19-26), all showing the well-known complement of symptoms consisting of reduced tolerance to exercise and compromise of pulmonary function at somewhat lower levels than was previously thought to be effective. Mild respiratory irritation was found in the whole group of heavily exercising healthy young men at 0.16 ppmv ozone; two men showed subjective responses at 0.14 ppmv and one of those two showed responses at 0.12 ppmv. Objective spirometric data, however, failed to show effects (24). Another study (25) showed on six groups of exercising healthy young men that forced expiratory spirometric variables were adversely affected by 0.12, 0.18 and 0.24 ppmv. Coughing was observed in all subjects. In yet another study (26) ten trained athletes, in conditions simulating competitive exercise, were exposed to 0.12, 0.18 and 0.24 ppmv ozone and to filtered air. One, five, and seven subjects, respectively, did not complete the exercise protocol, whereas all completed the protocol in filtered air. These studies led to the concept of the "effective dose"- the product of ozone concentration, time of exposure and minute ventilatory volume ($\dot{V}e$) (19). These authors emphasize, as was pointed out in 1980 (4), that ozone concentration is the predominant factor in determining the effective dose.

These latter studies indicate that ozone can cause symptoms and objectively-determined compromise of pulmonary function in heavily exercising people at levels well below current Environmental Protection Agency and FAA standards. More stringent urban air ozone standards have been urged (27).

Four studies were found that examined the effects of ozone on disease processes (28-31). In human beings, the general finding was that ozone (0.25 ppm) had no significant effect on exercising people with chronic obstructive pulmonary disease (28) or in selected patients with heart disease exposed to 0.20 to 0.30 ppmv (29). In mice infected with influenza and exposed to 1.0 ppmv ozone for 1, 2, 3, 4, or 5 days for 3 h/d, there was a twofold increase in mortality and a 3 d decrease in survival time after the second day of exposure (30). Van Louveren, et al. (31) exposed rats infected with Listeria monocytogenes to 0.25 or 2.0 ppmv ozone for one week. Ozone was found to suppress the capacity of lung macrophages to ingest and destroy Listeria; further, ozone had a suppressive effect on the development of cellular immune responses to Listeria, i.e., T-cell-dependent immunity.

Ozone still has not been shown convincingly to have any primary extrapulmonary effects. Gliner et al. (32) failed to show an effect of ozone (0.75 ppmv) on the human EEG.

Many papers have appeared in the recent literature regarding the site and mechanism of oxidant-induced damage. An interesting feature of some of these studies is the involvement of the parasympathetic nervous system in the early response of the airway to ozone. Gertner et al. (33, 34) studied the resistance in dogs' peripheral lung by way of a bronchoscope wedged in a segmental airway. Exposure of the lung segment to 1.0 ppmv ozone caused an increase in resistance of the lung collateral system (Rcs) in 2 min, which was prevented by bilateral vagotomy. Vagotomy, however, did not prevent a later increase in Rcs that was reduced by chlorpheniramine. There was no development of adaptation or tolerance to 1.0 ppmv as had been shown to occur with 0.1 ppmv. These workers interpreted their findings to mean that the early bronchoconstrictive response was mediated by the parasympathetics and the later congestive response by histamine. These investigators later showed that the lung response to histamine aerosols was increased by 1.0 ppmv ozone. Jones and associates (35) took strips of trachealis muscle from dogs that had shown hyper-responsiveness to ozone. The strips were studied *in vitro* for responsiveness to electric field stimulation, acetylcholine and potassium chloride. Excitatory junction potentials were measured with microelectrodes to determine if inhaled ozone affects acetylcholine release from parasympathetic nerve endings. Provocative doses of acetylcholine dropped from 4.11 mg/ml without ozone to 0.66 mg/ml with ozone. Electric field responsiveness was increased but not so with potassium chloride. The authors suggest that a postjunctional alteration in trachealis smooth muscle results from ozone exposure and accounts for subsequent airway hyper-responsiveness. Barry and associates (36) showed morphometrically that terminal bronchioles of the rat were particularly susceptible to low levels of ozone (0.25 ppmv), producing 20 to 30 percent loss of cilia; luminal surfaces of Clara cells were reduced by 16 to 25 percent. Dubick et al. (37) showed that young monkeys exposed to 0.25 ppmv ozone for 8 h/d on alternate months had significantly increased lung collagen content, chest wall compliance, and inspiratory capacity. All had bronchiolitis.

In human subjects, bronchioalveolar lavage of lungs of young men exposed earlier for 2 h to 0.4 ppmv ozone showed an 8.2-fold increase in percentage of polymorphonuclear leucocytes, with a small decrease in percentage of macrophages (38). Immunoreactive neutrophil elastase, often associated with inflammation and lung damage, increased 3.8-fold in the lavaged fluid and 20.6-fold in lavaged cells. Increased vascular

permeability of the lung was suggested by a 2-fold increase in albumin and IgG. Fibronectin 6 increased 6.4-fold and Factor VII increased 2.1-fold; both are coagulation factors. Urokinase plasminogen activator increased by 3.6-fold. The authors conclude that a fairly brief exposure to ozone (0.4 ppmv) with light exercise results in increases of several factors related to lung damage.

The damaging effects of ozone are well-known. The mechanism of such damage is, to some extent, speculative but undoubtedly involves the intracellular production of free radicals - defined as any species that contains one or more unpaired electrons (39). Examples of free radicals are the superoxide (O^{-2}) and hydroxyl (OH^{-}) radicals resulting from hyperoxia that participate in lung damage and a host of other conditions (40). Ozone is not a free radical nor does it form a free radical when it breaks down into biatomic oxygen molecule and an oxygen singlet; that is, neither ozone nor singlet oxygen is a partially reduced oxygen product because these species are at the same oxidation level as elemental oxygen (41). However, singlet oxygen is a highly reactive species and can produce free radicals that can have severe consequences as far as cellular metabolism is concerned. The superoxide radical is naturally produced when electrons from the electron transport system react with oxygen. This free radical, however, is quickly dismuted by enzymically active metalloproteins known as superoxide dismutases (SOD's) - Cu- , Zn- or Mn-containing enzymes specific to the purpose: to produce hydrogen peroxide, which is just as quickly broken down by catalase or peroxidase to water and biatomic oxygen. Because superoxide itself is a very short-lived species, SOD activity has been accepted as a reliable indicator of superoxide activity.

Dubick and associates (42) hypothesized that ozone acts as an oxidant stress that is exacerbated by Cu, Zn or Mn deficiency, which is expressed as impaired SOD activity; the implication being that ozone, upon breakdown, yields superoxide as an intermediate product which, in the absence of these metal ions, persists long enough to lead to cellular damage or death. Calabrese et al. (43) point to methyl oleate ozonide as an aberrant intermediate oxidative product of lipid metabolism caused by ozone-produced free radicals *in vitro*.

Intracellular free radicals have a variety of disruptive effects including the destruction of lysosomal membranes, thus liberating destructive enzymes into the cytosol, disrupting mitochondrial and endoplasmic reticular membranes, and destroying cytoskeletal tubules (44). In rat lung Type II cells exposed to ozone *in vitro*, surfactant production, as indicated by phosphatidylcholin synthesis, was reduced (45). Exposure of human

Type II pneumocytes to ozone *in vitro* caused an increase in the mitochondrial component of superoxide dismutase; electron microscopy, however, failed to reveal that cell membranes were damaged (46). Ozone *in vitro* increased the ability of human lung alveolar macrophages to secrete chemotactic agents that stimulate the migration of peripheral blood neutrophils and monocytes, implying that these macrophages play a role in recruiting of leucocytes in response to lung injury by ozone (47).

Cell membrane tryptophane is responsible for cell membrane native fluorescence. Ozone levels *in vitro* that cause a 50 to 75 p.rcent loss of fluorescence result in about a 10 percent decline in tryptophane, suggesting that ozone has a predilection for this hydrophilic amino acid. The authors claim that the red cell membrane is a primary site of ozone toxicity, as demonstrated by lipid peroxidation, increased osmotic fragility and loss of cell membrane acetylcholine esterase (48). It is suggested that ozone contributes to the development of emphysema by inactivation of alpha 1-proteinase inhibitor (49). Airway epithelium of the dog apparently releases a factor that promotes relaxation of trachealis smooth muscle. Hyper-responsiveness to ozone of dog airway smooth muscle was not accompanied by decreased quantities of this factor (50). It was shown that exposing rats lungs to 2.0 ppmv ozone *in vitro* led to an increased release of short chain fatty acids, indicating that ozone cau[illegible] destruction of cellular lipids (51). Several papers indicate that toxic peroxidation intermediates caused by ozone damage adversely affect adjacent cells (39). How far this spreading toxicity is effective is apparently not known. It was shown that a stream of ozone-containing air caused peroxidation of arachidonic acid; such peroxides had biological activity similar to prostaglandin endoperoxides, in that they caused contraction of smooth muscle strips and caused platelet aggregation. The effects were not inhibited by alpha tocopherol (52). It has been suggested that thyroxine may enhance ozone toxicity, in that erythrocytes *in vitro* show increased cation permeability when the hormone is added during ozone exposure (53).

CONCLUSIONS

The above studies, mainly *in vitro*, show that ozone causes a broad spectrum of nonspecific damage to cells and that the damage may be spread by toxic oxidative intermediate breakdown products. Although there is some dispute about whether ozone itself destroys cell membranes by lipid peroxidation or whether such destruction is secondary to intracellular free radical production, the end result is the same. Release of metallic ions from intracellular storage sites, peroxidation of lipids and proteins, destruction of cytoskeleton and DNA damage are all included in the repertoire of ozone effects. Yet, in spite of much work showing damage

to erythrocytes *in vitro*, there is still no compelling evidence that ozone affects extrapulmonary systems *in vivo*. It is simply too fragile, or reactive, a molecule to be transported in the blood or even, perhaps, to reach the blood in pulmonary vessels.

Regarding ozone-protective measures, it is claimed that cell lipids can be protected, at least to some extent, from peroxidation by the essential nutrients alpha tocopherol, ascorbic acid and beta carotene. All of these vitamins scavenge free radicals and singlet oxygen (54). Vitamin E supplementation was shown to protect erythrocytes *in vitro* from ozone-induced damage (55). Similarly, para-aminobenzoic acid (PABA), para-aminohippuric acid and anthranillic acid were shown to protect erythrocytes *in vitro* from damage by 40 (!) ppmv ozone. PABA-injected rats were protected *in vivo* from 15 ppmv ozone (56). Inhalation of albuterol, a bronchodilating agent, had no protective effect in athletes exposed to 0.21 ppmv ozone (57). Vitamin E supplementation did not protect human subjects from the respiratory effects of a 2 h exposure to 0.5 ppmv ozone (58). Exposure of conscious guinea pigs to 3.5 ppmv ozone for 30 min rendered their lower airway, but not their upper airway, more sensitive to intravenous. histamine administered under anesthesia; vagotomy had no effect on the response (59). Indomethacin, a prostaglandin synthetase inhibitor, significantly improved forced vital capacity and 1 sec forced expiratory volume in exercising healthy human subjects exposed to ozone. The findings suggest that cyclooxygenase products of arachidonic acid that play a prominent role in ozone-induced pulmonary decrements are sensitive to indomethacin inhibition (60).

Agents that are claimed to protect against ozone seem to be either ineffective or only weakly effective in humans. Dietary content of free radical scavengers likewise does not seem to have a marked effect on ozone toxicity *in vivo*. As pointed out earlier, responses to ozone appear to be divided into an early bronchoconstrictive phase that is parasympathetically mediated and a late phase that is histamine mediated. It would probably be profitable, or at least informative, to explore further the effectiveness of parasympatholytic agents and antihistamines on airway responses to ozone.

One persistently peculiar aspect of the pulmonary response to ozone is "adaptation," i.e., an attenuated response upon repeated or prolonged exposure to ozone (61). Such adaptation can be demonstrated at the cellular level *in vitro* (62) as well as in intact animals and humans (61, 63). Adaptation in humans appears to last only 4 to 5 d after cessation of ozone exposure (63). It has been suggested that the pulmonary irritation in response to ozone is reversible after about a week of exposure to ozone,

presumably by such defensive mechanisms as increased mucus secretion, epithelial mitosis, and enzyme induction (64). Because the inflammatory responses in the airway are considered to be, in some measure, protective, it has been questioned whether or not adaptation is a good thing (65).

RECOMMENDATIONS

In brief, this review/update does not reveal that earlier findings need to be corrected, except that, in a few experiments, subjective responses (respiratory irritation) in heavily exercising humans have been shown at levels of ozone as low as 0.12 ppm. There is, however, no strong evidence pointing to the need for review or revision of existing FAA ozone standards. The implication of a neurological component in the early response to ozone is interesting and significant and should be investigated further.

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