EXPERT REPORT OF

RICHARD A. PARENT, PHD, DABT, FATS, RAC, ERT

IN THE MATTER OF

[redacted]

VS.

[redacted] INC.

IN THE

U. S. DISTRICT COURT [redacted]

[redacted]

CASE NO: [redacted]

CONSULTOX, LIMITED

DAMARISCOTTA, MAINE

MAY 30, 2013

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QUALIFICATIONS

I, Richard A. Parent, PhD, DABT, FATS, RAC, ERT, am a board certified toxicologist with over 12 years' experience in the field of industrial toxicology and an additional 27 years' experience in litigation support for both the plaintiff and defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984, I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in a variety of products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as the defense. I am board certified by the American Board of Toxicology, the Academy of Toxicological Sciences, and the Regulatory Affairs Professional Society. I am a recognized expert in toxicology in France and the European Community. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Appendix A, cited literature references in Appendix B, and a list of past testimony in Appendix C

MATERIALS REVIEWED

- Air Quality Testing by Air Quality Research from December 11, 2008, to June 9, 2009
- State of Alaska H&SS Public Notice; Bulletin No. 36 "Ozone Generators-Warning - Not for Occupied Spaces; September 8, 1997
- Handwritten ozone monitoring data from January 2009 and supplied to me on a CD
- CPSC Health Sciences Staff Report from contract # CPSC-S-04-1369 entitled "Assessing Potential Health Effects and Establishing Ozone Exposure Limits for Ozone-Generating Air Cleaners", dated September 26, 2006, draft by Richard Shaughnessy, PhD
- CPSC "An Update on Formaldehyde", US Consumer Product Safety Commission, Washington, DC, 1997 Revision
- Home Advice Report by [redacted] Company; test period February 11 - February 17, 2009, prepared by [redacted]

$ Doc Air "Indoor Air Quality (IAQ) and Building Systems Evaluation Report Including Proposal for Building Performance Improvements - Bearden [redacted]", November 6, 2008, by [redacted] CIH

- Honeywell Owners Guide, F50F and F300E Electronic Air Cleaners
- "Indoor Air Chemistry: Cleaning Agents, Ozone and Toxic Air Contaminants", Final Report: Contract No 01-336; prepared for the California Air Resources Board by WW Nazaroff , *et al.*, April 2006

- California Air Resources Board (CARB) news release: California Cleans Up Indoor Air Cleaners; September 27, 2007
- Letter from Dr. [redacted] to Mr. and Mrs. Bearden from Metro Public Health Department, Nashville, Tennessee, August 14, 2009
- Research Highlight, "Influence of an Electronic Air Cleaner on Indoor Ozone" by CMHC/SCHL Canada dated July 2003; CMHC Research Highlight 99-108
- Hazardous Substance Databank File on Ozone, National Library of Medicine, Bethesda MD, June 22, 2011
- CAL EPA Air Resources Board, "Ozone and Health" dated August 24, 2005
- Ozone testing in [redacted] house with Ozone Monitor Model 202
- Deposition of [redacted] taken on February 22, 2011, prepared by [redacted] and conducted by CC Dickson Co.
- Medical Records of [redacted] from January 10, 2008, to January 24, 2011
- Deposition [redacted] taken on February 21, 2011
- Numerous peer-reviewed publications describing the toxic effects of ozone and ozone reaction products within the house environment
- U.S. Environmental Protection Agency (US EPA). 1995. Ozone Generators in Indoor Air Settings. Report prepared for the Office of Research and Development by Raymond Steiber. National Risk Management Research Laboratory. US EPA. Research Triangle Park. EPA-600/R-95-154
    - "Ozone Generators that are Sold as Air Cleaners", Indoor Air Quality Document, US EPA, September 30, 2010; [http://www.epa.gov/iaq/pubs/ozonegen.html]

INTRODUCTION

It is my understanding that [redacted] moved into their house located at [redacted], on or about May 7, 2008, and that within days a previously healthy Mrs. [redacted] began feeling ill with chest tightness and coughing. In addition, she developed upper respiratory irritation, sinus problems, non-productive cough, chronic bronchitis, and a sensitivity to odors. Her symptoms continued through the summer, and in early November her throat, eyes, and sinuses began to burn. Her physician, Dr. [redacted] suggested that her symptoms may be related to ozone exposure or toxic volatile materials such as formaldehyde or other aldehydes produced by reaction with ozone.

It should be noted that prior to residing at [redacted] Mrs. [redacted] did not have any respiratory problems of which I am aware. There were, however, two incidences which preceded her ozone problems, but these occurred years before. The first involved her reaction to the installation of new carpeting in one of her previous residences with a burning throat as a result. When the rug was removed, her symptoms abated. A similar incident occurred during the remodeling of an office. Both of these incidences would indicate that Mrs. [redacted] is in a class of sensitive individuals. This sensitivity as it relates to ozone is addressed below.

During the period in which the [redacted] inhabited the house, two Honeywell F300 Electronic Air Cleaners located in the two HVAC units in the house were operating continuously, generating and releasing ozone directly into the home environment (at times set to cycle in conjunction with the [redacted] air conditioner and heating system; at times set to cycle with system fans). In addition to ozone itself being a severe respiratory poison, it reacts with chemicals which are normally found in the household environment thus producing additional toxicants and even toxic fine dust (nanoparticles) which is thought to be the vehicle for carrying other toxicants into the deep lung. Mr. [redacted] was not affected in the same manner since he did not spend as much time in the house as Mrs. [redacted]; he was apparently less effected by the ozone found to be present.

Mrs. [redacted] contacted the Metropolitan Public Health Department in Nashville and received a written response from Dr. [redacted], the Director of Environmental Health Services, stating that they discourage the use of electronic air cleaners in homes because of the toxicity of ozone and its reaction products. The letter discusses a variety of health problems that can result from low-level exposures to ozone.

DISCUSSION

Before embarking on a discussion of the pertinent issues relating to this case, there first should be an understanding of some of the details that will drive that discussion. Electronic air cleaners for the home generate ozone which is discharged into the air of that home. Ozone then can react with whatever else is in the home environment such as volatiles from cleaning products, air fresheners, perfumes, detergents, off-gasses from rugs and upholstery, among others. While ozone is an extremely toxic gas, its reaction product may be even more toxic. Ozone and its reaction products react with cells lining the walls of the upper respiratory system resulting in damage and consequent respiratory deficits and compromise of the immune system which protects the deep lung from damage. In the [redacted]'s situation, they were exposed to low levels of ozone and its oxidation products, including formaldehyde, from May of 2008 to November 2008 at which point they turned off their ozone-generating air cleaners after six months of continuous exposure. Mrs. [redacted] was exposed day and night during the time that she spent inside of the house and, as a consequence, has suffered respiratory effects including non-productive cough with wheezing, shortness of breath, hyperreactivity of her upper airways, sensitivity to odors, among other symptoms which she attributes to her home environment. This pattern of symptoms was not experienced by Mrs. [redacted] prior to her occupying the house in question.

Air Cleaners (ozone generators)

The FDA has enacted recent guidelines for ozone generating machines[1] describing the machines as being adulterated if they generate more than 50 ppb ozone, but it was the California Air Resources Board (CARB) that first adopted the 50 ppb limit.[2] CARB indicates that ozone beyond this concentration range

can produce lung inflammation, impaired pulmonary function, chest tightness, shortness of breath, worsening of asthma symptoms, and other more severe consequences including death at higher concentrations. They acknowledge the reaction of ozone with indoor chemicals resulting in the formation of formaldehyde, a known human carcinogen, and ultra fine particulates which can penetrate the deep lung in addition to other toxic reaction products. In an earlier document CARB went into more detail describing ozone oxidation products with air fresheners, glycol ethers, d,l-limonene, terpenoids like pine oil, and linalool resulting in formaldehyde, hydroxyl radicals, and secondary organic aerosols.[3] A California Environmental Protection Agency document entitled "Ozone and Health" dated August 24, 2005, described the ability of ozone to damage tissues lining the respiratory tract resulting in irritation, coughing, chest tightness, and exacerbation of asthma.[4] It further stated that air purifiers that generate ozone should not be used in occupied spaces since they can emit unsafe levels of ozone. In a letter from Richard Bode of CARB dated December 6, 2006, he stated that the 50 ppb limit for ozone generating devices may not be adequate to provide protection in situations involving long-term exposure. He pointed out that recent epidemiology studies have suggested health effects at ozone levels between 20 and 30 ppb, while the National Research Council's (NRC) recommended limit for continuous exposure is 20 ppb.[5] The NRC has further stated "there is no scientifically valid reason to allow marketing of devices that intentionally generate ozone for the purpose of cleaning indoor air or surfaces in occupied spaces."*

The US EPA in a document (see the "Materials Reviewed" section of this report) entitled "Ozone Generators in Indoor Air Settings" addressing ozone-generating air cleaners and indoor air chemistry indicated that some units can generate ozone at concentrations of 300 ppb when they are contaminated with dust particles. They discuss indoor environments with particular emphasis on the reaction of ozone with fragrance materials and cleaning products containing terpenes resulting in the formation of ultrafine particulates which can be deposited in the deep lung. In an industry publication, Tanasomwang & Laf[6] noted many studies on the health effects of indoor air pollutants with ozone being identified as a pulmonary irritant that affects mucous membranes and may cause irreversible lung damage. They also noted increases by an order of magnitude in ozone generated when electrodes become contaminated. A 1994
publication by Dorsey and Davidson[7] reported that ozone emission rates from an electrostatic air cleaner increased five-fold when it operated several days under high dust load and ten-fold when the discharge wires were oxidized. Additional information on electronic air cleaners may be found in publications cited in the "Materials Reviewed" section of this report.

Ozone Toxicology

Controlled Human Studies

*Even the popular "Consumer Reports" in its December 2007 edition warns against the use of "air cleaners" that generate ozone.

Reviews covering various aspects of ozone toxicity have been published by Lippman,[8] Mustafa[9] and the US EPA,[10] but there are a number of controlled studies in man which should be noted. Gong, *et al.*,[11,12] was able to demonstrate decrements in pulmonary function parameters as well as bronchial hyperreactivity in both healthy subjects and those with chronic obstructive pulmonary disease (COPD) when exposed to ozone while Peden, *et al.*,[13] showed nasal inflammation and increased sensitivity to allergens in the airway mucosa of allergic asthmatics. Aris, *et al.*,[14] exposed healthy athletes to 0.2 ppm ozone for four hours during moderate exercise. Eighteen hours after exposure ceased, bronchial biopsies were conducted and histologic evidence of upper airway inflammation was discovered. These findings included increased neutrophils in the airway mucosa and increases in LDH (lactate dehydrogenase), IL-8 (interleukin-8), total cells, and epithelial cells in the proximal airways lavage fluid which caused them[13] to conclude that ozone can cause injury to proximal airways and distal lung tissue.

Follinsbee, *et al.*,[15] and Horvath, *et al.*,[16] exposed sedentary subjects to 0.12 ppm (120 ppb) ozone with exercise, and this resulted in significant deficits in flows, tidal volumes, FVC (forced vital capacity), FEV_1 (forced expiratory volume in one second), and specific airways resistance as well as symptoms of cough, pain on deep inspiration, shortness of breath, throat irritation, and wheezing. Adams[17] exposed subjects to 80 ppb ozone for 6.6 hours and demonstrated a decrease in FEV_1, while McDonnell[18] reported reductions in FVC, FEV_1, and FEV_{25-75} in 60 young adults exposed to identical conditions. Also using a similar exposure scenario, Horstman, *et al.*,[19] reported a significant increased response to methacholine challenge in exposed subjects. FEV_1 decrements have been reported at concentrations as low as 80 ppb in controlled studies and as low as 40 ppb in adults and 23ppb in children during ambient exposures (See US EPA document[10], paragraph 6.2.4 and table 7.1, respectively).

Another study[20] looked at sputum analysis after ozone exposure and found neutrophils and myeloperoxidase in healthy subjects exposed to 0.4 ppm for two hours, in addition to IL-6 and IL-8. Bronchioalveolar lavage fluid (BAL) in relation to ozone exposure has been the subject of other studies. Koren, *et al.*,[21] exposed 11 healthy non-smoking subjects to a single exposure of 0.4 ppm ozone for two hours with intermittent exercise. They found increased levels of inflammatory cells, prostaglandins, fibronectin, and increased tissue factor in the lower airways of exposed subjects.

Graham and Koren[22] exposed ten subjects to 0.4 ppm ozone with exercise for 2 hours and found significant numbers of PMNs (polymorphonuclear leukocytes) in nasal lavage and considered this to be a good predictor of acute inflammatory response. In a 1995 publication, Weinmann, *et al.,*[23] exposed subjects to 0.35 ppm ozone for 130 minutes with exercise and reported a decreased macrophage population but increased neutrophils with significant increases in fibrinogen and albumin in post-exposure lavage fluid, while Devlin, *et al.,*[24] exposed non-smoking male subjects to as little as 80 ppb to 100 ppb ozone for 6.6 hours with moderate exercise and extracted BAL fluid after 18 hours post exposure. They reported significant increases in PMNs, protein, prostaglandin E2, fibronectin, interleukin-6 (IL-6), and lactate dehydrogenase and concluded that exposure to as little as 100 ppb ozone results in inflammation and damage to the alveolar region of the lung.

Still other studies address pulmonary function in response to ozone. Volunteer cyclists were exposed to ozone at concentrations ranging from 0.08 ppm to 0.32 ppm for one hour, and decrements in FEV_1 were noted at 0.16 and above in a dose-dependent manner.[25] Older men and women exposed for two hours to 0.45 ppm ozone with alternative period of exercise demonstrated decrements in FVC, FEV_1, and FEV_3,[26] while Folinsbee, *et al.,*[27] exposed ten non-smoking males to 0.12 ppm ozone for 6.6 hours resulting in decrements in FEV_1 and FVC with increases in cough and pain on deep inspiration and indications of hyperreactive airways. The US EPA document on air quality criteria for ozone[10] contains a summary table relating pulmonary function deficits to ambient ozone concentrations at 40 ppb and below (see Tables in sections AX-6, 7 in this US EPA document).

Other investigations[28] also have produced decreases in lung function and increases in airway activity. Folinsbee & Horvath[29] exposed subjects to 0.25 ppm ozone in repeated doses separated by 12, 24, 48, and 72 hours and found hyperresponsiveness based on measurement of FEV_1. Other studies have shown that 2-hour exposures of greater than 120 ppb produced significant deficits in flows, tidal volume, FVC, FEV_1, and specific airway resistance with symptoms of cough, pain on deep inspiration, shortness of breath, throat irritation, and wheezing with longer exposure periods producing more severe effects.[15,16] Jorres, *et al.,*[30] exposed subjects to 0.25 ppm ozone for three hours and noted airway hyperresponsiveness. Increased responsiveness to bronchoconstrictor challenge in asthmatic patients is thought to result from a combination of structural and physiological factors that include increased inner-wall thickness, increases in smooth muscle responsiveness, and mucus secretion as well as genetically modulated innate airway responsiveness.[31] Many report pulmonary function deficits or increases in hyperreactivity at

ozone levels of 80 ppb.[17-19] There are many other studies[8,9,32] relating to the effects of ozone on healthy human subjects, but a comprehensive review of this vast body of literature is beyond the scope of this report. The US EPA[10] has summarized much of this work in its document on air quality criteria for ozone[10] (see Tables AX6.2, AX7-1 to AX7-7, Table AX-6-11 and paragraph AX6.8 in this US EPA document). There are, however, a number of publications suggesting a causal link between long-term ozone exposure and onset of asthma in exposed individuals.[33-35]

In most of the studies indicated above there is a gradient in the response to various exposure scenarios related to ozone exposure. An abundance of information demonstrating this variability is contained in the US EPA document cited above[10] and found in paragraphs AX6.4, AX6.5.1,2, in paragraph 7.6.10 of that document and elsewhere. The publications cited indicate a large degree of intersubject variability in response to ozone.[110-113] Variations in response and sensitivity to ozone include both respiratory symptoms and pulmonary function.[114] One study by Adams, *et al.*[110] involved exposure of 8 trained male subjects and involved various exercise protocols, while another[111] examined variability in the effect of ozone on 20 healthy non-smoking volunteers. McDonnell, *et al.*[112] studied six groups of healthy young males and observed FEV_1 decrements ranging from 3 to 48%. Drechsler-Parks, *et al.*[26] examined the effects of ozone on 8 men and 8 women and suggested that women may be more sensitive than men to the effects of ozone. Table AX6.6 in the cited US EPA document[10] addresses gender and hormonal influences on this sensitivity to ozone.

This variability in sensitivity to the respiratory effects of ozone is thought to be caused by a genetic polymorphism related to quinone-metabolizing enzymes[115] and a decreased level of antioxidant enzymes. Genetic polymorphism of various enzyme systems are thought to play an important role in attenuating oxidative stress on the airway epithelium.[116,117]

These are only a few of the numerous publications dealing with variance in individual susceptibility to ozone. The US EPA document[10] cites many other studies which show that not everyone reacts the same to various concentrations of ozone.

Animal Studies

Data from animal studies confirm the many effects found in human studies, but they also include vital histopathological information that provides a further understanding of the effects of ozone on the respiratory system. A 1993 study by Harkema, *et al.*,[36] exposed monkeys to 0.15 ppm or 0.30 ppm ozone for 90 days. Exposed monkeys showed hyperplasia of the nonciliated epithelial cells and intraluminal accumulation of

macrophages in respiratory bronchioles. The ozone exposed epithelium was 80/20 cuboidal versus squamous cells, but air controls showed a 40/60 ratio. Cuboidal epithelial cells increased with exposure time and level of ozone. Another monkey study[37] involving exposure to 0.64 ppm ozone for 8 hours per day for one year resulted in narrowing of the respiratory bronchioles by both inflammation and through hyperplasia of the cuboidal bronchiolar cells.

Rat studies show similar findings.[38,39] Mitotic activity was measured in ozone-exposed rats and showed increased activity of nonciliated bronchiolar cells, interstitial cells, and alveolar type II pneumocytes[40,41] reflecting an increase in cell turnover as a result of ozone exposure. Other studies in rats have observed the presence of various biochemical parameters in BAL fluid that are thought to be sensitive markers of ozone damage.[42-44] Multiple studies have been reported showing effects on alveolar macrophages and decreased expression of CD3 among lung lymphocytes at concentrations as low as 100 ppb.[45] The US EPA document on air quality criteria for ozone[10] also describes studies showing ozone effects on lung permeability and inflammation (see Table AX5-3 in this US EPA document); effects on lung structure (see Table AX5-5); effects on lung morphology (see Table AX5-6); and effects on airway responsiveness (see Table AX5-7). In addition, Table AX5-2 in the same document provides a summary of new animal studies examining the effects of ozone on lung host defenses including effects on the immune system.

Airway hyperresponsiveness also has been demonstrated in animals exposed to ozone. One study by Fabbri, *et al.*,[46] exposed dogs for 2 hours to 3 ppm ozone described desquamation of the airway epithelial cells, increases in neutrophils and epithelial cells in BAL fluid, and a 15-fold increase in airway hyperresponsiveness. Four studies in ozone-exposed guinea pigs[47-50] showed similar findings. Other studies have noted marked mucous cell metaplasia[51,52] and increases in collagen content in lungs of exposed rats indicating fibrotic changes.[53] Again, the US EPA document on air quality criteria for ozone[10] contains much more information on the effects of ozone on animal models (see Table AX5-7 in this US EPA document).

Mechanism of Action

While it is not my intention to delve deeply into the mechanistic aspects of ozone exposure, the issue should be addressed. A study by Ostro, *et al.*,[54] described the physiological reasons for the loss in FEV_1 after ozone exposure explaining that afferent nerve receptor stimulation in the larynx and airways results in both bronchoconstriction and initiation of cough reflex. One of the biochemical explanations of the toxic effects of ozone is described by Pryor, *et al.*[55] They indicated that the the toxic effects are due

in part to a cascade of lipid ozonation products rather than ozone itself. Ozone is thought to be very reactive; consequently, it only effects the first layer of tissue, the epithelial cell lining fluid (ELF), and the membranes of the epithelial cells themselves. The ELF is about 90% lipid and 10% protein and contains appreciable amounts of unsaturated fatty acids. Ozone reacts with those fatty acids producing lipid ozonation products including ozonides, aldehydes, and hydroperoxides which may trigger endogenous mediators of inflammation and a cascade effect. Others have investigated this phenomena.[56-58] This mechanism is consistent with intersubject variability of response and genetic polymorphisms related to the presence of metabolic antioxidants. This issue is addressed later in this document.

Bayram, *et al.*,[59] examined the release of inflammatory mediators in bronchial epithelial cells of non-atopic and atopic asthmatic subjects exposed to 0 to 100 ppb ozone. They reported that ozone concentrations as low as 50 ppb produced significant differences in inflammatory cytokines produced by cells from asthmatic subjects. This concentration of ozone also increased the release of mediators 24 hours after exposure. They concluded that ozone may modulate airway disease by having a negative influence on bronchial epithelial cells. These findings are supported in paragraph 6.8 of the US EPA document on air qualiaty criteria for ozone.[10]

In-vitro studies have demonstrated ozone concentrations as low as 100 ppb producing decreased expression of CD3 among lymphocytes,[45] while studies of P450 gene expression have suggested a genetic sensitivity to ozone.[60] There is evidence that inhaled oxidant pollutants produce oxidative stress coupled with up-regulation of inflammatory cytokine production in the airways of asthmatics, and genetic polymorphisms may predict susceptibility to cytotoxic tissue injury from oxidative stress.[61]

Threshold Exposures

In the case of air cleaners that generate ozone, we are dealing with concentrations of ozone which are generally around 80 ppb[10] or below, but we also are dealing with the potential for a 24-hour per day exposure over several months and the generation of much higher ozone levels when the equipment becomes contaminated with dust or corrosion. Most of the studies previously presented involve short-term exposures, but there are studies of ambient ozone concentrations that do involve long-term exposure scenarios. Bell, *et al.*, in 2004[62] using ambient 24-hour ozone concentrations of less than 60 ppb were able to show that for every 20 ppb increase in ozone, mortality increased by 0.36%, and they concluded that a

threshold for ozone health effects should be less than 60 ppb. In a recent study, Bell, *et al.*,[62] found that every 10 ppb increase in ambient ozone concentration increased daily mortality by 0.52%. Fairly[63] found a threshold for ozone mortality to be less than 40 ppb. Consistent with the findings in a study across 23 European cities, Gryparis, *et al.*,[64] found that the concentration-response curve for ozone did not differ from linearity; that is, health effects from ozone go to zero when the ozone concentration goes to zero. In support of the absence of a threshold for ozone, Vedal, *et al.*,[65] found an annual mean maximum concentration of ambient in Vancouver, BC, to be 27.3 ppb, a concentration that demonstrated statistically significant effects on total mortality and respiratory mortality. They concluded that there was no threshold for ozone relative to human health effects. Other suggested thresholds for ozone included 50 ppb,[66] <42 ppb in Australia[67] and 30 ppb in Toronto.[68] Similarly, McConnel, *et al.*, also concluded that research has not supported a threshold for adverse effects in humans[69] as did Weschler.[70]

Additional reports include a meta-analysis showing an 0.87% increase in mortality per 10 ppb increase in daily ozone concentration and a conclusion that ozone concentrations as low as 20 ppb have been shown to increase mortality and that the threshold may be as low as 10 ppb.[71] Similar studies have reported a 0.39% increase in mortality per 10 ppb ozone,[72] a 0.41% increase per 10 ppb,[73] a 0.66% increase per 10 ppb,[64] a 4% increase in mortality per 25 ppb increase in ozone concentration,[74] and a 0.45% increase per 5 ppb in ozone concentration.[75]

Bayram, *et al.*,[59] reported that ozone concentrations as low as 50 ppb produced significant differences in inflammatory cytokines produced by cells from asthmatics versus non-asthmatic subjects and found significant increases in human bronchial epithelial cell permeability in asthmatic subjects as evidenced by statistically significantly decreased electrical resistence 24 hours following a 10 ppb exposure when compared to healthy subjects, while the latter showed statistically significant changes at 50 ppb.

Reaction Products with Ozone

Ozone has been shown to react with chemicals normally found in the air of a household including personal care products, wood, carpets, paint, adhesives, perfumes, air fresheners, among others.[70] In a National Institute for Occupational Safety and Health (NIOSH) working group report, Weschler, *et al.*,[61] described the reaction of terpenoids, sesquiterpenes, and unsaturated fatty acids resulting in active intermediates, including allergenic peroxides and hydroperoxides. These reactions can result in products which may be more toxic than ozone[76] and

including formaldehyde and other aldehydes, acrolein, methacrolein, acids, organic peroxides and hydroperoxides, and ultrafine particles. There is indirect evidence to support a connection between exposure to these materials and health effects.[70] Ozone terpenoid reactions lead to co-occurance of peroxides and submicron particles which are thought to provide a mechanism for transport of toxicants to the deep lung.[77] Clausen, *et al.*,[78] reported finding strong irritants from a reaction between limonene and ozone. These products included 3-ispropenyl-6-ozoheptanal, formaldehyde, formic acid, acetone, acrolein, and acetic acid. When mice were exposed to this mixture, a 33% reduction in breathing rate was recorded.

Liu, *et al.*,[79] combined pine-scented air freshener with ozone in a control chamber and found concentrations of formaldehyde up to 28.2 μg/m^3 and assorted additional aldehydes, including benzaldehyde. They also found particulate concentrations up to 65 μg/m^3. Shu, *et al.*,[80] showed that linalool, an indoor fragrance material, reacted with ozone producing the following products: 6-methyl-5-heptene-2-one, 4-hydroxy-4-methyl-5-hexene-1-ol, 5-ethenyldihydro-5-methyl-2-(3H)-furanone, and formaldehyde. Wilkins, *et al.*,[81] exposed mice to a mixture of isoprene and terpene with ozone and produced formaldehyde, formic acid, acetone, acrolein, acetic acid, and other oxidation products which reduced the breathing rates of mice by 50% in 30 minutes of exposure. Li, *et al.*,[82] simulated an office environment with a reaction between ozone and d-limonene resulting in organic hydroperoxides and hydroscopic secondary organic aerosols in the range of 10 to 100 μm in size. They indicated that the reaction products were more irritating than the starting materials. Others have described long-lived radicals, ozonides, organic acids, and other unknown oxygenated intermediates;[61] and the cited US EPA document[10] also has a section on these interactions (see paragraph 5.4.3).

In an experiment involving the reconstruction of a B-767 aircraft containing human occupants and ozone,[83] the following reaction products were identified: acetone, nonanal, decanal, 4-oxypentanal, 6-methyl-5-hepten-2-one, formic acid, and acetic acid. Wainman, *et al.*,[84] conducted some studies in a smog chamber reacting ozone and terpenes and found high aerosol yields of sub-micron particulates in excess of 20 μg/m^3. Other studies include a mixture of 23 volatile organics including two terpenes reacted with ozone resulting in formaldehyde, glyoxal, hydrogen peroxide and secondary organic aerosols;[85] oxidation of limonene-producing allergens including limonene oxide, carvone, and a series of hydroperoxides;[86] oxidation of linalool yielding allergenic hydroperoxides;[87] oxidation of glycol ethers (ethoxylated surfactants) resulting in allergic oxidation products formed rapidly with ozone;[88] reaction of ozone with limonene-producing gaseous oxidation products and ultrafine particles, both irritants in a mouse bioassay;[89] and reaction of ozone with air fresheners, perfumes, and cleaning materials.[90] Even carpeting material can react with ozone to produce assorted aldehydes.[91,92] Other studies also demonstrate the strong irritant potential for these oxidation mixtures.[93-95]

In addition to reacting with household chemicals, ozone also reacts with human skin lipids,[96] thereby producing a long list of saturated and unsaturated ketones, acids, and aldehydes. When soiled T-shirts were used as a surrogate for human occupation in a simulated aircraft cabin, the following reaction products were identified: acetone, propanal, formaldehyde, nonanal, 4-oxypentanal, acetic acid, formic acid, acrolein, and crotonaldehyde.[84] Many of these oxidized fragrance components have demonstrated allergic reactions when applied using the human patch test on 1,511 dermatitis patients.[97]

There are numerous similar studies described in the literature,[78,98-107] most of which describe complex mixtures of aldehydes, ketones, and other oxidation products resulting from reaction of ozone with household chemicals, and most of the mixtures contain allergens which can produce respiratory sensitization in those exposed continuously to these complex mixtures of materials. There are even some studies showing neurobehavioral effects in rats exposed to reactive ozonation products resulting in effects on short- and long-term memory, and learning deficits with demonstrated disruption of brain neurotransmission.[108] An excellent combination of studies on ozone reaction products written for CARB by Nazaroff, W. W., *et al.*, dated April 2006 is cited in the "Materials Reviewed" section of this report. Much new data on this subject was presented: volatile oxidation products including formaldehyde, acetaldehyde, acetone, glycolaldehyde, formic acid and acetic acid from controlled chamber studies involving ozonation of alpha-terpinene, d-limonene, terpinoline, and gamma-terpineol. They also reported the generation of sub-micron particulate matter.

CAUSATION ANALYSIS - HILL CRITERIA

The ability of air purifiers to generate unsafe levels of ozone and its reaction products in the home environment has been adequately described above. In addition, the ability of ozone to produce health effects at very low levels of exposure has also been adequately described, but it is appropriate that this information be presented in the context of a formalized causation analysis. While I will not reiterate the information already presented, some comment on the Hill Criteria is noted.

The Hill Criteria[109] was suggested by Sir Bradford Hill as a set of criteria that would be appropriate for establishing causation. It has been used by the Surgeon General of the United States in establishing causation in his "Smoking and Health" reports and its elements have been suggested in the Federal Rules of Evidence by the U.S. Federal Court System. The elements of this criteria are indicated below.

1. Strength of Association

   The essence of this criteria involves an assessment of the extent to which a particular disease coincides with a particular exposure. The incidence of the disease does not have to be high in order to

establish a strong association. In the case of a rare disease, the finding of even a few cases within a small population that has been treated with a particular drug would be of great significance.

I have presented sufficient scientific evidence to support a causal relationship between exposure to ozone and damage to the human and animal respiratory systems. I have presented controlled human exposure studies involving effects of ozone on various aspects of the pulmonary system including pulmonary function, defense capability, respiratory symptomatology, airway hyperactivity, and biochemical changes at exposure concentrations near 80 ppb, but I also have gone beyond and looked at the effects on mortality of even lower exposure levels in large populations. Many of the studies cited report either no threshold for health effects from ozone or very low thresholds. These lower levels of exposure are particularly pertinent since they are easily produced by air purification devices which are operating properly.

In addition to the direct effects of ozone on the human respiratory system, I also have described scientific literature which demonstrates that ozone reacts with many of the airborne chemicals normally found in the home including fragrances and cleaning products. Several of the reports cited show numerous chemicals being generated in this manner, many of which are respiratory irritants and sensitizers. Some have reported that these chemicals are even more irritating than ozone itself. Again, the information available is sufficient to meet this criteria.

The following concluding remark is contained in paragraph 8.4.7.6 of the US EPA document on air quality criteria for ozone:[10] "In conclusion, the epidemiologic evidence continues to support likely causal associations between ozone and acute respiratory morbidity and mortality, based on strength, robustness, and consistency of results reported from numerous studies". Chapter 7 Annex contained in the same document[10] entitled "Epidemiologic Studies of Human Health Effects Associated with Ambient Ozone Exposure" contains a vast amount of pertinent information beyond the scope of this document.

With regard to Mrs. [redacted], I have clearly indicated experimental data that demonstrates her exposure to ozone from her air cleaners over a period of six months and the consistent symptoms and medical problems that have resulted from that exposure. Further, I have shown the presence of at least one reaction product of ozone in the house, namely formaldehyde. In addition, I have indicated that she did not have any respiratory problems prior to moving into the house in question but that she had experienced respiratory problems in relation to remodeling efforts in her prior residence.

There remains no doubt as to her exposure to ozone at levels shown to produce adverse effects in humans, and there remains no doubt as to the source of this ozone.

2. Consistency of Association

Hill[09] asks the question, "Has it been repeatedly observed by different persons in different circumstance and times?". In other words, have similar findings been observed by different observers.

The scientific literature that I have presented consistently demonstrates similar findings of upper respiratory damage from ozone in humans and in animals under a variety of exposure conditions. Further, reaction products of ozone and household chemicals, although not always identical, are generally oxidation products including aldehydes and hydroperoxides, among others; many of these chemicals are also respiratory irritants and allergens.

Since moving into her new house, Mrs. [redacted] has shown a pattern of health effects that did not pre-exist her moving into the house and that are consistent with her continuous exposure to low levels of ozone and possible reaction products of ozone.

3. Specificity of Association

The specificity of an association describes the precision with which the occurrence of one variable will predict the occurrence of another. This criterion overlaps the strength of association to some extent but focuses more on the direct link between a specific disease and a specific cause for that disease. When dealing with human populations, this specificity is rare.

This criteria is difficult to meet since ozone and its reaction products do not produce pulmonary effects that are particular to the specific toxicants. This is not an unusual situation since pulmonary injury may be caused by a number of factors. For this reason, Hill allows some leeway in meeting all of the criteria which he has put forth.

With regard to Mrs. [redacted], specificity may be addressed in that there are no indications of an alternative cause for her medical problems, nor did her medical problems pre-exist her moving into her house.

4. Temporality

Hill[09] asks "Which is the cart and which is the horse?" If a disease state exists prior to exposure to a medication, the exposure may exacerbate the

disease but may not have caused the disease. The appearance of a diseased state must follow treatment with the medication being addressed.

Clearly, one must be exposed before one experiences the effects of that exposure. That certainly is the case here; however, when performing a causation analysis it is important to determine the condition of the exposed organism prior to exposure in order to be compared to that subsequent to the exposure. In the controlled scientific studies that I have cited, there is usually an unexposed group for comparison. This is true for both the human and the animal studies. This approach provides a "before" and "after" assessment. In cases of individual causation, there are no control groups; consequently, the only comparison one has is the condition of health of the exposed person prior to any exposure. According to the medical records, Mrs. [redacted] had no pre-existing respiratory condition, and her symptoms began when she moved into the new house and was exposed to ozone from the air cleaners that operated continuously for the six-month period during which she inhabited the residence.

It is important to rule out other possible causes which could produce the same health effects. Timing is important also when considering temporality. If a person is exposed to a carcinogen a couple of weeks ago and then is diagnosed with cancer, the temporal relationship is not valid because of the time that is required for the cancer to develop. It is not plausible for a cancer to develop in such a short period of time. Ozone acts instantly on the tissues that it contacts and therefore does not require a latency period to observe the effects. Chronic effects can certainly result from ozone exposure, but although the effects of individual ozone exposures are instant, they may be cumulative.

5. Biological Gradient

Dose-response is the foundation of good toxicological studies. The higher the dose or the longer the treatment, the more severe the response or the more prevalent the response. Dose cannot only be expressed as a single dose producing an acute response, but also by specifying the daily dose and treatment period. The latter is more appropriate in this situation.

In the "Threshold Exposures" section of this report, I have taken great care to describe numerous studies which question the existence of a threshold for production of health effects by ozone. Biological gradient is described as a dose-related response relationship. One study suggested a linear dose-response for ozone which in essence is an indication that there is no dose of ozone that is without some damage to the human organism. In support of dose-related toxicity for ozone, I have described several animal studies which examine the dose-response relationship for ozone.

Ozone was measured at 30 ppb in the [redacted] house after it was vacated by Mrs. [redacted]. No measurements were taken while Mrs.[redacted] was living in the house. I previously have indicated that when air cleaners become contaminated with dust, very high levels of ozone may be produced. It is understandable that after six months of continuous operation, the air cleaners in the [redacted] house may have been contaminated resulting in higher levels of ozone being produced; however, the only measurements that we have are those taken after the house had been vacated by Mrs. [redacted] Additional testing has been carried out in the home, and similar findings have been reported. I have described studies that conclude there is no threshold for ozone concentrations that can produce respiratory damage at the levels found in the [redacted]s house and even at lower levels.

6. Plausibility and Coherence

I will consider these criteria together since they impinge on the same theme voiced by Hill[109] with regard to coherence ". . . the cause and effect interpretation of our data should not seriously conflict with generally known facts of the natural history or biology of the disease". In addition, hypotheses based on sound scientific principles should be presented to explain the phenomena under consideration to demonstrate the plausibility of the causal conclusions being reached. It is desirable to provide experimental evidence to support the hypothesis, but this is not always available.

In the above discussion, I have presented numerous scientific studies which described the various mechanisms by which ozone produces damage to the respiratory system, but I have barely touched the surface of the information which is available on that subject. Clearly, the methods used are based on sound scientific principles, and the resulting effects do not violate any natural biological processes. In paragraph 8.4.12 of the US EPA document on air quality criteria for ozone[10] are the following statements: ". . . the convergence of epidemiologic and toxicologic evidence related to respiratory health effects of ambient O_3 exposures argues for coherence and plausibility for this body of evidence"; and "Analysis of the body of toxicologic studies suggest plausible mechanism for epidemiologic findings"; ". . . support the general conclusion that O_3 is causally related to respiratory-related mortality and morbidity"; and ". . . may also be causally related to long-term respiratory-related health risks."

There is little question about the relationship between ozone exposure and respiratory damage; about Mrs. [redacted] being exposed to ozone continuously over a period of six months; and about Mrs. [redacted] suffering adverse health effects upon entering her house and being exposed to ozone emanating from her air cleaning units. That Mrs. [redacted] suffered health effects from ozone exposure is plausible and logical.

7. Experiment

Although human clinical trials are relied upon to establish the efficacy of drugs, and epidemiolgy studies are used in establishing causation relating to adverse drug reactions as we have done above, animal experimentation is extremely useful in demonstrating concepts used to explain some of the human findings. In addition, studies of the effects of chemicals on cellular processes have also proven useful in being able to understand the mechanisms involved in the toxicological processes being studied.

The number of experimental scientific studies that have been published on the effects of ozone include controlled human studies as well as hundreds of experiments involving rats, mice and primates. The effects of ozone on the ciliated as well as non-ciliated epithelial cells of the upper airways, resulting hyperplasia and biochemical changes, effects on alveolar macrophages as well as demonstrated airway hyperresponsiveness are just a few of the studies mentioned here. A whole section of this report describes mechanistic studies in animals and *in-vitro* studies of cells exposed to ozone. As already mentioned, studies of biological gradient (dose-response) also have been carried out. These are all experimental studies which add to the understanding of ozone toxicology.

The US EPA document on air quality criteria for ozone[10] contains several tables containing vast amounts of data from experimental studies. These include the following compilations: Table AX5-3: Effects of ozone on lung permeability and inflammation down to 100 ppb; Table AX5-5 Effects of ozone on lung structure from short-term assays down to 100 ppb; AX5-6 Effects of ozone on lung morphology; AX5-7 Effects of airway responsiveness down to 100 ppb.

Experimental studies measuring ozone and formaldehyde have been performed on the [redacted] house, and conclusions have been drawn based on these experimental measurements.

8. Analogy

Are there other drugs, chemicals, or conditions that simulate the causal relationship which is under scrutiny? Are there other similar situations that parallel the events relating to the causal connection addressed herein?

While there are no compounds that are analogous to ozone, there are other compounds that react with the bronchial epithelial tissue causing cell destruction. Most, however, react by totally different mechanisms and should not be considered direct analogies.

CONCLUSION AND OPINIONS

Based on the above discussion, it is clear that a causal relationship exists between exposure to ozone and a number of adverse effects on the human respiratory system. Ozone is capable of destroying tissue in the upper respiratory system resulting in a compromised defense capability, decrements in pulmonary function, and a change in the cellular population of the conducting airways resulting in a hypersensitivity of the upper airways to various other insults. While acute cellular damage to the conducting airways and deep lung usually occur only at concentrations which exceed 80 ppb, it is clear from the information presented above that damage from ozone can occur even at very low concentrations. Some believe that there is no threshold concentration related to the ability of ozone to cause damage to the respiratory system. There is a substantial base of scientific literature to support this "no threshold" conclusion for ozone, and some of these studies conducted in both animals and man have been cited above. I have presented considerable evidence to show that not only can ozone produce respiratory damage by itself, but it can react with common household chemicals producing numerous additional toxicants. Many of the toxicants produced by the reaction of household chemicals with ozone are sensitizers and deep lung irritants thereby exacerbating the indoor air quality situation caused by air cleaners. This situation results in an environment which can produce adverse effects on individuals who spend most of their time in such an environment. Superimposed on this complex exposure situation is the fact that individuals vary in their sensitivity to various chemicals, some being more sensitive than others. This phenomena has been described briefly above.

The Consumer Product Safety Commission, among other agencies, has indicated that electronic air cleaners can generate ozone concentrations which are capable of producing health effects. They, and others cited above, have recommended against the use of these devices in the home.

The [redacted] moved into their new house at [redacted] Nashville, Tennessee, on or about May of 2008 and stayed in the house until about November 2008, approximately six months. The [redacted] house was equipped with two Honeywell F300 Electronic Air Cleaners running continuously in two central HVAC units. Immediately upon entering the house for the first time, a previously healthy Mrs. [redacted] began experiencing various respiratory problems which eventually developed into chest tightness, upper respiratory irritation, coughing, sinus problems, non-productive cough, chronic bronchitis, and sensitivity to odors. No respiratory symptoms that I am aware of pre-existed her entering the house other than her demonstrated reactivity to other indoor pollutants years before as described above. No ozone testing was carried out during the time that Mrs. [redacted] occupied the house between May and November 2008, but ozone sampling was carried out in December of that year when the air cleaning units were run only intermittently. Although ozone concentrations as high as 30 ppb were measured in the air of the [redacted] house during the December 2008 sampling period, this is not necessarily an indication of the extent of ozone contamination during the six-months period that they occupied the house. When air cleaners are run continuously, the amount of ozone generated can increase significantly to levels as high as 300 ppb (See US EPA document entitled "Ozone Generators in

Indoor Air Settings" in the "Materials Reviewed" section of this report). Reaction products of ozone, particularly formaldehyde, also were measured in December and were found to be present at 0.45 ppm. Mrs. [redacted] was tested for dermal sensitization to formaldehyde, and the tests was found to be negative.

Mrs. [redacted]'s exposure to ozone and its reaction products has obviously had significant health effects as indicated by her development of a variety of respiratory symptoms not apparently evident in her pre-exposure medical records. Since her symptoms did not pre-exist her exposure in her new house, one can conclude that they are related to her exposure to her house environment which included exposure to ozone and its many reaction products produced by reaction with ozone. The symptoms that she experienced are consistent with upper respiratory irritation caused by ozone and its reaction products at concentration levels that were actually measured in her house.

I therefore opine that ozone is not only capable of damaging epithelial tissue of the upper airways but is also capable of reacting with various household chemicals resulting in a number of toxicants capable of causing respiratory damage and allergic reactions in those exposed. I also opine that air purification equipment such as the Honeywell F300 Air Cleaners installed in the Bearden's house are capable of producing concentrations of ozone that can cause significant health effects by direct exposure to ozone and its reaction products.

I further opine that it is more probable than not that Mrs. [redacted] has suffered respiratory health effects including chronic cough, bronchitis, burning throat and sinuses, hoarseness, and sensitivity to smells as a result of her exposure to her ozone- contaminated house for a period of six months. I support my opinion with the body of literature cited above and the specific causation analysis using the Hill Criteria.

I reserve the right to alter my opinions should additional information become available.

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CONSULTOX, LIMITED

Date

[redacted]