SOUTH COAST AIR QUALITY MANAGEMENT DISTRICT

Appendix I

Comments and Responses to Comments

2016 AIR QUALITY MANAGEMENT PLAN

March 2017

From: StanYoung <genetree@bellsouth.net>
Sent: Tuesday, July 26, 2016 1:43 PM
To: Jo Kay Ghosh
Cc: Anthony Oliver; har@indecon.com; Margarita Felix (Ben); Marie Patrick (Bur)
Subject: air quality and health effects in South Coast Air Basin
Attachments: Comments on South Coast air quality and acute mortality V02.pdf; Young Short Bio 2016.pdf

July 26, 2016

Jo Kay Ghosh, PhD
SCAQMD Health Effects Officer
jghosh@aqmd.gov

Dear Dr. Ghosh:

I am a statistician and for the past several years I have been examining air quality, PM2.5 and ozone, and acute mortality for California. I attach a report that should be of interest to you. I find no association of air quality and acute mortality in the South Coast Air Basin. Please let me know if you have any questions on the analysis. I can provide the data set used in my analysis.

I also note that this analysis examines daily deaths of people 65 and older. The literature supports that there are no mortality effects in younger people. That is my assessment also. My reading of the literature on the "value of a statistical life" is that VSL depends on age. For people younger than 18 or so, VSL is essentially zero. Same for people older than 65. All that means that the EPA nominal VSL of $9M is surely an overestimate of the value of a statistical life. IF anyone is dying (the CA data and my analysis says that no one is), it is older people that have a very low VSL. Any analysis of economic impact should take into account the age distribution of any claimed mortality effect.

Sincerely,

S. Stanley Young, PhD, FASA, FAAS
genetree@bellsouth.net
919 782 2759

CC: Anthony Oliver aoliver@aqmd.gov
Henry A. Roman har@indecon.com
John Benoit mafelix@rcbos.org
William A. Burke mwpatrick@aqmd.gov

Short Bio 2016

Dr. S. Stanley Young worked at Eli Lilly, GlaxoSmithKline and the National Institute of Statistical Sciences on questions of applied statistics. His current mission is the evaluation of statistical claims particularly from observational studies. His research indicates that well over 50% of claims made fail to replicate when tested rigorously. His current interest is air pollution environmental epidemiology.

Dr. Young graduated from North Carolina State University, BS, MES and a PhD in Statistics and Genetics. He worked in the pharmaceutical industry on all phases of pre-clinical research. He has authored or co-authored over 60 papers including six “best paper” awards, and a highly cited book, Resampling-Based Multiple Testing. He has three issued patents. He is interested in all aspects of applied statistics, with special interest in chemical and biological informatics. He conducts research in the area of data mining.

Dr. Young is a Fellow of the American Statistical Association and the American Association for the Advancement of Science. He is an adjunct professor of statistics at North Carolina State University, the University of Waterloo, and the University of British Columbia where he has co-directed thesis work. He is also an adjunct professor of biostatistics at Georgia Southern University.

From: StanYoung <genetree@bellsouth.net>
Sent: Thursday, August 4, 2016 7:09 AM
To: Jo Kay Ghosh
Cc: Ann Scagliola; alovera@aqmd.gov; Margarita Felix (Ben); Marie Patrick (Bur); JudyM@ci.Rolling-Hills-Estates.ca.us
Subject: Material related to lack of association of air quality variables and mortality
Attachments: 02 Wang 2015 case crossover BMJ Open.pdf; 03 Young 2016 South Coast air quality and acute mortality.pdf; 00 Cover Letter to Ghosh.pdf; 00 Young 2016 Short Bio.pdf; 01 Milojevic- 2014 acute effects Heart.pdf

Follow Up Flag: Follow up
Flag Status: Completed

Dear Dr. Ghosh:

Attached find a cover letter and materials related to air quality and health effects. Two of the papers are new and you may not have seen them. I only recently became aware of the Wang paper. I have highlighted and added notes to the items so that key findings are easily found.

Let me know that you have received this email.

I'm happy to discuss any of the items with you or with anyone on the cc list.

Sincerely,

Stan Young

Your message is ready to be sent with the following file or link
attachments:
02 Wang 2015 case crossover BMJ Open
03 Young 2016 South Coast air quality and acute mortality
00 Cover Letter to Ghosh
00 Young 2016 Short Bio
01 Milojevic- 2014 acute effects Heart

Note: To protect against computer viruses, e-mail programs may prevent sending or receiving certain types of file attachments. Check your e-mail security settings to determine how attachments are handled.

August 4, 2016

Jo Kay Ghosh, PhD
SCAQMD Health Effects Officer
jghosh@aqmd.gov

Dear Dr. Ghosh:

As noted previously in my letter to you, I am a statistician and for the past several years I have been examining air quality, PM2.5 and ozone, and acute mortality for California. I attach several papers a report that should be of interest to you. I have added highlights to each document and also some notes. I find no association of air quality and acute mortality in the South Coast Air Basin. Two of the papers are recent and may not have come to your attention, Milojev et al. (2014) and Wang et al. (2015). Both papers examine heart attacks and multiple air quality measurement. Both papers find no association of air quality variables and heart attacks.

I also include an analysis of data from the South Coast Air Basin. This analysis I sent to you previously; here I have added some highlights and notes.

Sincerely,

S. Stanley Young, PhD, FASA, FAAS

genetree@bellsouth.net
919 782 2759

CC: Anthony Oliver aoliver@aqmd.gov
Ann Scagliola ascagliola@aqmd.gov
Henry A. Roman har@indecon.com
John Benoit mafelix@rcbos.org
William A. Burke mwpatrick@aqmd.gov
Judy Mitchell JudyM@ci.Rolling-Hills-Estates.ca.us

Short Bio 2016

Dr. S. Stanley Young worked at Eli Lilly, GlaxoSmithKline and the National Institute of Statistical Sciences on questions of applied statistics. His current mission is the evaluation of statistical claims particularly from observational studies. His research indicates that well over 50% of claims made fail to replicate when tested rigorously. His current interest is air pollution environmental epidemiology.

Dr. Young graduated from North Carolina State University, BS, MES and a PhD in Statistics and Genetics. He worked in the pharmaceutical industry on all phases of pre-clinical research. He has authored or co-authored over 60 papers including six "best paper" awards, and a highly cited book, Resampling-Based Multiple Testing. He has three issued patents. He is interested in all aspects of applied statistics, with special interest in chemical and biological informatics. He conducts research in the area of data mining.

Dr. Young is a Fellow of the American Statistical Association and the American Association for the Advancement of Science. He is an adjunct professor of statistics at North Carolina State University, the University of Waterloo, and the University of British Columbia where he has co-directed thesis work. He is also an adjunct professor of biostatistics at Georgia Southern University.

From: Ann Scagliola
Sent: Friday, August 5, 2016 11:09 AM
To: Jo Kay Ghosh
Subject: FW: SCAQMD Advisory Council Meeting - August 18, 2016

Importance: High

A comment received today from Dr. Froines.

From: Froines, John [mailto:jfroines@ucla.edu]
Sent: Friday, August 5, 2016 11:05 AM
To: Ann Scagliola <ascagliola@aqmd.gov>
Subject: RE: SCAQMD Advisory Council Meeting - August 18, 2016

Comment on ozone for the Advisory Council meeting. Ozone may alter the chemical properties of ambient particles by ozonizing them to generate potential electrophiles. Electro[philes have the potential to act as carcinogens.

As little as a single ozone exposure (0.5 ppm, 4 hours) can induce lung inflammation without induction of HO-1.

I will have more to say later.
John

From: Ann Scagliola [mailto:ascagliola@aqmd.gov]
Sent: Wednesday, August 03, 2016 4:51 PM
To: Paul Avila; Dr. Ed Avol; Judy Chow; Curt Coleman; Dr. Afif El-Hasan; Froines, John; Sue Gornick; Dr. John Husing; Dr. Cameron Kaiser; Mary Ann Lutz; Dr. Emily Nelson; Dr. Greg Osterman; Erbie Phillips; William La Marr; William La Marr; Dr. Rhodes Rigsby
Cc: Jo Kay Ghosh
Subject: SCAQMD Advisory Council Meeting - August 18, 2016
Importance: High

Advisory Council Members:

I am preparing the agenda for the Advisory Council meeting which is scheduled for 10:00 a.m. Thursday, August 18, 2016 at SCAQMD in Conference Room CC-8. I have received requests from a couple members for the possible option of participation by conference call.

Please confirm whether you plan to participate by conference call. If you would like to participate in this meeting by conference call, please sent me an e-mail by noon tomorrow, August 4, 2016, with the address and room number if applicable. All teleconference locations must be accessible to the public and handicapped accessible. Agendas must also be posted at the teleconference locations at least 72 hours prior to the meeting to comply with the posting requirements of the Brown Act. Thank you.

Comments on Draft 2016 AQMP Appendix I: Health Effects

Ed Avol (USC Dept of Preventive Medicine)

General Comments:

What is the proposed purpose of this appendix document? The need for a Health Effects appendix is not completely clear, although it is not completely unreasonable to have some key supporting information readily handy. That said, there seems to be a lot of generic cutting and pasting from the previous USEPA Integrated Science Assessments (ISAs). This leads one to wonder why the respective ISAs are not just directly utilized as the health effects appendix (if one is needed), at least with regard to NAAQS pollutants? Since the prior ISA reviews largely occurred three to five years ago, it does make sense to conduct and report on an updated search of the more recent health literature, and some of that does appear in the document. A more current ISA has been released for oxides of nitrogen (2016), so that document should be used to summarize current knowledge of NOx health effects.

I generally found the document to be somewhat inconsistent in its approach. Sectional organization, level of detail, and approaches to summarizing cited work seemed to vary from pollutant to pollutant, without a clear rationale or reason. It seems like a similar approach could be applied for all pollutants – a summary from the most recent ISA, a summary of more recently published information, a discussion of health endpoints and judgements about confidence of association, some perspectives on susceptible sub-populations, and conclusions about the state of knowledge for the pollutant being discussed.

Additionally, the criteria for discussing health outcomes seems to shift around a bit. I think it is appropriate that the EPA tables on causal relationship status be discussed and used to prioritize presentation of health effects data. However, it should be clear what the threshold is for inclusion and discussion (in other words, outcomes determined to be “causal”, “likely causal”, or “suggestive of causal”?) are going to be discussed. This threshold seemed to vary from pollutant to pollutant…

An alternative approach would be to identify target organs or outcomes of interest (brain, heart, lungs, neonatal development, metabolic, etc), and then comment on whether the database supported any concern for health impact.

Specific Comments:

Table of Contents – question why Ultrafine Particles have their own separate section, rather than being a sub-section of Particle Matter. In a similar vein, PM2.5 (Fine PM) and PM10 (Coarse PM) arguably should have their own sub-section in the report (since for both historical and regulatory reasons, both metrics are of health and regulatory significance).

Table of Contents – should be “Conclusions” (plural), not singular…

Table of Contents – ATTACHMENT – not sure why this list of publications appears in this document; the information contained in the appendix presumably draws from the larger range of peer-reviewed published literature, of which any SCAQMD-funded work is a small subset. This

does not add to the focus of the document (a review of air pollution health effects), is a little self-serving, and is unnecessary – I suggest removing this.

I-1, Introduction, last sentence – It sounds like the Health and Safety Code requires a review of PM, and other pollutants have been added by choice. Most are NAAQS pollutants and make sense to include. In terms of regulatory policy, something might also be said about VOCs, which play an important role in photochemistry, pollution reduction strategies, and human health effects in their own right.

I-1, para 2, bulleted list of adverse health effects – I'm not sure that this bullet list is especially useful, effective, accurate, or worthwhile. Using bullet points focuses the Reader on specific issues as being especially important, and I think this does not serve the presentation well because it is a partial (and somewhat mis-directed) list. Air pollution health effects have arguably been identified with most every organ system in the body. The listing here is inconsistent in sometimes providing an explanation (which isn't appropriate or useful in this introductory passage). I suggest this bullet list be re-done to present the example information more clearly (for example, why say "increased health care utilization" when examples of that ae also included? Why not just say, "increased physicians' visits, emergency room visits, and hospitalizations"? Saying increased respiratory illness and other morbidity (symptoms, infections, and asthma exacerbation) is somewhat repetitive – just say increased respiratory symptoms, infections, and asthma exacerbation. Decreased lung function is not "just" breathing capacity, so the parenthetical comment here should be deleted for clarity. The extended explanation for increased airway reactivity is unnecessary here and should be changed to "increased airway reactivity" or "increased airway responsiveness" , or "bronchial hyper-reactivity…but using text space to explain the laboratory approach utilized to observe the response makes little sense here. It's not immediately clear to me what is meant by "a decreased tolerance for exercise"? Are you claiming that air pollution makes you tired? I think what you are talking about are secondary observations conditional upon respiratory, cardiovascular, and metabolic effects (and/or possible heat-related effects as well, given the frequent co-occurrence of pollution episodes in the SCAQMD with elevated temperatures…but I am skeptical this is a useful bullet listing. The note "adverse birth outcomes, such as low birth weight" is another inadequate mis-direction, in my opinion, since there have been a range of negative birth outcomes reported (including pre-term, neurological, and developmental) that I would think most might consider more substantive and important than low birth weight…so again, if the decision is to list a few examples, be careful to list important ones or illustrative ones, and be aware of what may be missing. Missing from this overall list are also more important topics to identify, such as neurological and neuro-developmental effects (behavior and learning), and metabolic effects (obesity, blood pressure, and even diabetes). The point is, this can be a considerable listing of outcomes, so one needs to be thoughtful of intent here.

I-2, para2, sentence 1 – Are you saying the only data used in preparation of this appendix were those from epi or clinical studies? Nothing from bench-top toxicology? Each of these three approaches (Epidemiology, toxicology, and clinical studies) provide unique and overlapping benefits to health research, thought the specific benefits and shortcomings of each approach differ (but overlap).

I-2, para2, sentence 2 – Arguably, the historical approach to understanding the health effects of air pollutants has, in the clinical and toxicological settings, been focused on specific pollutants and individual effects. In the past decade, there has been increasing pressure to investigate the combined effects of multiple pollutants on human health, since multi-pollutant exposures are a more accurate reflection of the "real" world. Given this is the case, I would delete the last half of this sentence in the text ("…and specific pollutants responsible for individual effects").

I-2, para3, sentence 4 ("Evidence for more than additive effects has not been strong…") – I am not sure you would get a consensus opinion on this claim, and more importantly, the claim is not central to the presentation here. I think the key point is that regulatory policy has, by in large, focused on individual pollutants without much regard for multi-pollutant exposures or effects. Accordingly, the document reviews the health information in an individual stepwise fashion. However, since it is acknowledged that there are multiple chemicals co-exposures occurring, a brief review of reported combined effects is also being presented herein.

I-3, para2 – The presentation of a criteria by which to gauge causal relationships of reported health data is useful here, but there is inadequate explanation as to context. I suggest adding a sentence or two prior to Table I-1 that says something like this: "Over the decades of national reviews of outdoor air pollution and their health impacts, the US EPA has developed a list of five criteria by which the strength and credibility of data can be judged. This five-tier weight-of-evidence approach provides an objective basis for assessing the breadth, specificity, and consistency of evidence concerning a particular health outcome."

I-4, Ozone, third sentence ("Since it is a gas, …") – This sentence is literally true but generally misleading to readers. Fine (and ultra-fine) particles can also penetrate into the gas-exchange regions of the lung, so I object to the phrasing "Since it is a gas,…" and suggest this qualification be removed.

I-6, Short-Term Effects of Ozone, para1, first sentence – This statement is partially true and incomplete. Increased physical activity increases both depth and frequency of inhalation. This results in higher ventilation rates ("more air and ozone" being breathed in) and increased surface areas of the lung becoming accessible to the inhaled air parcel. Therefore, additional portions of the lung are likely to come into contact with ozone during increased physical activity, compared to lower activity levels or rest.

I-6, Short-Term Effects of Ozone, para2, last sentence – The statement seems to purposely focus on respiratory outcomes. Is this because you are purposely limiting the discussion to a causal threshold of "likely to be causal"? Under a casual determination of "suggestive of a causal relationship", there are cardiovascular, reproductive, developmental, and central nervous system effects, as well. My concern here is that you are limiting the range of discussion to only respiratory endpoints, when there are many other target organs at risk.

I-7, para1, third sentence ("USEPA's recent review…") – Probably better to anchor this comment to a date rather than "recent" – suggest saying "USEPA's 2013 Integrated Science Assessment Review…" or something like that to link the comment to the data resource.

I-8, para1, inclusion of confidence intervals in discussion of CHS publication regarding school absences – This seems a little confusing and inconsistent with the previous discussion, where confidence intervals or p values have not been presented with reported observed changes in health status. In the interest of the report being consistent and accessible to a wide portion of the public, I suggest removing the confidence intervals from this passage; the citation provides a ready means of more detailed review of the research, should a Reader want more information.

I-8, para2, discussion on attenuation of response (adaptation, reduction in magnitude, …) – Not clear from your presentation what the intent or objective here, but you seem to be discrediting the notion of "adaptation", so a few comments are in order:

(1) Many researchers in the field would shy away from the phrase "adaptation", which denotes some positive evolutionary change; "toleration" or "tolerance" has been suggested as an alternative phrase, or something connoting reduced or diminished response;
(2) I don't discount what you have said in the text regarding the uncoupling of macro-system (i.e. lung function) and micro-system (i.e., biochemical) changes, but since I am one of the investigators who did several of the ozone toleration studies in controlled-exposure settings, I would note that there is a range of human response. Based on laboratory findings, it appeared that a portion of the population were "non-responders" (didn't really change much from baseline levels), a substantive portion of the population displayed some attributes of "toleration" (that is, developed some diminished response with recurring ozone exposure), and that another substantive portion did not seem to develop a diminished response (that is, with repeated challenge, there was fairly consistent and repeated loss of lung function). This was true with both consecutive (i.e. daily) and seasonal responses. Regarding seasonal response, it appeared that the observed capacity for "toleration" or diminished response was established during the early part of the "smog" season, persisted through it, and was "lost" through the winter…so the phenomenon seems to be repeatable (among certain people). I think this is what the last sentence in the paragraph is suggesting (that there is a seasonal aspect to toleration, but that it is somewhat ephemeral).

I-11, Long-Term Exposure Effects of Ozone, para2, line2 – should be "summer-only".

I-13, para2, line5 – "…Tumor Necrosis Factor α …"; add (TNF-α) to clarify (many readers may only know it by its shorthand symbol).
I-13, para2, last sentence – This paragraph is about laboratory studies of animals, but the least sentences is talking about humans (?). This last sentence seems more appropriate for I-8, para3, and should be removed from the current location.

I-13, next-to-last paragraph, first sentence – too long and awkwardly constructed. Should be broken into two sentences: "Some animal studies …changes of the lung. However, morphological, developmental, and immunological differences make it difficult to apply these results to humans."

I-13, last para, second sentence (In southern California communities with high ozone concentrations ,…") – should provide a number or range to the term "high". The key message

from the study was that children playing in currently-encountered ambient levels of ozone were at increased risk for developing asthma (not just making existing asthma worse).

I-14, para2, line7 ("…prenatal exposures and low birth weight…") – should read *on* low birth weight …

I-14, para3, first sentence – remove the word "newer" from the phrase 'other health endpoints"…

I-14, para3, second sentence – "One study of childhood autism was conducted in LA County and reported …" should be re-written to read, "A study of childhood autism conducted in LA County reported…" (…there has been more than one autism study conducted in LA County…)

I-14, last para, second-to-last sentence – should read 'first-trimester ozone", "second-trimester ozone", and "preconception-SO2 … (hyphens missing from existing text)

I-15, Sensitive Populations for Ozone-Related Health Effects – This is an important issue for the public, who always wonders who (if anyone) is at increased risk, so I think it is useful to take some care in getting this information out there in a useful way. One should probably specify which review you are drawing data from (i.e., the February 2013 USEPA Integrated Science Assessment for Ozone). Additionally, you summarized much (but not all) of the identified at-risk populations listed in Table 8 from the 2013 EPA ISA (see Table 8 below, cut and pasted from the 2013 ISA). It might also be useful to create a short table of Evidence Class, Risk Factor, short summary directional effect, and a link or citation (to either the ISA at the EPA website, or to individual peer-reviewed articles) for inclusion into the AQMP appendix.
additional

Table 8-6 Summary of evidence for potential increased risk of O_3-related health effects.

Evidence Classification	Potential At Risk Factor
Adequate evidence	Genetic factors (Section 8.1) Asthma (Section 8.2.2) Children (Section 8.3.1.1) Older adults (Section 8.3.1.2) Diet (Section 8.4.1) Outdoor workers (Section 8.4.4)
Suggestive evidence	Sex (Section 8.3.2) SES (Section 8.3.3) Obesity (Section 8.4.2)
Inadequate evidence	Influenza/Infection (Section 8.2.1) COPD (Section 8.2.3) CVD (Section 8.2.4) Diabetes (Section 8.2.5) Hyperthyroidism (Section 8.2.6) Race/ethnicity (Section 8.3.4) Smoking (Section 8.4.3) Air conditioning use (Section 8.4.5)
Evidence of no effect	--

Additional note: SES is mentioned twice in the paragraph – first as having adequate evidence, then as having suggestive. As Table above shows, it should be suggestive, based on the ISA.

I-15, Summary Ozone Health Effects, first sentence – I think this could be strengthened and clarified. I suggest the following replacement sentences: "In summary, outdoor ozone exposures have been associated with a range of negative human health effects. The strongest evidence for negative health impacts are on the respiratory system, and are measured by decreased lung function performance and increased cell injury. Effects on other organ systems, including cardiovascular, neurological, and metabolic have been shown to lead to heart disease, learning and developmental issues, and obesity. Although the specific mechanisms of action for ozone effects on the various health endpoints …

OBSERVATION: The PM Section (I-15 through mid-I-23) - The "feel" of the section discussing PM health effects in the report is different than the previous ozone section. In the PM section, there is greater reliance on and quotation of specific effect estimates from specific studies, often with study-by-study citation. In the ozone health effects section, it seemed to be a more general discussion, with less rote listing of estimates and citations. The "correct" presentation depends on the target audience and the level of intended detail. It might be sufficient to cite the EPA NAAQS documents and reproduce some of the key tables, rather than trying to cut and paste larger more detailed sections of the respective documents in to the current AQMP.

I-15, Particulate Matter, para1, first sentence – add the concept of particle toxicity and expand the impact of factors, by revising the first sentence to read: "…a complex group of pollutants that vary in physical, chemical, and biological dimensions. Physically, particles can vary by size, surface area and roughness, shape, and mass. Chemically, they vary by composition. Biologically, they can vary by toxicity. In addition to all these factors, particles vary by source, which can affect many of the previously identified factors. Particulate matter can come from anthropogenic (man-made, such as from combustion of fuels, or frictional abrasion) or "natural" (plants – for example, pollens and spores) origins."

I-15, Particulate Matter, last para, second sentence – replace "to cover particles" with "to focus on particles". This word change is necessary because PM10 was already a part of TSP, so it was already in the existing NAAQS. Based on the growing PM data base, it was determined that the health effects observed were caused by the smaller particles in TSP, so a portion of the previous NAAQS was identified for regulation.

I-15, Particulate Matter, last para, third sentence – Revise to read "These can be inhaled and deposited throughout the upper and lower respiratory system, depositing in both airways and gas-exchange areas of the lung.

I-16, para2, first sentence - Delete the "In more recent years,", and begin the paragraph this way: "As more health research data has become available, concerns have centered on smaller and smaller particles. Additional focus has been places on …"

I-16, para2, last sentence – “In 2002, the California Air Resources Board adopted an air quality standard for PM2.5 at a level of 12 ug/m3, in the form of an annual average.”

I-16, para3, first sentence – “since that time, ~~numerous~~ *additional* studies have been published…”

I-17, para1, second-to-last sentence – “Of note, there is currently no federal of California standard for PM10-2.5, *although a PM10 standard remains in effect (see Table I-6).*

I-19, last para, last sentence – replace “preexistent” with ‘preexisting”.

I-21, para1, second sentence (“The results indicated that the association of PM10 …) – what is it you are trying to say? This seems convoluted and confusing. Removal of this sentence in its entirety improves the text, in my opinion…

I-21 para1, last sentence – “these results suggest that the effects *reported* are likely due to …”

I-21, para2, lines 2 and on – Change to read “After the study was published, it was discovered that some of the study analyses had been performed with incorrect default values. When the investigators re-analyzed the data using revised settings for the data, the size of the effect diminished, but the results remained largely the same. The strong positive association between acute PM10 exposure and mortality remained, both upon reanalysis using revised software and using alternative modeling approaches.”

i-23, para1, first sentence – This sentence, while true on the face of it, is awkward because there are MANY reasons for variation in relative importance of PM2.5 or PM10-2.5. Several of these have already been discussed earlier in the text, so it is not clear why this subset (concentration, components, seasonal variation) is being reported here again. I recommend deletion of this sentence and beginning the paragraph with the following sentence: A major knowledge gap in understanding the relative importance of “fine” PM (PM2.5) and “coarse” PM (PM10-2.5) is the relative lack of direct PM10-2.5 measurements.”

I-23, para1, first & second sentences (and elsewhere in the document) – the denotation for coarse particles switches back and forth through the sections – sometimes PM10-2.5, sometimes PM2.5-10…pick one and be consistent.

I-23, last para, second sentence – “The effect estimates *for these various morbidities* are generally higher than the estimates for mortality.

I-23, last paragraph, last two sentences – change to read “Observed effects have been associated with PM10, PM2.5, and PM10-2.5.”

I-31, para2, second sentence – missing a hyphen from “distance-weighted”.

I-37, para2, third sentence – (Regarding Avol 2001 Movers’ Study…) It’s important to note that children who moved to areas of higher PM10 & NO2 showed declines in lung function growth rates. Another way of phrasing this is that the effects of exposure seemed to “work” both ways – more exposure led to poorer lung function growth rates, less exposure led to improved lung function growth rates.

I-37, para2, last sentence – “The risk of lower lung function was about ~~five~~ four times higher in children …:

I-37, last para and last sentence, AND I-38 first para, line 8 – in some places, the term “new-onset asthma” has a hyphen, while in other places it does not; be consistent.

I-39, para2, last sentence – low-term (not term low) …

I-40, first para, second sentence – should read “A couple *of* recent studies …”

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints – It might be easier for Readers to follow along and/or locate text of interest if there were sub-headings for these paragraphs – Metabolic Syndrome, Neurological Impacts, …

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints, para1, first sentence – Many who access this document may not be aware of what is meant by the term “metabolic syndrome”, so it would be useful to provide a working definition here. Additionally, it is my understanding that in describing this endpoint, insulin resistance, high cholesterol, obesity, hypertension, etc are *attributes, manifestations, or markers* of metabolic syndrome, not the syndrome itself (in other words, a syndrome is a collection of symptoms, not the presence of any one condition). Therefore, the phrasing in the final sentence of the first paragraph in the section should be reviewed and revised.

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints – The topic of metabolic syndrome and particle pollution is introduced, but very little is said. There have been several dozen publications to date (just search on Pub Med for metabolic syndrome & air pollution, or see Brook et al 2016 article in Hypertension, Eze et al 2015 in PLoS One, Devlin et al 2014 in Toxicol Sci, …).

I-41, para1 – (similar comment to above) – While there are a few studies documented in the area of neurological outcomes, not that much is said. There is a growing a broad literature on the topic, with work reported by Annette Peters’ group in Germany, Jordi Sunyer’s group at CREAL in Barcelona, and the Harvard Normative Aging Study group (perhaps search on “Joel Schwartz:, Normative Aging Study, or ?).

I-41, Sensitive Populations for PM-Related Health Effects – As was done earlier in the document with regard to ozone and sensitive sub-populations, you might consider summarizing more directly from the most recent PM review by EPA CASAC to summarize who is considered to be at elevated risk and the degree of confidence associated with the respective claim (Chapter 8 of the 2010 ISA).

I-42 – Summary Particulate Matter Health Effects – this is an important section, but doesn’t quite deliver on the promise. Rather than a summary of what has been presented, this section seems to present additional information from additional sources. While the information presented is useful, it is NOT a ***summary*** of what has been presented.

I-43, Ultrafine Particles – why is this being presented AFTER the summary of the chapter? There may not be a current standard by which ultrafines are judged, but this section still provides information regarding health effects of PM…?

I-48, para1, last two lines – layout has switched to centered lines, rather than left-justified…

I-62, para2, second-to-last sentence – “However, it is important to note that these results represent a more refined risk estimation methodology, not an increase in risk.” This sentence is absurd, on the face of it. If a more refined estimate approach results in a larger risk estimate,

how can one claim there is no increase in risk? This is NOT just a numerical exercise – the implication of the numerical correction is arguably precisely that the risk is higher than was previously calculated; the sentence should be deleted.

I-63, Conclusions – This section is incomplete, arguably inadequate, and seems to just stop without concluding much of anything. Comments could have been made about improvements in the health database for each of the NAAQS

Pollutants. Comments could have been made regarding TACs or ultrafines, or improved understanding of susceptible sub-populations. Comments could have been restricted to ozone and PM, since that seems to be much of the original intent of this appendix…but instead, not much is "concluded."

I-87 – Draft 2016 AQMP Appendix I Attachment, Publications from Health Related Research Projects Funded or Co-Funded by SCAQMD – what is this even doing in this document? What does it add to the presentation? How does it help us to evaluate the health effects information presented in the body of the appendix? Possibly an interesting side discussion, but not germane to the focus of the presentation (since the source of funding for the reviewed research is not at issue); this could be deleted.

From: John Dunn <jddmdjd@web-access.net>
Sent: Sunday, August 14, 2016 5:59 PM
To: Jo Kay Ghosh; 'Henry A. Roman'; 'George D. Thurston'; Elaine Shen; Philip Fine; Wayne Nastri; Anthony Oliver
Subject: Submission to South Coast Quality Air Management District on AQMP proposals for 2016 human health effects
Attachments: Dunn Letter to SCAQMD re 2016 AQMP PM2.5 Claims 081416.pdf

Dr. Ghosh,

Attached is my letter and attachments pertinent to that letter opposing the new additional air regs that are part of the 2016 plan.

Please make sure the Board sees my critique and also the scientists engaged by South Coast to put together "research" intended to support the new regulations, that I consider inadequate to support any such regulatory proposals.

Thank you for your consideration of these matters
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Civilian Faculty Emergency Medicine
Carl R. Darnall Army Med Center
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325 784 6697
325 642 5073 (cell)

John Dale Dunn MD JD
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8-14-16

Air Quality Management Plan (AQMP) Staff
South Coast Air Quality Management District
Diamond Bar, CA
aqmp@aqmd.gov

Re: Public Comments on Draft 2016 AQMP

Ladies and Gentlemen,

As a follow-up to my unanswered public comments on the 2012 AQMP, I am submitting these public comments on the Draft 2016 AQMP. In particular, I protest the efforts of the SCAQMD staff to try to make the air pollution research pig's ear that uses unreliable, sometimes risible claims of deaths from small particle air pollution (PM2.5) into silky purse of evidence that justifies more expensive and onerous air regulations.

I think it deceitful that the South Coast would allow small associations as evidence of their claims of thousands of deaths annually in the South Coast area from research that shows small associations of deaths from small particle air pollution. Such claims are riven with deceit. So many papers used by the SCAQMD staff contain small associations and confidence intervals that cannot support the death claims.

I have attached to this cover letter the following items as detailed criticism of the PM2.5 premature death claims made in the Draft 2016 AQMP. 5-1

1. My 15-page January 19, 2016 letter to Mr. Henry A. Roman of Industrial Economics, Inc., takes down the laughable claims of the 2015 Thurston EHP paper that has only small associations (not proof of lethality or toxicity at all) and confidence intervals that cross 1.0 and fail to prove any death effect at all from small particles air pollution. Dr. Thurston admits the weakness of his evidence in the abstract. He can't make his lack of evidence of deaths from air pollution go away. Data torturing and harvesting noise in the variability of death rates can't fix his problem.

2. The 53-page October 4, 2012 sworn declaration of US EPA senior research scientist Robert B. Devlin in human exposure experiments with small particles, who admits at Paragraph 7 that observational epidemiological studies can't prove causation. I would emphasize that Dr. Devlin fails to point out that small association/low Relative Risk or Odds Ratio results don't even achieve the level of association that allows for a researcher to assert a hypothesis of causation. You might say, a robust result from epidemiology isn't proof, a small association result is even less than that.

3. The 25-page Reference Manual chapter on Epidemiology articulates the rules on proof of causation from observational studies and I highlighted those sections on proof of causation, general causation beginning at page 597 et.seq. and specific causation at page 608 et.seq. I will not discuss the scientific deceit that is used so often trying to make statistical significance into a claim that the evidence is reliable—the scientists in the group know the deceit involved in p value cheating—which doesn't make unreliable evidence proof of anything.

4. Two pages of basic information from the website of the GRADE Working Group (http://www.gradeworkinggroup.org/), particularly regarding "Grading the quality of evidence and the strength of recommendations". This international group is focused on the need for reliable epidemiological evidence. In the 9th paper on quality of evidence in epidemiology, on page 2 item 2, read what they say about small associations and why quality of evidence depends on Relative Risks of more than 2. Every researcher in the air pollution business would be out of business if they followed the rules suggested about the strength of association to prove lethality of pollutants.

5. The 14-page September 28, 2012 American Statistical Association Proceedings paper by Dr. James E. Enstrom "Particulate Matter is Not Killing Californians", which he presented on August 1, 2012 to the ASA 2012 Joint Statistical Meeting Section on Risk Analysis. Dr. Enstrom's analysis of all sources of evidence on PM2.5 deaths relevant to California provides proof that there is no death effect in California. Tables on pages 2331 and 2332 show small associations with confidence intervals that include 1.0. On page 2333, a US map of PM2.5 mortality risk from the 2000 HEI Reanalysis Report of Krewski also shows that there is no small particle death effect in California. This paper is permanently posted on Dr. Enstrom's website (http://www.scientificintegrityinstitute.org/ASAS092812.pdf). 5-1 Con't

6. My three-page June 8, 2011 letter to CARB about the clownish performance of Michael Jerrett, trying to rehabilitate his air pollution research in California, after initially he admitted in public that his analysis showed no death effect at all. His trickster attitude shows what lots of research money and time can do to put lipstick on a research pig.

7. The 5-page August 13, 2015 SCIENCE manuscript, "Particulate Matter Does Not Cause Premature Deaths", that includes me with nine other coauthors, provides evidence, wide and deep that the claims of the South Coast researchers are faulty, and unreliable—that there is no death effect to be shown. This manuscript is permanently posted on the National Association of Scholars website (https://www.nas.org/articles/nas_letter).

Conclusions

I have provided a short version of my objections to research used to support the SCAQMD Draft 2016 AQMP claims about PM2.5 premature deaths.

I hope you read the objections see that the Thurston research cannot be cobbled together with the rest of the research, including the flawed conurbation paper of Michael Jerrett in support of any new small particle regulations BECAUSE the research shows that new air regs will not save lives because there are no deaths.

Thurston, Jerrett, and all the papers on air pollution death studies in California show an overall small particle air pollution death effect of ZERO. What you gonna do—change the rules on how to study toxicity to justify more aggressive and burdensome air regs for Southern California—to achieve what? and at what cost?

I will provide, anytime, anywhere, in any forum, responses to South Coast staff or their hired researchers on their proposed small particle proposals and asserted justifications, when necessary, and depending on what you do with the sorry Thurston results.

You also have a big problem with the other show horses you have in the air pollution research community, all of them generating small association studies that don't prove up the South Coast claims about deaths. Not at all. In fact the studies show no death effect is likely, or the associations on the studies would be more consistently robust.

The scientists reading know what I am talking about, a pile of studies with no proof of causation at all, not even a whiff of good evidence for arguments about deaths makes a good argument that the South Coast portfolio is my best exhibit to prove that South Coast is making claims that are not supported by good evidence—evidence that doesn't pass the laugh or smell test.

5-1
Con't

Dr. Thurston and his now very old small particles paper that admits extremely small Hazard Risks and even Confidence Intervals that include 1.0 is no proof. The Jerrett conurbation gambit is silliness, expensive silliness, but still no proof of a death effect.

I am happy to expand on this letter and attachments by webinar, teleconference or further correspondence in response to questions.

Please make sure this letter and the attachments are made available to the SCAQMD Governing Board.

Cordially,

/s/JDunn MD

John Dale Dunn MD JD

The following attachment(s) were included with Comment Letter #5 submitted by Dr. John Dale Dunn, and was/were duplicate entries on previous comment letter(s) received:

- Letter from Dr. John Dale Dunn to Henry Roman, dated January 19, 2016. This corresponds to Comment letter #5 under the draft Socioeconomic Report.

The following attachments were also included with Comment Letter #5 submitted by Dr. John Dale Dunn. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachments, however, interested parties can obtain access at the links provided below:

- Pages 21 – 23 of the Devlin Declaration Exhibit 1, which includes several copied pages of the following text: Committee on Research Priorities for Airborne Particulate Matter; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council. "Research Priorities for Airborne Particulate Matter: IV. Continuing Research Progress". Washington, DC: National Academies Press, 2004. https://www.nap.edu/catalog/10957/research-priorities-for-airborne-particulate-matter-iv-continuing-research-progress
- Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence; Federal Judicial Center; National Research Council. "Reference Manual on Scientific Evidence: Third Edition". Washington, DC: National Academies Press, 2011. https://www.nap.edu/catalog/13163/reference-manual-on-scientific-evidence-third-edition
- GRADE working group webpage titled "Introduction"
- Joint Statistical Meeting 2012 Online Program, session 546 (Wed, 8/1/2012, 2:00PM – 3:50PM), titled "Are Fine Particulates Killing Californians?", and abstract by James Enstrom titled "Particulate Matter is Not Killing Californians". http://www.amstat.org/meetings/jsm/2012/onlineprogram/ActivityDetails.cfm?SessionID=207510 and http://www.amstat.org/meetings/jsm/2012/onlineprogram/AbstractDetails.cfm?abstractid=303741
- Joint Statistical Meeting 2012 Section on Risk Analysis paper by James Enstrom, titled "Particulate Matter is Not Killing Californians", dated September 28, 2012. http://www.scientificintegrityinstitute.org/ASA092812.pdf
- Enstrom et al. manuscript titled "Particulate Matter Does Not Cause Premature Deaths", dated August 17, 2015. Available within this link, on pages 13-17: https://www.nas.org/images/documents/PM2.5.pdf

A hard copy of all materials included in the comment letters, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

Appendix A, Dr. Robert Devlin admission under oath
Case 1:12-cv-01066-AJT-TCB Filed 10/04/12
(53 pages)

DECLARATION OF ROBERT DEVLIN

I, Robert B. Devlin, pursuant to 28 U.S.C. § 1746, declare, under penalty of perjury, that the following statements are true and correct based upon my personal knowledge, experience or upon information provided to me by persons under my supervision:

1. I am a **Senior Scientist (ST) for the Environmental Public Health Division (EPHD), National Health and Environmental Research Laboratory (NHEERL), Office of Research and Development (ORD), U.S. Environmental Protection Agency.** As one ofthree STs in NHEERL I am expected to be a scientific leader in the area of air pollution research, to define important areas of research, assemble teams to carry out that research and ensure it is completed in a timely manner and published in peer-reviewed journals. I am currently on detail as Acting Associated Director for Health for NHEERL. Prior to my current position, I was Chief of the Clinical Research Branch (CRB) ofthe EPHD from 1994 – 2008. The CRB is responsible for doing nearly all controlled human exposure studies within NHEERL. I as also acting Director of
EPHD (then call Human Studies Division) in 2007; the Director oversees all research in the Division including epidemiology, clinical and in vitro studies. **I was acting National Program**

Director for ORD's Air Research Program in 2000. This position is the lead for developing research plans related to air pollution for all of ORD and representing the program to groups outside the EPA. I hold adjunct faculty appointments at the University ofNorth Carolina (Chapel Hill) and North Carolina State University. I have been engaged in performing controlled human exposure studies as an EPA investigator since 1986. I have authored or co-authored more than 190 scientific articles, 53 of which involved controlled exposure of human volunteers to air pollutants. The quality of my work at EPA has been recognized by several awards, including one gold and 9 bronze medals, and 8 EPA Scientific and Technological Achievement Awards. I have been invited to present my research at more than 100 Universities, Workshops, and International Meetings.

2. I have a B.S. Degree from the University of Texas (El Paso) that was granted in 1969 and a **Ph.D. degree from the University of Virginia** that was granted in 1976. I was a member of the faculty at Emory University (Atlanta) from 1979 – 1986.

3. I have reviewed the Complaint and exhibits filed in the above-captioned case

4. The term particulate matter (PM) covers a broad class of discrete, but chemically and physically diverse, particles that are ubiquitously pres nt in the ambient air and are emitted from different sources such as power plants, mobile sources, biomass burning, and dust generated by mechanical processes. There are three generally recognized modes of PM defined by particle diameter: very small so-called ultrafine particles that result from the primary emissions related to engine combustion and which are usually in close proximity to those sources; large (coarse) particles primarily generated by abrasive processes and from wind-blown dust; and so-called fme particles which derive from combustion by-products that volatilize and quickly condense or from gases (such as sulfur oxides and nitrogen oxides) that react and transform in the atmosphere after

being emitted. PM2.5 is roughly synonymous with fine PM, and generally includes all particulate matter with an aerodynamic diameter of2.5 micrometers or less. 40 CFR § 50.7(a). Principal sources of PM2.5 are fossil fuel combustion, including motor vehicle and power plant emissions, natural and anthropogenic biomass burning, as well as other industrial processes such smelting The EPA has specific regulations to control levels of both fine and coarse particles.

5. **In December 2009 EPA issued the Integrated Science Assessment (ISA) for Particulate Matter, pursuant to section 108 ofthe Clean Air Act (CAA), 42 U.S.C. § 7408.** The ISA is an update of prior science assessments of PM, and reflects the state of the science at that time. The ISA was developed after lengthy review by the Clean Air Scientific Advisory Committee, a federally mandated body charged with advising EPA about scientific matters relating to particulate matter and other forms of air pollution. CAA § 109(d)(2), 42 U.S.C. § 7409(d)(2). Development of an ISA typically involves the consideration of thousands of scientific studies conducted in the U.S. and around the world as part of assessing the relationship between air pollutant exposures and health effects. In the ISA, the entire body of scientific evidence, including epidemiological, controlled human exposure, animal toxicological studies, studies with cultured cells, as well as other sources of information, is assessed and an overall judgment is made on the causal relationship between exposure to ambient PM2.5 and health effects. The ISA provides the scientific basis for development of the National Ambient Air Quality Standards (NAAQS) for an air pollutant. CAA § 109(b).[1]

6. Epidemiological studies typically use data from large populations of people with varying susceptibility to PM2.5 and evaluate the relationship between short or long-term changes in ambient levels ofPM2.5, e.g. changes in the 24-hour average level ofPM2.5 measured at

[1] Ambient air refers to outdoor air in places that members of the public have access to. 40 C.F.R. § 50.1.

monitors in a metropolitan area, with changes in mortality and morbidity such as the numbers of emergency department visits and hospital admissions. This generally involves the use of complex statistical methods to evaluate the mathematical relationship between variations in measured ambient air pollution levels and health data.

7. **Epidemiological observations are the primary tool in the discovery of risks to public health such as that presented by ambient PM2.5. However, epidemiological studies do not generally provide direct evidence of causation. They indicate the existence or lack of a statistical relationship between ambient levels of PM2.5 and adverse health outcomes**. Large population studies cannot assess the biological mechanisms (called biological plausibility) that could explain how inhaling ambient air pollution particles can cause illness or death in susceptible individuals. This sometimes leaves open the question of whether the observed association in the epidemiological study is causal or whether PM2.5 is merely a marker for some other unknown substance.

8. **Controlled human exposure studies conducted by EPA scientists and EPA funded scientists at multiple universities in the United States fill an information gap that cannot be filled by large population studies. In 1998 the Committee on Research Priorities for Airborne Particulate Matter was established by the National Research Council in response to a request from Congress. The committee was charged with producing four reports over a five-year period which describe a conceptual framework for an integrated national program of particulate-matter research and identified the most critical research needs linked to key policy-related scientific uncertainties. Excerpts from their most recent report (published in 2004) are attached as Exhibit**

1 to this Declaration. On page 36 the Committee says:

Controlled human exposure studies offer the opportunity to study small numbers of human subjects under carefully controlled exposure conditions and gain valuable insights

into both the relative deposition of inhaled particles and the resulting health effects. Individuals studied can range from healthy people to individuals with cardiac or respiratory diseases of varying degrees of severity. In all cases, the specific protocols defining the subjects, the exposure conditions, and the evaluation procedures must be reviewed and approved by institutional review boards providing oversight for human experimentation. The exposure atmospheres studied vary, ranging from well-defined, single-component aerosols (such as black carbon or sulfuric acid) to atmospheres produced by recently developed particle concentrators, which concentrate the particles present in ambient air. The concentrations of particles studied are limited by ethical considerations and by concern for the range of concentrations, from the experimental setting to typical ambient concentration, over which findings need to be extrapolated.

Exhibit 1 at 36. Controlled human exposures studies have been conducted for decades on important pollutants such as ozone, particulate matter, nitrogen dioxide (NO_2), sulfur dioxide (S02), VOCs emitted in from new homes, and carbon monoxide (CO).

9. **Controlled human exposure studies assess the biological plausibility of the associations observed in the large-population epidemiological studies.** Controlled human exposure studies usually compare the response of an individual following exposure to clean air with their response following exposure to a pollutant that was generated or prepared under carefully controlled conditions, thus providing direct causal evidence that observed effects are related to the pollutant of interest. These studies are done under conditions that are controlled to ensure safety, with measurable, reversible physiological responses. **They are not meant to cause clinically significant adverse health effects, but rather reversible physiological responses can be indicators of the potential for more serious outcomes in susceptible populations identified in epidemiology studies.** As such, controlled human exposure studies do not study individuals felt to be at significant risk; they almost always study healthy individuals or people with conditions such as mild asthma. Controlled human exposure studies, together with toxicological studies, provide important insights which can improve our understanding of the potential biological mechanisms or pathways for effects observed in epidemiological studies (e.g., respiratory symptoms or

cardiovascular events, hospital admissions or emergency department visits, or premature death).

10. **Obtaining information on the biological impacts of exposure to PM2.5 from controlled human exposure studies such as the CAPTAIN study is a very important element in developing an integrated body of scientific knowledge to evaluate the impact on health from exposure to PM**

2.5 air pollution. The CAPTAIN study is particularly important in that it addresses an area of PM research where there are still important questions related to fully understanding the role of specific components included in the mixtures of fine particles represented by PM2.s that may be more closely related to the cardiovascular health effects observed in epidemiological studies. PM2.5 is a complex mixture derived from several different sources**. There is still uncertainty as to which components or sources of PM2.5 are most responsible for causing effects people and if different components or sources cause effects by different biological mechanisms. This type of research can help address existing uncertainties in the PM scientific literature, providing important evidence for informing future PM NAAQS reviews and, in particular, consideration of possible alternative particle indicators and/or standard levels.** In some cases, research in these areas can go beyond aiding standard setting to informing the development of more efficient and effective control strategies.

11. **For ethical and safety reasons, controlled human exposure studies to air pollution conducted by NHEERL are initiated only if there is evidence that any effects to the subjects resulting from exposure will be mild, transient, and reversible, and if there is prior data from one or more of the following types of research:**

a. Testing in laboratory animals.

b. Observational research involving only naturally occurring human exposures.

c. Human studies involving a closely related air pollutant.

12. Based on the entire body of scientific evidence, including epidemiological, controlled human exposure, and toxicological studies, the ISA for PM drew several important conclusions about the relationship between exposure to PM2.5 and health effects. For short-term exposures to PM2.5, the ISA concluded there was a causal relationship between ambient PM and cardiovascular effects. The epidemiologic evidence showed that increases in 24-hour levels of ambient PM2.5 was mathematically associated with an increase in hospital admission or emergency room visits, predominantly for ischemic heart disease [IHD] and congestive heart failure [CHF]). See ISA p. 2-9, attached as Exhibit 2 to this Declaration. **There was also evidence from a small number of toxicological and controlled human exposure studies that supported the biological plausibility of this conclusion, although these studies needed to be duplicated and expanded to identify specific PM components and sources which are of most concern. The ISA also concluded there was a causal relationship between ambient PM and mortality. An evaluation of the epidemiological literature indicates consistent positive associations between short-term exposure to PM2.5 and all-cause, cardiovascular-, and respiratory-related mortality. ISA p. 2-10, Exhibit 2 to this Declaration. Finally, the ISA concluded that there was a likely casual relationship between ambient PM and respiratory effects. The recent epidemiological studies that have been evaluated report consistent positive associations between short-term exposure to PM2.5 and respiratory emergency department visits and hospital admissions for chronic obstructive pulmonary disease (COPD) and respiratory infections. ISA p.2-10, Exhibit 2 to this Declaration. The evidence of serious health effects such as hospital admissions, emergency department visits, and death, all derived from a large body of epidemiological studies.**

13. The risk of serious health effects from exposure to typical levels ofPM2.5 is largely focused on people with preexisting illnesses, such as elderly people with cardiovascular diseases or COPD. Even for people with preexisting diseases, there is no evidence that all persons are affected the same way or have the same degree of risk.

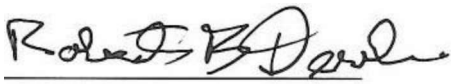
14. The body of scientific evidence also informs us on what risks there are to an individual that is exposed to PM2.5. For example, **it is clear that PM2.5 is not lethal or toxic to all people. The risk of serious health effects is clearly focused on people such as those with pre-existing cardio or respiratory illness. When very large numbers of people are exposed, as occurs in major population centers, the overall risk to the public is large enough to present a serious public health problem in the form of increased mortality and morbidity. It is this serious risk to the overall public health that leads EPA to describe PM as a serious public health problem.**

15. **However, the risk to an individual is very different from the overall public health risk associated with exposures of large populations of people to ambient air levels of PM2.5. This is especially true if the individual does not have pre-existing health conditions such as preexisting cardiovascular disease. While it is impossible to say there is no risk to a healthy individual, epidemiology studies provide evidence that the risk to healthy individuals is considered to be very small. Institutional review boards (IRBs) are charged with overseeing the safe and ethical conduct of human studies. IRBs from the University of North Carolina Medical School (which oversee EPA studies done on the campus of the University ofNorth Carolina) as well as those which oversee human studies at several universities throughout the US, in Canada, England, and Sweden have all examined the risk posed to individuals exposed to particulate air pollution and concluded that these studies are safe and ethical to perform.**

16. EPA relies on the entire body of scientific evidence to draw judgments about the risk to the

public health from exposure to ambient PM. In settings the NAAQS, EPA exercise it scientific and public health judgment and determines levels that will protect the public health, including groups of people that are more at risk to the air pollutant under consideration, with an adequate margin of safety. In the case ofPM2.5, the people most at risk from exposure to ambient PM2.5 include those with pre-existing cardiovascular illness or respiratory illness. The current NAAQS is 15.0 ug/m3 annual average, and a 35 *uglm3* 24-hour average. The 24 hour average is met if the 3 year average of the 98th percentile is 35 ug/m3 or below. The 98th percentile means that approximately 6 or 7 days in the year can have higher concentrations than the day used to compare to the 35 ug/m3. [2]

Dated: October 3, 2012



Robert B. Devlin

[2] The air quality in Chapel Hill, NC, where the subjects are tested, is wel1 within the levels that attain the current NAAQS.

Devlin Declaration Exhibit 1

Devlin Declaration Exhibit 2

Chapter 2. Integrative Health and Welfare Effects Overview

The subsequent chapters of this ISA will present the most policy-relevant information related to this review of the NAAQS for PM. This chapter integrates the key findings from the disciplines evaluated in this current assessment of the PM scientific literature, which includes the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, health studies (e.g., toxicological, controlled human exposure, and epidemiologic), and welfare effects. The EPA framework for causal determinations described in Chapter 1 has been applied to the body of scientific evidence in order to collectively examine the health or welfare effects attributed to PM exposure in a two-step process.

As described in Chapter 1, EPA assesses the results of recent relevant publications, building upon evidence available during the previous NAAQS reviews, to draw conclusions on the causal relationships between relevant pollutant exposures and health or environmental effects. This ISA uses a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

Beyond judgments regarding causality are questions relevant to quantifying health or environmental risks based on our understanding of the quantitative relationships between pollutant exposures and health or welfare effects. Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response or dose-response relationship?
- Under what exposure conditions (amount deposited, dose or concentration, duration and pattern) are effects observed?
- What populations appear to be differentially affected (i.e., more susceptible) to effects?
- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected, or are more sensitive to effects?

To address these questions, in the second step of the EPA framework, the entirety of quantitative evidence is evaluated to identify and characterize potential concentration-response relationships. This requires evaluation of levels of pollutant and exposure durations at which effects were observed for exposed populations including potentially susceptible populations.

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this assessment, presented in Chapter 1. Section 2.1 discusses the trends in ambient concentrations and sources of PM and provides a brief summary of ambient air quality. Section 2.2 presents the evidence regarding personal exposure to ambient PM in outdoor and indoor microenvironments, and it discusses the

[10] Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

relationship between ambient PM concentrations and exposure to PM from ambient sources. Section 2.3 integrates the evidence for studies that examine the health effects associated with short- and long-term exposure to PM and discusses important uncertainties identified in the interpretation of the scientific evidence. **Section 2.4 provides a discussion of policy-relevant considerations, such as potentially susceptible populations, lag structure, and the PM concentration-response relationship, and PM sources and constituents linked to health effects. Section 2.5 summarizes the evidence for welfare effects related to PM exposure. Finally, Section 2.6 provides all of the causal determinations reached for each of the health outcomes and PM exposure durations evaluated in this ISA.**

2.1. Concentrations and Sources of Atmospheric PM

2.1.1. Ambient PM Variability and Correlations

Recently, advances in understanding the spatiotemporal distribution of PM mass and its constituents have been made, particularly with regard to $PM_{2.5}$ and its components as well as ultrafine particles (UFPs). Emphasis in this ISA is placed on the period from 2005-2007, incorporating the most recent validated EPA Air Quality System (AQS) data. The AQS is EPA's repository for ambient monitoring data reported by the national, and state and local air monitoring networks. Measurements of $PM_{2.5}$ and PM_{10} are reported into AQS, while $PM_{10-2.5}$ concentrations are obtained as the difference between PM_{10} and $PM_{2.5}$ (after converting PM_{10} concentrations from STP to local conditions; Section 3.5). Note, however, that a majority of U.S. counties were not represented in AQS because their population fell below the regulatory monitoring threshold. Moreover, monitors reporting to AQS were not uniformly distributed across the U.S. or within counties, and conclusions drawn from AQS data may not apply equally to all parts of a geographic region. Furthermore, biases can exist for some PM constituents (and hence total mass) owing to volatilization losses of nitrates and other semi-volatile compounds, and, conversely, to retention of particle-bound water by hygroscopic species. The degree of spatial variability in PM was likely to be region-specific and strongly influenced by local sources and meteorological and topographic conditions.

2.1.1.1. Spatial Variability across the U.S.

AQS data for daily average concentrations of $PM_{2.5}$ for 2005-2007 showed considerable variability across the U.S. (Section 3.5.1.1). Counties with the highest average concentrations of $PM_{2.5}$ (>18 $\mu g/m^3$) were reported for several counties in the San Joaquin Valley and inland southern California as well as Jefferson County, AL (containing Birmingham) and Allegheny County, PA (containing Pittsburgh). Relatively few regulatory monitoring sites have the appropriate co-located monitors for computing $PM_{10-2.5}$, resulting in poor geographic coverage on a national scale (Figure 3-10). Although the general understanding of PM differential settling leads to an expectation of greater spatial heterogeneity in the $PM_{10-2.5}$ fraction, deposition of particles as a function of size depends strongly on local meteorological conditions. Better geographic coverage is available for PM_{10}, where the highest reported annual average concentrations (>50 $\mu g/m^3$) occurred in southern California, southern Arizona and central New Mexico. The size distribution of PM varied substantially by location, with a generally larger fraction of PM_{10} mass in the $PM_{10-2.5}$ size range in western cities (e.g., Phoenix and Denver) and a larger fraction of PM_{10} in the $PM_{2.5}$ size range in eastern U.S. cities (e.g., Pittsburgh and Philadelphia). UFPs are not measured as part of AQS or any other routine regulatory network in the U.S. Therefore, limited information is available regarding regional variability in the spatiotemporal distribution of UFPs.

Spatial variability in $PM_{2.5}$ components obtained from the Chemical Speciation Network (CSN) varied considerably by species from 2005-2007 (Figures 3-12 through 3-18). The highest annual average organic carbon (OC) concentrations were observed in the western and southeastern U.S. OC concentrations in the western U.S. peaked in the fall and winter, while OC concentrations in the Southeast peaked anytime between spring and fall. Elemental carbon (EC) exhibited less seasonality than OC and showed lowest seasonal variability in the eastern half of the U.S. The

highest annual average EC concentrations were present in Los Angeles, Pittsburgh, New York, and El Paso. Concentrations of sulfate (SO_4^{2-}) were higher in the eastern U.S. as a result of higher SO_2 emissions in the East compared with the West. There is also considerable seasonal variability with higher SO_4^{2-} concentrations in the summer months when the oxidation of SO_2 proceeds at a faster rate than during the winter. Nitrate (NO_3^-) concentrations were highest in California and during the winter in the Upper Midwest. In general, NO_3^- was higher in the winter across the country, in part as a result of temperature-driven partitioning and volatilization. Exceptions existed in Los Angeles and Riverside, CA, where high NO_3^- concentrations appeared year-round. There is variation in both
$PM_{2.5}$ mass and composition among cities, some of which might be due to regional differences in meteorology, sources, and topography.

2.1.1.2. Spatial Variability on the Urban and Neighborhood Scales

In general, $PM_{2.5}$ has a longer atmospheric lifetime than $PM_{10-2.5}$. As a result, $PM_{2.5}$ is more homogeneously distributed than $PM_{10-2.5}$, whose concentrations more closely reflect proximity to local sources (Section 3.5.1.2). Because PM_{10} encompasses $PM_{10-2.5}$ in addition to $PM_{2.5}$, it also exhibits more spatial heterogeneity than $PM_{2.5}$. Urban- and neighborhood-scale variability in PM mass and composition was examined by focusing on 15 metropolitan areas, which were chosen based on their geographic distribution and coverage in recent health effects studies. The urban areas selected were Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Inter-monitor correlation remained higher over long distances for $PM_{2.5}$ as compared with PM_{10} in these 15 urban areas. To a large extent, greater variation in $PM_{2.5}$ and PM_{10} concentrations within cities was observed in areas with lower ratios of $PM_{2.5}$ to PM_{10}. When the data was limited to only sampler pairs with less than
4 km separation (i.e., on a neighborhood scale), inter-sampler correlations remained higher for $PM_{2.5}$ than for PM_{10}. The average inter-sampler correlation was 0.93 for $PM_{2.5}$, while it dropped to 0.70 for PM_{10} (Section 3.5.1.3). Insufficient data were available in the 15 metropolitan areas to perform similar analyses for $PM_{10-2.5}$ using co-located, low volume FRM monitors.

As previously mentioned, UFPs are not measured as part of AQS or any other routine regulatory network in the U.S. Therefore, information about the spatial variability of UFPs is sparse; however, their number concentrations are expected to be highly spatially and temporally variable. This has been shown on the urban scale in studies in which UFP number concentrations drop off quickly with distance from roads compared to accumulation mode particle numbers.

2.1.2. Trends and Temporal Variability

Overall, $PM_{2.5}$ concentrations decreased from 1999 (the beginning of nationwide monitoring for $PM_{2.5}$) to 2007 in all ten EPA Regions, with the 3-yr avg of the 98th percentile of 24-h $PM_{2.5}$ concentrations dropping 10% over this time period. However from 2002-2007, concentrations of $PM_{2.5}$ were nearly constant with decreases observed in only some EPA Regions (Section 3.5.2.1).
Concentrations of $PM_{2.5}$ components were only available for 2002-2007 using CSN data and showed little decline over this time period. This trend in $PM_{2.5}$ components is consistent with trends in $PM_{2.5}$ mass concentration observed after 2002 (shown in Figures 3-44 through 3-47). Concentrations of PM_{10} also declined from 1988 to 2007 in all ten EPA Regions.

Using hourly PM observations in the 15 metropolitan areas, diel variation showed average hourly peaks that differ by size fraction and region (Section 3.5.2.3). For both $PM_{2.5}$ and PM_{10}, a morning peak was typically observed starting at approximately 6:00 a.m., corresponding with the start of morning rush hour. There was also an evening concentration peak that was broader than the morning peak and extended into the overnight period, reflecting the concentration increase caused by the usual collapse of the mixing layer after sundown. The magnitude and duration of these peaks varied considerably by metropolitan area investigated.

UFPs were found to exhibit similar two-peaked diel patterns in Los Angeles and the San Joaquin Valley of CA and Rochester, NY as well as in Kawasaki City, Japan, and Copenhagen, Denmark. The morning peak in UFPs likely represents primary source emissions, such as rush-hour traffic, while the afternoon peak likely represents the combination of primary source emissions and nucleation of new particles.

2.1.3. Correlations between Copollutants

Correlations between PM and gaseous copollutants, including SO_2, NO_2, carbon monoxide (CO) and O_3, varied both seasonally and spatially between and within metropolitan areas (Section 3.5.3). On average, $PM_{2.5}$ and PM_{10} were correlated with each other better than with the gaseous copollutants. Although data are limited for $PM_{10-2.5}$, the available data suggest a stronger correlation between PM_{10} and $PM_{10-2.5}$ than between $PM_{2.5}$ and $PM_{10-2.5}$ on a national basis.There was relatively little seasonal variability in the mean correlation between PM in both size fractions and SO_2 and NO_2. CO, however, showed higher correlations with $PM_{2.5}$ and PM_{10} on average in the winter compared with the other seasons. This seasonality results in part because a larger fraction of PM is primary in origin during the winter. To the extent that this primary component of PM is associated with common combustion sources of NO_2 and CO, then higher correlations with these gaseous copollutants are to be expected. Increased atmospheric stability in colder months also results in higher correlations between primary pollutants (Section 3.5).

The correlation between daily maximum 8-h avg O_3 and 24-h avg $PM_{2.5}$ showed the highest degree of seasonal variability with positive correlations on average in summer (avg = 0.56) and negative correlations on average in the winter (avg = -0.30). During the transition seasons, spring and fall, correlations were mixed but on average were still positive. $PM_{2.5}$ is both primary and secondary in origin, whereas O_3 is only secondary. Photochemical production of O_3 and secondary PM in the planetary boundary layer (PBL) is much slower during the winter than during other seasons. Primary pollutant concentrations (e.g., primary $PM_{2.5}$ components, NO and NO_2) in many urban areas are elevated in winter as the result of heating emissions, cold starts and low mixing heights. O_3 in the PBL during winter is mainly associated with air subsiding from above the boundary layer following the passage of cold fronts, and this subsiding air has much lower PM concentrations than are present in the PBL. Therefore, a negative association between O_3 and $PM_{2.5}$ is frequently observed in the winter. During summer, both O_3 and secondary $PM_{2.5}$ are produced in the PBL and in the lower free troposphere at faster rates compared to winter, and so they tend to be positively correlated.

2.1.4. Measurement Techniques

The federal reference methods (FRMs) for $PM_{2.5}$ and PM_{10} are based on criteria outlined in the Code of Federal Regulations. They are, however, subject to several limitations that should be kept in mind when using compliance monitoring data for health studies. For example, FRM techniques are subject to the loss of semi-volatile species such as organic compounds and ammonium nitrate (especially in the West). Since FRMs based on gravimetry use 24-h integrated filter samples to collect PM mass, no information is available for variations over shorter averaging times from these instruments. However, methods have been developed to measure real-time PM mass concentrations. Real-time (or continuous and semi-continuous) measurement techniques are also available for PM species, such as particle into liquid sampler (PILS) for multiple ions analysis and aerosol mass spectrometer (AMS) for multiple components analysis (Section 3.4.1). Advances have also been achieved in PM organic speciation. New 24-h FRMs and Federal Equivalent Methods (FEMs) based on gravimetry and continuous FEMs for $PM_{10-2.5}$ are available. FRMs for $PM_{10-2.5}$ rely on calculating the difference between co-located PM_{10} and $PM_{2.5}$ measurements while a dichotomous sampler is designated as an FEM.

2.1.5. PM Formation in the Atmosphere and Removal

PM in the atmosphere contains both primary (i.e., emitted directly by sources) and secondary components, which can be anthropogenic or natural in origin. Secondary PM components can be produced by the oxidation of precursor gases such as SO_2 and NO_X to acids followed by neutralization with ammonia (NH_3) and the partial oxidation of organic compounds. In addition to being emitted as primary particles, UFPs are produced by the nucleation of H_2SO_4 vapor, H_2O vapor, and perhaps NH_3 and certain organic compounds. Over most of the earth's surface, nucleation is probably the major mechanism forming new UFPs. New UFP formation has been observed in environments ranging from relatively unpolluted marine and continental environments to polluted

urban areas as an ongoing background process and during nucleation events. However, as noted above, a large percentage of UFPs come from combustion-related sources such as motor vehicles.
Developments in the chemistry of formation of secondary organic aerosol (SOA) indicate that oligomers are likely a major component of OC in aerosol samples. Recent observations also suggest that small but significant quantities of SOA are formed from the oxidation of isoprene in addition to the oxidation of terpenes and organic hydrocarbons with six or more carbon atoms. Gasoline engines have been found to emit a mix of nucleation-mode heavy and large polycyclic aromatic hydrocarbons on which unspent fuel and trace metals can condense, while diesel particles are composed of a soot nucleus on which sulfates and hydrocarbons can condense. To the extent that the primary component of organic aerosol is overestimated in emissions from combustion sources, the semi-volatile components are underestimated. This situation results from the lack of capture of evaporated semi-volatile components upon dilution in common emissions tests. As a result, near-traffic sources of precursors to SOA would be underestimated. The oxidation of these precursors results in more oxidized forms of SOA than previously considered, in both near source urban environments and further downwind. Primary organic aerosol can also be further oxidized to forms that have many characteristics in common with oxidized SOA formed from gaseous precursors. Organic peroxides constitute a significant fraction of SOA and represent an important class of reactive oxygen species (ROS) that have high oxidizing potential. More information on sources, emissions and deposition of PM are included in Section 3.3.
Wet and dry deposition are important processes for removing PM and other pollutants from the atmosphere on urban, regional, and global scales. Wet deposition includes incorporation of particles into cloud droplets that fall as rain (rainout) and collisions with falling rain (washout). Other hydrometeors (snow, ice) can also serve the same purpose. Dry deposition involves transfer of particles through gravitational settling and/or by impaction on surfaces by turbulent motions. The effects of deposition of PM on ecosystems and materials are discussed in Section 2.5 and in Chapter 9.

2.1.6. Source Contributions to PM

Results of receptor modeling calculations indicate that $PM_{2.5}$ is produced mainly by combustion of fossil fuel, either by stationary sources or by transportation. A relatively small number of broadly defined source categories, compared to the total number of chemical species that typically are measured in ambient monitoring source receptor studies, account for the majority of the observed PM mass. Some ambiguity is inherent in identifying source categories. For example, quite different mobile sources such as trucks, farm equipment, and locomotives rely on diesel engines and ancillary data is often required to resolve these sources. A compilation of study results shows that secondary SO_4^{2-} (derived mainly from SO_2 emitted by Electricity Generating Units [EGUs]), NO_3^- (from the oxidation of NO_x emitted mainly from transportation sources and EGUs), and primary mobile source categories, constitute most of $PM_{2.5}$ (and PM_{10}) in the East. $PM_{10-2.5}$ is mainly primary in origin, having been emitted as fully formed particles derived from abrasion and crushing processes, soil disturbances, plant and insect fragments, pollens and other microorganisms, desiccation of marine aerosol emitted from bursting bubbles, and hygroscopic fine PM expanding with humidity to coarse mode. Gases such as HNO_3 can also condense directly onto preexisting coarse particles. Suspended primary coarse PM can contain Fe, Si, Al, and base cations from soil, plant and insect fragments, pollen, fungal spores, bacteria, and viruses, as well as fly ash, brake lining particles, debris, and automobile tire fragments. Quoted uncertainties in the source apportionment of constituents in ambient aerosol samples typically range from 10 to 50%. An intercomparison of source apportionment techniques indicated that the same major source categories of $PM_{2.5}$ were consistently identified by several independent groups working with the same data sets. Soil-, sulfate-, residual oil-, and salt-associated mass were most clearly identified by the groups. Other sources with more ambiguous signatures, such as vegetative burning and traffic-related emissions were less consistently identified.
Spatial variability in source contributions across urban areas is an important consideration in assessing the likelihood of exposure error in epidemiologic studies relating health outcomes to sources. Concepts similar to those for using ambient concentrations as surrogates for personal exposures apply here. Some source attribution studies for $PM_{2.5}$ indicate that intra-urban variability increases in the following order: regional sources (e.g., secondary SO_4^{2-} originating from EGUs) < area sources (e.g., on-road mobile sources) < point sources (e.g., metals from stacks of smelters).

Although limited information was available for $PM_{10-2.5}$, it does indicate a similar ordering, but without a regional component (resulting from the short lifetime of $PM_{10-2.5}$ compared to transport times on the regional scale). More discussion on source contributions to PM is available in Section 3.6.

2.1.7. Policy-Relevant Background

The background concentrations of PM that are useful for risk and policy assessments, which inform decisions about the NAAQS are referred to as policy-relevant background (PRB) concentrations. PRB concentrations have historically been defined by EPA as those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America defined here as the U.S., Canada, and Mexico. For this document, PRB concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside continental North America. Background concentrations so defined facilitated separation of pollution that can be controlled by U.S. regulations or through international agreements with neighboring countries from those that were judged to be generally uncontrollable by the U.S. Over time, consideration of potential broader ranging international agreements may lead to alternative determinations of which PM source contributions should be considered by EPA as part of PRB. Contributions to PRB concentrations of PM include both primary and secondary natural and anthropogenic components. For this document, PRB concentrations of $PM_{2.5}$ for the continental U.S. were estimated using EPA's Community Multi-scale Air Quality (CMAQ) modeling system, a deterministic, chemical-transport model (CTM), using output from GEOS-Chem a global-scale model for CMAQ boundary conditions. PRB concentrations of $PM_{2.5}$ were estimated to be less than 1 $\mu g/m^3$ on an annual basis, with maximum daily average values in a range from 3.1 to 20 $\mu g/m^3$ and having a peak of 63 $\mu g/m^3$ at the nine national park sites across the U.S. used to evaluate model performance for this analysis. A description of the models and evaluation of their performance is given in Section 3.6 and further details about the calculations of PRB concentrations are given in Section 3.7.

2.2. Human Exposure

This section summarizes the findings from the recent exposure assessment literature. This summary is intended to support the interpretation of the findings from epidemiologic studies and reflects the material presented in Section 3.8. Attention is given to how concentration metrics can be used in exposure assessment and what errors and uncertainties are incurred for different approaches. Understanding of exposure errors is important because exposure error can potentially bias an estimate of a health effect or increase the size of confidence intervals around a health effect estimate.

2.2.1. Spatial Scales of PM Exposure Assessment

Assessing population-level exposure at the urban scale is particularly relevant for time-series epidemiologic studies, which provide information on the relationship between health effects and community-average exposure, rather than an individual's exposure. PM concentrations measured at a central-site ambient monitor are used as surrogates for personal PM exposure. However, the correlation between the PM concentration measured at central-site ambient monitor(s) and the unknown true community average concentration depends on the spatial distribution of PM, the location of the monitoring site(s) chosen to represent the community average, and division of the community by terrain features or local sources into several sub-communities that differ in the temporal pattern of pollution. Concentrations of SO_4^{2-} and some components of SOA measured at central-site monitors are expected to be uniform in urban areas because of the regional nature of their sources. However, this is not true for primary components like EC whose sources are strongly spatially variable in urban areas.

At micro-to-neighborhood scales, heterogeneity of sources and topography contribute to variability in exposure. This is particularly true for $PM_{10-2.5}$ and for UFPs, which have spatially

variable urban sources and loss processes (mainly gravitational settling for $PM_{10-2.5}$ and coagulation for UFPs) that also limit their transport from sources more readily than for $PM_{2.5}$. Personal activity patterns also vary across urban areas and across regions. Some studies, conducted mainly in Europe, have found personal $PM_{2.5}$ and PM_{10} exposures for pedestrians in street canyons to be higher than ambient concentrations measured by urban central site ambient monitors. Likewise, microenvironmental UFP concentrations were observed to be substantially higher in near-road environments, street canyons, and tunnels when compared with urban background concentrations.

In-vehicle UFP and $PM_{2.5}$ exposures can also be important. As a result, concentrations measured by ambient monitors likely do not reflect the contributions of UFP or $PM_{2.5}$ exposures to individuals while commuting. There is significant variability within and across regions of the country with respect to indoor exposures to ambient PM. Infiltrated ambient PM concentrations depend in part on the ventilation properties of the building or vehicle in which the person is exposed. PM infiltration factors depend on particle size, chemical composition, season, and region of the country. Infiltration can best be modeled dynamically rather than being represented by a single value. Season is important to PM infiltration because it affects the ventilation practices (e.g., open windows) used. In addition, ambient temperature and humidity conditions affect the transport, dispersion, and size distribution of PM. Residential air exchange rates have been observed to be higher in the summer for regions with low air conditioning usage. Regional differences in air exchange rates (Southwest < Southeast < Northeast < Northwest) also reflect ventilation practices. Differential infiltration occurs as a function of PM size and composition (the latter of which is described below). PM infiltration is larger for accumulation mode particles than for UFPs and $PM_{10-2.5}$. Differential infiltration by size fraction can affect exposure estimates if not accurately characterized.

2.2.2. Exposure to PM Components and Copollutants

Emission inventories and source apportionment studies suggest that sources of PM exposure vary by region. Comparison of studies performed in the eastern U.S. with studies performed in the western U.S. suggest that the contribution of SO_4^{2-} to exposure is higher for the East (16-46%) compared with the West (~4%) and that motor vehicle emissions and secondary NO_3^- are larger sources of exposure for the West (~9%) as compared with the East (~4%). Results of source apportionment studies of exposure to SO_4^{2-} indicate that SO_4^{2-} exposures are mainly attributable to ambient sources. Source apportionment for OC and EC is difficult because they originate from both indoor and outdoor sources. Exposure to OC of indoor and outdoor origin can be distinguished by the presence of aliphatic C-H groups generated indoors, since outdoor concentrations of aliphatic C-H are low. Studies of personal exposure to ambient trace metal have shown significant variation among cities and over seasons. This is in response to geographic and seasonal variability in sources including incinerator operation, fossil fuel combustion, biomass combustion (wildfires), and the resuspension of crustal materials in the built environment. Differential infiltration is also affected by variations in particle composition and volatility. For example, EC infiltrates more readily than OC. This can lead to outdoor-indoor differentials in PM composition.

Some studies have explored the relationship between PM and copollutant gases and suggested that certain gases can serve as surrogates for describing exposure to other air pollutants. The findings indicate that ambient concentrations of gaseous copollutants can act as surrogates for personal exposure to ambient PM. Several studies have concluded that ambient concentrations of O_3, NO_2, and SO_2 are associated with the ambient component of personal exposure to total $PM_{2.5}$. If associations between ambient gases and personal exposure to $PM_{2.5}$ of ambient origin exist, such associations are complex and vary by season and location.

2.2.3. Implications for Epidemiologic Studies

In epidemiologic studies, exposure may be estimated using various approaches, most of which rely on measurements obtained using central site monitors. The magnitude and direction of the biases introduced through error in exposure measurement depend on the extent to which the error is associated with the measured PM concentration. In general, when exposure error is not strongly correlated with the measured PM concentration, bias is toward the null and effect estimates are

underestimated. Moreover, lack of information regarding exposure measurement error can also add uncertainty to the health effects estimate.

One important factor to be considered is the spatial variation in PM concentrations. The degree of urban-scale spatial variability in PM concentrations varies across the country and by size fraction. $PM_{2.5}$ concentrations are relatively well-correlated across monitors in the urban areas examined for this assessment. The limited available evidence indicates that there is greater spatial variability in $PM_{10-2.5}$ concentrations than $PM_{2.5}$ concentrations, resulting in increased exposure error for the larger size fraction. Likewise, studies have shown UFPs to be more spatially variable across urban areas compared to $PM_{2.5}$. Even if $PM_{2.5}$, $PM_{10-2.5}$, or UFP concentrations measured at sites within an urban area are generally highly correlated, significant spatial variation in their concentrations can occur on any given day. In addition, there can be differential exposure errors for PM components (e.g., SO_4^{2-}, OC, EC). Current information suggests that UFPs, $PM_{10-2.5,}$ and some PM components are more spatially variable than $PM_{2.5}$. Spatial variability of these PM indicators adds uncertainty to exposure estimates.

Overall, recent studies generally confirm and build upon the key conclusions of the 2004 PM AQCD: separation of total PM exposures into ambient and nonambient components reduces potential uncertainties in the analysis and interpretation of PM health effects data; and ambient PM concentration can be used as a surrogate for ambient PM exposure in community time-series epidemiologic studies because the change in ambient PM concentration should be reflected in the change in the health risk coefficient. The use of the community average ambient $PM_{2.5}$ concentration as a surrogate for the community average personal exposure to ambient $PM_{2.5}$ is not expected to change the principal conclusions from time-series and most panel epidemiologic studies that use community average health and pollution data. Several recent studies support this by showing how the ambient component of personal exposure to $PM_{2.5}$ could be estimated using various tracer and source apportionment techniques and by showing that the ambient component is highly correlated with ambient concentrations of $PM_{2.5}$. These studies show that the non-ambient component of personal exposure to $PM_{2.5}$ is largely uncorrelated with ambient $PM_{2.5}$ concentrations. A few panel epidemiologic studies have included personal as well as ambient monitoring data, and generally reported associations with all types of PM measurements. Epidemiologic studies of long-term exposure typically exploit the differences in PM concentration across space, as well as time, to estimate the effect of PM on the health outcome of interest. Long-term exposure estimates are most accurate for pollutants that do not vary substantially within the geographic area studied.

2.3. Health Effects

This section evaluates the evidence from toxicological, controlled human exposure, and epidemiologic studies that examined the health effects associated with short- and long-term exposure to PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$ and UFPs). The results from the health studies evaluated in combination with the evidence from atmospheric chemistry and exposure assessment studies contribute to the causal determinations made for the health outcomes discussed in this assessment (a description of the causal framework can be found in Section 1.5.4). In the following sections a discussion of the causal determinations will be presented by PM size fraction and exposure duration (i.e., short- or long-term exposure) for the health effects for which sufficient evidence was available to conclude a causal, likely to be causal or suggestive relationship. Although not presented in depth in this chapter, a detailed discussion of the underlying evidence used to formulate each causal determination can be found in Chapters 6 and 7.

2.3.1. Exposure to $PM_{2.5}$

2.3.1.1. Effects of Short-Term Exposure to $PM_{2.5}$

Table 2-1. Summary of causal determinations for short-term exposure to $PM_{2.5}$.

Size Fraction	Outcome	Causality Determination
$PM_{2.5}$	Cardiovascular Effects	Causal
	Respiratory Effects	Likely to be causal
Mortality		Causal

Cardiovascular Effects

Epidemiologic studies that examined the effect of $PM_{2.5}$ on cardiovascular emergency department (ED) visits and hospital admissions reported consistent positive associations (predominantly for ischemic heart disease [IHD] and congestive heart failure [CHF]), with the majority of studies reporting increases ranging from 0.5 to 3.4% per 10 µg/m^3 increase in $PM_{2.5}$. These effects were observed in study locations with mean[1] 24-h avg $PM_{2.5}$ concentrations ranging from 7-18 µg/m^3 (Section 6.2.10). The largest U.S.-based multicity study evaluated, Medicare Air Pollution Study (MCAPS), provided evidence of regional heterogeneity (e.g., the largest excess risks occurred in the Northeast [1.08%]) and seasonal variation (e.g., the largest excess risks occurred during the winter season [1.49%]) in $PM_{2.5}$ cardiovascular disease (CVD) risk estimates, which is consistent with the null findings of several single-city studies conducted in the western U.S. These associations are supported by multicity epidemiologic studies that observed consistent positive associations between short-term exposure to $PM_{2.5}$ and cardiovascular mortality and also reported regional and seasonal variability in risk estimates. The multicity studies evaluated reported consistent increases in cardiovascular mortality ranging from 0.47 to 0.85% in study locations with mean 24-h avg $PM_{2.5}$ concentrations above 12.8 µg/m^3 (Table 6-15).

Controlled human exposure studies have demonstrated $PM_{2.5}$-induced changes in various measures of cardiovascular function among healthy and health-compromised adults. The most consistent evidence is for altered vasomotor function following exposure to diesel exhaust (DE) or CAPs with O_3 (Section 6.2.4.2). Although these findings provide biological plausibility for the observations from epidemiologic studies, the fresh DE used in the controlled human exposure studies evaluated contains gaseous components (e.g., CO, NO_x), and therefore, the possibility that some of the changes in vasomotor function might be due to gaseous components cannot be ruled out. Furthermore, the prevalence of UFPs in fresh DE limits the ability to conclusively attribute the observed effects to either the UF fraction or $PM_{2.5}$ as a whole. An evaluation of toxicological studies found evidence for altered vessel tone and microvascular reactivity, which provide coherence and biological plausibility for the vasomotor effects that have been observed in both the controlled human exposure and epidemiologic studies (Section 6.2.4.3). However, most of these toxicological studies exposed animals via intratracheal (IT) instillation or using relatively high inhalation concentrations. In addition to the effects observed on vasomotor function, myocardial ischemia has been observed across disciplines through $PM_{2.5}$ effects on ST-segment depression, with toxicological studies providing biological plausibility by demonstrating reduced blood flow during ischemia (Section 6.2.3). There is also a growing body of evidence from controlled human exposure and toxicological studies demonstrating $PM_{2.5}$-induced changes on heart rate variability (HRV) and

[1] In this context mean represents the arithmetic mean of 24-h avg PM concentrations.

markers of systemic oxidative stress (Sections 6.2.1 and 6.2.9, respectively). Additional but inconsistent effects of $PM_{2.5}$ on blood pressure (BP), blood coagulation markers, and markers of systemic inflammation have also been reported across disciplines. Toxicological studies have provided biologically plausible mechanisms (e.g., increased right ventricular pressure and diminished cardiac contractility) for the associations observed between $PM_{2.5}$ and CHF in epidemiologic studies. Together, the collective evidence from epidemiologic, controlled human exposure, and toxicological studies is sufficient to conclude that **a causal relationship exists between short- term exposures to $PM_{2.5}$ and cardiovascular effects.**

Respiratory Effects

The recent epidemiologic studies evaluated report consistent positive associations between short-term exposure to $PM_{2.5}$ and respiratory ED visits and hospital admissions for chronic obstructive pulmonary disease (COPD) and respiratory infections (Section 6.3). Positive associations were also observed for asthma ED visits and hospital admissions for adults and children combined, but effect estimates are imprecise and not consistently positive for children alone. Most studies reported effects in the range of ~1% to 4% increase in respiratory hospital admissions and ED visits and were observed in study locations with mean 24-h avg $PM_{2.5}$ concentrations ranging from 6.1-22 $\mu g/m^3$. Additionally, multicity epidemiologic studies reported consistent positive associations between short-term exposure to $PM_{2.5}$ and respiratory mortality as well as regional and seasonal variability in risk estimates. The multicity studies evaluated reported consistent, precise increases in respiratory mortality ranging from 1.67 to 2.20% in study locations with mean 24-h avg $PM_{2.5}$ concentrations above 12.8 $\mu g/m^3$ (Table 6-15). Evidence for $PM_{2.5}$-related respiratory effects was also observed in panel studies, which indicate associations with respiratory symptoms, pulmonary function, and pulmonary inflammation among asthmatic children. Although not consistently observed, some controlled human exposure studies have reported small decrements in various measures of pulmonary function following controlled exposures to $PM_{2.5}$ (Section 6.3.2.2). Controlled human exposure studies using adult volunteers have demonstrated increased markers of pulmonary inflammation following exposure to a variety of different particle types; oxidative responses to DE and wood smoke; and exacerbations of allergic responses and allergic sensitization following exposure to DE particles (Section 6.3). Toxicological studies have provided additional support for $PM_{2.5}$-related respiratory effects through inhalation exposures of animals to CAPs, DE, other traffic-related PM and wood smoke. These studies reported an array of respiratory effects including altered pulmonary function, mild pulmonary inflammation and injury, oxidative responses, airway hyperresponsiveness (AHR) in allergic and non-allergic animals, exacerbations of allergic responses, and increased susceptibility to infections (Section 6.3).
Overall, the evidence for an effect of $PM_{2.5}$ on respiratory outcomes is somewhat restricted by limited coherence between some of the findings from epidemiologic and controlled human exposure studies for the specific health outcomes reported and the sub-populations in which those health outcomes occur. Epidemiologic studies have reported variable results among specific respiratory outcomes, specifically in asthmatics (e.g., increased respiratory symptoms in asthmatic children, but not increased asthma hospital admissions and ED visits) (Section 6.3.8). Additionally, respiratory effects have not been consistently demonstrated following controlled exposures to $PM_{2.5}$ among asthmatics or individuals with COPD. Collectively, the epidemiologic, controlled human exposure, and toxicological studies evaluated demonstrate a wide range of respiratory responses, and although results are not fully consistent and coherent across studies the evidence is sufficient to conclude that **a causal relationship is likely to exist between short-term exposures to $PM_{2.5}$ and respiratory effects.**

Mortality

An evaluation of the epidemiologic literature indicates consistent positive associations between short-term exposure to $PM_{2.5}$ and all-cause, cardiovascular-, and respiratory-related mortality (Section 6.5.2.2.). The evaluation of multicity studies found that consistent and precise risk estimates for all-cause (nonaccidental) mortality that ranged from 0.29 to 1.21% per 10 $\mu g/m^3$

increase in $PM_{2.5}$ at lags of 1 and 0-1 days. In these study locations, mean 24-h avg $PM_{2.5}$ concentrations were 12.8 µg/m^3 and above (Table 6-15). Cardiovascular-related mortality risk estimates were found to be similar to those for all-cause mortality; whereas, the risk estimates for respiratory-related mortality were consistently larger (i.e., 1.01-2.2%) using the same lag periods and averaging indices. The studies evaluated that examined the relationship between short-term exposure to $PM_{2.5}$ and cardiovascular effects (Section 6.2) provide coherence and biological plausibility for $PM_{2.5}$-induced cardiovascular mortality, which represents the largest component of total (nonaccidental) mortality (~ 35%) (American Heart Association, 2009, 198920). However, as noted in Section 6.3, there is limited coherence between some of the respiratory morbidity findings from epidemiologic and controlled human exposure studies for the specific health outcomes reported and the subpopultions in which those health outcomes occur, complicating the interpretation of the $PM_{2.5}$ respiratory mortality effects observed. Regional and seasonal patterns in $PM_{2.5}$ risk estimates were observed with the greatest effect estimates occurring in the eastern U.S. and during the spring. Of the studies evaluated only Burnett et al. (2004, 086247), a Canadian multicity study, analyzed gaseous pollutants and found mixed results, with possible confounding of $PM_{2.5}$ risk estimates by NO_2. Although the recently evaluated U.S.-based multicity studies did not analyze potential confounding of $PM_{2.5}$ risk estimates by gaseous pollutants, evidence from the limited number of single-city studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggest that gaseous copollutants do not confound the $PM_{2.5}$-mortality association. This is further supported by studies that examined the PM_{10}-mortality relationship. An examination of effect modifiers (e.g., demographic and socioeconomic factors), specifically air conditioning use as an indicator for decreased pollutant penetration indoors, has suggested that $PM_{2.5}$ risk estimates increase as the percent of the population with access to air conditioning decreases. Collectively, the epidemiologic literature provides evidence that **a causal relationship exists between short-term exposures to $PM_{2.5}$ and mortality.**

2.3.1.2. Effects of Long-Term Exposure to $PM_{2.5}$

Table 2-2. Summary of causal determinations for long-term exposure to $PM_{2.5}$.

Size Fraction	Outcome	Causality Determination
$PM_{2.5}$	Cardiovascular Effects	Causal
	Respiratory Effects	Likely to be causal
	Mortality	Causal
	Reproductive and Developmental	Suggestive
Cancer, Mutagenicity, and Genotoxicity		Suggestive

Cardiovascular Effects

The strongest evidence for cardiovascular health effects related to long-term exposure to $PM_{2.5}$ comes from large, multicity U.S.-based studies, which provide consistent evidence of an association between long-term exposure to $PM_{2.5}$ and cardiovascular mortality (Section 7.2.10). These associations are supported by a large U.S.-based epidemiologic study (i.e., Women's Health Initiative [WHI] study) that reports associations between $PM_{2.5}$ and CVDs among post-menopausal women using a 1-yr avg $PM_{2.5}$ concentration (mean = 13.5 µg/m^3) (Section 7.2). However, epidemiologic studies that examined subclinical markers of CVD report inconsistent findings. Epidemiologic studies have also provided some evidence for potential modification of the $PM_{2.5}$-CVD association when examining individual-level data, specifically smoking status and the use of anti-

hyperlipidemics. Although epidemiologic studies have not consistently detected effects on markers of atherosclerosis due to long-term exposure to $PM_{2.5}$, toxicological studies have provided strong evidence for accelerated development of atherosclerosis in $ApoE^{-/-}$ mice exposed to CAPs and have shown effects on coagulation, experimentally-induced hypertension, and vascular reactivity (Section 7.2.1.2). Evidence from toxicological studies provides biological plausibility and coherence with studies of short-term exposure and cardiovascular morbidity and mortality, as well as with studies that examined long-term exposure to $PM_{2.5}$ and cardiovascular mortality. Taken together, the evidence from epidemiologic and toxicological studies is sufficient to conclude that **a causal relationship exists between long-term exposures to $PM_{2.5}$ and cardiovascular effects.**

Respiratory Effects

Recent epidemiologic studies conducted in the U.S. and abroad provide evidence of associations between long-term exposure to $PM_{2.5}$ and decrements in lung function growth, increased respiratory symptoms, and asthma development in study locations with mean $PM_{2.5}$ concentrations ranging from 13.8 to 30 $\mu g/m^3$ during the study periods (Section 7.3.1.1 and Section 7.3.2.1). These results are supported by studies that observed associations between long-term exposure to PM_{10} **and an increase in respiratory symptoms and reductions in lung function growth in areas where PM_{10} is dominated by $PM_{2.5}$. However, the evidence to support an association with long-term exposure to $PM_{2.5}$ and respiratory mortality is limited (Figure 7-7). Subchronic and chronic toxicological studies of CAPs, DE, roadway air and woodsmoke provide coherence and biological plausibility for the effects observed in the epidemiologic studies. These toxicological studies have presented some evidence for altered pulmonary function, mild inflammation, oxidative responses, immune suppression, and histopathological changes including mucus cell hyperplasia** (Section 7.3). Exacerbated allergic responses have been demonstrated in animals exposed to DE and wood smoke. In addition, pre- and postnatal exposure to ambient levels of urban particles was found to affect lung development in an animal model. This finding is important because impaired lung development is one mechanism by which PM exposure may decrease lung function growth in children. Collectively, the evidence from epidemiologic and toxicological studies is sufficient to conclude that **a causal relationship is likely to exist between long-term exposures to $PM_{2.5}$ and respiratory effects.**

Mortality

The recent epidemiologic literature reports associations between long-term $PM_{2.5}$ exposure and increased **risk of mortality. Mean $PM_{2.5}$ concentrations ranged from 13.2 to 29 $\mu g/m^3$ during the study period in these areas (Section 7.6). When evaluating cause-specific mortality, the strongest evidence can be found when examining associations between $PM_{2.5}$ and cardiovascular mortality, and positive associations were also reported between $PM_{2.5}$ and lung cancer mortality (Figure 7-7). The cardiovascular mortality association has been confirmed further by the extended Harvard Six Cities and American Cancer Society studies, which both report strong associations between long- term exposure to $PM_{2.5}$ and cardiopulmonary and IHD mortality (Figure 7-7). Additional new evidence from a study that used the WHI cohort found a particularly strong association between long-term exposure to $PM_{2.5}$ and CVD mortality in post-menopausal women. Fewer studies have evaluated the respiratory component of cardiopulmonary mortality, and, as a result, the evidence to support an association with long-term exposure to $PM_{2.5}$ and respiratory mortality is limited (Figure 7-7). The evidence for cardiovascular and respiratory morbidity due to short- and long-term exposure to $PM_{2.5}$ provides biological plausibility for cardiovascular- and respiratory-related mortality. Collectively, the evidence is sufficient to conclude that a causal relationship exists between long-term exposures to $PM_{2.5}$ and mortality.**

Reproductive and Developmental Effects

Evidence is accumulating for $PM_{2.5}$ effects on low birth weight and infant mortality, especially due to respiratory causes during the post-neonatal period. The mean $PM_{2.5}$ concentrations during the study periods ranged from 5.3-27.4 $\mu g/m^3$ (Section 7.4), with effects becoming more precise and consistently positive in locations with mean $PM_{2.5}$ concentrations of 15 $\mu g/m^3$ and above (Section 7.4). Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth weight than exposure to PM_{10}. The evidence from a few U.S. studies that investigated PM_{10} effects on fetal growth, which reported similar decrements in birth weight, provide consistency for the $PM_{2.5}$ associations observed and strengthen the interpretation that particle exposure may be causally related to reductions in birth weight. The epidemiologic literature does not consistently report associations between long-term exposure to PM and preterm birth, growth restriction, birth defects or decreased sperm quality. Toxicological evidence supports an association between $PM_{2.5}$ and PM_{10} exposure and adverse reproductive and developmental outcomes, but provide little mechanistic information or biological plausibility for an association between long-term PM exposure and adverse birth outcomes (e.g., low birth weight or infant mortality). New evidence from animal toxicological studies on heritable mutations is of great interest, and warrants further investigation. Overall, the epidemiologic and toxicological evidence is **suggestive of a causal relationship between long-term exposures to $PM_{2.5}$ and reproductive and developmental outcomes.**

Cancer, Mutagenicity, and Genotoxicity

Multiple epidemiologic studies have shown a consistent positive association between $PM_{2.5}$ and lung cancer mortality, but studies have generally not reported associations between $PM_{2.5}$ and lung cancer incidence (Section 7.5). Animal toxicological studies have examined the potential relationship between PM and cancer, but have not focused on specific size fractions of PM. Instead they have examined ambient PM, wood smoke, and DEP. A number of studies indicate that ambient urban PM, emissions from wood/biomass burning, emissions from coal combustion, and gasoline and DE are mutagenic, and that PAHs are genotoxic. These findings are consistent with earlier studies that concluded that ambient PM and PM from specific combustion sources are mutagenic and genotoxic and provide biological plausibility for the results observed in the epidemiologic studies. A limited number of epidemiologic and toxicological studies examined epigenetic effects, and demonstrate that PM induces some changes in methylation. However, it has yet to be determined **how these alterations in the genome could influence the initiation and promotion of cancer. Additionally, inflammation and immune suppression induced by exposure to PM may confer susceptibility to cancer. Collectively, the evidence from epidemiologic studies, primarily those of lung cancer mortality, along with the toxicological studies that show some evidence of the mutagenic and genotoxic effects of PM is suggestive of a causal relationship between long-term exposures to $PM_{2.5}$ and cancer.**

2.3.2. Integration of $PM_{2.5}$ Health Effects

In epidemiologic studies, short-term exposure to $PM_{2.5}$ is associated with a broad range of respiratory and cardiovascular effects, as well as mortality. For cardiovascular effects and mortality, the evidence supports the existence of a causal relationship with short-term $PM_{2.5}$ exposure; while the evidence indicates that a causal relationship is likely to exist between short-term $PM_{2.5}$ exposure and respiratory effects. The effect estimates from recent and older U.S. and Canadian-based epidemiologic studies that examined the relationship between short-term exposure to $PM_{2.5}$ and health outcomes with mean 24-h avg $PM_{2.5}$ concentrations <17 $\mu g/m^3$ are shown in Figure 2-1. **A number of different health effects are included in Figure 2-1 to provide an integration of the range of effects by mean concentration, with a focus on cardiovascular and respiratory effects and all-cause (nonaccidental) mortality (i.e., health effects categories with at least a suggestive causal determination). A pattern of consistent positive associations with mortality and morbidity effects can be seen in this figure. Mean $PM_{2.5}$ concentrations ranged from 6.1 to 16.8 $\mu g/m^3$.in these study locations.**

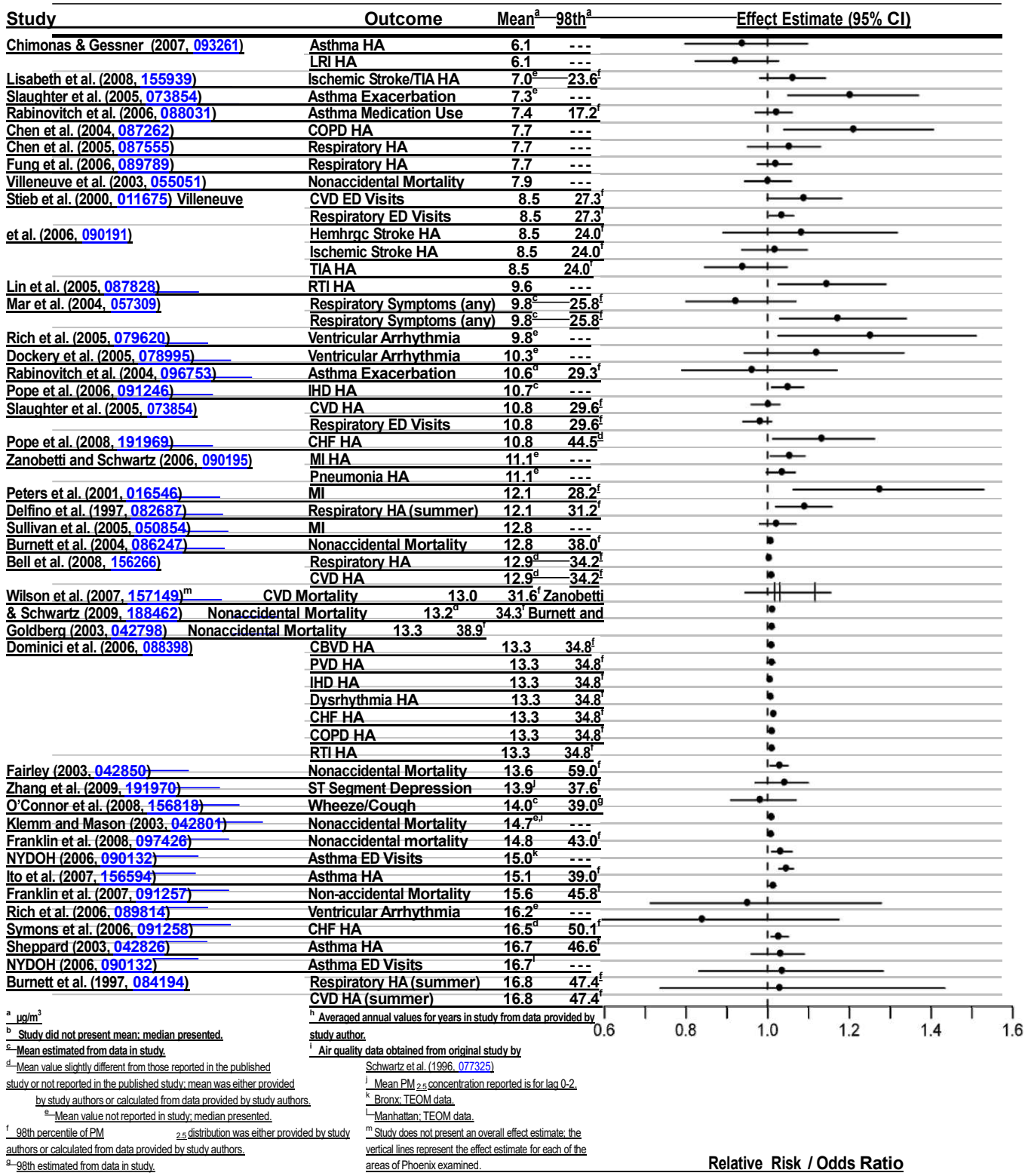


Figure 2-1. Summary of effect estimates (per 10 µg/m^3) by increasing concentration from U.S. studies examining the association between short-term exposure to $PM_{2.5}$ and cardiovascular and respiratory effects, and mortality, conducted in locations where the reported mean 24-h avg $PM_{2.5}$ concentrations were <17 µg/m^3.

Long-term exposure to $PM_{2.5}$ has been associated with health outcomes similar to those found in the short-term exposure studies, specifically for respiratory and cardiovascular effects and mortality. As found for short-term $PM_{2.5}$ exposure, the evidence indicates that a causal relationship exists between long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality, and that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and effects on the respiratory system.

Figure 2-2 highlights the findings of epidemiologic studies where the long-term mean $PM_{2.5}$ concentrations were ≤ 29 µg/m^3. A range of health outcomes are displayed (including cardiovascular mortality, all-cause mortality, infant mortaltiy, and bronchitis) ordered by mean concentration. The range of mean $PM_{2.5}$ concentrations in these studies was 10.7-29 µg/m^3 during the study periods. Additional studies not included in this figure that focus on subclinical outcomes, such as changes in lung function or atherosclerotic markers also report effects in areas with similar concentrations (Sections 7.2 and 7.3). Although not highlighted in the summary figure, long-term $PM_{2.5}$ exposure studies also provide evidence for reproductive and developmental effects (i.e., low birth weight) and
cancer (i.e., lung cancer mortality) in response to to exposure to $PM_{2.5}$.

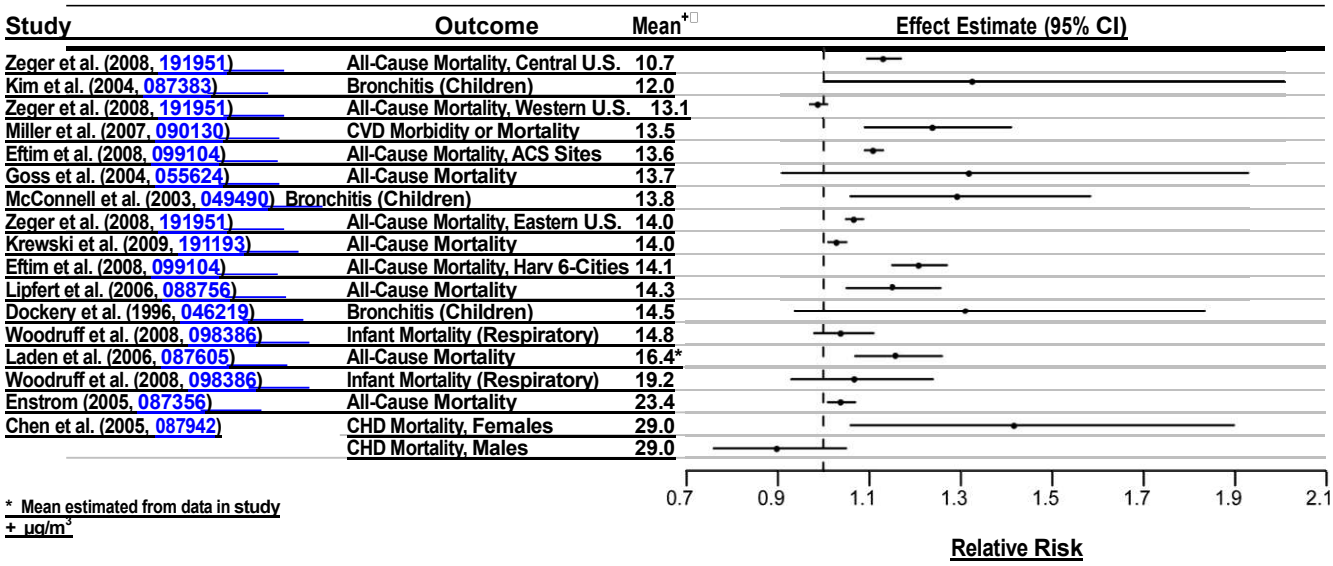


Figure 2-2. Summary of effect estimates (per 10 µg/m^3) by increasing concentration from U.S. studies examining the association between long-term exposure to $PM_{2.5}$ and cardiovascular and respiratory effects, and mortality.

The observations from both the short- and long-term exposure studies are supported by experimental findings of $PM_{2.5}$-induced subclinical and clinical cardiovascular effects. Epidemiologic studies have shown an increase in ED visits and hospital admissions for IHD upon exposure to $PM_{2.5}$. These effects are coherent with the changes in vasomotor function and ST- segment depression observed in both toxicological and controlled human exposure studies. It has been postulated that exposure to $PM_{2.5}$ can lead to myocardial ischemia through an effect on the autonomic nervous system or by altering vasomotor function. PM-induced systemic inflammation, oxidative stress and/or endothelial dysfunction may contribute to altered vasomotor function. These effects have been demonstrated in recent animal toxicological studies, along with altered microvascular reactivity, altered vessel tone, and reduced blood flow during ischemia. Toxicological studies demonstrating increased right ventricular pressure and diminished cardiac contractility also provide biological plausibility for the associations observed between $PM_{2.5}$ and CHF in epidemiologic studies. Thus, the overall evidence from the short-term epidemiologic, controlled human exposure, and toxicological studies evaluated provide coherence and biological plausibility for cardiovascular effects related to myocardial ischemia and CHF. Coherence in the cardiovascular effects observed

can be found in long-term exposure studies, especially for CVDs among post-menopausal women. Additional studies provide limited evidence for subclinical measures of atherosclerosis in epidemiologic studies with stronger evidence from toxicological studies that have demonstrated accelerated development of atherosclerosis in ApoE$^{-/-}$ mice exposed to $PM_{2.5}$ CAPs along with effects on coagulation, experimentally-induced hypertension, and vascular reactivity. Repeated acute responses to PM may lead to cumulative effects that manifest as chronic disease, such as atherosclerosis. Contributing factors to atherosclerosis development include systemic inflammation, endothelial dysfunction, and oxidative stress all of which are associated with $PM_{2.5}$ exposure. However, it has not yet been determined whether PM initiates or promotes atherosclerosis. The evidence from both short- and long-term exposure studies on cardiovascular morbidity provide coherence and biological plausibility for the cardiovascular mortality effects observed when examining both exposure durations. In addition, cardiovascular hospital admission and mortality studies that examined the PM_{10} concentration-response relationship found evidence of a log-linear no-threshold relationship between PM exposure and cardiovascular-related morbidity (Section 6.2) and mortality (Section 6.5). Epidemiologic studies have also reported respiratory effects related to short-term exposure to $PM_{2.5}$, which include increased ED visits and hospital admissions, as well as alterations in lung function and respiratory symptoms in asthmatic children. These respiratory effects were found to be generally robust to the inclusion of gaseous pollutants in copollutant models with the strongest evidence from the higher powered studies (Figure 6-9 and Figure 6-15). Consistent positive associations were also reported between short-term exposure to $PM_{2.5}$ and respiratory mortality in epidemiologic studies. However, uncertainties exist in the $PM_{2.5}$-respiratory mortality associations reported due to the limited number of studies that examined potential confounders of the $PM_{2.5}$- respiratory mortality relationship, and the limited information regarding the biological plausibility of the clinical and subclinical respiratory outcomes observed in the epidemiologic and controlled human exposure studies (Section 6.3) resulting in the progression to $PM_{2.5}$-induced respiratory mortality. Important new findings, which support the $PM_{2.5}$-induced respiratory effects mentioned above, include associations with post-neonatal (between 1 mo and 1 yr of age) respiratory mortality. Controlled human exposure studies provide some support for the respiratory findings from epidemiologic studies, with demonstrated increases in pulmonary inflammation following short-term exposure. However, there is limited and inconsistent evidence of effects in response to controlled exposures to $PM_{2.5}$ on respiratory symptoms or pulmonary function among healthy adults or adults with respiratory disease. Long-term exposure epidemiologic studies provide additional evidence for $PM_{2.5}$-induced respiratory morbidity, but little evidence for an association with respiratory mortality. These epidemiologic morbidity studies have found decrements in lung function growth, as well as increased respiratory symptoms, and asthma. Toxicological studies provide coherence and biological plausibility for the respiratory effects observed in response to short and long-term exposures to PM by demonstrating a wide array of biological responses including: altered pulmonary function, mild pulmonary inflammation and injury, oxidative responses, and histopathological changes in animals exposed by inhalation to $PM_{2.5}$ derived from a wide variety of sources. In some cases, prolonged exposures led to adaptive responses. Important evidence was also found in an animal model for altered lung development following pre- and post-natal exposure to urban air, which may provide a mechanism to explain the reduction in lung function growth observed in children in response to long-term exposure to PM.

Additional respiratory-related effects have been tied to allergic responses. Epidemiologic studies have provided evidence for increased hospital admissions for allergic symptoms (e.g., allergic rhinitis) in response to short- and long-term exposure to $PM_{2.5}$. Panel studies also positively associate long-term exposure to $PM_{2.5}$ and PM_{10} with indicators of allergic sensitization. Controlled human exposure and toxicological studies provide coherence for the exacerbation of allergic symptoms, by showing that $PM_{2.5}$ can promote allergic responses and intensify existing allergies. Allergic responses require repeated exposures to antigen over time and co-exposure to an adjuvant (possibly DE particles or UF CAPs) can enhance this response. Allergic sensitization often underlies allergic asthma, characterized by inflammation and AHR. In this way, repeated or chronic exposures involving multifactorial responses (immune system activation, oxidative stress, inflammation) can lead to irreversible outcomes. Epidemiologic studies have also reported evidence for increased hospital admissions for respiratory infections in response to both short- and long-term exposures to $PM_{2.5}$. Toxicological studies suggest that PM impairs innate immunity, which is the first line of

defense against infection, providing coherence for the respiratory infection effects observed in epidemiologic studies.

The difference in effects observed across studies and between cities may be attributed, at least in part, to the differences in PM composition across the U.S. Differences in PM toxicity may result from regionally varying PM composition and size distribution, which in turn reflects differences in sources and PM volatility. A person's exposure to ambient PM will also vary due to regional differences in personal activity patterns, microenvironmental characteristics and the spatial variability of PM concentrations in urban areas. Regional differences in $PM_{2.5}$ composition are outlined briefly in Section 2.1 above and in more detail in Section 3.5. An examination of data from the CSN indicates that East-West gradients exist for a number of PM components. Specifically, SO_4^{2-} concentrations are higher in the East, OC constitutes a larger fraction of PM in the West, and NO_3^- concentrations are highest in the valleys of central California and during the winter in the Midwest. However, the available evidence and the limited amount of city-specific speciated $PM_{2.5}$ data does not allow conclusions to be drawn that specifically differentiate effects of PM in different locations.

It remains a challenge to determine relationships between specific constituents, combinations of constituents, or sources of $PM_{2.5}$ and the various health effects observed. Source apportionment studies of $PM_{2.5}$ have attempted to decipher some of these relationships and in the process have identified associations between multiple sources and various respiratory and cardiovascular health effects, as well as mortality. Although different source apportionment methods have been used across these studies, the methods used have been evaluated and found generally to identify the same sources and associations between sources and health effects (Section 6.6). While uncertainty remains, it has been recognized that many sources and components of $PM_{2.5}$ contribute to health effects. Overall, the results displayed in Table 6-18 indicate that many constituents of $PM_{2.5}$ can be linked with multiple health effects, and the evidence is not yet sufficient to allow differentiation of those constituents or sources that are more closely related to specific health outcomes.

Variability in the associations observed across $PM_{2.5}$ epidemiologic studies may be due in part to exposure error related to the use of county-level air quality data. Because western U.S. counties tend to be much larger and more topographically diverse than eastern U.S. counties, the day-to-day variations in concentration at one site, or even for the average of several sites, may not correlate well with the day-to-day variations in all parts of the county. For example, site-to-site correlations as a function of distance between sites (Section 3.5.1.2) fall off rapidly with distance in Los Angeles, but high correlations extend to larger distances in eastern cities such as Boston and Pittsburgh. These differences may be attributed to a number of factors including topography, the built environment, climate, source characteristics, ventilation usage, and personal activity patterns. For instance, regional differences in climate and infrastructure can affect time spent outdoors or indoors, air conditioning usage, and personal activity patterns. Characteristics of housing stock may also cause regional differences in effect estimates because new homes tend to have lower infiltration factors than older homes. Biases and uncertainties in exposure estimates resulting from these aspects can, in turn, cause bias and uncertainty in associated health effects estimates.

The new evidence reviewed in this ISA greatly expands upon the evidence available in the 2004 PM AQCD particularly in providing greater understanding of the underlying mechanisms for $PM_{2.5}$ induced cardiovascular and respiratory effects for both short- and long-term exposures. Recent studies have provided new evidence linking long-term exposure to $PM_{2.5}$ with cardiovascular outcomes that has expanded upon the continuum of effects ranging from the more subtle subclinical measures to cardiopulmonary mortality.

2.3.3. Exposure to $PM_{10-2.5}$

2.3.3.1. Effects of Short-Term Exposure to $PM_{10-2.5}$

Table 2-3. Summary of causal determinations for short-term exposure to $PM_{10-2.5}$.

Size Fraction	Outcome	Causality Determination
$PM_{10-2.5}$	Cardiovascular Effects	Suggestive
	Respiratory Effects	Suggestive
Mortality		Suggestive

Cardiovascular Effects

Generally positive associations were reported between short-term exposure to $PM_{10-2.5}$ and hospital admissions or ED visits for cardiovascular causes. These results are supported by a large U.S. multicity study of older adults that reported $PM_{10-2.5}$ associations with CVD hospital admissions, and only a slight reduction in the $PM_{10-2.5}$ risk estimate when included in a copollutant model with $PM_{2.5}$ (Section 6.2.10). The $PM_{10-2.5}$ associations with cardiovascular hospital admissions and ED visits were observed in study locations with mean 24-h avg $PM_{10-2.5}$ concentrations ranging from 7.4 to 13 $\mu g/m^3$. These results are supported by the associations observed between $PM_{10-2.5}$ and cardiovascular mortality in areas with 24-h avg $PM_{10-2.5}$ concentrations ranging from 6.1-16.4 $\mu g/m^3$ (Section 6.2.11). The results of the epidemiologic studies were further confirmed by studies that examined dust storm events, which contain high concentrations of crustal material, and found an increase in cardiovascular-related ED visits and hospital admissions. Additional epidemiologic studies have reported $PM_{10-2.5}$ associations with other cardiovascular health effects including supraventricular ectopy and changes in HRV (Section 6.2.1.1). Although limited in number, studies of controlled human exposures provide some evidence to support the alterations in HRV observed in the epidemiologic studies (Section 6.2.1.2). The few toxicological studies that examined the effect of $PM_{10-2.5}$ on cardiovascular health effects used IT instillation due to the technical challenges in exposing rodents via inhalation to $PM_{10-2.5}$, and, as a result, provide only limited evidence on the biological plausibility of $PM_{10-2.5}$ induced cardiovascular effects. The potential for $PM_{10-2.5}$ to elicit an effect is supported by dosimetry studies, which show that a large proportion of inhaled particles in the 3-6 micron (d_{ae}) range can reach and deposit in the lower respiratory tract, particularly the tracheobronchial (TB) airways (Figures 4-3 and 4-4). Collectively, the evidence from epidemiologic studies, along with the more limited evidence from controlled human exposure and toxicological studies **is suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and cardiovascular effects.**

Respiratory Effects

A number of recent epidemiologic studies conducted in Canada and France found consistent, positive associations between respiratory ED visits and hospital admissions and short-term exposure to $PM_{10-2.5}$ in studies with mean 24-h avg concentrations ranging from 5.6-16.2 $\mu g/m^3$ (Section 6.3.8). In these studies, the strongest relationships were observed among children, with less consistent evidence for adults and older adults (i.e., $\geq$ 65). In a large multicity study of older adults, $PM_{10-2.5}$ was positively associated with respiratory hospital admissions in both single and copollutant models with $PM_{2.5}$. In addition, a U.S.-based multicity study found evidence for an increase in respiratory mortality upon short-term exposure to $PM_{10-2.5}$, but these associations have not been consistently

observed in single-city studies (Section 6.3.9). A limited number of epidemiologic studies have focused on specific respiratory morbidity outcomes, and found no evidence of an association with lower respiratory symptoms, wheeze, and medication use (Section 6.3.1.1). While controlled human exposure studies have not observed an effect on lung function or respiratory symptoms in healthy or asthmatic adults in response to short-term exposure to $PM_{10-2.5}$, healthy volunteers have exhibited an increase in markers of pulmonary inflammation. Toxicological studies using inhalation exposures are still lacking, but pulmonary injury has been observed in animals after IT instillation exposure (Section 6.3.5.3). In some cases, $PM_{10-2.5}$ was found to be more potent than $PM_{2.5}$ and effects were not attributable to endotoxin. Both rural and urban $PM_{10-2.5}$ have induced inflammation and injury responses in rats or mice exposed via IT instillation, making it difficult to distinguish the health effects of $PM_{10-2.5}$ from different environments. Overall, epidemiologic studies, along with the
limited number of controlled human exposure and toxicological studies that examined $PM_{10-2.5}$ respiratory effects provide evidence that **is suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and respiratory effects.**

Mortality

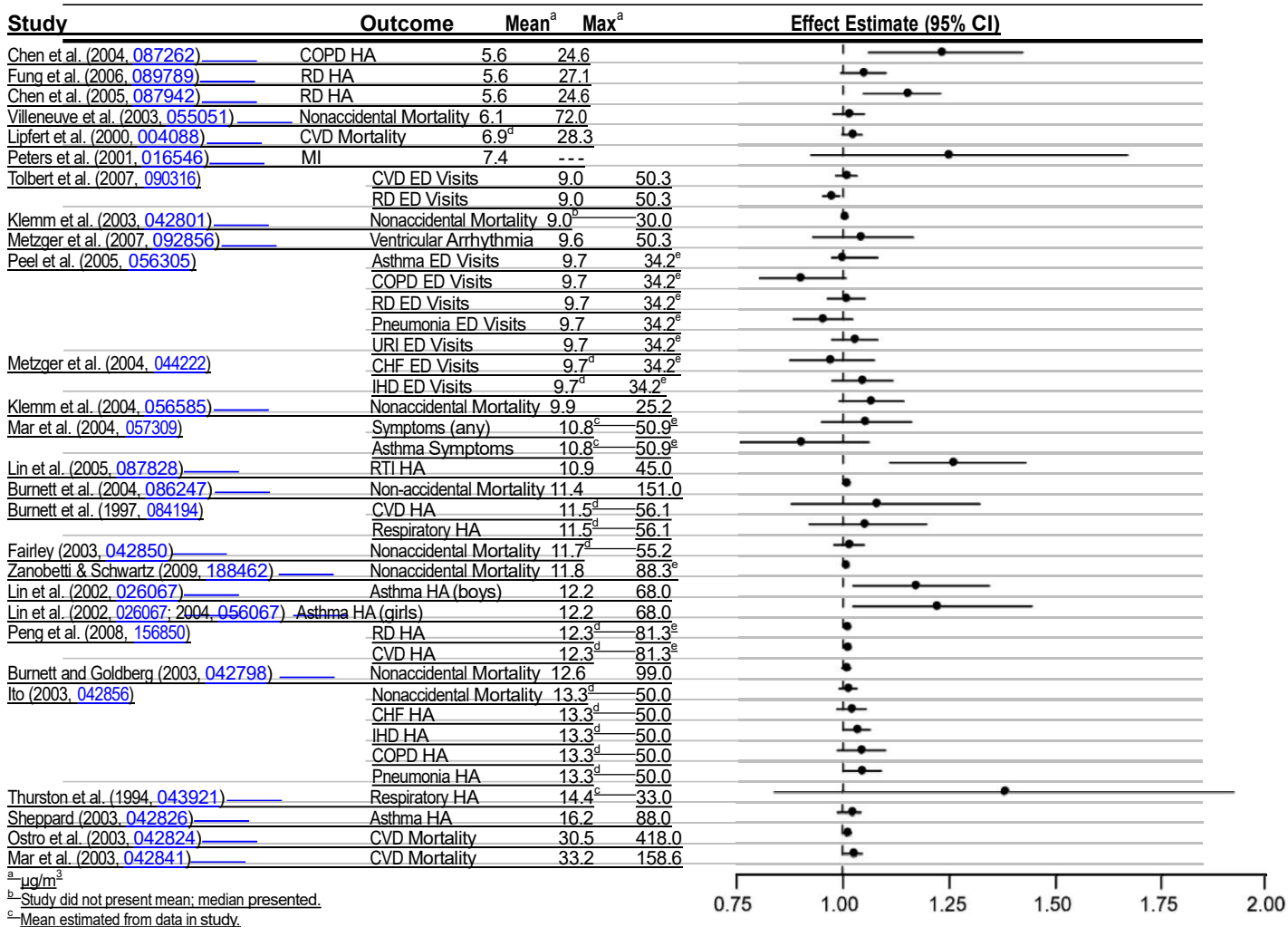
The majority of studies evaluated in this review provide some evidence for mortality associations with $PM_{10-2.5}$ in areas with mean 24-h avg concentrations ranging from 6.1-16.4 $\mu g/m^3$. However, uncertainty surrounds the $PM_{10-2.5}$ associations reported in the studies evaluated due to the different methods used to estimate $PM_{10-2.5}$ concentrations across studies (e.g., direct measurement of $PM_{10-2.5}$ using dichotomous samplers, calculating the difference between PM_{10} and $PM_{2.5}$ concentrations). In addition, only a limited number of $PM_{10-2.5}$ studies have investigated potential confounding by gaseous copollutants or the influence of model specification on $PM_{10-2.5}$ risk estimates.
A new U.S.-based multicity study, which estimated $PM_{10-2.5}$ concentrations by calculating the difference between the county-average PM_{10} and $PM_{2.5}$, found associations between $PM_{10-2.5}$ and mortality across the U.S., including evidence for regional variability in $PM_{10-2.5}$ risk estimates (Section 6.5.2.3). Additionally, the U.S.-based multicity study provides preliminary evidence for greater effects occurring during the warmer months (i.e., spring and summer). A multicity Canadian study provides additional evidence for an association between short-term exposure to $PM_{10-2.5}$ and mortality (Section 6.5.2.3). Although consistent positive associations have been observed across both multi- and single-city studies, more data are needed to adequately characterize the chemical and biological components that may modify the potential toxicity of $PM_{10-2.5}$ and compare the different methods used to estimate exposure. Overall, the evidence evaluated **is suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and mortality.**

2.3.4. Integration of $PM_{10-2.5}$ Effects

Epidemiologic, controlled human exposure, and toxicological studies have provided evidence that is suggestive for relationships between short-term exposure to $PM_{10-2.5}$ and cardiovascular effects, respiratory effects, and mortality. Conclusions regarding causation for the various health effects and outcomes were made for $PM_{10-2.5}$ as a whole regardless of origin, since $PM_{10-2.5}$-related effects have been demonstrated for a number of different environments (e.g., cities reflecting a wide range of environmental conditions). Associations between short-term exposure to $PM_{10-2.5}$ and cardiovascular and respiratory effects, and mortality have been observed in locations with mean $PM_{10-2.5}$ concentrations ranging from 5.6 to 33.2 $\mu g/m^3$, and maximum $PM_{10-2.5}$ concentrations ranging from
24.6 to 418.0 $\mu g/m^3$) (Figure 2-3). A number of different health effects are included in Figure 2-3 to provide an integration of the range of effects by mean concentration, with a focus on cardiovascular and respiratory effects, and mortality (i.e., health effects categories with at least a suggestive causal determination). To date, a sufficient amount of evidence does not exist in order to draw conclusions regarding the health effects and outcomes associated with long-term exposure to $PM_{10-2.5}$.

In epidemiologic studies, associations between short-term exposure to $PM_{10-2.5}$ and cardiovascular outcomes (i.e., IHD hospital admissions, supraventricular ectopy, and changes in HRV) have been found that are similar in magnitude to those observed in $PM_{2.5}$ studies. Controlled human exposure studies have also observed alterations in HRV, providing consistency and coherence

for the effects observed in the epidemiologic studies. To date, only a limited number of toxicological studies have been conducted to examine the effects of $PM_{10-2.5}$ on cardiovascular effects. All of these studies involved IT instillation due to the technical challenges of using $PM_{10-2.5}$ for rodent inhalation studies. As a result, the toxicological studies evaluated provide limited biological plausibility for the $PM_{10-2.5}$ effects observed in the epidemiologic and controlled human exposure studies.



[a] µg/m^3
[b] Study did not present mean; median presented.
[c] Mean estimated from data in study.
[d] Mean value slightly different from those reported in the published study; mean was either provided by study authors or calculated from data provided by study authors.
[e] Maximum $PM_{10-2.5}$ concentration provided by study authors or calculated from data provided by study authors.

Figure 2-3. Summary of U.S. studies examining the association between short-term exposure to $PM_{10-2.5}$ and cardiovascular morbidity/mortality and respiratory morbidity/mortality. All effect estimates have been standardized to reflect a 10 µg/m^3 increase in mean 24-h avg $PM_{10-2.5}$ concentration and ordered by increasing concentration.

Limited evidence is available from epidemiologic studies for respiratory health effects and outcomes in response to short-term exposure to $PM_{10-2.5}$. An increase in respiratory hospital admissions and ED visits has been observed, but primarily in studies conducted in Canada and Europe. In addition, associations are not reported for lower respiratory symptoms, wheeze, or medication use. Controlled human exposure studies have not observed an effect on lung function or respiratory symptoms in healthy or asthmatic adults, but healthy volunteers have exhibited pulmonary inflammation. The toxicological studies (all IT instillation) provide evidence of

pulmonary injury and inflammation. In some cases, $PM_{10-2.5}$ was found to be more potent than $PM_{2.5}$ and effects were not solely attributable to endotoxin.
Currently, a national network is not in place to monitor $PM_{10-2.5}$ concentrations. As a result, uncertainties surround the concentration at which the observed associations occur. Ambient concentrations of $PM_{10-2.5}$ are generally determined by the subtraction of PM_{10} and $PM_{2.5}$ measurements, using various methods. For example, some epidemiologic studies estimate $PM_{10-2.5}$ by taking the difference between collocated PM_{10} and $PM_{2.5}$ monitors while other studies have taken the difference between county average PM_{10} and $PM_{2.5}$ concentrations. Moreover, there are potential differences among operational flow rates and temperatures for PM_{10} and $PM_{2.5}$ monitors used to calculate $PM_{10-2.5}$. Therefore, there is greater error in ambient exposure to $PM_{10-2.5}$ compared to $PM_{2.5}$. This would tend to increase uncertainty and make it more difficult to detect effects of $PM_{10-2.5}$ in epidemiologic studies. In addition, the various differences between eastern and western U.S. counties can lead to exposure misclassification, and the potential underestimation of effects in western counties (as discussed for $PM_{2.5}$ in Section 2.3.2).
It is also important to note that the chemical composition of $PM_{10-2.5}$ can vary considerably by location, but city-specific speciated $PM_{10-2.5}$ data are limited. $PM_{10-2.5}$ may contain Fe, Si, Al, and base cations from soil, plant and insect fragments, pollen, fungal spores, bacteria, and viruses, as well as fly ash, brake lining particles, debris, and automobile tire fragments.
The 2004 PM AQCD presented the limited amount of evidence available that examined the potential association between exposure to $PM_{10-2.5}$ and health effects and outcomes. The current evidence, primarily from epidemiologic studies, builds upon the results from the 2004 PM AQCD and indicates that short-term exposure to $PM_{10-2.5}$ is associated with effects on both the cardiovascular and respiratory systems. However, variability in the chemical and biological composition of $PM_{10-2.5}$, limited evidence regarding effects of the various components of $PM_{10-2.5}$, and lack of clearly defined biological mechanisms for $PM_{10-2.5}$-related effects are important sources of uncertainty.

2.3.5. Exposure to UFPs

2.3.5.1. Effects of Short-Term Exposure to UFPs

Table 2-4. Summary of causal determinations for short-term exposure to UFPs.

Size Fraction	Outcome	Causality Determination
UFPs	Cardiovascular Effects	Suggestive
	Respiratory Effects	Suggestive

Cardiovascular Effects

Controlled human exposure studies provide the majority of the evidence for cardiovascular health effects in response to short-term exposure to UFPs. While there are a limited number of studies that have examined the association between UFPs and cardiovascular morbidity, there is a larger body of evidence from studies that exposed subjects to fresh DE, which is typically dominated by UFPs. These studies have consistently demonstrated changes in vasomotor function following exposure to atmospheres containing relatively high concentrations of particles (Section 6.2.4.2). Markers of systemic oxidative stress have also been observed to increase after exposure to various particle types that are predominantly in the UFP size range. In addition, alterations in HRV parameters have been observed in response to controlled human exposure to UF CAPs, with inconsistent evidence for changes in markers of blood coagulation following exposure to UF CAPs

and DE (Sections 6.2.1.2 and 6.2.8.2). A few toxicological studies have also found consistent changes in vasomotor function, which provides coherence with the effects demonstrated in the controlled human exposure studies (Section 6.2.4.3). Additional UFP-induced effects observed in toxicological studies include alterations in HRV, with less consistent effects observed for systemic inflammation and blood coagulation. Only a few epidemiologic studies have examined the effect of UFPs on cardiovascular morbidity and collectively they found inconsistent evidence for an association between UFPs and CVD hospital admissions, but some positive associations for subclinical cardiovascular measures (i.e., arrhythmias and supraventricular beats) (Section 6.2.2.1). These studies were conducted in the U.S. and Europe in areas with mean particle number concentration ranging from ~8,500 to 36,000 particles/cm^3. However, UFP number concentrations are highly variable (i.e., concentrations drop off quickly from the road compared to accumulation mode particles), and therefore, more subject to exposure error than accumulation mode particles. In conclusion, the evidence from the studies evaluated **is suggestive of a causal relationship between short-term exposures to UFPs and cardiovascular effects.**

Respiratory Effects

A limited number of epidemiologic studies have examined the potential association between short-term exposure to UFPs and respiratory morbidity. Of the studies evaluated, there is limited, and inconsistent evidence for an association between short-term exposure to UFPs and respiratory symptoms, as well as asthma hospital admissions in locations a median particle number concentration of ~6,200 to a mean of 38,000 particles/cm^3 (Section 6.3.10). The spatial and temporal variability of UFPs also affects these associations. Toxicological studies have reported respiratory effects including oxidative, inflammatory, and allergic responses using a number of different UFP types (Section 6.3). Although controlled human exposure studies have not extensively examined the effect of UFPs on respiratory outcomes, a few studies have observed small UFP-induced asymptomatic decreases in pulmonary function. Markers of pulmonary inflammation have been observed to increase in healthy adults following controlled exposures to UFPs, particularly in studies using fresh DE. However, it is important to note that for both controlled human exposure and animal toxicological studies of exposures to fresh DE, the relative contributions of gaseous copollutants to the respiratory effects observed remain unresolved. Thus, the current collective evidence **is suggestive of a causal relationship between short-term exposures to UFPs and respiratory effects.**

2.3.6. Integration of UFP Effects

The controlled human exposure studies evaluated have consistently demonstrated effects on vasomotor function and systemic oxidative stress with additional evidence for alterations in HRV parameters in response to exposure to UF CAPs. The toxicological studies provide coherence for the changes in vasomotor function observed in the controlled human exposure studies. Epidemiologic studies are limited because a national network is not in place to measure UFP in the U.S. UFP concentrations are spatially and temporally variable, which would increase uncertainty and make it difficult to detect associations between health effects and UFPs in epidemiologic studies. In addition, data on the composition of UFPs, the spatial and temporal evolution of UFP size distribution and chemical composition, and potential effects of UFP constituents are sparse. More limited evidence is available regarding the effect of UFPs on respiratory effects. Controlled human exposure studies have not extensively examined the effect of UFPs on respiratory measurements, but a few studies have observed small decrements in pulmonary function and increases in pulmonary inflammation. Additional effects including oxidative, inflammatory, and pro- allergic outcomes have been demonstrated in toxicological studies. Epidemiologic studies have found limited and inconsistent evidence for associations between UFPs and respiratory effects. Overall, a limited number of studies have examined the association between exposure to UFPs and morbidity and mortality. Of the studies evaluated, controlled human exposure and toxicological studies provide the most evidence for UFP-induced cardiovascular and respiratory effects; however, many studies focus on exposure to DE. As a result, it is unclear if the effects observed are due to UFP, larger particles (i.e., $PM_{2.5}$), or the gaseous components of DE. Additionally, UF CAPs systems

are limited as the atmospheric UFP composition is modified when concentrated, which adds uncertainty to the health effects observed in controlled human exposure studies (Section 1.5.3).

2.4. Policy Relevant Considerations

2.4.1. Potentially Susceptible Populations

Upon evaluating the association between short- and long-term exposure to PM and various health outcomes, studies also attempted to identify populations that are more susceptible to PM (i.e., populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., PM) due to a variety of factors including, but not limited to: genetic or developmental factors, race, gender, life stage, lifestyle (e.g., smoking status and nutrition) or preexisting disease; as well as, population-level factors that can increase an individual's exposure to an air pollutant (e.g., PM) such as socioeconomic status [SES], which encompasses reduced access to health care, low educational attainment, residential location, and other factors). These studies did so by conducting stratified analyses; by examining effects in individuals with an underlying health condition; or by developing animal models that mimic the pathophysiologic conditions associated with an adverse health effect. In addition, numerous studies that focus on only one potentially susceptible population provide supporting evidence on whether a population is susceptible to PM exposure. These studies identified a multitude of factors that could potentially contribute to whether an individual is susceptible to PM (Table 8-2). Although studies have primarily used exposures to $PM_{2.5}$ or PM_{10}, the available evidence suggests that the identified factors may also enhance susceptibility to $PM_{10-2.5}$.

The examination of susceptible populations to PM exposure allows for the NAAQS to provide an adequate margin of safety for both the general population and for susceptible populations.

During specific periods of life (i.e., childhood and advanced age), individuals may be more susceptible to environmental exposures, which in turn can render them more susceptible to PM-related health effects. An evaluation of age-related health effects suggests that older adults have heightened responses for cardiovascular morbidity with PM exposure. In addition, epidemiologic and toxicological studies provide evidence that indicates children are at an increased risk of PM-related respiratory effects. It should be noted that the health effects observed in children could be initiated by exposures to PM that occurred during key windows of development, such as in utero. Epidemiologic studies that focus on exposures during development have reported inconsistent findings (Section 7.4), but a recent toxicological study suggests that inflammatory responses in pregnant women due to exposure to PM could result in health effects in the developing fetus.

Epidemiologic studies have also examined whether additional factors, such as gender, race, or ethnicity modify the association between PM and morbidity and mortality outcomes. Although gender and race do not seem to modify PM risk estimates, limited evidence from two studies conducted in California suggest that Hispanic ethnicity may modify the association between PM and mortality.

Recent epidemiologic and toxicological studies provided evidence that individuals with null alleles or polymorphisms in genes that mediate the antioxidant response to oxidative stress (i.e., GSTM1), regulate enzyme activity (i.e., MTHFR and cSHMT), or regulate levels of procoagulants (i.e., fibrinogen) are more susceptible to PM exposure. However, some studies have shown that polymorphisms in genes (e.g., HFE) can have a protective effect against effects of PM exposure. Additionally, preliminary evidence suggests that PM exposure can impart epigenetic effects (i.e., DNA methylation); however, this requires further investigation.

Collectively, the evidence from epidemiologic and toxicological, and to a lesser extent, controlled human exposure studies, indicate increased susceptibility of individuals with underlying CVDs and respiratory illnesses (i.e., asthma) to PM exposure. Controlled human exposure and toxicological studies provide additional evidence for increased PM-related cardiovascular effects in individuals with underlying respiratory health conditions.

Recently studies have begun to examine the influence of preexisting chronic inflammatory conditions, such as diabetes and obesity, on PM-related health effects. These studies have found some evidence for increased associations for cardiovascular outcomes along with pathophysiologic alterations in markers of inflammation, oxidative stress, and acute phase response. However, more

research is needed to thoroughly examine the affect of PM exposure on obese individuals and to identify the biological pathway(s) that could increase the susceptibility of diabetic and obese individuals to PM. There is also evidence that SES, measured using surrogates such as educational attainment or residential location, modifies the association between PM and morbidity and mortality outcomes. In addition, nutritional status, another surrogate measure of SES, has been shown to have protective effects against PM exposure in individuals that have a higher intake of some vitamins and nutrients. Overall, the epidemiologic, controlled human exposure, and toxicological studies evaluated in this review provide evidence for increased susceptibility for various populations, including children and older adults, people with pre-existing cardiopulmonary diseases, and people with lower SES.

2.4.2. Lag Structure of PM-Morbidity and PM-Mortality Associations

Epidemiologic studies have evaluated the time-frame in which exposure to PM can impart a health effect. PM exposure-response relationships can potentially be influenced by a multitude of factors, such as the underlying susceptibility of an individual (e.g., age, pre-existing diseases), which could increase or decrease the lag times observed.

An attempt has been made to identify whether certain lag periods are more strongly associated with specific health outcomes. The epidemiologic evidence evaluated in the 2004 PM AQCD supported the use of lags of 0-1 days for cardiovascular effects and longer moving averages or distributed lags for respiratory diseases (U.S. EPA, 2004, 056905). However, currently, little consensus exists as to the most appropriate a priori lag times to use when examining morbidity and mortality **outcomes. As a result, many investigators have chosen to examine the lag structure of associations between PM concentration and health outcome instead of focusing on a priori lag times. This approach is informative because if effects are cumulative, higher overall risks may exist than would be observed for any given single-day lag.**

2.4.2.1. PM-Cardiovascular Morbidity Associations

Most of the studies evaluated that examined the association between cardiovascular hospital admissions and ED visits report associations with short-term PM exposure at lags 0- to 2-days, with more limited evidence for shorter durations (i.e., hours) between exposure and response for some health effects (e.g., onset of MI) (Section 6.2.10). However, these studies have rarely examined alternative lag structures. Controlled human exposure and toxicological studies provide biological plausibility for the health effects observed in the epidemiologic studies at immediate or concurrent day lags. Although the majority of the evidence supports shorter lag times for cardiovascular health effects, a recent study has provided preliminary evidence suggesting that longer lag times (i.e., 14- day distributed lag model) may be plausible for non-ischemic cardiovascular conditions (Section 6.2.10). Panel studies of short-term exposure to PM and cardiovascular endpoints have also examined the time frame from exposure to health effect using a wide range of lag times. Studies of ECG changes indicating ischemia show effects at lags from several hours to 2 days, while lag times ranging from hours to several week moving averages have been observed in studies of arrhythmias, vasomotor function and blood markers of inflammation, coagulation and oxidative stress (Section 6.2). The longer lags observed in these panel studies may be explained if the effects of PM are cumulative. Although few studies of cumulative effects have been conducted, toxicological studies have demonstrated PM-dependent progression of atherosclerosis. **It should be noted that PM exposure could also lead to an acute event (e.g., infarction or stroke) in individuals with atherosclerosis that may have progressed in response to cumulative PM exposure. Therefore, effects have been observed at a range of lag periods from a few hours to several days with no clear evidence for any lag period having stronger associations then another.**

2.4.2.2. PM-Respiratory Morbidity Associations

Generally, recent studies of respiratory hospital admissions that evaluate multiple lags, have found effect sizes to be larger when using longer moving averages or distributed lag models. For example, when examining hospital admissions for all respiratory diseases among older adults, the strongest associations were observed when using PM concentrations 2 days prior to the hospital

admission (Section 6.3.8). Longer lag periods were also found to be most strongly associated with asthma hospital admissions and ED visits in children (3-5 days) with some evidence for more immediate effects in older adults (lags of 0 and 1 day), but these observations were not consistent across studies (Section 6.3.8). These variable results could be due to the biological complexity of asthma, which inhibits the identification of a specific lag period. The longer lag times identified in the epidemiologic studies evaluated are biologically plausible considering that PM effects on allergic sensitization and lung immune defenses have been observed in controlled human exposure and toxicological studies. These effects could lead to respiratory illnesses over a longer time course (e.g., within several days respiratory infection may become evident, resulting in respiratory symptoms or a hospital admission). However, inflammatory responses, which contribute to some forms of asthma, may result in symptoms requiring medical care within a shorter time frame (e.g., 0-1 days).

2.4.2.3. PM-Mortality Associations

Epidemiologic studies that focused on the association between short-term PM exposure and mortality (i.e., all-cause, cardiovascular, and respiratory) mostly examined a priori lag structures of either 1 or 0-1 days. Although mortality studies do not often examine alternative lag structures, the selection of the aforementioned a priori lag days has been confirmed in additional studies, with the strongest PM-mortality associations consistently being observed at lag 1 and 0-1-days (Section 6.5). However, of note is recent evidence for larger effect estimates when using a distributed lag model.
Epidemiologic studies that examined the association between long-term exposure to PM and mortality have also attempted to identify the latency period from PM exposure to death
(Section 7.6.4). **Results of the lag comparisons from several cohort studies indicate that the effects of changes in exposure on mortality are seen within five years, with the strongest evidence for effects observed within the first two years. Additionally, there is evidence, albeit from one study, that the mortality effect had larger cumulative effects spread over the follow-up year and three preceding years.**

2.4.3. PM Concentration-Response Relationship

An important consideration in characterizing the PM-morbidity and mortality association is whether the concentration-response relationship is linear across the full concentration range that is encountered or if there are concentration ranges where there are departures from linearity
(i.e., nonlinearity). In this ISA studies have been identified that attempt to characterize the shape of the concentration-response curve along with possible PM "thresholds" (i.e., levels which PM concentrations must exceed in order to elicit a health response). The epidemiologic studies evaluated that examined the shape of the concentration-response curve and the potential presence of a threshold have focused on cardiovascular hospital admissions and ED visits and mortality associated with short-term exposure to PM_{10} and mortality associated with long-term exposure to $PM_{2.5}$.

A limited number of studies have been identified that examined the shape of the PM-cardiovascular hospital admission and ED visit concentration-response relationship. Of these studies, some conducted an exploratory analysis during model selection to determine if a linear curve most adequately represented the concentration-response relationship; whereas, only one study conducted an extensive analysis to examine the shape of the concentration-response curve at different concentrations (Section 6.2.10.10). Overall, the limited evidence from the studies evaluated supports the use of a no-threshold, log-linear model, which is consistent with the observations made in studies that examined the PM-mortality relationship.
Although multiple studies have previously examined the PM-mortality concentration-response relationship and whether a threshold exists, more complex statistical analyses continue to be developed to analyze this association. Using a variety of methods and models, most of the studies evaluated support the use of a no-threshold, log-linear model; however, one study did observe heterogeneity in the shape of the concentration-response curve across cities (Section 6.5). Overall, the studies evaluated further support the use of a no-threshold log-linear model, but additional issues such as the influence of heterogeneity in estimates between cities, and the effect of seasonal and regional differences in PM on the concentration-response relationship still require further investigation.

In addition to examining the concentration-response relationship between short-term exposure to PM and mortality, Schwartz et al. (2008, 156963) conducted an analysis of the shape of the concentration-response relationship associated with long-term exposure to PM. Using a variety of statistical methods, the concentration-response curve was found to be indistinguishable from linear, and, therefore, little evidence was observed to suggest that a threshold exists in the association between long-term exposure to $PM_{2.5}$ and the risk of death (Section 7.6).

2.4.4. PM Sources and Constituents Linked to Health Effects

Recent epidemiologic, toxicological, and controlled human exposure studies have evaluated the health effects associated with ambient PM constituents and sources, using a variety of quantitative methods applied to a broad set of PM constituents, rather than selecting a few constituents a priori (Section 6.6). There is some evidence for trends and patterns that link particular ambient PM constituents or sources with specific health outcomes, but there is insufficient evidence to determine whether these patterns are consistent or robust.

For cardiovascular effects, multiple outcomes have been linked to a $PM_{2.5}$ crustal/soil/road dust source, including cardiovascular mortality and ST-segment changes. Additional studies have reported associations between other sources (i.e., traffic and wood smoke/vegetative burning) and cardiovascular outcomes (i.e., mortality and ED visits). Studies that only examined the effects of individual $PM_{2.5}$ constituents found evidence for an association between EC and cardiovascular hospital admissions and cardiovascular mortality. Many studies have also observed associations between other sources (i.e., salt, secondary SO_4^{2-}/long-range transport, other metals) and cardiovascular effects, but at this time, there does not appear to be a consistent trend or pattern of effects for those factors.

There is less consistent evidence for associations between PM sources and respiratory health effects, which may be partially due to the fact that fewer source apportionment studies have been conducted that examined respiratory-related outcomes (e.g., hospital admissions) and measures (e.g., lung function). However, there is some evidence for associations between respiratory ED visits and decrements in lung function with secondary SO_4^{2-} $PM_{2.5}$. In addition, crustal/soil/road dust and traffic sources of PM have been found to be associated with increased respiratory symptoms in asthmatic children and decreased PEF in asthmatic adults. Inconsistent results were observed in those $PM_{2.5}$ studies that used individual constituents to examine associations with respiratory morbidity and mortality, although Cu, Pb, OC, and Zn were related to respiratory health effects in two or more studies.

A few studies have identified $PM_{2.5}$ sources associated with total mortality. These studies found an association between mortality and the $PM_{2.5}$ sources: secondary SO_4^{2-}/long-range transport, traffic, and salt. In addition, studies have evaluated whether the variation in associations between $PM_{2.5}$ and mortality or PM_{10} and mortality reflects differences in $PM_{2.5}$ constituents. PM_{10}-mortality effect estimates were greater in areas with a higher proportion of Ni in $PM_{2.5}$, but the overall PM_{10}-mortality association was diminished when New York City was excluded in sensitivity analyses in two of the studies. V was also found to modify PM_{10}-mortality effect estimates. When examining the effect of species-to-$PM_{2.5}$ mass proportion on $PM_{2.5}$-mortality effect estimates, Ni, but not V, was also found to modify the association.

Overall, the results indicate that many constituents of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those constituents or sources that are more closely related to specific health outcomes. These findings are consistent with the conclusions of the 2004 PM AQCD (U.S. EPA, 2004, 056905) (i.e., that a number of source types, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning, are associated with health effects). Although the crustal factor of fine particles was not associated with mortality in the 2004 PM AQCD (U.S. EPA, 2004, 056905), recent studies have suggested that PM (both $PM_{2.5}$ and $PM_{10-2.5}$) from crustal, soil or road dust sources or PM tracers linked to these sources are associated with cardiovascular effects. In addition, $PM_{2.5}$ secondary SO_4^{2-} has been associated with both cardiovascular and respiratory effects.

2.5. Welfare Effects

This section presents key conclusions and scientific judgments regarding causality for welfare effects of PM as discussed in Chapter 9. The effects of particulate NO_X and SO_X have recently been evaluated in the ISA for Oxides of Nitrogen and Sulfur – Ecological Criteria (U.S. EPA, 2008, 157074). That ISA focused on the effects from deposition of gas- and particle-phase pollutants related to ambient NO_X and SO_X concentrations that can lead to acidification and nutrient enrichment. Thus, emphasis in Chapter 9 is placed on the effects of airborne PM, including NO_X and SO_X, on visibility and climate, and on the effects of deposition of PM constituents other than NO_X and SO_X, primarily metals and carbonaceous compounds. EPA's framework for causality, described in Chapter 1, was applied and the causal determinations are highlighted.

Table 2-5. Summary of causality determination for welfare effects.

Welfare Effects	Causality Determination
Effects on Visibility	Causal
Effects on Climate	Causal
Ecological Effects	Likely to be causal
Effects on Materials	Causal

2.5.1. Summary of Effects on Visibility

Visibility impairment is caused by light scattering and absorption by suspended particles and gases. There is strong and consistent evidence that PM is the overwhelming source of visibility impairment in both urban and remote areas. EC and some crustal minerals are the only commonly occurring airborne particle components that absorb light. All particles scatter light, and generally light scattering by particles is the largest of the four light extinction components (i.e., absorption and scattering by gases and particles). Although a larger particle scatters more light than a similarly shaped smaller particle of the same composition, the light scattered per unit of mass is greatest for particles with diameters from ~0.3-1.0 μm. For studies where detailed data on particle composition by size are available, accurate calculations of light extinction can be made. However, routinely available PM speciation data can be used to make reasonable estimates of light extinction using relatively simple algorithms that multiply the concentrations of each of the major PM species by its dry extinction efficiency and by a water growth term that accounts for particle size change as a function of relative humidity for hygroscopic species (e.g., sulfate, nitrate, and sea salt). This permits the visibility impairment associated with each of the major PM components to be separately approximated from PM speciation monitoring data.

Direct optical measurement of light extinction measured by transmissometer, or by combining the PM light scattering measured by integrating nephelometers with the PM light absorption measured by an aethalometer, offer a number of advantages compared to algorithm estimates of light extinction based on PM composition and relative humidity data. The direct measurements are not subject to the uncertainties associated with assumed scattering and absorption efficiencies used in the PM algorithm approach. The direct measurements have higher time resolution (i.e., minutes to hours), which is more commensurate with visibility effects compared with calculated light extinction using routinely available PM speciation data (i.e., 24-h duration).

Particulate sulfate and nitrate have comparable light extinction efficiencies (haze impacts per unit mass concentration) at any relative humidity value. Their light scattering per unit mass concentration increases with increasing relative humidity, and at sufficiently high humidity values (RH>85%) they are the most efficient particulate species contributing to haze. Particulate sulfate is

the dominant source of regional haze in the eastern U.S. (>50% of the particulate light extinction) and an important contributor to haze elsewhere in the country (>20% of particulate light extinction). Particulate nitrate is a minor component of remote-area regional haze in the non-California western and eastern U.S., but an important contributor in much of California and in the upper Midwestern U.S., especially during winter when it is the dominant contributor to particulate light extinction.

EC and OC have the highest dry extinction efficiencies of the major PM species and are responsible for a large fraction of the haze, especially in the northwestern U.S., though absolute concentrations are as high in the eastern U.S. Smoke plume impacts from large wildfires dominate many of the worst haze periods in the western U.S. Carbonaceous PM is generally the largest component of urban excess $PM_{2.5}$ (i.e., the difference between urban and regional background concentration). Western urban areas have more than twice the average concentrations of carbonaceous PM than remote areas sites in the same region. In eastern urban areas $PM_{2.5}$ is dominated by about equal concentrations of carbonaceous and sulfate components, though the usually high relative humidity in the East causes the hydrated sulfate particles to be responsible for about twice as much of the urban haze as that caused by the carbonaceous PM.

$PM_{2.5}$ crustal material (referred to as fine soil) and $PM_{10-2.5}$ are significant contributors to haze for remote areas sites in the arid southwestern U.S. where they contribute a quarter to a third of the haze, with $PM_{10-2.5}$ usually contributing twice that of fine soil. Coarse mass concentrations are as high in the Central Great Plains as in the deserts though there are no corresponding high concentrations of fine soil as in the Southwest. Also the relative contribution to haze by the high coarse mass in the Great Plains is much smaller because of the generally higher haze values caused by the high concentrations of sulfate and nitrate PM in that region.

Visibility has direct significance to people's enjoyment of daily activities and their overall sense of wellbeing. For example, psychological research has demonstrated that people are emotionally affected by poor VAQ such that their overall sense of wellbeing is diminished. Urban visibility has been examined in two types of studies directly relevant to the NAAQS review process: urban visibility preference studies and urban visibility valuation studies. Both types of studies are designed to evaluate individuals' desire for good VAQ where they live, using different metrics. Urban visibility preference studies examine individuals' preferences by investigating the amount of visibility degradation considered unacceptable, while economic studies examine the value an individual places on improving VAQ by eliciting how much the individual would be willing to pay for different amounts of VAQ improvement.

There are three urban visibility preference studies and two additional pilot studies that have been conducted to date that provide useful information on individuals' preferences for good VAQ in the urban setting. The completed studies were conducted in Denver, Colorado, two cities in British Columbia, Canada, and Phoenix, AZ. The additional studies were conducted in Washington, DC. The range of median preference values for an acceptable amount of visibility degradation from the 4 urban areas was approximately 19-33 dv. Measured in terms of visual range (VR), these median acceptable values were between approximately 59 and 20 km.

The economic importance of urban visibility has been examined by a number of studies designed to quantify the benefits (or willingness to pay) associated with potential improvements in urban visibility. Urban visibility valuation research was described in the 2004 PM AQCD (U.S. EPA, 2004, 056905) and the 2005 PM Staff Paper (U.S. EPA, 2005, 090209). Since the mid-1990s, little new information has become available regarding urban visibility valuation (Section 9.2.4).

Collectively, the evidence is sufficient to conclude that **a causal relationship exists between PM and visibility impairment.**

2.5.2. Summary of Effects on Climate

Aerosols affect climate through direct and indirect effects. The direct effect is primarily realized as planet brightening when seen from space because most aerosols scatter most of the visible spectrum light that reaches them. The Intergovernmental Panel on Climate Change (IPCC) Fourth Assessment Report (AR4) (IPCC, 2007, 092765), hereafter IPCC AR4, reported that the radiative forcing from this direct effect was -0.5 (±0.4) W/m^2 and identified the level of scientific understanding of this effect as 'Medium-low'. The global mean direct radiative forcing effect from individual components of aerosols was estimated for the first time in the IPCC AR4 where they were reported to be (all in W/m^2 units): -0.4 (±0.2) for sulfate, -0.05 (±0.05) for fossil fuel-derived organic

carbon, +0.2 (±0.15) for fossil fuel-derived black carbon (BC), +0.03 (±0.12) for biomass burning, -0.1 (±0.1) for nitrates, and -0.1 (±0.2) for mineral dust. Global loadings of anthropogenic dust and nitrates remain very troublesome to estimate, making the radiative forcing estimates for these constituents particularly uncertain.

Numerical modeling of aerosol effects on climate has sustained remarkable progress since the time of the 2004 PM AQCD (U.S. EPA, 2004, 056905), PM AQCD, though model solutions still display large heterogeneity in their estimates of the direct radiative forcing effect from anthropogenic aerosols. The clear-sky direct radiative forcing over ocean due to anthropogenic aerosols is estimated from satellite instruments to be on the order of -1.1 (±0.37) W/m^2 while model estimates are -0.6 W/m^2. The models' low bias over ocean is carried through for the global average: global average direct radiative forcing from anthropogenic aerosols is estimated from measurements to range from -0.9 to -1.9 W/m^2, larger than the estimate of -0.8 W/m^2 from the models.

Aerosol indirect effects on climate are primarily realized as an increase in cloud brightness (termed the 'first indirect' or Twomey effect), changes in precipitation, and possible changes in cloud lifetime. The IPCC AR4 reported that the radiative forcing from the Twomey effect was -0.7 (range: -1.1 to +4) and identified the level of scientific understanding of this effect as “Low” in part owing to the very large unknowns concerning aerosol size distributions and important interactions with clouds. Other indirect effects from aerosols are not considered to be radiative forcing.

Taken together, direct and indirect effects from aerosols increase Earth's shortwave albedo or reflectance thereby reducing the radiative flux reaching the surface from the Sun. This produces net climate cooling from aerosols. The current scientific consensus reported by IPCC AR4 is that the direct and indirect radiative forcing from anthropogenic aerosols computed at the top of the atmosphere, on a global average, is about -1.3 (range: -2.2 to -0.5) W/m^2. While the overall global average effect of aerosols at the top of the atmosphere and at the surface is negative, absorption and scattering by aerosols within the atmospheric column warms the atmosphere between the Earth's surface and top of the atmosphere. In part, this is owing to differences in the distribution of aerosol type and size within the vertical atmospheric column since aerosol type and size distributions strongly affect the aerosol scattering and reradiation efficiencies at different altitudes and atmospheric temperatures. And, although the magnitude of the overall negative radiative forcing at the top of the atmosphere appears large in comparison to the analogous IPCC AR4 estimate of positive radiative forcing from anthropogenic GHG of about +2.9 (± 0.3) W/m^2, the horizontal, vertical, and temporal distributions and the physical lifetimes of these two very different radiative forcing agents are not similar; therefore, the effects do not simply off-set one another.

Overall, the evidence is sufficient to conclude that a causal relationship exists between PM and effects on climate, including both direct effects on radiative forcing and indirect effects that involve cloud feedbacks that influence precipitation formation and cloud lifetimes.

2.5.3. Summary of Ecological Effects of PM

Ecological effects of PM include direct effects to metabolic processes of plant foliage; contribution to total metal loading resulting in alteration of soil biogeochemistry and microbiology, plant growth and animal growth and reproduction; and contribution to total organics loading resulting in bioaccumulation and biomagnification across trophic levels. These effects were well- characterized in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Thus, the summary below builds upon the conclusions provided in that review.

PM deposition comprises a heterogeneous mixture of particles differing in origin, size, and chemical composition. Exposure to a given concentration of PM may, depending on the mix of deposited particles, lead to a variety of phytotoxic responses and ecosystem effects. Moreover, many of the ecological effects of PM are due to the chemical constituents (e.g., metals, organics, and ions) and their contribution to total loading within an ecosystem.

Investigations of the direct effects of PM deposition on foliage have suggested little or no effects on foliar processes, unless deposition levels were higher than is typically found in the ambient environment. However, consistent and coherent evidence of direct effects of PM has been found in heavily polluted areas adjacent to industrial point sources such as limestone quarries, cement kilns, and metal smelters (Sections 9.4.3 and 9.4.5.7). Where toxic responses have been

documented, they generally have been associated with the acidity, trace metal content, surfactant properties, or salinity of the deposited materials.

An important characteristic of fine particles is their ability to affect the flux of solar radiation passing through the atmosphere, which can be considered in both its direct and diffuse components. Foliar interception by canopy elements occurs for both up- and down-welling radiation. Therefore, the effect of atmospheric PM on atmospheric turbidity influences canopy processes both by radiation attenuation and by changing the efficiency of radiation interception in the canopy through conversion of direct to diffuse radiation. Crop yields can be sensitive to the amount of radiation received, and crop losses have been attributed to increased regional haze in some areas of the world such as China (Section 9.4.4). On the other hand, diffuse radiation is more uniformly distributed throughout the canopy and may increase canopy photosynthetic productivity by distributing radiation to lower leaves. The enrichment in photosynthetically active radiation (PAR) present in diffuse radiation may offset a portion of the effect of an increased atmospheric albedo due to atmospheric particles. Further research is needed to determine the effects of PM alteration of radiative flux on the growth of vegetation in the U.S.

The deposition of PM onto vegetation and soil, depending on its chemical composition, can produce responses within an ecosystem. The ecosystem response to pollutant deposition is a direct function of the level of sensitivity of the ecosystem and its ability to ameliorate resulting change. Many of the most important ecosystem effects of PM deposition occur in the soil. Upon entering the soil environment, PM pollutants can alter ecological processes of energy flow and nutrient cycling, inhibit nutrient uptake, change ecosystem structure, and affect ecosystem biodiversity. The soil environment is one of the most dynamic sites of biological interaction in nature. It is inhabited by microbial communities of bacteria, fungi, and actinomycetes, in addition to plant roots and soil macro-fauna. These organisms are essential participants in the nutrient cycles that make elements available for plant uptake. Changes in the soil environment can be important in determining plant and ultimately ecosystem response to PM inputs.

There is strong and consistent evidence from field and laboratory experiments that metal components of PM alter numerous aspects of ecosystem structure and function. Changes in the soil chemistry, microbial communities and nutrient cycling, can result from the deposition of trace metals. Exposures to trace metals are highly variable, depending on whether deposition is by wet or dry processes. Although metals can cause phytotoxicity at high concentrations, few heavy metals (e.g., Cu, Ni, Zn) have been documented to cause direct phytotoxicity under field conditions. Exposure to coarse particles and elements such as Fe and Mg are more likely to occur via dry deposition, while fine particles, which are more often deposited by wet deposition, are more likely to contain elements such as Ca, Cr, Pb, Ni, and V. Ecosystems immediately downwind of major emissions sources can receive locally heavy deposition inputs. Phytochelatins produced by plants as a response to sublethal concentrations of heavy metals are indicators of metal stress to plants. Increased concentrations of phytochelatins across regions and at greater elevation have been associated with increased amounts of forest injury in the northeastern U.S.

Overall, the ecological evidence is sufficient to conclude that **a causal relationship is likely to exist between deposition of PM and a variety of effects on individual organisms and ecosystems, based on information from the previous review and limited new findings in this review.** However, in many cases, it is difficult to characterize the nature and magnitude of effects and to quantify relationships between ambient concentrations of PM and ecosystem response due to significant data gaps and uncertainties as well as considerable variability that exists in the components of PM and their various ecological effects.

2.5.4. Summary of Effects on Materials

Building materials (metals, stones, cements, and paints) undergo natural weathering processes from exposure to environmental elements (wind, moisture, temperature fluctuations, sunlight, etc.). Metals form a protective film of oxidized metal (e.g., rust) that slows environmentally induced corrosion. However, the natural process of metal corrosion is enhanced by exposure to anthropogenic pollutants. For example, formation of hygroscopic salts increases the duration of surface wetness and enhances corrosion.

A significant detrimental effect of particle pollution is the soiling of painted surfaces and other building materials. Soiling changes the reflectance of opaque materials and reduces the transmission

of light through transparent materials. Soiling is a degradation process that requires remediation by cleaning or washing, and, depending on the soiled surface, repainting. Particulate deposition can result in increased cleaning frequency of the exposed surface and may reduce the usefulness of the soiled material. Attempts have been made to quantify the pollutant exposure levels at which materials damage and soiling have been perceived. However, to date, insufficient data are available to advance the knowledge regarding perception thresholds with respect to pollutant concentration, particle size, and chemical composition. Nevertheless, the evidence is sufficient to conclude that **a causal relationship exists between PM and effects on materials.**

2.6. Summary of Health Effects and Welfare Effects Causal Determinations

This chapter has provided an overview of the underlying evidence used in making the causal determinations for the health and welfare effects and PM size fractions evaluated. This review builds upon the main conclusions of the last PM AQCD (U.S. EPA, 2004, 056905):

- "A growing body of evidence both from epidemiological and toxicological studies… supports the general conclusion that $PM_{2.5}$ (or one or more $PM_{2.5}$ components), acting alone and/or in combination with gaseous copollutants, are likely causally related to cardiovascular and respiratory mortality and morbidity." (pg 9-79)

- "A much more limited body of evidence is suggestive of associations between short-term (but not long-term) exposures to ambient coarse-fraction thoracic particles… and various mortality and morbidity effects observed at times in some locations. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may contribute under some circumstances to increased human health risks… with somewhat stronger evidence for… associations with morbidity (especially respiratory) endpoints than for mortality." (pg 9-79 and 9-80)

- "Impairment of visibility in rural and urban areas is directly related to ambient concentrations of fine particles, as modulated by particle composition, size, and hygroscopic characteristics, and by relative humidity." (pg 9-99)

- "Available evidence, ranging from satellite to in situ measurements of aerosol effects on incoming solar radiation and cloud properties, is strongly indicative of an important role in climate for aerosols, but this role is still poorly quantified." (pg 9-111)

The evaluation of the epidemiologic, toxicological, and controlled human exposure studies published since the completion of the 2004 PM AQCD have provided additional evidence for PM-related health effects. Table 2-6 provides an overview of the causal determinations for all PM size fractions and health effects. Causal determinations for PM and welfare effects, including visibility, climate, ecological effects, and materials are included in Table 2-7. Detailed discussions of the scientific evidence and rationale for these causal determinations are provided in the subsequent chapters of this ISA.

Table 2-6. Summary of PM causal determinations by exposure duration and health outcome.

Size Fraction	Exposure	Outcome	Causality Determination
$PM_{2.5}$	Short-term	Cardiovascular Effects	Causal
		Respiratory Effects	Likely to be causal
		Central Nervous System	Inadequate
		Mortality	Causal
	Long-term	Cardiovascular Effects	Causal
		Respiratory Effects	Likely to be Causal
		Mortality	Causal
		Reproductive and Developmental	Suggestive
	Cancer, Mutagenicity, Genotoxicity		Suggestive
$PM_{10-2.5}$	Short-term	Cardiovascular Effects	Suggestive
		Respiratory Effects	Suggestive
		Central Nervous System	Inadequate
		Mortality	Suggestive
	Long-term	Cardiovascular Effects	Inadequate
		Respiratory Effects	Inadequate
		Mortality	Inadequate
	Reproductive and Developmental		Inadequate
	Cancer, Mutagenicity, Genotoxicity		Inadequate
UFPs	Short-term	Cardiovascular Effects	Suggestive
		Respiratory Effects	Suggestive
		Central Nervous System	Inadequate
		Mortality	Inadequate
	Long-term	Cardiovascular Effects	Inadequate
		Respiratory Effects	Inadequate
		Mortality	Inadequate
		Reproductive and Developmental	Inadequate
	Cancer, Mutagenicity, Genotoxicity		Inadequate

Table 2-7. Summary of PM causal determinations for welfare effects

Welfare Effects	Causality Determination
Effects on Visibility	Causal
Effects on Climate	Causal
Ecological Effects	Likely to be causal
Effects on Materials	Causal

Chapter 2 References

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June 8, 2011

Research Screening Committee Members

California Air Resources Board
1001 I Street
P.O. Box 2815
Sacramento, CA 95812

RE: Draft report for the contract No. 06-332 "Spatiotemporal Analysis of Air Pollution and Mortality in California Based on the American Cancer Society Cohort"

Ladies and Gentlemen of the Screening Committee,

Your have a choice in your consideration of this study by Dr. Michael Jerrett and many Co-Authors on whether you will properly execute your duties to assure good science informs good policy making, or you can be complicit in a scientific fraud of great magnitude. This study and report, particularly its conclusions, are a scientific fraud that not only ignores the rules of epidemiology and good human health effects science, but are complicit in fraudulent activity that uses public moneys, by faculty members of the University of California and others who put their names to the study.

I have reviewed the "Jarrett" study, paid for by 750,000 taxpayer dollars, which is an important consideration expanded on herein below. The Jarrett 3 year effort is based on assumptions that are derivative of previous studies, but in the main it is a modeling exercise intended to dredge for proof that there are small particle air pollution deaths that justify a California Air Resources Board small particle regulatory regime. Nothing in this expensive desk top computer modeling study is adequate to the task. After all is said and done, now looking at the Jarrett study, it shows no evidence that current ambient small particles in the air of California air are killing anyone.

Here is where the fraud begins, members of the Screening Committee.

The models failed to provide the proof that Dr. Enstrom was wrong in 2005 when he said there is no small particle death effect in California. The elaborate Jarrett study confirms what Jarrett admitted in February of 2010, that he could find no human health effect from California small particle air pollution. The study presented to the committee fails to disprove or contradict the assertion of Dr. Enstrom in 2005 or the admission of Dr. Jarrett in 2010 that CARB claims of deaths from small particles were not evident in his research. Dr. Jarrett in 2010 was admitting that, even as the chosen researcher for CARB, he could not find evidence to show

death effects from small particles in the air.

The only model in the elaborate and thick Jarrett study before you that provides even a glimmer, A GLIMMER, for the CARB agenda of small particle regulations failed when the minor relative risk of 1.08 was combined with a confidence interval that included 1.0. ATTENTION, LADIES AND GENTLEMEN OF THE SCREENING COMMITTEE—THAT MEANS THAT THE JARRETT STUDY SHOWS NO SMALL PARTICLE EFFECTS. PERIOD. NONE, IN ANY OF THE MODELS OR ALTERNATIVE SCENARIOS.

However, because this is such a scandal, and because criticizing Dr. Jarrett's study is so easy, I would like to list a few points for your consideration: ,

1. The Jarrett study, if intended to show small particles kill, came a cropper (that means it failed, folks), since it fails in every effort to find significant evidence that small particles kill Californians. In fact it shows what we all knew, that Californians are not dying from small particles. All of the studies showed effects with a confidence interval that crossed or included 1.0. As Bugs Bunny would say—that's all folks! You have nothing to hang your hat on and approval of this study will show your lack of good faith.
2. All 9 modeling exercises, intended to dredge for proof to support CARB had no effects that escaped the confidence interval that made them mean nothing—NOTHING. The studies showed the confidence intervals meeting or crossing 1.0, confirming that there is of NO EFFECT of small particles on premature death in California from small particles of 2.5 microns or less.
3. When the 9 studies offered by the Jarrett study show no effect, any CARB decision to pursue the Small Particle regulations would not only violate a committee public duty to pursue policies that are based on sound science, I WOULD ARGUE THAT SUCH A DECISION BY CARB WOULD INDICATE COMPLICITY BY THE COMMITTEE AND BY CARB LEADERSHIP IN A FRAUD, A FRAUDULENT STUDY PAID FOR BY THE BELEAGURED TAXPAYERS OF CALIFORNIA WHO COULD HAVE BEEN SPARED THE THREE QUARTERS OF A MILLION DOLLARS WASTED ON THE STUDY.
4. I would remind the review committee that complicity in a fraud exposes individuals, either in their official or their individual capacities as parties to misuse of taxpayer funds.

I will not belabor the members of the committee with the epidemiological rules and the toxicology rules that are applicable to studies such as the Jarrett study. Suffice it to say that Federal Judicial Rules of Evidence specify that scientific evidence such as that contained in the Jarrett study should be reliable and relevant for the case in hand—the question of whether CARB has the science to justify its policy decisions.

<u>The misrepresentation and fraud of the Jarrett group and the Jarrett study is most evident in the conclusions.</u> The authors state "We conclude that combustion-source air pollution, especially from traffic, is significantly associated with premature death in this large cohort of Californians." A reasonable citizen reviewer of the study, knowledgeable in the science of epidemiology would ask--how could the authors use words like "conclude" or "significantly associated" when they have nothing in the study to support an assertion?

Have the authors sold their scientific integrity for $750,000? Are they implicated in a fraud on the citizens of California, claiming their "show nothing" study is adequate to support a new ambitious and onerous CARB regulatory regime focused on small particles?

There is retribution in the law for fraud on the taxpayers. Laws were enacted to prevent dishonest and

fraudulent use of public moneys. Committees that fail to recognize their responsibility as fiduciaries for the taxpayers could also be considered complicit in the fraud if they have been properly warned.

This letter is proper warning to the members of the review committee.

Consider your options when I am telling you, as an experienced and knowledgeable man of science and the law. You and the CARB and the scientists involved in this disgraceful study may have to answer questions on whether the study was properly conducted, but more importantly, were the conclusions proper, given the evidence or, were those conclusions bought and paid for?

Respectfully,

John Dale Dunn MD JD

GORDON J. FULKS, PHD
PORTLAND, OREGON USA

August 15, 2016

South Coast Air Quality Management District
Attn: Health Effects Officer Jo Kay Chan Ghosh, PhD
Air Quality Specialist Anthony Oliver, PhD
21865 Copley Drive
Diamond Bar, CA 91765

Ladies and Gentlemen,

We all want to live in a clean environment, and I applaud your efforts to improve air quality in Southern California. As someone who lived in the severe air pollution in Chicago in the 1950s through the 1970s and then experienced the different but still severe air pollution in Southern California in later decades, I appreciate clean air.

But at some point we reach diminishing returns for dollars expended. That point is clearly reached when there are no further health benefits to be realized from trying to control the last tiny amount of man-made pollution that becomes lost in natural background levels or in artificial background levels floating over from China.

6-1

Of course, 'Linear No-Threshold' (LNT) arguments insist that there is no threshold below which poisons become unimportant. Hence, it is possible to extrapolate fatalities at high doses to far less but still finite fatalities at low doses. **This is nonsense**, as was shown, for instance, in studies of those clearly exposed to radiation from the nuclear weapons that devastated Hiroshima and Nagasaki. There was a radiation exposure below which the population suffered no increased risk of premature death. **The LNT arguments are bad science.**

Yet we still see far too many attempts to apply LNT arguments based on statistical techniques trying to correlate mortality records with vague low level exposures. This is bad science on top of bad science. **Entirely random data sets will still show clusters of false positives, because random data is never completely smooth.** Every gambler in Las Vegas playing a game of pure chance will have good and bad nights.

And then there is the problem of confusing correlation with causation. Even if researchers are able to spot legitimate correlations, they MUST go further to establish whether A causes B or B causes A or C causes both of them. Failing to do this is bad science on top of bad science on top of bad science.

Five years ago, I pointed out that the PM 2.5 studies of small particulate air pollution performed by Michael Jerrett et al. (2011), for the California Air Resources Board did NOT meet elementary scientific standards and should be rejected. Please see my attached 10/26/2011 letter. Yet Jerrett et al. is still alive in a revised 2013 version that ignored our criticism and even ignored their own previous findings of no effect in eight of nine statistical models. Such bad behavior has no place in science.

To be fair to Jerrett et al., I do not place all the blame on them, because they were just doing what CARB and SCAQMD paid them to do, and that was not science. Both agencies wanted to regulate diesel engines. **That is a poor reason to support heavily flawed scientific studies. It gives both the regulators and the scientists a bad name.** While peer-review is the weakest of the validation criteria for scientific theories, it is far better than just ignoring scientific criticism and compounding the bad science with bad regulations.

I hope you will do what CARB failed to do: pay attention to criticism from those of us qualified to critique the studies you propose to rely upon. Failing to do so will come back to haunt you. The Devil always comes to collect on Faustian Bargains.

Since my critical comments about Jerrett et al five years ago, others have pointed out that we face an epidemic of poor science that has overwhelmed the field of Epidemiology. Too many researchers try to make a name for themselves by pointing out the false positives to be found in completely random data. And while they can get past peer-review when it is merely 'pal-review', they fail replication tests run by truly independent researchers. Such bad behavior from those who should know better costs our society dearly. **Regulators MUST ask the hard questions to weed out the bad science** that does not meet basic requirements for honesty, let alone the "Utter Honesty" expected of scientists.*

It is long past time for California air pollution agencies to reject the defective work of Jerrett at al and stop imposing even more draconian regulations on the citizens of California. If Southern Californians really have $38 billion dollars to spend on environmental improvements, surely you can find more productive ways to improve the environment in Southern California.

Gordon J. Fulks, PhD
Portland, Oregon USA

P.S. I am an astrophysicist, originally from the University of Chicago Laboratory for Astrophysics and Space Research. I have a Bachelors, Masters, and PhD, all in Physics and all from the University of Chicago. As with many physicists, I have a strong interest in the integrity of science. I also have no conflicts of interest in this matter. No one is paying me to critique your work. We realize that science is much more than a good story. It is a story that must survive verification tests. If it does not, it must be scrapped! There are no exceptions for stories that please regulatory agencies.

* "Utter Honesty" is a term coined by the great Southern California Physicist, Nobel Laureate, and Professor at Cal-Tech Richard Feynman. He used it to explain to students of science what would be expected of them in their careers. Too many missed that lecture.

From: James E. Enstrom <jenstrom@ucla.edu>
Sent: Monday, August 15, 2016 11:55 PM
To: Jo Kay Ghosh
Cc: Elaine Shen; Shah Dabirian; Anthony Oliver; Philip Fine; Wayne Nastri; 'Henry A. Roman'; 'George D. Thurston'; 'Kevin R. Cromar'; AQMP Inquiries
Subject: Enstrom Comments re SCAQMD 2016 AQMP Health Effects
Attachments: Enstrom Comments re SCAQMD 2016 AQMP Health Effects 081516.pdf

August 15, 2016

Jo Kay Chan Ghosh, Ph.D.
Health Effects Officer
South Coast Air Quality Management District
jghosh@aqmd.gov

Dear Dr. Ghosh,

Attached are my public comments regarding the SCAQMD Draft 2016 AQMP Appendix I Health Effects. I plan to speak about these comments at the August 18, 2016 SCAQMD AQMP Advisory Council meeting in Diamond Bar. Please acknowledge receipt of these comments.

Thank you very much.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

cc: Elaine Shen <eshen@aqmd.gov>
Shah Dabirian <sdabirian@aqmd.gov>
Anthony Oliver <aoliver@aqmd.gov>
Philip M. Fine <pfine@aqmd.gov>
Wayne Nastri <wnastri@aqmd.gov>
Henry A. Roman <har@indecon.com>
George D. Thurston <George.Thurston@nyumc.org>
Kevin R. Cromar <kevin.cromar@nyu.edu>
AQMP Comment <aqmp@aqmd.gov>

August 15, 2016

Jo Kay Chan Ghosh, Ph.D.
Health Effects Officer
South Coast Air Quality Management District
jghosh@aqmd.gov

Dear Dr. Ghosh,

I am writing to express serious concern that my July 26, 2016 public comments below regarding the health effects/impacts of particulate matter in the South Coast Air Basin (SCAB) are not being addressed. In particular, the August 16, 2016 PPT by Dr. Elaine Shen Update on the Preliminary Draft Socioeconomic Report claims that there will be 2,111 premature deaths due to PM2.5 in 2023. This is the same number of deaths shown in the attached July 28, 2016 PPT slide by Dr. Anthony Oliver Preliminary Public Health Benefits of the Draft 2016 AQMP . This scientifically invalid claim does not provide valid public health justification for a 2016 AQMP that will impose an estimated $38.2 billion in compliance costs on the SCAB economy. 7-1

Since 2006 I have repeatedly presented to CARB and SCAQMD strong epidemiologic evidence that there is no relationship between PM2.5 and total mortality in California. The latest version of this evidence is the attached table with 16 null results and 1 essentially null result from six different California cohorts (http://scientificintegrityinstitute.org/NoPMDeaths081516.pdf). Seven of the null results come from studies that were partially funded by SCAQMD. In addition, a very strong case has recently been made by nine accomplished experts, including myself, that "Particulate Matter Does Not *Cause* Premature Deaths" (https://www.nas.org/articles/nas_letter). Furthermore, I have now submitted for publication a manuscript with null findings that invalidate the positive nationwide relationship between PM2.5 and total mortality published in the seminal Pope 1995 paper, which is based on the American Cancer Society Cancer Prevention Study II (CPS II) cohort. My null CPS II cohort findings raise serious doubts about validity of the positive CPS II cohort findings in Jerrett 2005, Jerrett 2009, and Jerrett 2013, which have been used as the basis for the PM2.5 premature death claims in the PPTs of Drs. Oliver and Shen. 7-2

All epidemiologic evidence relevant to the SCAB must be properly presented and summarized in the revised Draft 2016 AQMP Appendix I Health Effects (http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2016-air-quality-management-plan/DRAFT2016AQMP/appi.pdf?sfvrsn=2). Indeed, Appendix I must be finalized in strict compliance with all provisions of California Health and Safety Code (CHSC) Section 40471 (b): "On or before December 31, 2001, and every three years thereafter, as part of the preparation of the air quality management plan revisions, the south coast district board, in conjunction with a public health organization or agency, shall prepare a report on the health impacts of particulate matter air pollution in the South Coast Air Basin. The south coast district board shall submit its report to the advisory council appointed pursuant to Section 40428 for review and comment. The advisory council shall undertake peer review concerning the report prior to its finalization and public release. The south coast district board shall hold public hearings concerning the report and the peer review, and shall append to the report any additional material or information that results from the peer review and public hearings." (http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=40001-41000&file=40460-40471). 7-3

As I have previously requested, the 2016 AQMP must present current data on the average human exposure levels for PM2.5, ozone, and NOx in the SCAB. My evidence dating back decades indicates that the actual human exposure levels are far below the EPA National Ambient Air Quality Standards (NAAQS) and well below the levels for which there are proven adverse health effects. Furthermore, the tiny health effects of air pollution must be put into perspective with all the factors that influence human health, such as, employment, and with the fact that the SCAB has 2014 age-adjusted death rates for all causes, all cancer, and all respiratory diseases that are among the lowest in the entire US. These low death rates are summarized the attached table.

7-3 Con't

The ultimate scientific and regulatory fate of the 2016 depends upon the scientists who have conducted air pollution epidemiology research and upon the SCAQMD scientists who summarize these research findings in Appendix I Health Effects. We will soon find out if the SCAQMD scientists have the honesty and integrity to state that air pollution *does not cause* premature deaths in the SCAB, that the average daily human exposures to PM2.5, ozone, and NOx in the SCAB are well below the levels that *cause* adverse health effects, and that tougher air pollution regulations in the already healthy SCAB are not justified on a public health or socioeconomic basis.

In closing, please read my attached July 19, 2016 statement to the BizFed Southern California Business Coalition "AQMD Must Reassess Its Air Quality Regulations" and the attached page summarizing my scientific credentials and academic career.

Thank you very much for your consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

cc: Elaine Shen <eshen@aqmd.gov>
Shah Dabirian <sdabirian@aqmd.gov>
Anthony Oliver <aoliver@aqmd.gov>
Philip M. Fine <pfine@aqmd.gov>
Wayne Nastri <wnastri@aqmd.gov>
Henry A. Roman <har@indecon.com>
George D. Thurston <George.Thurston@nyumc.org>
Kevin R. Cromar <kevin.cromar@nyu.edu>
AQMP Comment <aqmp@aqmd.gov>

The following attachment(s) were included with Comment Letter #7 submitted by Dr. James Enstrom, and was/were duplicate entries on previous comment letter(s) received:

- Letter from Dr. James Enstrom to Dr. Anthony Oliver, dated July 26, 2016. This corresponds to Comment letter #10 under the draft Socioeconomic Report.

The following attachments were also included with Comment Letter #7 submitted by Dr. James Enstrom, and we are pending permission from the author to post to the website.

- Summary table of epidemiologic cohort studies of PM2.5 and total mortality in California, 2000-2016
- Table of 2014 age-adjusted death rates by state and county
- Presentation by James Enstrom titled “AQMD must reassess its air quality regulations” dated July 19, 2016

A hard copy of all materials included in the comment letters, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

July 26, 2016

Anthony Oliver, Ph.D.
SCAQMD Air Quality Specialist
aoliver@aqmd.gov

Dear Dr. Oliver,

I am an environmental epidemiologist and physicist who has had a long career at UCLA and I am an expert in the health effects of air pollution in California. I am writing regarding your planned presentation "Item #3: Preliminary Public Health Benefits of the Draft 2016 AQMP" at the July 28, 2016 SCAQMD Scientific, Technical & Modeling Peer Review Advisory Group (STMPR) Socioeconomic Meeting (http://www.aqmd.gov/home/library/meeting-agendas-minutes/agenda?title=STMPRSocio_072816). I challenge the validity of your "Preliminary Health Impacts – Mortality" and your selective use of Jerrett 2005, Jerrett 2009, and Jerrett 2013.

Key aspects of my prior criticism of SCAQMD STMPR claims regarding the health impacts of PM2.5 and ozone in the South Coast Air Basin (SCAB) are contained in these three documents:

November 16, 2015 Enstrom Email to Cassmassi and SMTPR Staff re Ozone and PM in SCAB (http://www.scientificintegrityinstitute.org/Cassmassi111615.pdf)
November 22, 2015 Enstrom Table with 2000-2015 Results Showing NO PM2.5 Premature Deaths in CA (http://www.scientificintegrityinstitute.org/NoPMDeaths112215.pdf)
December 15, 2015 Enstrom Email to Roman Requesting NO IEc PM2.5 and Ozone Deaths for 2016 AQMP (http://www.scientificintegrityinstitute.org/Roman121515.pdf)

I strongly recommend that you carefully read all three documents, as well as all the weblinks that they contain. Then I strongly recommend that you discuss these documents with me, as well as with SCAQMD Health Effects Officer Jo Kay Chan Ghosh and IEc Principal Henry A. Roman. Finally, I strongly recommend that you announce during your presentation that several highly qualified doctoral-level scientists, including myself, are challenging the validity of your presentation, particularly your claims of "Premature Mortalities" in the SCAB.

Thank you very much for your attention to this important matter.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

cc: Jo Kay Chan Ghosh <jghosh@aqmd.gov>
Henry A. Roman <har@indecon.com>
George D. Thurston <George.Thurston@nyumc.org>
Elaine Shen <eshen@aqmd.gov>
Philip M. Fine <pfine@aqmd.gov>
Wayne Nastri <wnastri@aqmd.gov>

Preliminary Health Impacts - Mortality

- Health impacts for mortality are based on the previous data and:
  - Ozone: Pooling of L.A.-specific NMMAPS and meta-analysis estimates from Bell et al. (2005).
  - $PM_{2.5}$: Pooling of Jerrett et al. (2005), Jerrett et al. (2013), and Kriging and LUR estimates from Krewski et al. (2009).

- No threshold effects assumed for either pollutant
  - IEc recommendation based on latest scientific evidence
  - U.S. EPA's practice

> In the absence of substantial information in the scientific literature on alternative forms of C-R functions at low O3 concentrations, the best estimate of the C-R function is a linear, no-threshold function.
>
> U.S. EPA, 2014 Health Risk and Exposure Assessment for Ozone

Note: Confidence intervals provided on supplementary handout.

Preliminary Health Impacts – Mortality (cont'd)

Premature Mortalities Avoided		
	2023	**2031**
Mortality, All Cause	**2193**	**2563**
Short-term Ozone Exposure	**51**	**87**
Los Angeles	22	40
Orange	10	14
Riverside	11	16
San Bernardino	9	15
Long-term $PM_{2.5}$ Exposure	**2111**	**2425**
Los Angeles	1481	1707
Orange	321	356
Riverside	141	166
San Bernardino	169	197

Note: Confidence intervals provided on supplementary handout.

Summary Table. Epidemiologic cohort studies of $PM_{2.5}$ and total mortality in California, 2000-2016
Relative risk of death from all causes (RR and 95% CI) associated with increase of 10 µg/m³ in PM2.5
(http://scientificintegrityinstitute.org/NoPMDeaths112215.pdf)

Krewski 2000 & 2010 CA CPS II Cohort N=40,408 RR = 0.872 (0.805-0.944) 1982-1989
(N=[18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM2.5; 44 covariates)

McDonnell 2000 CA AHSMOG Cohort N~3,800 RR ~ 1.00 (0.95 – 1.05) 1977-1992
(N~[1,347 M + 2,422 F]; SC&SD&SF AB; M RR=1.09(0.98-1.21) & F RR~0.98(0.92-1.03))

Jerrett 2005 CPS II Cohort in LA Basin N=22,905 RR = 1.11 (0.99 - 1.25) 1982-2000
(N=22,905 M & F; 267 zip code areas; 1999-2000 PM2.5; 44 cov + max confounders)

Enstrom 2005 CA CPS I Cohort N=35,783 RR = 1.039 (1.010-1.069) 1973-1982
(N=[15,573 M + 20,210 F]; 11 counties; 1979-1983 PM2.5) RR = 0.997 (0.978-1.016) 1983-2002

Enstrom 2006 CA CPS I Cohort N=35,783 RR = 1.061 (1.017-1.106) 1973-1982
(11 counties; 1979-1983 & 1999-2001 PM2.5) RR = 0.995 (0.968-1.024) 1983-2002

Zeger 2008 MCAPS Cohort "West" N=3,100,000 RR = 0.989 (0.970-1.008) 2000-2005
(N=[1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA (CA=73%); 2000-2005 PM2.5)

Jerrett 2010 CA CPS II Cohort N=77,767 RR ~ 0.994 (0.965-1.025) 1982-2000
(N=[34,367 M + 43,400 F]; 54 counties; 2000 PM2.5; KRG ZIP; 20 ind cov+7 eco var; Slide 12)

Krewski 2010 (2009) CA CPS II Cohort
(4 MSAs; 1979-1983 PM2.5; 44 cov) N=40,408 RR = 0.960 (0.920-1.002) 1982-2000
(7 MSAs; 1999-2000 PM2.5; 44 cov) N=50,930 RR = 0.968 (0.916-1.022) 1982-2000

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 0.994 (0.965-1.024) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 1.002 (0.992-1.012) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)

Lipsett 2011 CA Teachers Cohort N=73,489 RR = 1.01 (0.95 – 1.09) 2000-2005
(N=[73,489 F]; 2000-2005 PM2.5)

Ostro 2011 CA Teachers Cohort N=43,220 RR = 1.06 (0.96 – 1.16) 2002-2007
(N=[43,220 F]; 2002-2007 PM2.5)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.060 (1.003–1.120) 1982-2000
(N=[~32,550 M + ~41,161 F]; 54 counties; 2000 PM2.5; LUR Conurb Model; 42 ind cov+7 eco var+5 metro; Table 6)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.028 (0.957-1.104) 1982-2000
(same parameters and model as above, except including co-pollutants NO2 and Ozone; Table 5)

Ostro 2015 CA Teachers Cohort N=101,884 RR = 1.01 (0.98 -1.05) 2001-2007
(N=[101,881 F]; 2002-2007 PM2.5) (all natural causes of death)

Thurston 2016 CA NIH-AARP Cohort N=160,209 RR = 1.02 (0.99 -1.04) 2000-2009
(N=[~95,965 M + ~64,245 F]; full baseline model: PM2.5 by zip code; Table 3) (all natural causes of death)

Enstrom 2016 unpub CA NIH-AARP Cohort N=160,368 RR = 1.001 (0.949-1.055) 2000-2009
(N=[~96,059 M + ~64,309 F]; full baseline model: 2000 PM2.5 by county)

2014 Age-Adjusted Death Rates by State and County

Deaths per 1,000 persons (age-adjusted using 2000 U.S. Standard Population)
with 95% Confidence Interval shown in parentheses
(http://wonder.cdc.gov/ucd-icd10.html)

August 6, 2016

Location	2014 Age-Adjusted Death Rate (95% Confidence Interval)		
	All Causes	All Cancer	All Respiratory
	ICD-10=All Codes	ICD-10=C00-D48	ICD-10=J00-J98
United States (50 States + DC)	7.25 (7.24-7.26)	1.66 (1.65-1.66)	0.71 (0.71-0.71)
California (2nd lowest State)	6.06 (6.03-6.08)	1.48 (1.46-1.49)	0.57 (0.56-0.57)
South Coast Air Basin (Los Angeles, Orange, Riverside, and San Bernardino Counties)	5.93	1.46	0.55
Hawaii (Lowest State)	5.89 (5.77-6.00)	1.44 (1.38-1.49)	0.53 (0.50-0.56)
Los Angeles County	5.71 (5.66-5.75)	1.42 (1.40-1.44)	0.53 (0.52-0.55)
Orange County	5.48 (5.40-5.56)	1.38 (1.34-1.42)	0.47 (0.45-0.49)

Presentation to Southern California Business Coalition on SCAQMD and 2016 AQMP

"**AQMD Must Reassess Its Air Quality Regulations**"

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu

July 19, 2016

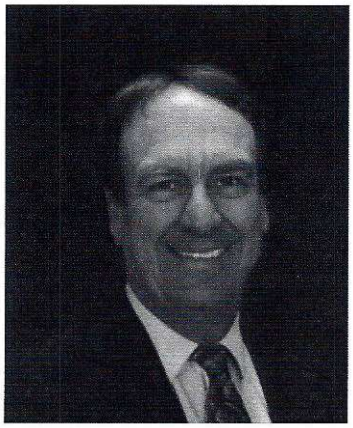
The South Coast Air Quality Management District (AQMD), one of the most powerful regulatory agencies in the United States, has just proposed tightening its regulations. During the past 40 years it has implemented strong air quality regulations in the 11,000 square-mile South Coast Air Basin (SCAB), which includes the 17 million people who live in the populated areas of Los Angeles, Orange, Riverside, and San Bernardino counties. These increasingly aggressive and costly regulations have impacted all sectors of the economy, from utility power plants, oil refineries, the ports, and all manufacturers to restaurants, dry cleaners, printers, and auto repair shops. While these regulations have improved air quality substantially, they have been excessive and have contributed to the loss of more than half of the manufacturing jobs in Southern California.

The regulation of fine particulate matter ($PM_{2.5}$), ozone (O_3), and nitrogen oxides (NO_x) has been largely justified on a cost-benefit basis by the claim that air pollution causes 5,000 premature deaths per year in the SCAB. This claim relies on the implausible and unproven hypothesis that inhalation over a lifetime of about one teaspoon of $PM_{2.5}$ (particles less than 2.5 microns in diameter) causes premature death. For perspective, inhaling this amount of $PM_{2.5}$ is roughly equivalent to smoking two cigarettes a year, certainly not a lethal dose. Moreover, there is overwhelming epidemiological evidence, including two large 2011 AQMD-funded epidemiological studies, that air pollution does not cause any premature deaths in California. Furthermore, the SCAB has an age-adjusted total death rate that is lower than the death rate in every state except Hawaii. It has a similarly low total cancer death rate.

Regarding exposures, the average ambient levels of 8-hour ozone and 24-hour $PM_{2.5}$ in the SCAB, as measured by AQMD monitors, are below the current Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS) for ozone and $PM_{2.5}$. Furthermore, the average personal exposures to ozone and $PM_{2.5}$ among SCAB residents are much lower than the ambient levels measured by AQMD monitors. These average personal exposure levels are far below the levels associated with adverse health effects. Air pollutants are now at record low levels and close to natural background levels. The last Stage 3 smog alert was in 1974 and the last Stage 2 smog alert was in 1988. Much of the remaining SCAB pollution comes across the Pacific Ocean from China, which ignores air pollution regulations and which does much of the manufacturing that used to be done here.

Unfortunately, the AQMD staff, led since 1997 by Executive Officer Barry R. Wallerstein, has ignored the extremely positive air quality evidence above. Instead of acting in the best public health and socioeconomic interest of the SCAB residents, AQMD staff has implemented scientifically unjustified regulations in conjunction with the EPA, the California Air Resources Board, and powerful environmental activist groups (like Coalition for Clean Air, American Lung Association, Natural Resources Defense Council, and Sierra Club). The AQMD Board justifiably fired Wallerstein on March 4. There is now an opportunity for the remaining AQMD staff to work with numerous qualified experts like myself in order to reassess the scientific validity of all their regulations. The REgional CLean Air Incentives Market (RECLAIM), the Multiple Air Toxics Exposure Study (MATES), and the 2012 Air Quality Management Plan (AQMP) all need to be reassessed. These reassessments must be made before the 2016 AQMP is finalized and, if they are not made, the AQMD Board should not approve the 2016 AQMP. It is time to stop unjustified regulations in Southern California and to bring manufacturing jobs back.

Guest Speaker: James E. Enstrom, Ph.D., M.P.H.



Dr. Enstrom is a native Californian who has lived most of his life in Los Angeles County. In 1965 He graduated co-valedictorian of his class at Harvey Mudd College in Claremont, CA, where he obtained a B.S. in physics. In 1970 Dr. Enstrom obtained his Ph.D. in experimental elementary particle physics at Stanford University from Nobel Laureate Melvin Schwartz. During 1971-1973 he worked as a physicist at the Lawrence Berkeley Laboratory in research group of Nobel Laureate Luis Alvarez. He then came to the UCLA School of Public Health as a postdoctoral fellow in cancer epidemiology and received an M.P.H. and postdoctoral certificate in 1976 from renowned public health epidemiologist Dr. Lester Breslow.

He then joined the UCLA School of Public Health faculty as a Research Professor / Researcher and he held that position for 36 years until June 2012. He currently retains a similar affiliation with UCLA, although he is now drawing retirement. He has been a Fellow of the American College of Epidemiology since 1981, he has been listed in Who's Who in America since 1990, and he has been President of the Scientific Integrity Institute in Los Angeles since 2005.

During his long career, he has explored many important epidemiological issues, particularly focusing on California. A major theme of his research has been identifying healthy lifestyles. He has shown that it is possible to reduce mortality risk from cancer and heart disease by 70% in the middle age range and to increase longevity by as much as 10 years. Examples of healthy populations that he has examined include religiously active California Mormons, California Cancer Prevention Study subjects, California PREVENTION Magazine Readers, and California and national samples of adults adhering to good health practices.

He has also examined the influence of environmental factors on mortality. In December 2005 he published a major paper on fine particulate matter and mortality in California and he has numerous other fm. Since then he has conclusively documented that fine particulate matter does not cause premature death in California. Since 2013, following the lead of the US House Science Committee, he has been involved with efforts to obtain the access to the "secret science" data that EPA has used to justify its fine particulate and ozone air pollution regulations in California and the United States. These efforts include the August 1, 2013 House subpoena of EPA, as well as the Secret Science Reform Acts of 2014 and 2015.

He is currently conducting important new air pollution epidemiology research that is relevant to the EPA, CARB, and SCAQMD regulations. More information can be found at his Scientific Integrity Institute website (http://www.scientificintegrityinstitute.org/).

Angela Kim

From: StanYoung <genetree@bellsouth.net>
Sent: Tuesday, August 16, 2016 7:48 PM
To: Jo Kay Ghosh
Cc: Margarita Felix (Ben); James E. Enstrom
Subject: Enstrom 2005 data and analysis
Attachments: Enstrom 2005 data and analysis.docx

Dear Dr. Ghosh:

I was reading ISA 2009 and I came across this data set for California. I dropped it into SAS JMP and just looked at the data.

You and the staff really need to look at the actual data for California.
Enstrom published in 2005. I've looked at all the data from 2000 to 2012. It is available. There are no excess statistical deaths. You really need to talk to the rest of the staff and fill them in.

8-1

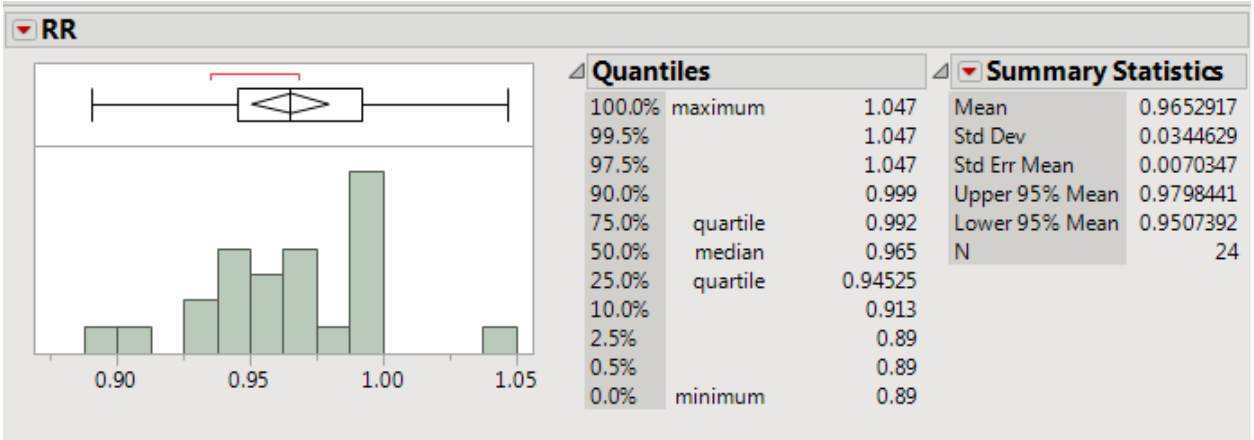
You need to take Jim Enstrom seriously. Look at the things I have sent to you.

Eventually, it will all come out.

Stan Young

Enstrom 2005 data and analysis

This data came from Enstrom (2005) as given in EPA ISA 2009, page E-503. Risk ratios, RR. A RR of 1.00 is no effect. RR<1.00 is beneficial side and RR>1.00 is detrimental. Trace down the RR col of the data table looking at the various California counties and note that all but one RR are less than 1.00. There is no increase in deaths due to PM2.5. The average level of the RR is 0.965.



	County	RR	CIL	CLH
1	Alameda	0.962	0.926	0.999
2	Butte	0.999	0.910	1.096
3	Contra Costa	0.999	0.943	1.058
4	Fresno	0.935	0.872	1.002
5	Humboldt	0.992	0.900	1.092
6	Kern	0.944	0.872	1.023
7	Marin	0.939	0.867	1.016
8	Napa	0.949	0.868	1.038
9	Orange	0.990	0.948	1.034
10	Riverside	0.959	0.906	1.015
11	Sacramento	0.998	0.944	1.055
12	San Bernardino	0.992	0.938	1.049
13	San Diego	0.992	0.954	1.033
14	San Francisco	0.963	0.914	1.014
15	San Joaquin	0.925	0.816	1.049
16	San Mateo	0.949	0.899	1.003
17	Santa Barbara	0.968	0.878	1.068
18	Santa Clara	0.955	0.910	1.003
19	Santa Cruz	0.890	0.793	0.999
20	Solano	0.901	0.815	0.995
21	Sonoma	0.968	0.884	1.060
22	Stanislaus	0.984	0.904	1.072
23	Tulare	1.047	0.979	1.119
24	Ventura	0.967	0.872	1.072

From: Michael T. Kleinman <mtkleinm@uci.edu>
Sent: Tuesday, August 16, 2016 5:28 PM
To: Jo Kay Ghosh
Subject: enstrom
Attachments: Some background on PM and mortality.docx

I disagree with Enstrom's conclusion that "Particulate Matter Does Not *Cause* Premature Deaths" I selected a few papers from reputable scientists that counter Enstrom's, as yet unpublished remarks. Epidemiology studies are always hard pressed when it comes to determining causality. However EPA has gone with a weight of evidence approach that has been peer reviewed by CASAC.

As stated in the 2009 US EPA Integrated Scientific Assessment for PM2.5,
"Regional and seasonal patterns in PM2.5 risk estimates were observed with results similar to those presented for PM10 (Dominici et al., 2007, 097361; Peng et al., 2005, 087463; Zeka et al., 2006, 088749), with the greatest effects occurring in the eastern U.S. (Franklin et al., 2007, 091257; Franklin et al., 2008, 097426) and during the spring (Franklin et al., 2007, 091257; Zanobetti and Schwartz, 2009, 188462). Of the studies evaluated only Burnett et al. (2004, 086247), a Canadian multicity study, analyzed gaseous pollutants and found mixed results, with possible confounding of PM2.5 risk estimates by NO2. Although the recently evaluated U.S.-based multicity studies did not analyze potential confounding of PM2.5 risk estimates by gaseous pollutants, evidence from singlecity studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggest that gaseous copollutants do not confound the PM2.5-mortality association, which is further supported by studies that examined the PM10-mortality relationship. An examination of effect modifiers (e.g., demographic and socioeconomic factors), specifically AC use which is sometimes used as a surrogate for decreased pollutant penetration indoors, has suggested that PM2.5 risk estimates increase as the percent of the population with access to AC decreases (Franklin et al., 2007, 091257; 2008, 097426). Collectively, the epidemiologic evidence is sufficient to conclude that a causal relationship exists between short-term exposure to PM2.5 and mortality." 9-1

A new ISA is in the works.

Michael Kleinman
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Occupational and Environmental Medicine
100 Theory STE 100
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(949)824-4765

"Despite important gaps in scientific knowledge and continued reasons for some skepticism, a comprehensive evaluation of the research findings provides persuasive evidence that exposure to fine particulate air pollution has adverse effects on cardiopulmonary health" [1]. "PM2.5 exposure was associated with CVD mortality, with the hazards ratios (95% confidence interval) per 10 µg/m(3) increase in PM2.5 equal to 1.12 (1.10-1.15). Pollution-induced CVD mortality risk is observed for those with and without existing cardiometabolic disorders. Long-term exposure may also contribute to the development or exacerbation of cardiometabolic disorders, increasing risk of CVD, and cardiometabolic disease mortality" [2]. "In [a] large national cohort of nonimmigrant Canadians, mortality was associated with long-term exposure to PM(2.5). Associations were observed with exposures to PM(2.5) at concentrations that were predominantly lower (mean, 8.7 mug/m(3); interquartile range, 6.2 mug/m(3)) than those reported previously" [3].

In a study of Canadian women, "a 10 mug/m(3) increase in PM2.5 exposure was associated with elevated risks of nonaccidental (HR: 1.12; 95% CI = 1.04, 1.19), and ischemic heart disease mortality (HR: 1.34; 95% CI = 1.09, 1.66)" [4].

"The association between PM(2.5) and lung cancer mortality was similar in men and women and across categories of attained age and educational attainment, but was stronger in those with a normal body mass index and a history of chronic lung disease at enrollment (P < 0.05). CONCLUSIONS: The … findings strengthen the evidence that ambient concentrations of PM(2.5) measured in recent decades are associated with small but measurable increases in lung cancer mortality." [5]

"Long-term exposure to particulate matter less than 10 mum in aerodynamic diameter (PM10) was associated with elevated risks for IHD mortality (1.06; 95% CI, 0.99-1.14) and incident stroke (1.06; 95% CI, 1.00-1.13), while exposure to nitrogen oxides was associated with elevated risks for IHD and all cardiovascular mortality. CONCLUSIONS: This study provides evidence linking long-term exposure to PM2.5 and PM10 with increased risks of incident stroke as well as IHD mortality; exposure to nitrogen oxides was also related to death from cardiovascular diseases. [6]"

1. Pope CA, 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manage. 2006; 56:709-42.
2. Pope CA, 3rd, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, et al. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ Res. 2015; 116:108-15.
3. Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environmental Health Perspectives. 2012; 120:708-14.
4. Villeneuve PJ, Weichenthal SA, Crouse D, Miller AB, To T, Martin RV, et al. Long-term Exposure to Fine Particulate Matter Air Pollution and Mortality Among Canadian Women. Epidemiology. 2015; 26:536-45.
5. Turner MC, Krewski D, Pope CA, 3rd, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med. 2011; 184:1374-81.
6. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. American Journal of Respiratory and Critical Care Medicine. 2011; 184:828-35.

From: Froines, John <jfroines@ucla.edu>
Sent: Wednesday, August 17, 2016 11:52 AM
To: Jo Kay Ghosh
Subject: FW: HO-1
Attachments: 160408 AQMD final summary V5.docx

Please delete my name from progress report. My involvement was earlier. Thanks.
John

From: Froines, John
Sent: Wednesday, August 17, 2016 10:49 AM
To: jghosh@aqmd.gov
Subject: FW: HO-1

For interest and relevant to Appendix 1.
John Froines

Quantitative assays in the characterization of ambient air.

A report to the South Coast Air Quality Management District for Contra

Arthur K. Cho

Summary

1. Quantitative chemical reactivity and cellular assays have been performed on ambient air particles and their corresponding volatile components collected in three sites in the Los Angles Basin. The chemical results indicate that the particle (PM2.5) phase contains most (~75-80%) of the DTT based prooxidants and the vapor phase, defined as the dichloromethane soluble semivolatile organic species, contain most of the electrophiles (80-95%). The assoicated cellular assays showed that these reactive species exhibited caused inflammatory and adaptive responses by a mouse macrophage cell line to which the samples were exposed.

2. Most of the prooxidants present in the particle phase were associated with metals, as shown by the sensitivity of the DTT activity to a metal chelator, whereas the electrophiles were organic compounds. Seasonal differences in prooxidant content were also noticed, with the winter season PM2.5 higher for Commerce and Long Beach than that for the summer. Samples from San Bernardino differed from the other two sites in that levels of both reactive species in the summer samples were elevated. This observation was attributed to greater photochemical alterations of the air mass generated in the western end of the Los Angeles Basin as it moved east with the prevailing winds during the summer months.

3. The cellular actions of the ambient samples on cells were assessed in terms of two general responses, inflammation and adaptation. The inflammatory response is associated with, for example, the exacerbation of asthma and atherosclerosis, two dieseases with which air pollution has been associated. The adaptive response reflects an attempt by the cell to minimize the chemical insult associated

with the pollutants through the increased expression of antioxidant and foreign compound eliminated proteins.

4. The two cellular responses were monitored with tumor necrosis factor alpha (TNFa) as the inflammatory marker and heme oxygenase-1 (HO-1) as the adaptive marker. The summer particle phase from San Bernardino was the most potent in inducing the inflammatory respose and its corresponding vapor phase the most potent in inducing adaptation. Subsequent experiments showed that the semivolatile components of the vapor phase were capable of suppressing the inflammatory response of the particle phase and an inverse relationship was observed, with increasing adaptation suppressing the inflammatory response. Taken together, the results suggest that the inflammatory effects of ambient air may be less than would be expected from assessment of PM2.5 phase alone and point out the critical importance of analysis of both particle and vapor phases in studies of air pollutants. It should be pointed out however, that suppression of the inflammatory response could result in a reduced ability to respond to pathogenic microbial infections.

5. Analogous observations were with biodiesel exhaust and of cooking oil smoke samples obtained from the University of California Riverside College of Engineering Center for Environmental Research and Training (CE-CERT). Particle and vapor phases were also examined and the results showed an inverse relationship between the expression of TNFa and HO-1 by components of the vapor phase which had a high content of HO-1 inducers and a positive correlaton between samples with low levels of HO-1 and TNFa found in the particle phases. Thus, these data also support the notion that the response by cells to the chemical insults provided by the particle phase components are inflammatory but that this action is suppressed by adaptation which, when sufficiently intense, can suppress even baseline cellular TNFa expression.

6. The unique aspect of this work was its quantitative approach. The quantitative nature of each analysis allowed us to compare samples across locations, between seasons and in a limited study, comparing different biodiesel fuels. This approach

provided evidence for an antagonistic relationship between the inflammatory and adaptive responses by cells which could determine the net health outcome of exposure of air pollution in terms of exacerbation of vascular and pulmonary diseases on the one hand and a compromisd immune system on the other.

Objective

The objective of the project was to develop protocols for quantitatively assessing potential adverse biological effects of emission samples from vehicles and ambient air. The quantitative output of the assays could then be archived and compared with data from subsequent studies. A second objective was to develop a protocol for the fractionation of diesel exhaust to characterize the chemical classes involved in the biological responses observed for the total exhaust as a whole. This objective was dependent on a large scale collection of diesel exhaust particles and vapors to be made by the Center for Environmental Research Technology of the College of Engineering at the University of California at Riverside (CE-CERT). However, CE-CERT did not deliver the sample to us and our results for this objective were limited to preliminary procedural experiments with a diesel exhaust sample collected by Japanese colleagues in an earlier study.

The samples used in the first objective were:

1. Ambient air samples collected in the communities of Commerce, Long Beach and San Bernardino in the Los Angeles Basin. Collections were made in the summer and winter months and included particulate and vapor phase components. The latter were the volatile organic species collected in XAD resin beds placed below the filter holders which trapped PM2.5 particles.
2. Selected particle and vapor samples collected at the CE-CERT. These samples included biodiesel exhaust, cooking oil smoke and ethanol fuel exhaust from vehicles.

The samples were subjected to two sets of analytical procedures, chemical reactivity assays measuring pro-oxidant and electrophilic activities and cellular assays that determined the

capacity of the samples to initiate inflammatory and adaptive responses. The hypothesis leading to the assays is described in the background section.

Methods

Chemical assays

We used the DTT based prooxidant (1; 2)and the GAPDH based electrophile assay (3; 4)to measure chemical reactivity. The DTT assay measures the ability of the sample to transfer electrons from dithiothreitol (DTT) to oxygen in a reaction analogous to that occurring in cells. Electrophiles, as defined by the GAPDH assay, are organic compounds with the ability to form covalent bonds with the thiol of glyceraldehyde-3-phosphate dehydrogenase, a reaction that would occur with other available thiols in cells. In studies of ambient air mixtures collected with the VACES concentrator, we have shown that the DTT activity correlates with the ability of the sample to induce HO-1 in macrophages and with the polynuclear aromatic hydrocarbon content of the sample (1).

Cellular assays

Cells

Raw 264.7 cells were cultured in DMEM, supplemented by 1% penicillin-streptomycin and 10% FBS as described by Li et al. (5) with slight modifications. Cells were exposed to the entire particle suspension or to the DMSO solution of the dichloromethane extract of the XAD resin as the particle and vapor phases, respectively. The samples were added to the media to attain air volume equivalent concentrations from 0.1 to 2.0 m^3/mL. A filter blank suspension and DMSO in volumes corresponding to the particle and vapor samples, respectively, were used as controls. The stimulation was allowed to proceed for time periods of 3, 6 or 16 hours and the cells and media collected for subsequent ELISA analysis.

In a 2 phase exposure study with the summer San Bernardino samples, cells were exposed to the vapor phase components at 1 m^3/mL and relevant controls for 24 hours, the DMEM removed and replaced with fresh DMEM containing the challenge agent, or PM2.5, also at 1 m^3/mL. This mixture was cultured for 16 hours after which the cells and media were processed as above for analysis of HO-1 and TNFα.

The shorter stimulation period of 3 hours was used in subsequent studies because at this time levels of marker proteins were found to be high and the time period more suitable for multiple sample studies.

ELISA assay for markers

The ELISA assays were performed following instructions provided by the manufacturers (HO-1; Enzo Life Sciences; TNFα, BD Pharmingen). The results reported are the difference between the control and the experimental cultures. The HO-1 results were expressed as ng/mg protein and the TNFα results were expressed as pg/mL medium.

Data analysis

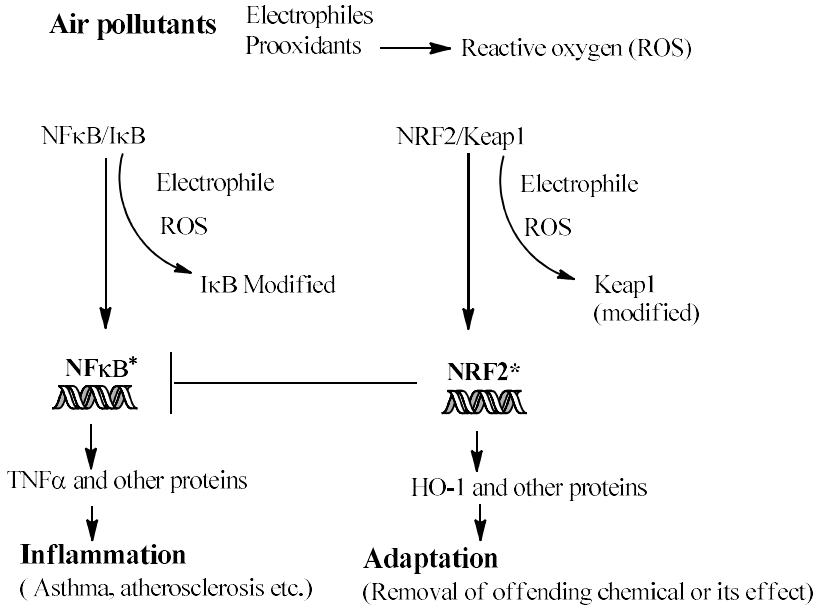
Whenever possible, attempts were made to conduct experiments using three concentrations of test sample to assess concentration dependency of the response. The multiplicity of components involved in the responses measured can result in a non-linear response reflecting issues such as saturation and possible hormetic responses or a "U" shaped dose response relationship. Linear concentration dependency is thus critical in comparing cellular responses.

Background

Although air pollutants include precursors to toxins such as polynuclear aromatic hydrocarbons (e.g., (6-8)) that can be bioactivated to their toxic metabolites, the focus of our research has been the reactive substances present in air pollution mixtures. In our view, these reactive substances can have immediate health effects on humans by undergoing chemical reactions with available biological molecules. These chemical reactions are of two types, the generation of so called reactive oxygen species, superoxide, hydrogen peroxide and hydroxyl radical and the formation of covalent, irreversible bonds between the pollutant and a protein. There are two types of cellular responses to these chemical insults, adaptation and inflammation. In the adaptive response, levels of antioxidant molecules, proteins or small molecules that convert the oxygen species to water, are increased together with increases in levels of biological "traps", substances such as glutathione that reduce the concentration of the reactive substance by converting the offending agent to an inactive metabolite that can be excreted (9; 10). Inflammation is a more general process, in which phagocytic cells remove the offending particle or microorganism from the general circulation by internalizing them and rendering them inactive(11). It is also the

process by which the organism protects itself from the invasion of pathogenic microorganisms, using the immune system. The overall process is a cascade of cellular events involving multiple cells and is initiated by the expression of triggering proteins called cytokines. Adaptation and inflammation are mediated by distinct pathways and like most biological responses, are dependent on the concentration of the triggering agent(s). It should also be pointed out that both adaptation and inflammation can be considered adverse health responses. Adaptation can increase organism sensitivity to microbial attack by suppressing the immune response and inflammation can result in exacerbation of chronic diseases such as asthma and atherosclerosis through the increased expression of cytokines. Figure 1 is a highly simplified summary of the interrelationship between the two processes.

Figure 1 Air pollutants and cellular targets



Two cellular signaling cascades are summarized in the figure, a proinflammatory cascade, mediated by the transcription factor NFκB and an adaptive cascade with Nrf2 as the transcription factor. These cascades have a "ying-yang" relationship in that the adaptive response antagonizes the inflammatory response, shown by the line. In the resting state the transcription factors are complexed with inhibitory regulators which dissociate upon reaction with electrophiles or ROS generated by the prooxidants of the pollutant mixture. The result of the activation can be inflammation or adaptation, depending on the concentrations and nature of the offending chemical mixture. The line between Nrf2 and NFkB is meant to indicate an antagonistic relationship between the actions of the two factors.

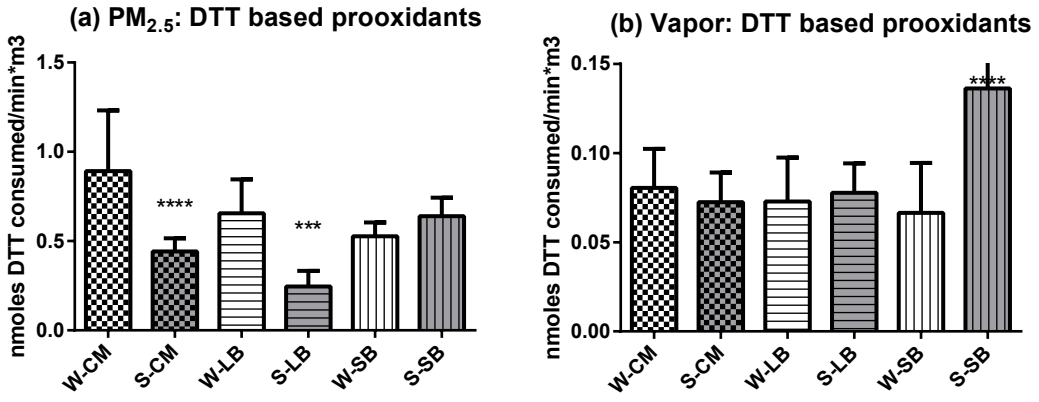
The cytokine, tumor necrosis factor alpha (TNFa), is a marker for NFkappaB activation and the antioxidant enzyme, hemeoxygenase-1 (HO-1) as a marker for Nrf2 activation, the transcription factors associated with the inflammatory and adaptive responses, respectively. We have used lipopolysaccharide (LPS) and a Japanese diesel exhaust sample (J-DEP) used by many investigators as a HO-1 stimulant, as standards. As such, levels of TNFa and HO-1 were shown to increase with increasing concentration of the LPS and J-DEP.

We hypothesize that the chemical species in air pollutant mixtures involved in these interactions are prooxidants and electrophiles. Prooxidants are compounds that engage in electron transfer reactions or the reduction of molecular oxygen to the ROS using endogenous biological antioxidants such as NADPH, NADH and ascorbate as reducing agents (12). Prooxidants generate ROS from oxygen and biochemical agents such as NADPH. These ROS, most notably hydrogen peroxide modify cysteine thiols, causing the breakdown of inactive complexes of transcription factors to their active forms indicated by asterisks in figure 1. Electrophiles are compounds that react with electron rich functionalities such as cysteine thiol and lysine amino groups of proteins to form irreversible covalent bonds (13-15). By this reaction, then electrophiles also modify the same thiols but irreversibly and dissociate the transcription factor complex to active factor. The transcription factors then enter the nucleus and stimulate expression of multiple proteins including the two marker proteins, TNFa and HO-1. Thus, the relative quantities of the two proteins reflects the activation status of the processes. A recent review of the inflammatory actions of DEPs relevant to atherosclerosis, indicates the increase in TNFa and HO-1 can be antagonized by N-acetyl cysteine (16). Although commonly referred to as an “antioxidant”, this compound is actually a neucleophile, reacting with sulfenic acids to form disulfides (17) and covalent bonds with electrophiles such as quinones (18). In addition to electrophiles, air pollutants include prooxidants and there is evidence to suggest that metals play an important role in this component of air toxicant (4; 19; 20).

Results

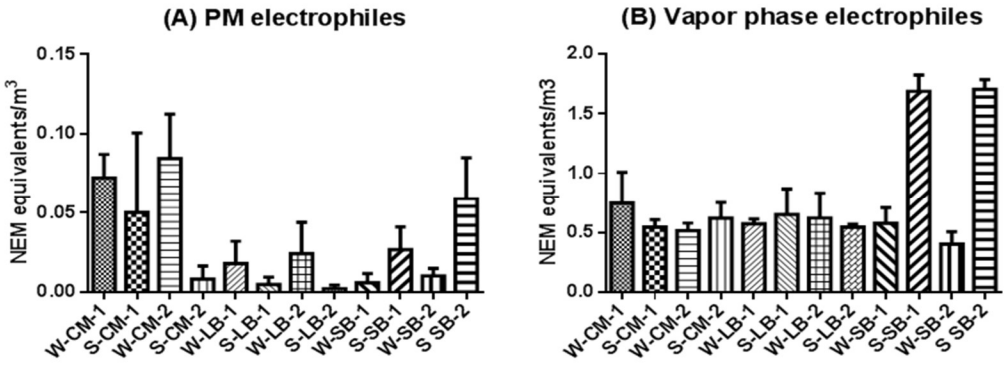
Figure 2 shows the chemical reactivities of particulate (PM2.5) and semi volatile organic species (XAD) in samples collected from sites neighboring railyards in Commerce, Long Beach and San Bernardino using a Tisch sampler to collect filter and XAD resin based volatile organic species (21).

Figure 2a Prooxidant content in PM2.5 and semivolatile organics (XAD) .



*The abbreviations used are W- winter, S-summer, CM Commerce, LB, Long Beach and SB, San Bernardino. Asterisks are used to denote p values for significance: 0.01 to 0.05, *; 0.001 to 0.01, **; < 0.001 *** to ****.*

Figure 2b Electrophile content in content in PM2.5 and semivolatile organics (XAD)



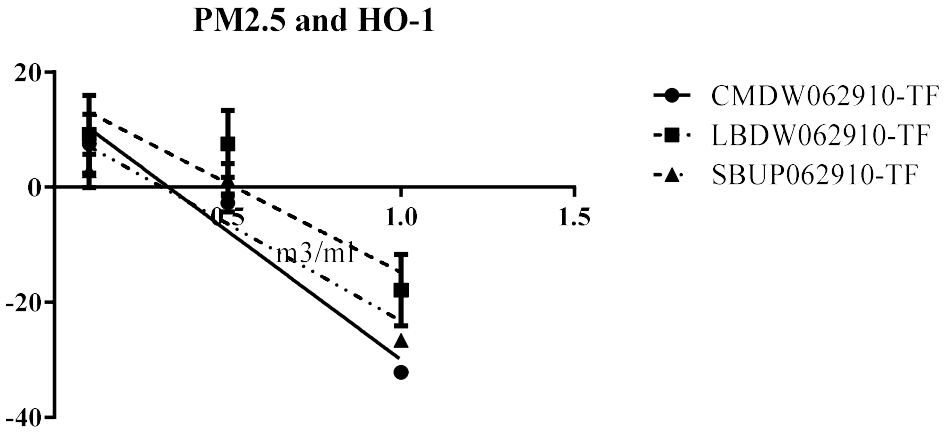
Wide differences in the distribution of the two reactivities were observed (note differences in Y axis scale) between the particle and vapor or semi-volatile organic phases. The ambient electrophiles were mostly in the vapor phase but the prooxidants were mostly in the particle

phase. Significant seasonal differences were observed for Commerce and Long Beach with the winter samples containing higher levels of prooxidant compared to the summer. The San Bernardino samples exhibited the opposite trend but it was not significant. The high winter sample prooxidant content could reflect the influence of the Santa Ana winds common in the Basin during the fall and winter. These winds typically move easterly from the mountains to the coast and could limit the movement of pollutants from downtown traffic and railyards in Commerce and Long Beach. That effect and the slightly lower temperature may result in retention of the reactive chemicals by the particles from these locations.

Celllular responses to PM2.5 and XAD resin extracts of summer samples collected in the Basin

The availability of the large scale samples of ambient air samples allowed us to examine cellular effects of selected samples with measured chemical reactivities. The first study examined the actions of summer San Bernardino samples because of their high reactivity compared to those from Commerce or Long Beach. Responses were measured at three different concentrations to permit analysis for linear relationships between concentration and response and expression of the potency of a given sample by the regression slope. This approach allowed us to identify a negative concentration response for particles and HO-1 expression, i.e., the particles exhibited a negative concentration dependency with minimal differences between the slopes of the concentration response curves (see figure 2). The negative values observed reflect differences between the “filter blank” and the particles on the sample filters and indicate the samples suppressed normal HO-1 expression. As the concentration of PM2.5 was increased, HO-12 levels decreased and at 1 m3/mL, were significantly lower than the control expression.

Figure 2 Effect of PM2.5 concentration on HO-1 induction.



Net expression, based on differences between PM2.5 and corresponding filter blanks, of HO-1 by cells following stimulation by PM2.5 samples.

This observation supported the notion of antagonism between inflammation and adaptation (figure 1), as the PM2.5 fractions increased TNFa expression (table 2). Furthermore, the biological potency of the samples on a per volume basis reflected the chemical reactivity. TNFa expression induced in macrophages by the particle phase increased in the order SB>CM≥LB which followed the order of prooxidant content, although the responses from the CM and LB samples were mostly if not altogether due to the lipopolysaccharide contents of the samples with minimal contributions from chemical sources. Table 2. Slopes of the concentration-marker protein concentration following a 16 hour stimulation by PM2.5 and XAD resin extracts of the 6/29 samples.

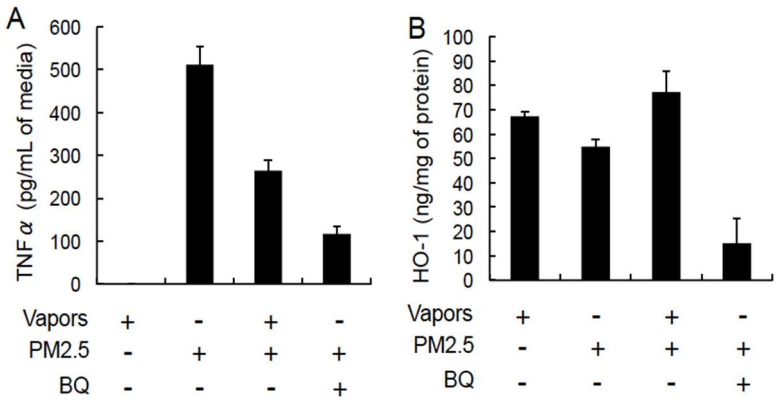
From samples of 6/29	**Commerce**	**Long Beach**	**San Bernardino**
PM 2.5 TNFa expression	18.7*X + 0.07	11.1*X - 0.38	413.9*X - 16.64
PM2.5 HO-1 expression	-44.69*X + 14.71	-30.88*X + 16.09	-33.67*X + 10.46
XAD HO-1 expression	34.49*X - 10.98	43.23*X - 12.14	182.4*X - 22.49
Units are ng HO-1 or pg TNFa per mg protein/m3 per mL			

We then tested whether the notion of TNFa and HO-1 antagonism could be demonstrated in PM2.5 and XAD extracts from the same air sample. Since the PM2.5 samples were

proinflammatory and the XAD samples adaptive, the inflammatory response should be suppressed if the cells were first exposed to the adaptive XAD sample. In the experiment, summarized in figure 3, cells were exposed to blank XAD extract and XAD extract from sample for 16 hours then the cells were washed and challenge with the particle phase for 16 hours and TNFa response measured (figure 3).

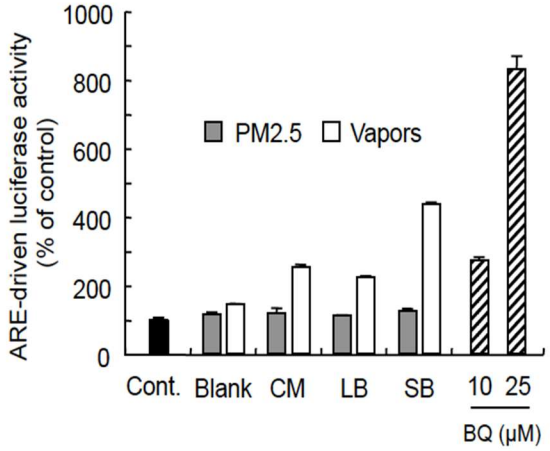
Interaction between XAD and PM2.5 samples; inhibition of the inflammatory response.

Figure 3



The results of the experiment showed indeed, that preexposure to XAD extract (identified as Vapors), reduced the subsequent TNFa response to PM2.5 exposure, i.e., components of the XAD extract suppressed the inflammatory response to the PM2.5 components by about 50%. The suppression is likely due to activation of the antioxidant/antielectrophile response element (ARE) as shown in experiments in which only vapor phase components activate the ARE (figure 4). This DNA element binds the transcription factor Nrf2 following its dissociation from the Nrf2-keap-1 complex, and in turn, increases the expression of HO-1 and other antioxidant proteins that serve to reduce the oxidative stress caused by prooxidants. In the figure, only the vapor phase increased the ARE driven luciferase activity. BQ is benzoquinone, which was used as a reference electrophile.

Figure 4. Stimulation of the ARE by XAD extracts (vapors) and benzoquinone (BQ).



Conclusions

The results of this study showed:

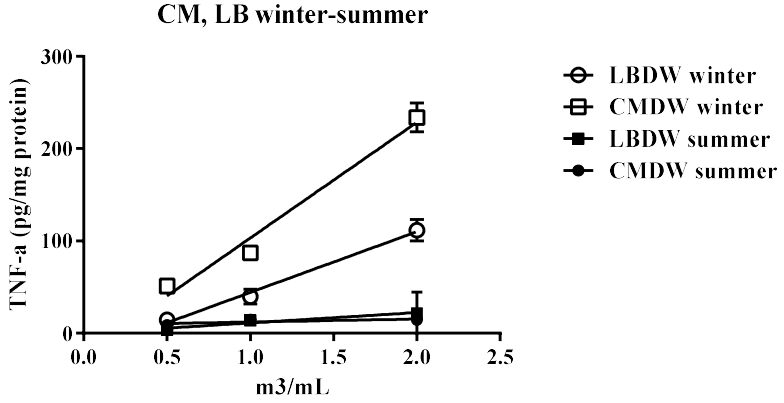
1. That the PM2.5 and semi-volatile organic components of ambient air samples with varying levels of prooxidants and electrophiles were capable of affecting the internal cell biology of macrophages with potencies that reflected chemical reactivity.
2. The PM2.5 prooxidants in the SB sample induced an inflammatory response, indicated by higher levels of TNFa and the semi-volatile organics induced HO-1 in a mouse macrophage preparation.
3. The induction of HO-1 by the semi-volatile organics reflects activation of the ARE through dissociation of the Nrf2/keap 1 complex. ARE activation results in increased antioxidant enzymes and other proteins that can serve to attenuate an inflammatory response, as demonstrated by preexposure of the cells to XAD extracts which suppressed the inflammatory response to PM2.5.
4. This result points out the role of volatile organics in the overall effects of ambient air on cells and, by extrapolation to, intact organisms. The net effect of chronic exposure to the mixture of particles and vapors could be an anti-inflammatory response resulting in a greater susceptibility to infections.

Seasonal differences in the cellular effects of PM2.5 from the Los Angeles Basin.

In contrast to the SB samples, the winter CM and LB PM2.5 samples had significantly higher prooxidant content compared to the summer samples (figure 1) and based on the results above, would be expected to exhibit greater inflammatory responses than those from the corresponding

summer. The sample from 11/12/2009 was used for this study. The values of the PM2.5 samples are shown in table XX

Winter PM2.5	DTT Activity	DTT/DTPA	DHBA	GAPDH
Commerce	0.960	0.147	0.336	0.128
Lomg Beach	0.590	0.000	0.451	0.000



Linear regression results

	LBDW winter	CMDW winter	LBDW summer	CMDW summer
Equation	Y = 65.81*X - 21.58	Y = 125.4*X - 22.30	Y = 11.25*X - 0.07500	Y = 3.264*X + 8.875
R square	0.974	0.9719	0.3437	0.4762

Linear regression analysis of the concentration-TNFa expression data indicated that the winter samples exhibited slopes that followed prooxidant content with Commerce higher than Long Beach. In contrast, the concentration dependency of TNFa expression was not deemed to have a significant slope, i.e, TNFa expression did not increase with concentration. In summary, winter samples from both CM and LB were proinflammatory with potencies that reflected their prooxidant content and the corresponding summer samples were inactive.

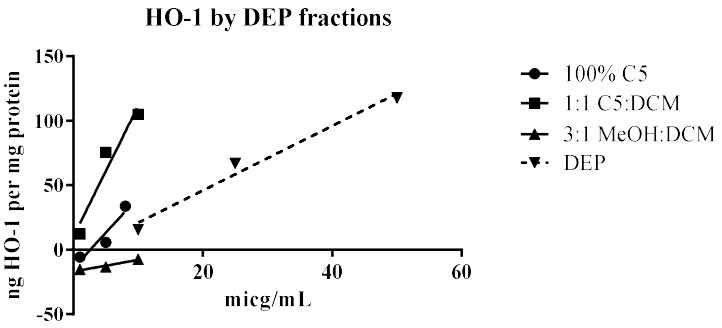
Fractionation of Japanese diesel exhaust particle (J-DEP) preparation

As stated above, we did not receive the DEP – vapor preparation that was to be provided by CE-CERT and were therefore unable to perform a fractionation as originally planned. However, to prepare for the samples, we began experiments to establish a fractionation protocol that could be used to prepare fractions for chemical and cellular analyses that could provide useful information

on the physical properties of the biologically active components of a test air pollutant sample. The procedure was a conventional sequential extraction that used solvents of increasing polarity starting with pentane then dichloromethane then methanol with mixtures of the solvents (Table 3). The cellular activities of each fraction were determined and recoveries determined using the mass following evaporation. The total cellular activity for a given fraction was defined as the product of the slope of HO-1 regression curve and the fraction mass. The nature of the chemical components of each fraction is shown in the 6th column. The TNFa responses were positive for the most polar fraction and the residue. DATA MISSING

Solvent	HO-1 regression	mass	total per fraction	% of total activity	Chemical groups present
	ng HO-1/micgmL^-1	mg	micg		
100% Pentane	Y = 5.508*X - 14.44	44.18	243.4	71%	Low MW PAHs, olefins, alkanes
50% Pentane/CH2Cl2	Y = 10.12*X + 10.20	8.66	87.5	25%	Quinones, PAHs
75% methanol/CH2Cl2*	Y = 0.8910*X - 16.89	14.97	13.3	4%	Quinones, phenols
Residue*	Negative values				Polar organics, metals
DEP	Y = 2.503*X - 4.132	67.81	344.2	100%	

The relationship between the HO-1 inducing capacity of the different fractions is shown in Figure 5.

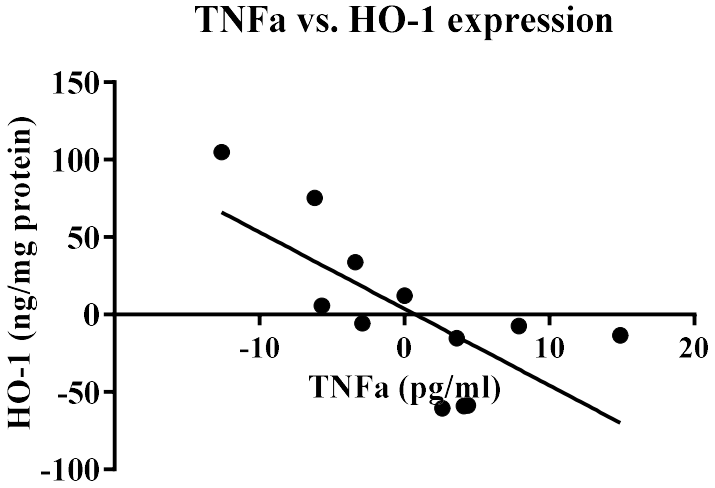


A DEP sample of about 100 mg was sequentially extracted with the indicated solvent mixtures and the extracts evaporated and used in subsequent cell assays. The cells were exposed to the fractions in concentrations that reflected the original sample

mass so that total activities could be estimated. The high recovery (327/256 or ~127%) may be due to the separation of the fractions, for example removal of TNFa inducing agents may increase the HO-1 inducing ability of the sample. .

Most of the HO-1 inducing capacity is associated with the non-polar solvent extracts, i.e., pentane and dichloromethane-pentane mixtures. The only significant TNF inducing activity was observed in the more polar methanol/DMC fraction and residue. These results suggest HO-1 induction is due primarily to non-polar compounds which include low molecular weight electrophiles such as reactive olefins and quinones that are active in the GAPDH assay. TNFa induction appears to be due to the more polar fraction and may be due to some quinones but more likely metals which are insoluble in non polar organic solvents but may be extractable by methanol if complexed with organic compounds such as polyphenols (4; 22). It should be pointed out that this DEP preparation has a high content of organic compounds, particularly quinones compared to other preparations we have examined (23) which may account for the dominant HO-1 response which could be suppressing the inflammatory response, as shown in figure 6.

Figure 6 Relationship between TNFa and HO-1 inducing abilities of the fractions of table XX



The HO-1 and TNFa expression values for the different concentrations of fractions used to generate table XX are shown with a regression line. Although the regression fit was poor (r2 = 0.49) the Pearson correlation coefficient (0.7) and p value (<.011) indicate they correlated well. This relationship has been observed with other samples examined in this study.

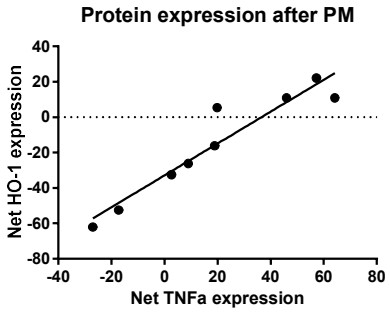
Conclusions

Preliminary extraction experiments using the cellular assay procedures on selected fractions of a commonly used Japanese DEP preparation (e.g., (10; 24-27)) showed the adaptive response to be associated with non-polar organic components and the inflammatory response with more polar organic and metal components. These observations suggest that this DEP preparation, with its high polar organic content, may be less inflammatory and more adaptive than ambient particles such as those found in the LA Basin. If this is a general property of diesel exhaust particles compared to ambient air PM2.5, there may be a difference in the primary response, i.e., the higher adaptive response associated with DEPs may contrast with the proinflammatory ambient PM2.5 from multiple sources.

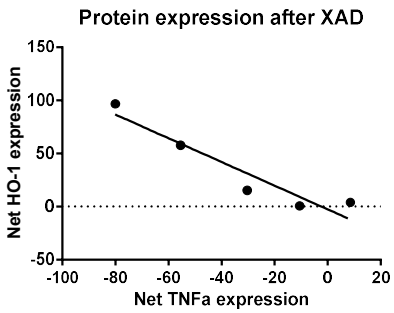
1. Studies of other air pollution samples

The notion of attenuation of inflammation by components of air samples was consistent with observations made in studies of biodiesel (figure 3) and cooking oil (figure 4) samples as part of collaborative study with the UCR College of Engineering Center for Environmental Research and Training (C E-CERT). Thus, analysis of the two phases, particulate and vapor (semivolatile organic species) of biodiesel exhaust showed that the volatile components were much stronger inducers of HO-1 (note difference in the values of the Y axis) , the adaptation marker and in the case of the vapor phase, were able to suppress the normal or background level of TNFa expression by the cells, evidenced by a negative correlation between the expression levels of the proteins. In contrast, the particle phase was capable of increasing TNFa expression beyond background levels but with much lower efficacy in HO-1 induction.

Figure 8A Comparison of adaptive and inflammatory responses to PM2.5 and vapors from biodiesel exhaust.



Plot of respective protein expression following exposure to PM from ULSD, AFME, Soy and WCO. r^2 + 0.952, p<0.0001



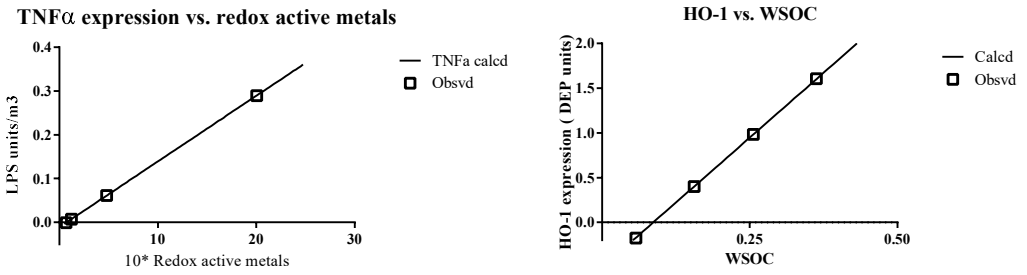
Plot of respective protein expression following exposure to XAD from ULSD, AFME, Soy and WCO. r^2 = 0.899, p<0.0014

The values shown are cellular responses to a fixed concentration of a different sample. Note the smaller negative values for TNFa expression from PM2.5 (-30 is smallest value) compared to XAD samples (-80 is the smallest value). Although the control expression of TNFa is suppressed by both phases, PM2.5 are weaker in their ability to induce HO-1 or promote adaptation. An inverse correlation between the expression of HO-1 and TNFa is shown, consistent with the antagonistic relationship between the two responses shown in figure 1.

In an attempt to assess the roles of redox active metals and water soluble organic species in the PM2.5, averaged values from the samples used here for the cell studies and those from the different samples used by CE-CERT were compared with the assumption that exhaust samples

from the same fuels would, on average contain the same components. The results from that assessment are shown in figure 8B, together with the best fit line from regression analysis. This analysis indicates that TNFa expression correlated with redox metal content and the HO-1 response correlated with water soluble organic compound content (WSOC).

Figure 8B Regression of HO-1 and TNFa responses of PM2.5 against chemical analyses (N = 4) .



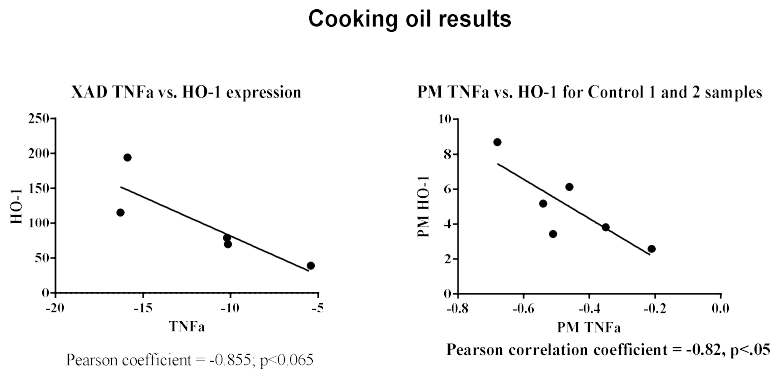
TNFα = 0.015*[Redox active metals] -0.011

HO-1 = 4.65*[WSOC] -0.41

The averaged TNFa response to the particle samples (expressed as LPS units) were compared to averaged redox active metal content for samples from the same fuels (Correlation coefficient was 0.95, with p<.05). Analogously, the HO-1 response with WSOC content of the sample with a correlation coefficient of 0.953 and p<.047)

Similar observations were made with samples from cooking oil smoke (figure 9). The chemical constituents of cooking oil smoke contain prooxidants and electrophiles but not necessarily the same compounds as those from engine exhaust. The vapor phase components induced HO-1 much more strongly than the particle phase but the relationship between the two protein markers was an inverse one with higher levels of HO-1 expression associated with greater suppression of TNFa expression.

Figure 9. Cellular responses to cooking oil particle and vapor phase samples.



Cells were exposed to the samples at fixed concentrations and the proteins measured by ELISA procedures. The negative values reflect the differences between the sample effect and that of a filter (PM) or the solvent (XAD) and are interpreted to reflect a net suppression of TNFa expression.

Chemical properties and cell responses

Using the available data, the potential for the DTT and GAPDH assays as predictors of the cellular response was assessed by determining Pearson correlation coefficients for the DTT values and the cell responses. We found positive correlations for DTT activity-based prooxidant content with particle based HO-1 (0.86; $p<.016$), TNFa (0.96; $p<.04$) for the biodiesel samples and HO-1 (0.905; $p<0.013$) for the cooking smoke samples. The vapor phase chemical reactivities did not correlate with either cell response. These results suggest that the prooxidant content of the particles could be predictors of cell responses but there is insufficient data to be conclusive.

Conclusions

The quantitative nature of the data obtained has provided the ability to compare and further characterize combustion based air pollutants from different locations, seasons and fuel sources. The results show that the analyzed samples contained common chemical reactivities and elicited similar biological activities but with quantitative differences. The major findings from the application of the assays are the following:

1. There are seasonal differences in the nature of ambient air samples which can affect the potential health effects. Specifically, the decrease in volatile organic species associated with the winter season may enhance the potential adverse effects of the particle phase.

2. The vapor phase with its semi volatile organic components has been largely ignored in studies of air pollution because of the focus on particulates. The results here show that the volatile fraction includes both prooxidants and electrophiles and reacts in the chemical and biological assays accordingly. The higher electrophile content observed may be responsible for adaptive responses associated with this fraction. It is possible however, that adaptation could result in suppression of the immune system resulting in a greater susceptibility to infections. Thus, the vapor phase of air pollution mixtures is clearly an important component of the exposome that should be monitored and studied.
3. There appears to be an inverse relationship between the inflammatory and adaptive responses by the cells upon exposure to the samples, with the vapor phase components more effective in promoting the adaptive response. One interpretation of this finding is that the vapor phase components reduce the inflammatory or potential adverse health effects of the particles. Thus, when assessing the health effects of air pollution mixtures, the combined effect of both particle and vapor phases need to be examined.
4. The relationship between the inflammatory and adaptive responses were discernable because of the quantitative nature of the assays performed and demonstrate the importance of quantitative data. However, cellular responses are variable so that values from separate experiments are often difficult to compare. To address this variability, we are now collecting data with selected agents to identify appropriate standards.

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From: Froines, John <jfroines@ucla.edu>
Sent: Wednesday, August 17, 2016 3:40 PM
To: Jo Kay Ghosh
Subject: FW: View your article Chemical reactivities of ambient air samples in three Southern California communities on the new Taylor & Francis Online

See below for reference on air pollutants from three communities. The article is relevant to health issues and relevant to Appendix 1. Thank you.
John

From: Taylor and Francis Group [mailto:TaylorandFrancis@tandf.msgfocus.com]
Sent: Monday, August 15, 2016 10:01 AM
To: Froines, John
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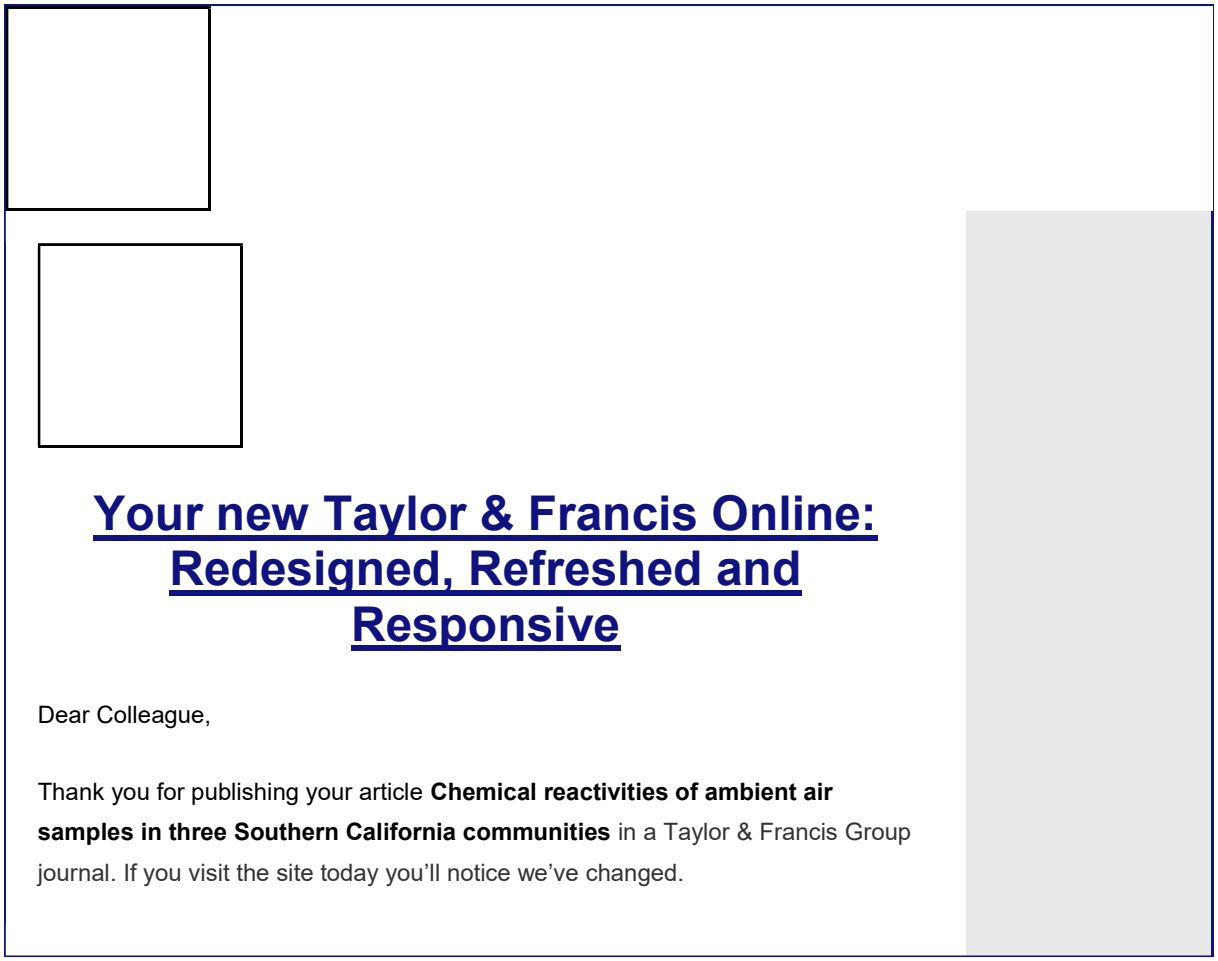

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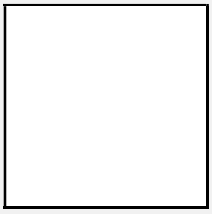

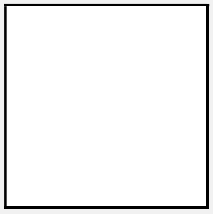

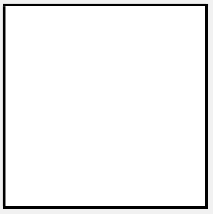

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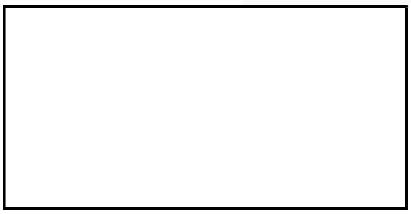

From: Emily Nelson <dremilynelson@gmail.com>
Sent: Friday, August 19, 2016 11:46 AM
To: John J. Benoit (GBM)
Cc: Jo Kay Ghosh; Philip Fine; Barbara Baird
Subject: Draft AQMP 2016 Appendix I Health Effects Advisory Council Comment

Dear Supervisor Benoit,
Thank you for the opportunity to participate on the Advisory Council for the review of the Draft 2016 AQMP Appendix I Health Effects. Our meeting yesterday was meaningful and I believe the SCAQMD staff have done an excellent job. Since I have participated on the AQMD review of Health Effects for the third or fourth time, I just have a few conceptual comments to contribute to the Final Draft.
Dr. Jo Kay Ghosh, SCAQMD Health Effects Officer, and her staff have admirably expanded the prior Health Effects summaries to include the latest research available. This job was made more difficult since the U.S. EPA is also updating their Integrated Science Assessment review for Particulate Matter which was last completed in 2009. Their soon to be published more recent review would have made the job much easier. Since I was once the only biologist on staff at the District and served as the prototype for Health Effects Officer, I know that I would not want to tackle some of this work with this matter of timing.
Overall, my comments are:

1) Explain the purpose of this appendix more clearly in the Introduction. Also state that it is not the purpose of this appendix to present data on ambient air quality statistics, attainment status, air pollution geographic distribution, environmental justice, socioeconomic impacts, preferred control strategies, or cost effectiveness. All of these discussions can be found in the complete AQMP document and its other appendices. Unfortunately, some of the Advisory Council members seemed to be unclear on the purpose of Appendix I and there was much discussion that did not belong to yesterday's meeting.

2) Since most of the readers of Appendix I will not have scientific health effects background, it might be most useful to define some additional regulatory and medical terms. Specifically, EPA's designations for weight of evidence presented in Table I-1 were apparently unclear to some Advisory Council members. Perhaps a statement that these are determined by EPA and are a result of scientific evaluation of the research studies they have reviewed. I'm still waiting for a creative numbering system that would more clearly identify weight of evidence that the public would understand. Perhaps a Richter scale of weight of evidence? Also, a quick definition of FEV1 could be very useful for some readers.

3) The introduction should also describe the legislative and regulatory mandates for each agency involved in this scientific review. It should be clear that the SCAQMD, while commenting on and contributing to proposed ambient air quality standards, must do all in its power to attempt to attain those standards once they are adopted by EPA. Once the CA state standards are mentioned, it would be useful to quote the Health and Safety Code that only requires the SCAQMD to attain these usually more stringent standards at the earliest practicable time with no specific deadlines codified.

One final comment would be to carefully select the Advisory Council members for each appendix based on their expertise. I truly was hoping for more discussion of the latest health effects research from others such as DRI or Dr. Froines.
Again, thank you for this opportunity to be a small part of your AQMP review process.
Sincerely, Emily Nelson, D.Env.
Health and Environmental Risk Consultant

From: Edward Lawrence Avol <avol@usc.edu>
Sent: Sunday, August 21, 2016 2:53 PM
To: Jo Kay Ghosh
Subject: RE: DEADLINE EXTENDED - AQMP, Appendix I Comments
Attachments: AQMD 2016 AQMP Health Section AVOL rev.docx

Jo Kay,

Please find attached my slightly revised comments on the AQMP Appendix devoted to Health Impacts (Appendix I). The meeting discussion did help to clarify a few points, and I have made one or two small changes to my previously-submitted draft comments based on the meeting discussions.

Thank you for the opportunity to participate in this important process. Understanding the basis for strategies and actions, and effectively communicating complex scientific information in a way that becomes accessible and useful to the public is a critically-important task; I hope these comments, and the comments of my colleagues on the committee, help you in that objective.

Take care,
Ed

From: Ann Scagliola [mailto:ascagliola@aqmd.gov] **On Behalf Of** Jo Kay Ghosh
Sent: Friday, August 19, 2016 10:15 AM
To: Bill LaMarr <billlamarr@msn.com>; Bill LaMarr <billlamarr113@gmail.com>; Curtis Coleman <colemanlaw@earthlink.net>; Dr. Afif El-Hasan <afif.h.el-hasan@kp.org>; Dr. Cameron Kaiser <ckaiser@rivcocha.org>; Dr. Emily Nelson <dremilynelson@gmail.com>; Dr. Greg Osterman <gregory.b.osterman@jpl.nasa.gov>; Dr. John Froines <jfroines@ucla.edu>; Dr. John Husing <john@johnhusing.com>; Dr. Rhodes Rigsby <rrigsby@llu.edu>; Erbie Phillips <erbiejr@gmail.com>; Judy Chow <judy.chow@dri.edu>; Mary Ann Lutz <maryann@lutz-co.com>; Paul Avila <paulavila51@aol.com>; Edward Lawrence Avol <avol@usc.edu>; Sue Gornick <sgornick@wspa.org>
Cc: Jo Kay Ghosh <jghosh@aqmd.gov>
Subject: DEADLINE EXTENDED - AQMP, Appendix I Comments
Importance: High

Sent on Behalf of Jo Kay Ghosh

Advisory Council Members,

As discussed in yesterday's Advisory Council meeting, the deadline for submitting comments for the draft 2016 AQMP, Appendix I has been extended to August 26, 2016. Please send your comments to the attention of Jo Kay Ghosh (jghosh@aqmd.gov).

Thank you,

Ann Scagliola
South Coast Air Quality Management District
Planning, Rule Development & Area Sources
ph: 909.396.2423 | fax: 909.396.3931
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Revised Comments on Draft 2016 AQMP Appendix I: Health Effects

Ed Avol (USC Dept of Preventive Medicine)

(19Aug2016)

General Comments:

The purpose and format of this appendix document is not clear. There may be a legal requirement for a Health Effects appendix, but the public should have a better sense (with a clear statement of purpose and approach) of why this is being provided beyond, "it's required."

That said, there seems to be a lot of generic cutting and pasting from previous USEPA Integrated Science Assessments (ISAs). However, because the ISAs are thousands of pages, there needs to be some careful selection and decisions regarding what is brought forward from the EPA efforts. Since the prior ISA reviews largely occurred three to five years ago, it does make sense to conduct and report on an updated search of the more recent health literature, and some of that does appear in the document. A more current ISA has been released for oxides of nitrogen (2016), so that document should be used to summarize current knowledge of NOx health effects.

I generally found the document to be somewhat inconsistent in its approach. Sectional organization, level of detail, and approaches to summarizing cited work seemed to vary from pollutant to pollutant, without a clear rationale or reason. Order of presentation was odd (ozone, then PM, then NOx, then SOx, then lead, then CO, then HAPs seems more sensible, based on control strategies and interactive photochemical impacts). Organizationally, it seems like a similar approach could be applied for all pollutants – a summary from the most recent ISA, a summary of more recently published information, a discussion of health endpoints and judgements about confidence of association, some perspectives on susceptible sub-populations, and conclusions about the state of knowledge for the pollutant being discussed.

Additionally, the criteria for discussing health outcomes seems to shift around a bit. I think it is appropriate that the EPA tables on causal relationship status be discussed and used to prioritize presentation of health effects data. However, there needs to be a brief discussion about what the causality table means, so that the different thresholds are understandable to the public. It also needs to be made clearer what the causality threshold selection criteria is for inclusion of data in this document (in other words, is there only going to be discussion regarding outcomes determined to be "causal", "likely causal", or "suggestive of causal"?). This decision regarding causality threshold seemed to vary from pollutant to pollutant…but was not explained or discussed in the text.

An alternative approach would be to identify target organs or outcomes of interest (brain, heart, lungs, neonatal development, metabolic, etc), and then comment on whether the database supported any concern for health impact.

I think it is useful to inform the public that health concerns extend well beyond respiratory alone…and provide the data to support the claim. It certainly makes sense to think about air pollution affecting breathing, but the impacts go far beyond that…and that does come across as clearly as one would expect in appendix devoted to health outcomes of air pollution.

Specific Comments:

Table of Contents – I question why “Ultrafine Particles” have their own separate section, rather than being a sub-section of Particle Matter. If one were being consistent and logical, an introductory section would talk generically about PM, then individual sub-sections would talk about PM10, PM2.5, PM 10-2.5, and ultrafines. PM2.5 (Fine PM) and PM10 (Coarse PM) arguably should have their own sub-section in the report (since for both historical and regulatory reasons, both metrics are of health and regulatory significance).

Table of Contents – should be “Conclusions” (plural), not singular…

Table of Contents – ATTACHMENT – not sure why this list of SCAQMD efforts appears in this health appendix document. The information contained in the appendix obviously draws from a larger range of peer-reviewed published literature beyond SCAQMD-funded work. Inclusions of this section does not add to the focus of the document (a review of air pollution health effects), is a little self-serving, and seems unnecessary. If the intent is to demonstrate that the SCAQMD has and does fund health research, then this might merit another separate appendix, with an explanatory paragraph or two.

I-1, Introduction, last sentence – It sounds like the Health and Safety Code requires a review of PM, and other pollutants have been added by choice. Most are NAAQS pollutants and make sense to include. In terms of regulatory policy, something might also be said about VOCs, which play an important role in photochemistry, pollution reduction strategies, and human health effects in their own right.

I-1, para 2, bulleted list of adverse health effects – I’m not sure that this bullet list is especially useful, effective, accurate, or worthwhile. Using bullet points focuses the Reader on specific issues as being especially important, and I think this does not serve the presentation well because it is a partial (and somewhat mis-directed) list. Air pollution health effects have arguably been identified with most every organ system in the body. The listing here is inconsistent in sometimes providing an explanation (which isn’t appropriate or useful in this introductory passage). I suggest this bullet list be re-done to present the example information more clearly (for example, why say “increased health care utilization” when examples of that are also included? Why not just say, “increased physicians’ visits, emergency room visits, and hospitalizations”? Saying increased respiratory illness and other morbidity (symptoms, infections, and asthma exacerbation) is somewhat repetitive – just say increased respiratory symptoms, infections, and asthma exacerbation. Decreased lung function is not “just” breathing capacity, so the parenthetical comment here should be deleted for clarity. The extended explanation for increased airway reactivity is unnecessary here and should be changed to “increased airway reactivity” or “increased airway responsiveness” , or “bronchial hyper-reactivity…but using text space to explain the laboratory approach utilized to observe the response makes little sense here. It’s not immediately clear to me what is meant by “a decreased tolerance for exercise”? Are you claiming that air pollution makes you tired? I think what you are talking about are secondary observations conditional upon respiratory, cardiovascular, and metabolic effects (and/or possible heat-related effects as well, given the frequent co-occurrence of pollution episodes in the SCAQMD with elevated temperatures)…but I am skeptical this is a useful bullet listing. The note “adverse birth outcomes, such as low birth weight” is another inadequate mis-direction, in my opinion, since there have been a range of

negative birth outcomes reported (including pre-term, neurological, and developmental) that I would think most might consider more substantive and important than low birth weight…so again, if the decision is to list a few examples, be careful to list important ones or illustrative ones, and be aware of what may be missing. Missing from this overall list are also more important topics to identify, such as neurological and neuro-developmental effects (behavior and learning), and metabolic effects (obesity, blood pressure, and even diabetes). The point is, this can be a considerable listing of outcomes, so one needs to be thoughtful of intent here.

I-2, para2, sentence 1 – Are you saying the only data used in preparation of this appendix were those from epi or clinical studies? Nothing from bench-top toxicology? Each of these three approaches (epidemiology, toxicology, and clinical studies) provide unique and overlapping benefits to health research, thought the specific benefits and shortcomings of each approach differ (but overlap).

I-2, para2, sentence 2 – Arguably, the historical approach to understanding the health effects of air pollutants has, in the clinical and toxicological settings, been focused on specific pollutants and individual effects. In the past decade, there has been increasing pressure to investigate the combined effects of multiple pollutants on human health, since multi-pollutant exposures are a more accurate reflection of the "real" world. Given this is the case, I would delete the last half of this sentence in the text ("…and specific pollutants responsible for individual effects").

I-2, para3, sentence 4 ("Evidence for more than additive effects has not been strong…") – I am not sure you would get a consensus opinion on this claim, and more importantly, the claim is not central to the presentation here. I think the key point is that regulatory policy has, by in large, focused on individual pollutants without much regard for multi-pollutant exposures or effects. Accordingly, the document reviews the health information in an individual stepwise fashion. However, since it is acknowledged that there are multiple chemicals co-exposures occurring, a brief review of reported combined effects is also being presented herein.

I-3, para2 – The presentation of a criteria by which to gauge causal relationships of reported health data is useful here, but there is inadequate explanation as to context. I suggest adding a sentence or two prior to Table I-1 that says something like this: "Over the decades of national reviews of outdoor air pollution and their health impacts, the US EPA has developed a list of five criteria by which the strength and credibility of data can be judged. This five-tier weight-of-evidence approach provides an objective basis for assessing the breadth, specificity, and consistency of evidence concerning a particular health outcome."

I-4, Ozone, third sentence ("Since it is a gas, …") – This sentence is literally true but generally misleading to readers. Fine (and ultra-fine) particles can also penetrate into the gas-exchange regions of the lung, so I object to the phrasing "Since it is a gas,…" and suggest this qualification be removed.

I-6, Short-Term Effects of Ozone, para1, first sentence – This statement is partially true and incomplete. Increased physical activity increases both depth and frequency of inhalation. This results in higher ventilation rates ("more air and ozone" being breathed in) and increased surface areas of the lung becoming accessible to the inhaled air parcel. Therefore, additional

portions of the lung are likely to come into contact with ozone during increased physical activity, compared to lower activity levels or rest.

I-6, Short-Term Effects of Ozone, para2, last sentence – The statement seems to purposely focus on respiratory outcomes. Is this because you are purposely limiting the discussion to a causal threshold of "likely to be causal"? Under a casual determination of "suggestive of a causal relationship", there are cardiovascular, reproductive, developmental, and central nervous system effects, as well. My concern here is that you are limiting the range of discussion to only respiratory endpoints, when there are many other target organs at risk.

I-7, para1, third sentence ("USEPA's recent review…") – Probably better to anchor this comment to a date rather than "recent" – suggest saying "USEPA's 2013 Integrated Science Assessment Review…" or something like that to link the comment to the data resource.

I-8, para1, inclusion of confidence intervals in discussion of CHS publication regarding school absences – This seems a little confusing and inconsistent with the previous discussion, where confidence intervals or p values have not been presented with reported observed changes in health status. In the interest of the report being consistent and accessible to a wide portion of the public, I suggest removing the confidence intervals from this passage; the citation provides a ready means of more detailed review of the research, should a Reader want more information.

I-8, para2, discussion on attenuation of response (adaptation, reduction in magnitude, …) – Not clear from your presentation what the intent or objective here, but you seem to be discrediting the notion of "adaptation", so a few comments are in order:

(1) Many researchers in the field would shy away from the phrase "adaptation", which denotes some positive evolutionary change; "toleration" or "tolerance" has been suggested as an alternative phrase, or something connoting reduced or diminished response;
(2) I don't discount what you have said in the text regarding the uncoupling of macro-system (i.e. lung function) and micro-system (i.e., biochemical) changes, but since I am one of the investigators who did several of the ozone toleration studies in controlled-exposure settings, I would note that there is a range of human response. Based on laboratory findings, it appeared that a portion of the population were "non-responders" (didn't really change much from baseline levels), a substantive portion of the population displayed some attributes of "toleration" (that is, developed some diminished response with recurring ozone exposure), and that another substantive portion did not seem to develop a diminished response (that is, with repeated challenge, there was fairly consistent and repeated loss of lung function). This was true with both consecutive (i.e. daily) and seasonal responses. Regarding seasonal response, it appeared that the observed capacity for "toleration" or diminished response was established during the early part of the "smog" season, persisted through it, and was "lost" through the winter…so the phenomenon seems to be repeatable (among certain people). I think this is what the last sentence in the paragraph is suggesting (that there is a seasonal aspect to toleration, but that it is somewhat ephemeral).

I-11, Long-Term Exposure Effects of Ozone, para2, line2 – should be "summer-only".

I-13, para2, line5 – "…Tumor Necrosis Factor α …"; add (TNF-α) to clarify (many readers may only know it by its shorthand symbol).
I-13, para2, last sentence – This paragraph is about laboratory studies of animals, but the last sentences is talking about humans (?). This last sentence seems more appropriate for I-8, para3, and should be removed from the current location.

I-13, next-to-last paragraph, first sentence – too long and awkwardly constructed. Should be broken into two sentences: "Some animal studies …changes of the lung. However, morphological, developmental, and immunological differences make it difficult to apply these results to humans."

I-13, last para, second sentence (In southern California communities with high ozone concentrations ,…") – should provide a number or range to the term "high". The key message from the study was that children playing in currently-encountered ambient levels of ozone were at increased risk for developing asthma (not just making existing asthma worse).

I-14, para2, line7 ("…prenatal exposures and low birth weight…") – should read ***on*** low birth weight …

I-14, para3, first sentence – remove the word "newer" from the phrase 'other health endpoints"…

I-14, para3, second sentence – "One study of childhood autism was conducted in LA County and reported …" should be re-written to read, "A study of childhood autism conducted in LA County reported…" (…there has been more than one autism study conducted in LA County…)

I-14, last para, second-to-last sentence – should read 'first-trimester ozone", "second-trimester ozone", and "preconception-SO2 … (hyphens missing from existing text)

I-15, Sensitive Populations for Ozone-Related Health Effects – This is an important issue for the public, who always wonders who (if anyone) is at increased risk, so I think it is useful to take some care in getting this information out there in a useful way. One should probably specify which review you are drawing data from (i.e., the February 2013 USEPA Integrated Science Assessment for Ozone). Additionally, you summarized much (but not all) of the identified at-risk populations listed in Table 8 from the 2013 EPA ISA (see Table 8 below, cut and pasted from the 2013 ISA). It might also be useful to create a short table of Evidence Class, Risk Factor, short summary directional effect, and a link or citation (to either the ISA at the EPA website, or to individual peer-reviewed articles) for inclusion into the AQMP appendix.

additional

Table 8-6 Summary of evidence for potential increased risk of O_3-related health effects.

Evidence Classification	Potential At Risk Factor
Adequate evidence	Genetic factors (Section 8.1) Asthma (Section 8.2.2) Children (Section 8.3.1.1) Older adults (Section 8.3.1.2) Diet (Section 8.4.1) Outdoor workers (Section 8.4.4)
Suggestive evidence	Sex (Section 8.3.2) SES (Section 8.3.3) Obesity (Section 8.4.2)
Inadequate evidence	Influenza/Infection (Section 8.2.1) COPD (Section 8.2.3) CVD (Section 8.2.4) Diabetes (Section 8.2.5) Hyperthyroidism (Section 8.2.6) Race/ethnicity (Section 8.3.4) Smoking (Section 8.4.3) Air conditioning use (Section 8.4.5)
Evidence of no effect	--

Additional note: SES is mentioned twice in the paragraph – first as having adequate evidence, then as having suggestive. As Table above shows, it should be suggestive, based on the ISA.

I-15, Summary Ozone Health Effects, first sentence – I think this could be strengthened and clarified. I suggest the following replacement sentences: “In summary, outdoor ozone exposures have been associated with a range of negative human health effects. The strongest evidence for negative health impacts are on the respiratory system, and are measured by decreased lung function performance and increased cell injury. Effects on other organ systems, including cardiovascular, neurological, and metabolic have been shown to lead to heart disease, learning and developmental issues, and obesity. Although the specific mechanisms of action for ozone effects on the various health endpoints …

OBSERVATION: The PM Section (I-15 through mid-I-23) - The “feel” of the section discussing PM health effects in the report is different than the previous ozone section. In the PM section, there is greater reliance on and quotation of specific effect estimates from specific studies, often with study-by-study citation. In the ozone health effects section, it seemed to be a more general discussion, with less rote listing of estimates and citations. The “correct” presentation depends on the target audience and the level of intended detail. It might be sufficient to cite the EPA NAAQS documents and reproduce some of the key tables, rather than trying to cut and paste larger, more detailed sections of the respective documents into the current AQMP.

I-15, Particulate Matter, para1, first sentence – add the concept of particle toxicity and expand the impact of factors, by revising the first sentence to read: "…a complex group of pollutants that vary in physical, chemical, and biological dimensions. Physically, particles can vary by size, surface area and roughness, shape, and mass. Chemically, they vary by composition. Biologically, they can vary by toxicity (and even by biological availability [i.e., what chemical form] of the chemicals present). In addition to all these factors, particles vary by source, which can affect many of the previously identified factors. Particulate matter can come from anthropogenic (man-made, such as from combustion of fuels, or frictional abrasion) or "natural" (plants – for example, pollens and spores) origins."

I-15, Particulate Matter, last para, second sentence – replace "to cover particles" with "to focus on particles". This word change is necessary because PM10 was already a part of TSP, so it was already in the existing NAAQS. Based on the growing PM data base, it was determined that the health effects observed were caused by the smaller particles in TSP, so a portion of the previous NAAQS was identified for regulation.

I-15, Particulate Matter, last para, third sentence – Revise to read "These can be inhaled and deposited throughout the upper and lower respiratory system, depositing in both airways and gas-exchange areas of the lung.

I-16, para2, first sentence - Delete the "In more recent years,", and begin the paragraph this way: "As more health research data has become available, concerns have centered on smaller and smaller particles. Additional focus has been places on …"

I-16, para2, last sentence – "In 2002, the California Air Resources Board adopted an air quality standard for PM2.5 at a level of 12 ug/m3, in the form of an annual average."

I-16, para3, first sentence – "since that time, ~~numerous~~ *additional* studies have been published…"

I-17, para1, second-to-last sentence – "Of note, there is currently no federal or California standard for PM10-2.5, *although a PM10 standard remains in effect (see Table I-6).*

I-19, last para, last sentence – replace "preexistent" with 'preexisting".

I-21, para1, second sentence ("The results indicated that the association of PM10 …) – what is it you are trying to say? This seems convoluted and confusing. Removal of this sentence in its entirety improves the text, in my opinion…

I-21 para1, last sentence – "these results suggest that the effects *reported* are likely due to …"

I-21, para2, lines 2 and on – Change to read "After the study was published, it was discovered that some of the study analyses had been performed with incorrect default values. When the investigators re-analyzed the data using revised settings for the data, the size of the effect diminished, but the results remained largely the same. The strong positive association between acute PM10 exposure and mortality remained, both upon reanalysis using revised software and using alternative modeling approaches."

i-23, para1, first sentence – This sentence, while true on the face of it, is awkward because there are MANY reasons for variation in relative importance of PM2.5 or PM10-2.5. Several of these have already been discussed earlier in the text, so it is not clear why this subset (concentration, components, seasonal variation) is being reported here again. I recommend

deletion of this sentence and beginning the paragraph with the following sentence: A major knowledge gap in understanding the relative importance of “fine” PM (PM2.5) and “coarse” PM (PM10-2.5) is the relative lack of direct PM10-2.5 measurements.”

I-23, para1, first & second sentences (and elsewhere in the document) – the denotation for coarse particles switches back and forth through the sections – sometimes PM10-2.5, sometimes PM2.5-10…pick one and be consistent.

I-23, last para, second sentence – “The effect estimates *for these various morbidities* are generally higher than the estimates for mortality.

I-23, last paragraph, last two sentences – change to read “Observed effects have been associated with PM10, PM2.5, and PM10-2.5.”

I-31, para2, second sentence – missing a hyphen from “distance-weighted”.

I-37, para2, third sentence – (Regarding Avol 2001 Movers’ Study…) It’s important to note that children who moved to areas of higher PM10 & NO2 showed declines in lung function growth rates. Another way of phrasing this is that the effects of exposure seemed to “work” both ways – more exposure led to poorer lung function growth rates, less exposure led to improved lung function growth rates.

I-37, para2, last sentence – “The risk of lower lung function was about ~~five~~ four times higher in children …:

I-37, last para and last sentence, AND I-38 first para, line 8 – in some places, the term “new-onset asthma” has a hyphen, while in other places it does not; be consistent.

I-39, para2, last sentence – low-term (not term low) …

I-40, first para, second sentence – should read “A couple *of* recent studies …”

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints – It might be easier for Readers to follow along and/or locate text of interest if there were sub-headings for these paragraphs – Metabolic Syndrome, Neurological Impacts, …

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints, para1, first sentence – Many who access this document may not be aware of what is meant by the term “metabolic syndrome”, so it would be useful to provide a working definition here. Additionally, it is my understanding that in describing this endpoint, insulin resistance, high cholesterol, obesity, hypertension, etc are *attributes, manifestations, or markers* of metabolic syndrome, not the syndrome itself (in other words, a syndrome is a collection of symptoms, not the presence of any one condition). Therefore, the phrasing in the final sentence of the first paragraph in the section should be reviewed and revised.

I-40, Long-Term Particulate Matter Exposures and Newer Health Endpoints – The topic of metabolic syndrome and particle pollution is introduced, but very little is said. There have been several dozen publications to date (just search on Pub Med for metabolic syndrome & air pollution, or see Brook et al 2016 article in Hypertension, Eze et al 2015 in PLoS One, Devlin et al 2014 in Toxicol Sci, …).

I-41, para1 – (similar comment to above) – While there are a few studies documented in the area of neurological outcomes, not that much is said. There is a growing and broad literature on the topic, with work reported by Annette Peters' group in Germany, Jordi Sunyer's group at CREAL in Barcelona, and the Harvard Normative Aging Study group (perhaps search on "Joel Schwartz:, Normative Aging Study, or ?).

I-41, Sensitive Populations for PM-Related Health Effects – As was done earlier in the document with regard to ozone and sensitive sub-populations, you might consider summarizing more directly from the most recent PM review by EPA CASAC to summarize who is considered to be at elevated risk and the degree of confidence associated with the respective claim (Chapter 8 of the 2010 ISA).

I-42 – Summary Particulate Matter Health Effects – this is an important section, but doesn't quite deliver on the promise. Rather than a summary of what has been presented, this section seems to present additional information from additional sources. While the information presented is useful, it is NOT a ***summary*** of what has been presented.

I-43, Ultrafine Particles – why is this being presented AFTER the summary of the chapter? There may not be a current standard by which ultrafines are judged, but this section still provides information regarding health effects of PM…?

I-48, para1, last two lines – layout has switched to centered lines, rather than left-justified…

I-62, para2, second-to-last sentence – "However, it is important to note that these results represent a more refined risk estimation methodology, not an increase in risk." This sentence is absurd, on the face of it. If a more refined estimate approach results in a larger risk estimate, how can one claim there is no increase in risk? This is NOT just a numerical exercise – the implication of the numerical correction is arguably precisely that the risk is higher than was previously calculated; the sentence should be deleted.

I-63, Conclusions – This section is incomplete, arguably inadequate, and seems to just stop without concluding much of anything. Comments could have been made about improvements in the health database for each of the NAAQS

Pollutants. Comments could have been made regarding TACs or ultrafines, or improved understanding of susceptible sub-populations. Comments could have been restricted to ozone and PM, since that seems to be much of the original intent of this appendix…but instead, not much is "concluded."

I-87 – Draft 2016 AQMP Appendix I Attachment, Publications from Health Related Research Projects Funded or Co-Funded by SCAQMD – what is this even doing in this document? What does it add to the presentation? How does it help us to evaluate the health effects information presented in the body of the appendix? Possibly an interesting side discussion, but not germane to the focus of the presentation (since the source of funding for the reviewed research is not at issue); this could be deleted.

From: John Husing <john@johnhusing.com>
Sent: Wednesday, August 24, 2016 12:13 PM
To: Jo Kay Ghosh; Larry McCallon (GBM); Ben Benoit (GBM); Margarita Felix (Ben); Ben Benoit (GBM)
Subject: Missing appendix item or discussion

As a member of the AQMP Advisory group, I note that in your 26 pages of references to studies on the health impacts of pollution, I the only study (*title and summary below*) that directly measured the impact of the 2007 and later diesel engines on long term health and cancer was not listed. This despite the fact that it concludes no cancer risk and was paid for, among others, by CARB, NRDC and EPA. It appears to be research that AQMD does not even want to acknowledge exists.

Advanced Collaborative Emissions Study (ACES): Lifetime Cancer and Non-Cancer Assessment in Rats Exposed to New-Technology Diesel Exhaust Jacob D McDonaldJeffrey C BemisLance M HallbergDaniel J ConklinResearch Report 184, January 2015 Health Effects Institute

ww

FOR RELEASE TUESDAY, JANUARY 27, 2015

For More Information:

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STUDY OF LIFETIME ANIMAL EXPOSURE TO NEW TECHNOLOGY DIESEL ENGINE EXHAUST FINDS NO LUNG CANCER

(Boston, January 27. 2015) The first study to conduct a comprehensive evaluation of lifetime exposure to new technology diesel exhaust (NTDE) has found no evidence of carcinogenic lung tumors.
The Advanced Collaborative Emissions Study (ACES), issued today by the Health Effects Institute
(HEI)1also confirmed that the concentrations of particulate matter and toxic air pollutants emitted from
NTDE are more than 90% lower than emissions from traditional older diesel engines (TDE).
The study exposed laboratory rats 80 hoursa week, for up to 30 months, to emissions from a heavy-
duty diesel engine meeting stringent 2007 US EPA standards that use new filters and oth
er control technology to reduce emissions significantly. In contrast to previous health studies of TDE, the ACES
study found that lifetime exposure did not induce tumors or pre-cancerous changes in the lung and did not
increase tumors related to NTDE in any other tissue. A few mild changes were seen in the lungs,
consistent with long-term exposure to NO2, a component of NTDE that has been further substantially
reduced in 2010-and later model year engines compliant with US EPA rules.

The ACES results are expected to play an important role in future risk reviews of diesel engines by
international and US agencies. "We are already seeing a transition in America's roads with over 30% of
the trucks and buses in use today meeting these new standards and the trend is growing in Europe as
well," said Dan Greenbaum, President of HEI. "These results confirm the great strides that government
and industry have made to reduce diesel risk – and argue for even greater efforts to accelerate the
replacement of older diesel engines."

From: Froines, John <jfroines@ucla.edu>
Sent: Thursday, August 25, 2016 8:30 AM
To: Jo Kay Ghosh
Subject: FW: relevant references
Attachments: UFP_NP_AAAAI report_Highlighted.pdf

Hello: I work as a colleague with two other investigators, Dr. Arthur Cho and Dr. Ning Li. We have had AQMD funded research in the past. I will be sending a few documents that may have use in Appendix 1. Hopefully they will be useful. More to come.
John

The following attachment(s) were included with Comment Letter #16 submitted by Dr. John Froines. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachments, however, interested parties can obtain access at the links provided below:

Li, N., S. Georas, N. Alexis, P. Fritz, T. Xia, M. A. Williams, E. Horner and A. Nel (2016). "A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects." J Allergy Clin Immunol **138**(2): 386-396.

http://linkinghub.elsevier.com/retrieve/pii/S0091-6749(16)30011-2

A hard copy of copyrighted material, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

From: Froines, John <jfroines@ucla.edu>
Sent: Thursday, August 25, 2016 8:36 AM
To: Jo Kay Ghosh
Subject: report
Attachments: 160408 AQMD final summary V5.docx

An older report.
John

Quantitative assays in the characterization of ambient air.

A report to the South Coast Air Quality Management District for Contra

Arthur K. Cho

Summary

1. Quantitative chemical reactivity and cellular assays have been performed on ambient air particles and their corresponding volatile components collected in three sites in the Los Angles Basin. The chemical results indicate that the particle (PM2.5) phase contains most (~75-80%) of the DTT based prooxidants and the vapor phase, defined as the dichloromethane soluble semivolatile organic species, contain most of the electrophiles (80-95%). The assoicated cellular assays showed that these reactive species exhibited caused inflammatory and adaptive responses by a mouse macrophage cell line to which the samples were exposed.

2. Most of the prooxidants present in the particle phase were associated with metals, as shown by the sensitivity of the DTT activity to a metal chelator, whereas the electrophiles were organic compounds. Seasonal differences in prooxidant content were also noticed, with the winter season PM2.5 higher for Commerce and Long Beach than that for the summer. Samples from San Bernardino differed from the other two sites in that levels of both reactive species in the summer samples were elevated. This observation was attributed to greater photochemical alterations of the air mass generated in the western end of the Los Angeles Basin as it moved east with the prevailing winds during the summer months.

3. The cellular actions of the ambient samples on cells were assessed in terms of two general responses, inflammation and adaptation. The inflammatory response is associated with, for example, the exacerbation of asthma and atherosclerosis, two dieseases with which air pollution has been associated. The adaptive response reflects an attempt by the cell to minimize the chemical insult associated

with the pollutants through the increased expression of antioxidant and foreign compound eliminated proteins.

4. The two cellular responses were monitored with tumor necrosis factor alpha (TNFa) as the inflammatory marker and heme oxygenase-1 (HO-1) as the adaptive marker. The summer particle phase from San Bernardino was the most potent in inducing the inflammatory respose and its corresponding vapor phase the most potent in inducing adaptation. Subsequent experiments showed that the semivolatile components of the vapor phase were capable of suppressing the inflammatory response of the particle phase and an inverse relationship was observed, with increasing adaptation suppressing the inflammatory response. Taken together, the results suggest that the inflammatory effects of ambient air may be less than would be expected from assessment of PM2.5 phase alone and point out the critical importance of analysis of both particle and vapor phases in studies of air pollutants. It should be pointed out however, that suppression of the inflammatory response could result in a reduced ability to respond to pathogenic microbial infections.

5. Analogous observations were with biodiesel exhaust and of cooking oil smoke samples obtained from the University of California Riverside College of Engineering Center for Environmental Research and Training (CE-CERT). Particle and vapor phases were also examined and the results showed an inverse relationship between the expression of TNFa and HO-1 by components of the vapor phase which had a high content of HO-1 inducers and a positive correlaton between samples with low levels of HO-1 and TNFa found in the particle phases. Thus, these data also support the notion that the response by cells to the chemical insults provided by the particle phase components are inflammatory but that this action is suppressed by adaptation which, when sufficiently intense, can suppress even baseline cellular TNFa expression.

6. The unique aspect of this work was its quantitative approach. The quantitative nature of each analysis allowed us to compare samples across locations, between seasons and in a limited study, comparing different biodiesel fuels. This approach

provided evidence for an antagonistic relationship between the inflammatory and adaptive responses by cells which could determine the net health outcome of exposure of air pollution in terms of exacerbation of vascular and pulmonary diseases on the one hand and a compromisd immune system on the other.

Objective

The objective of the project was to develop protocols for quantitatively assessing potential adverse biological effects of emission samples from vehicles and ambient air. The quantitative output of the assays could then be archived and compared with data from subsequent studies. A second objective was to develop a protocol for the fractionation of diesel exhaust to characterize the chemical classes involved in the biological responses observed for the total exhaust as a whole. This objective was dependent on a large scale collection of diesel exhaust particles and vapors to be made by the Center for Environmental Research Technology of the College of Engineering at the University of California at Riverside (CE-CERT). However, CE-CERT did not deliver the sample to us and our results for this objective were limited to preliminary procedural experiments with a diesel exhaust sample collected by Japanese colleagues in an earlier study.

The samples used in the first objective were:

1. Ambient air samples collected in the communities of Commerce, Long Beach and San Bernardino in the Los Angeles Basin. Collections were made in the summer and winter months and included particulate and vapor phase components. The latter were the volatile organic species collected in XAD resin beds placed below the filter holders which trapped PM2.5 particles.
2. Selected particle and vapor samples collected at the CE-CERT. These samples included biodiesel exhaust, cooking oil smoke and ethanol fuel exhaust from vehicles.

The samples were subjected to two sets of analytical procedures, chemical reactivity assays measuring pro-oxidant and electrophilic activities and cellular assays that determined the

capacity of the samples to initiate inflammatory and adaptive responses. The hypothesis leading to the assays is described in the background section.

Methods

Chemical assays

We used the DTT based prooxidant (1; 2)and the GAPDH based electrophile assay (3; 4)to measure chemical reactivity. The DTT assay measures the ability of the sample to transfer electrons from dithiothreitol (DTT) to oxygen in a reaction analogous to that occurring in cells. Electrophiles, as defined by the GAPDH assay, are organic compounds with the ability to form covalent bonds with the thiol of glyceraldehyde-3-phosphate dehydrogenase, a reaction that would occur with other available thiols in cells. In studies of ambient air mixtures collected with the VACES concentrator, we have shown that the DTT activity correlates with the ability of the sample to induce HO-1 in macrophages and with the polynuclear aromatic hydrocarbon content of the sample (1).

Cellular assays

Cells

Raw 264.7 cells were cultured in DMEM, supplemented by 1% penicillin-streptomycin and 10% FBS as described by Li et al. (5) with slight modifications. Cells were exposed to the entire particle suspension or to the DMSO solution of the dichloromethane extract of the XAD resin as the particle and vapor phases, respectively. The samples were added to the media to attain air volume equivalent concentrations from 0.1 to 2.0 m^3/mL. A filter blank suspension and DMSO in volumes corresponding to the particle and vapor samples, respectively, were used as controls. The stimulation was allowed to proceed for time periods of 3, 6 or 16 hours and the cells and media collected for subsequent ELISA analysis.

In a 2 phase exposure study with the summer San Bernardino samples, cells were exposed to the vapor phase components at 1 m^3/mL and relevant controls for 24 hours, the DMEM removed and replaced with fresh DMEM containing the challenge agent, or PM2.5, also at 1 m^3/mL. This mixture was cultured for 16 hours after which the cells and media were processed as above for analysis of HO-1 and TNFα.

The shorter stimulation period of 3 hours was used in subsequent studies because at this time levels of marker proteins were found to be high and the time period more suitable for multiple sample studies.

ELISA assay for markers

The ELISA assays were performed following instructions provided by the manufacturers (HO-1; Enzo Life Sciences; TNFα, BD Pharmingen). The results reported are the difference between the control and the experimental cultures. The HO-1 results were expressed as ng/mg protein and the TNFα results were expressed as pg/mL medium.

Data analysis

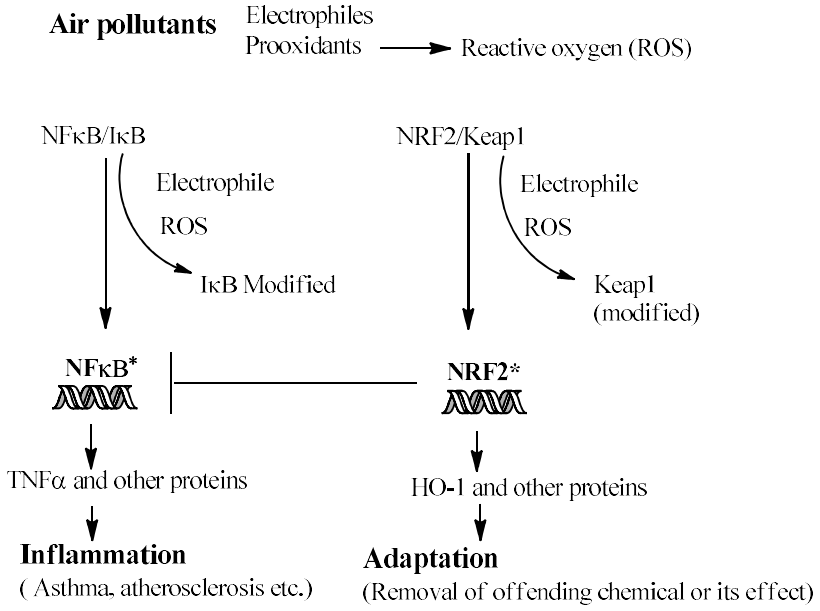
Whenever possible, attempts were made to conduct experiments using three concentrations of test sample to assess concentration dependency of the response. The multiplicity of components involved in the responses measured can result in a non-linear response reflecting issues such as saturation and possible hormetic responses or a "U" shaped dose response relationship. Linear concentration dependency is thus critical in comparing cellular responses.

Background

Although air pollutants include precursors to toxins such as polynuclear aromatic hydrocarbons (e.g., (6-8)) that can be bioactivated to their toxic metabolites, the focus of our research has been the reactive substances present in air pollution mixtures. In our view, these reactive substances can have immediate health effects on humans by undergoing chemical reactions with available biological molecules. These chemical reactions are of two types, the generation of so called reactive oxygen species, superoxide, hydrogen peroxide and hydroxyl radical and the formation of covalent, irreversible bonds between the pollutant and a protein. There are two types of cellular responses to these chemical insults, adaptation and inflammation. In the adaptive response, levels of antioxidant molecules, proteins or small molecules that convert the oxygen species to water, are increased together with increases in levels of biological "traps", substances such as glutathione that reduce the concentration of the reactive substance by converting the offending agent to an inactive metabolite that can be excreted (9; 10). Inflammation is a more general process, in which phagocytic cells remove the offending particle or microorganism from the general circulation by internalizing them and rendering them inactive(11). It is also the

process by which the organism protects itself from the invasion of pathogenic microorganisms, using the immune system. The overall process is a cascade of cellular events involving multiple cells and is initiated by the expression of triggering proteins called cytokines. Adaptation and inflammation are mediated by distinct pathways and like most biological responses, are dependent on the concentration of the triggering agent(s). It should also be pointed out that both adaptation and inflammation can be considered adverse health responses. Adaptation can increase organism sensitivity to microbial attack by suppressing the immune response and inflammation can result in exacerbation of chronic diseases such as asthma and atherosclerosis through the increased expression of cytokines. Figure 1 is a highly simplified summary of the interrelationship between the two processes.

Figure 1 Air pollutants and cellular targets



Two cellular signaling cascades are summarized in the figure, a proinflammatory cascade, mediated by the transcription factor NFκB and an adaptive cascade with Nrf2 as the transcription factor. These cascades have a "ying-yang" relationship in that the adaptive response antagonizes the inflammatory response, shown by the line. In the resting state the transcription factors are complexed with inhibitory regulators which dissociate upon reaction with electrophiles or ROS generated by the prooxidants of the pollutant mixture. The result of the activation can be inflammation or adaptation, depending on the concentrations and nature of the offending chemical mixture. The line between Nrf2 and NFkB is meant to indicate an antagonistic relationship between the actions of the two factors.

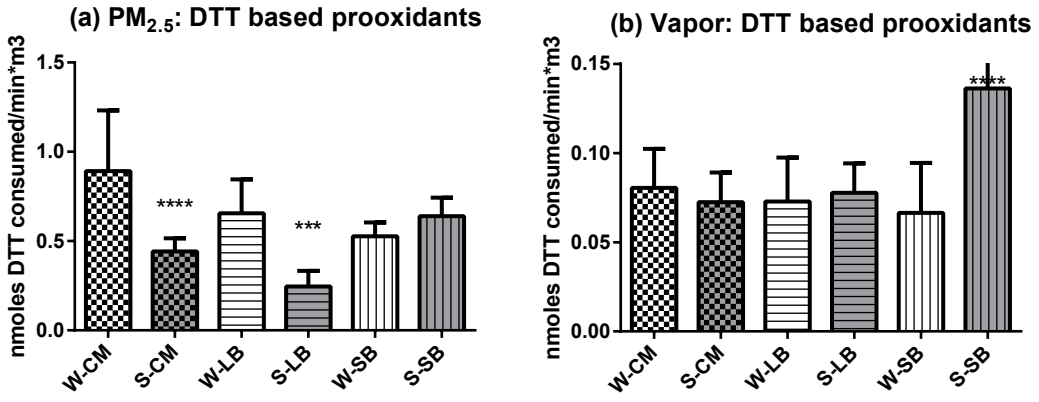
The cytokine, tumor necrosis factor alpha (TNFa), is a marker for NFkappaB activation and the antioxidant enzyme, hemeoxygenase-1 (HO-1) as a marker for Nrf2 activation, the transcription factors associated with the inflammatory and adaptive responses, respectively. We have used lipopolysaccharide (LPS) and a Japanese diesel exhaust sample (J-DEP) used by many investigators as a HO-1 stimulant, as standards. As such, levels of TNFa and HO-1 were shown to increase with increasing concentration of the LPS and J-DEP.

We hypothesize that the chemical species in air pollutant mixtures involved in these interactions are prooxidants and electrophiles. Prooxidants are compounds that engage in electron transfer reactions or the reduction of molecular oxygen to the ROS using endogenous biological antioxidants such as NADPH, NADH and ascorbate as reducing agents (12). Prooxidants generate ROS from oxygen and biochemical agents such as NADPH. These ROS, most notably hydrogen peroxide modify cysteine thiols, causing the breakdown of inactive complexes of transcription factors to their active forms indicated by asterisks in figure 1. Electrophiles are compounds that react with electron rich functionalities such as cysteine thiol and lysine amino groups of proteins to form irreversible covalent bonds (13-15). By this reaction, then electrophiles also modify the same thiols but irreversibly and dissociate the transcription factor complex to active factor. The transcription factors then enter the nucleus and stimulate expression of multiple proteins including the two marker proteins, TNFa and HO-1. Thus, the relative quantities of the two proteins reflects the activation status of the processes. A recent review of the inflammatory actions of DEPs relevant to atherosclerosis, indicates the increase in TNFa and HO-1 can be antagonized by N-acetyl cysteine (16). Although commonly referred to as an “antioxidant”, this compound is actually a neucleophile, reacting with sulfenic acids to form disulfides (17) and covalent bonds with electrophiles such as quinones (18). In addition to electrophiles, air pollutants include prooxidants and there is evidence to suggest that metals play an important role in this component of air toxicant (4; 19; 20).

Results

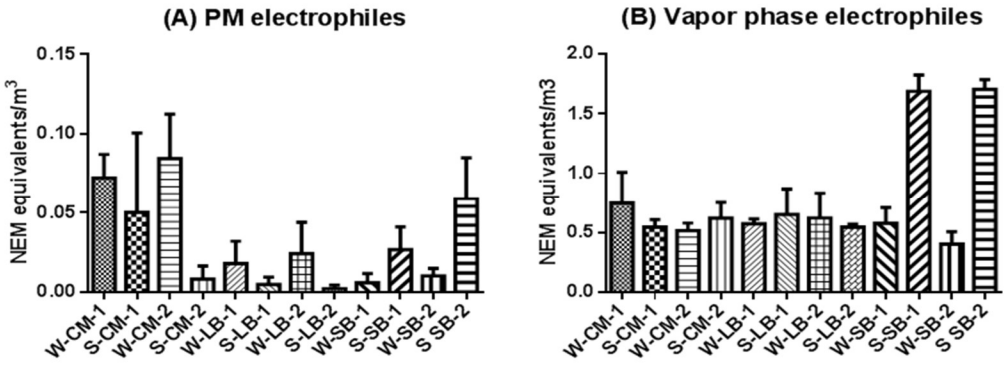
Figure 2 shows the chemical reactivities of particulate (PM2.5) and semi volatile organic species (XAD) in samples collected from sites neighboring railyards in Commerce, Long Beach and San Bernardino using a Tisch sampler to collect filter and XAD resin based volatile organic species (21).

Figure 2a Prooxidant content in PM2.5 and semivolatile organics (XAD) .



*The abbreviations used are W- winter, S-summer, CM Commerce, LB, Long Beach and SB, San Bernardino. Asterisks are used to denote p values for significance: 0.01 to 0.05, *; 0.001 to 0.01, **; < 0.001 *** to ****.*

Figure 2b Electrophile content in content in PM2.5 and semivolatile organics (XAD)



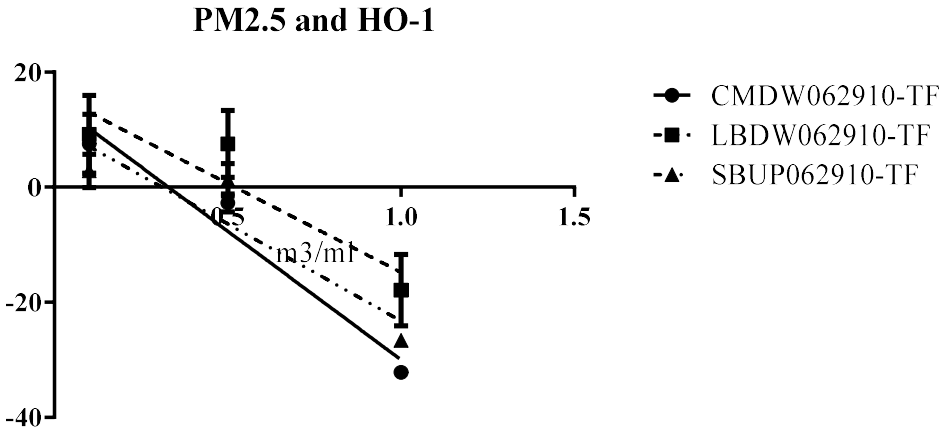
Wide differences in the distribution of the two reactivities were observed (note differences in Y axis scale) between the particle and vapor or semi-volatile organic phases. The ambient electrophiles were mostly in the vapor phase but the prooxidants were mostly in the particle

phase. Significant seasonal differences were observed for Commerce and Long Beach with the winter samples containing higher levels of prooxidant compared to the summer. The San Bernardino samples exhibited the opposite trend but it was not significant. The high winter sample prooxidant content could reflect the influence of the Santa Ana winds common in the Basin during the fall and winter. These winds typically move easterly from the mountains to the coast and could limit the movement of pollutants from downtown traffic and railyards in Commerce and Long Beach. That effect and the slightly lower temperature may result in retention of the reactive chemicals by the particles from these locations.

Celllular responses to PM2.5 and XAD resin extracts of summer samples collected in the Basin

The availability of the large scale samples of ambient air samples allowed us to examine cellular effects of selected samples with measured chemical reactivities. The first study examined the actions of summer San Bernardino samples because of their high reactivity compared to those from Commerce or Long Beach. Responses were measured at three different concentrations to permit analysis for linear relationships between concentration and response and expression of the potency of a given sample by the regression slope. This approach allowed us to identify a negative concentration response for particles and HO-1 expression, i.e., the particles exhibited a negative concentration dependency with minimal differences between the slopes of the concentration response curves (see figure 2). The negative values observed reflect differences between the “filter blank” and the particles on the sample filters and indicate the samples suppressed normal HO-1 expression. As the concentration of PM2.5 was increased, HO-12 levels decreased and at 1 m3/mL, were significantly lower than the control expression.

Figure 2 Effect of PM2.5 concentration on HO-1 induction.



Net expression, based on differences between PM2.5 and corresponding filter blanks, of HO-1 by cells following stimulation by PM2.5 samples.

This observation supported the notion of antagonism between inflammation and adaptation (figure 1), as the PM2.5 fractions increased TNFa expression (table 2). Furthermore, the biological potency of the samples on a per volume basis reflected the chemical reactivity. TNFa expression induced in macrophages by the particle phase increased in the order SB>CM≥LB which followed the order of prooxidant content, although the responses from the CM and LB samples were mostly if not altogether due to the lipopolysaccharide contents of the samples with minimal contributions from chemical sources. Table 2. Slopes of the concentration-marker protein concentration following a 16 hour stimulation by PM2.5 and XAD resin extracts of the 6/29 samples.

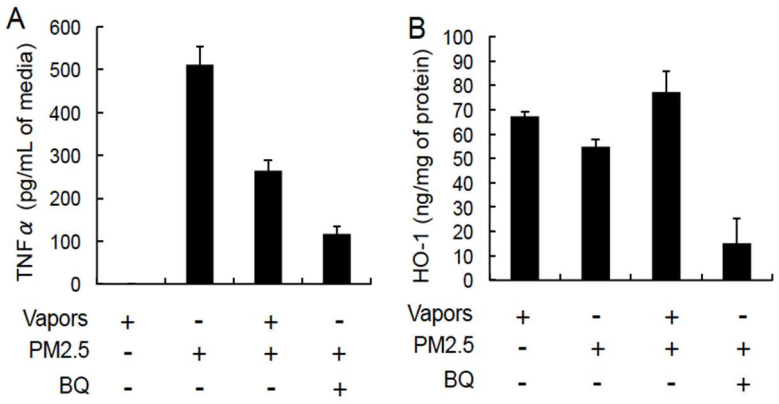
From samples of 6/29	**Commerce**	**Long Beach**	**San Bernardino**
PM 2.5 TNFa expression	18.7*X + 0.07	11.1*X - 0.38	413.9*X - 16.64
PM2.5 HO-1 expression	-44.69*X + 14.71	-30.88*X + 16.09	-33.67*X + 10.46
XAD HO-1 expression	34.49*X - 10.98	43.23*X - 12.14	182.4*X - 22.49
Units are ng HO-1 or pg TNFa per mg protein/m3 per mL			

We then tested whether the notion of TNFa and HO-1 antagonism could be demonstrated in PM2.5 and XAD extracts from the same air sample. Since the PM2.5 samples were

proinflammatory and the XAD samples adaptive, the inflammatory response should be suppressed if the cells were first exposed to the adaptive XAD sample. In the experiment, summarized in figure 3, cells were exposed to blank XAD extract and XAD extract from sample for 16 hours then the cells were washed and challenge with the particle phase for 16 hours and TNFa response measured (figure 3).

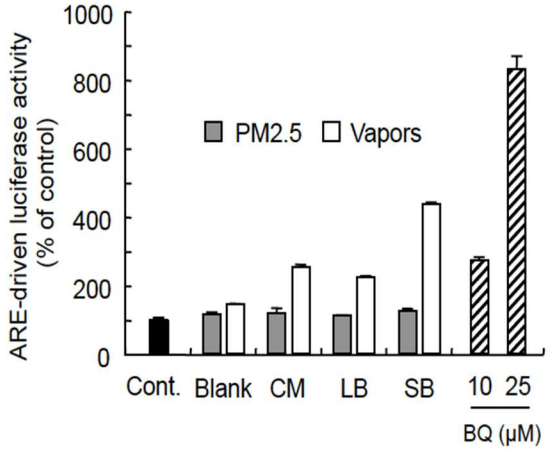
Interaction between XAD and PM2.5 samples; inhibition of the inflammatory response.

Figure 3



The results of the experiment showed indeed, that preexposure to XAD extract (identified as Vapors), reduced the subsequent TNFa response to PM2.5 exposure, i.e., components of the XAD extract suppressed the inflammatory response to the PM2.5 components by about 50%. The suppression is likely due to activation of the antioxidant/antielectrophile response element (ARE) as shown in experiments in which only vapor phase components activate the ARE (figure 4). This DNA element binds the transcription factor Nrf2 following its dissociation from the Nrf2-keap-1 complex, and in turn, increases the expression of HO-1 and other antioxidant proteins that serve to reduce the oxidative stress caused by prooxidants. In the figure, only the vapor phase increased the ARE driven luciferase activity. BQ is benzoquinone, which was used as a reference electrophile.

Figure 4. Stimulation of the ARE by XAD extracts (vapors) and benzoquinone (BQ).



Conclusions

The results of this study showed:

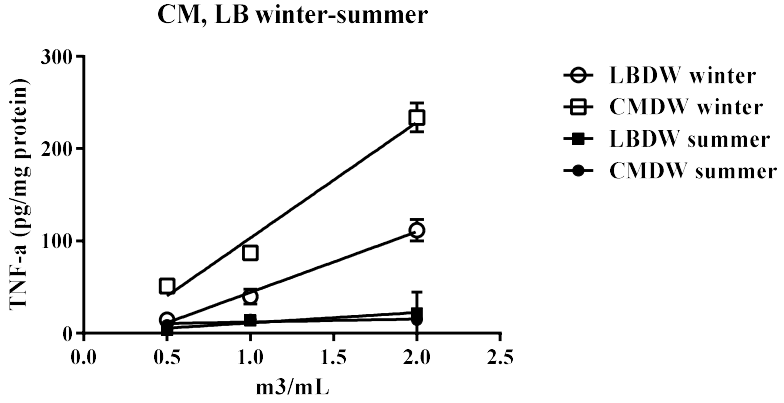
1. That the PM2.5 and semi-volatile organic components of ambient air samples with varying levels of prooxidants and electrophiles were capable of affecting the internal cell biology of macrophages with potencies that reflected chemical reactivity.
2. The PM2.5 prooxidants in the SB sample induced an inflammatory response, indicated by higher levels of TNFa and the semi-volatile organics induced HO-1 in a mouse macrophage preparation.
3. The induction of HO-1 by the semi-volatile organics reflects activation of the ARE through dissociation of the Nrf2/keap 1 complex. ARE activation results in increased antioxidant enzymes and other proteins that can serve to attenuate an inflammatory response, as demonstrated by preexposure of the cells to XAD extracts which suppressed the inflammatory response to PM2.5.
4. This result points out the role of volatile organics in the overall effects of ambient air on cells and, by extrapolation to, intact organisms. The net effect of chronic exposure to the mixture of particles and vapors could be an anti-inflammatory response resulting in a greater susceptibility to infections.

Seasonal differences in the cellular effects of PM2.5 from the Los Angeles Basin.

In contrast to the SB samples, the winter CM and LB PM2.5 samples had significantly higher prooxidant content compared to the summer samples (figure 1) and based on the results above, would be expected to exhibit greater inflammatory responses than those from the corresponding

summer. The sample from 11/12/2009 was used for this study. The values of the PM2.5 samples are shown in table XX

Winter PM2.5	DTT Activity	DTT/DTPA	DHBA	GAPDH
Commerce	0.960	0.147	0.336	0.128
Lomg Beach	0.590	0.000	0.451	0.000



Linear regression results

	LBDW winter	CMDW winter	LBDW summer	CMDW summer
Equation	Y = 65.81*X - 21.58	Y = 125.4*X - 22.30	Y = 11.25*X - 0.07500	Y = 3.264*X + 8.875
R square	0.974	0.9719	0.3437	0.4762

Linear regression analysis of the concentration-TNFa expression data indicated that the winter samples exhibited slopes that followed prooxidant content with Commerce higher than Long Beach. In contrast, the concentration dependency of TNFa expression was not deemed to have a significant slope, i.e, TNFa expression did not increase with concentration. In summary, winter samples from both CM and LB were proinflammatory with potencies that reflected their prooxidant content and the corresponding summer samples were inactive.

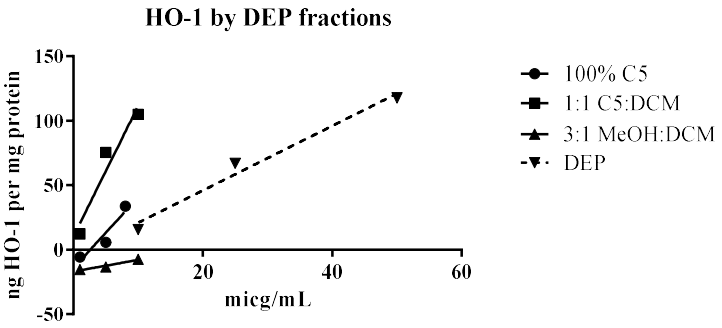
Fractionation of Japanese diesel exhaust particle (J-DEP) preparation

As stated above, we did not receive the DEP – vapor preparation that was to be provided by CE-CERT and were therefore unable to perform a fractionation as originally planned. However, to prepare for the samples, we began experiments to establish a fractionation protocol that could be used to prepare fractions for chemical and cellular analyses that could provide useful information

on the physical properties of the biologically active components of a test air pollutant sample. The procedure was a conventional sequential extraction that used solvents of increasing polarity starting with pentane then dichloromethane then methanol with mixtures of the solvents (Table 3). The cellular activities of each fraction were determined and recoveries determined using the mass following evaporation. The total cellular activity for a given fraction was defined as the product of the slope of HO-1 regression curve and the fraction mass. The nature of the chemical components of each fraction is shown in the 6th column. The TNFa responses were positive for the most polar fraction and the residue. DATA MISSING

Solvent	HO-1 regression	mass	total per fraction	% of total activity	Chemical groups present
	ng HO-1/micgmL^-1	mg	micg		
100% Pentane	Y = 5.508*X - 14.44	44.18	243.4	71%	Low MW PAHs, olefins, alkanes
50% Pentane/CH2Cl2	Y = 10.12*X + 10.20	8.66	87.5	25%	Quinones, PAHs
75% methanol/CH2Cl2*	Y = 0.8910*X - 16.89	14.97	13.3	4%	Quinones, phenols
Residue*	Negative values				Polar organics, metals
DEP	Y = 2.503*X - 4.132	67.81	344.2	100%	

The relationship between the HO-1 inducing capacity of the different fractions is shown in Figure 5.

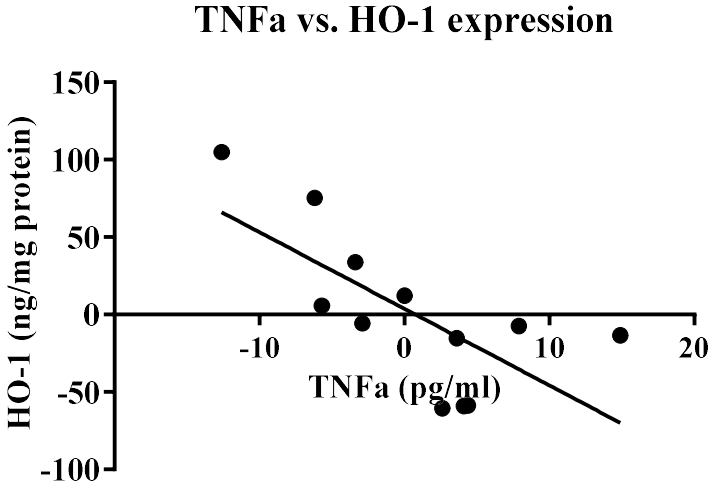


A DEP sample of about 100 mg was sequentially extracted with the indicated solvent mixtures and the extracts evaporated and used in subsequent cell assays. The cells were exposed to the fractions in concentrations that reflected the original sample

mass so that total activities could be estimated. The high recovery (327/256 or ~127%) may be due to the separation of the fractions, for example removal of TNFa inducing agents may increase the HO-1 inducing ability of the sample. .

Most of the HO-1 inducing capacity is associated with the non-polar solvent extracts, i.e., pentane and dichloromethane-pentane mixtures. The only significant TNF inducing activity was observed in the more polar methanol/DMC fraction and residue. These results suggest HO-1 induction is due primarily to non-polar compounds which include low molecular weight electrophiles such as reactive olefins and quinones that are active in the GAPDH assay. TNFa induction appears to be due to the more polar fraction and may be due to some quinones but more likely metals which are insoluble in non polar organic solvents but may be extractable by methanol if complexed with organic compounds such as polyphenols (4; 22). It should be pointed out that this DEP preparation has a high content of organic compounds, particularly quinones compared to other preparations we have examined (23) which may account for the dominant HO-1 response which could be suppressing the inflammatory response, as shown in figure 6.

Figure 6 Relationship between TNFa and HO-1 inducing abilities of the fractions of table XX



The HO-1 and TNFa expression values for the different concentrations of fractions used to generate table XX are shown with a regression line. Although the regression fit was poor (r2 = 0.49) the Pearson correlation coefficient (0.7) and p value (<.011) indicate they correlated well. This relationship has been observed with other samples examined in this study.

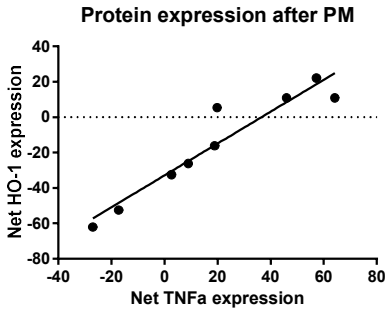
Conclusions

Preliminary extraction experiments using the cellular assay procedures on selected fractions of a commonly used Japanese DEP preparation (e.g., (10; 24-27)) showed the adaptive response to be associated with non-polar organic components and the inflammatory response with more polar organic and metal components. These observations suggest that this DEP preparation, with its high polar organic content, may be less inflammatory and more adaptive than ambient particles such as those found in the LA Basin. If this is a general property of diesel exhaust particles compared to ambient air PM2.5, there may be a difference in the primary response, i.e., the higher adaptive response associated with DEPs may contrast with the proinflammatory ambient PM2.5 from multiple sources.

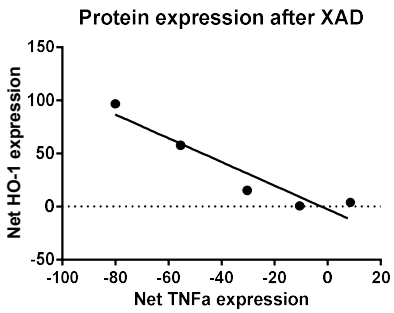
1. Studies of other air pollution samples

The notion of attenuation of inflammation by components of air samples was consistent with observations made in studies of biodiesel (figure 3) and cooking oil (figure 4) samples as part of collaborative study with the UCR College of Engineering Center for Environmental Research and Training (C E-CERT). Thus, analysis of the two phases, particulate and vapor (semivolatile organic species) of biodiesel exhaust showed that the volatile components were much stronger inducers of HO-1 (note difference in the values of the Y axis) , the adaptation marker and in the case of the vapor phase, were able to suppress the normal or background level of TNFa expression by the cells, evidenced by a negative correlation between the expression levels of the proteins. In contrast, the particle phase was capable of increasing TNFa expression beyond background levels but with much lower efficacy in HO-1 induction.

Figure 8A Comparison of adaptive and inflammatory responses to PM2.5 and vapors from biodiesel exhaust.



Plot of respective protein expression following exposure to PM from ULSD, AFME, Soy and WCO. r^2 + 0.952, p<0.0001



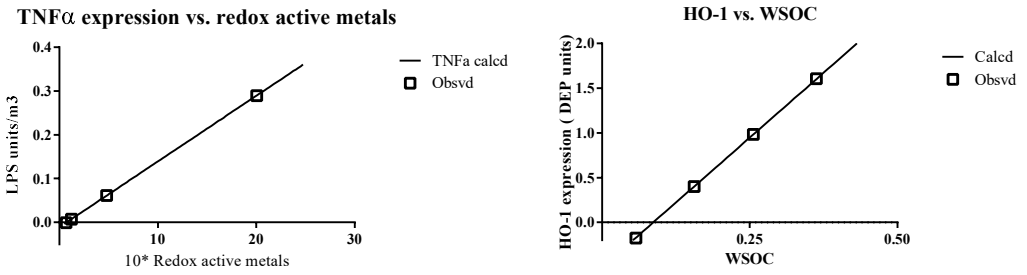
Plot of respective protein expression following exposure to XAD from ULSD, AFME, Soy and WCO. r^2 = 0.899, p<0.0014

The values shown are cellular responses to a fixed concentration of a different sample. Note the smaller negative values for TNFa expression from PM2.5 (-30 is smallest value) compared to XAD samples (-80 is the smallest value). Although the control expression of TNFa is suppressed by both phases, PM2.5 are weaker in their ability to induce HO-1 or promote adaptation. An inverse correlation between the expression of HO-1 and TNFa is shown, consistent with the antagonistic relationship between the two responses shown in figure 1.

In an attempt to assess the roles of redox active metals and water soluble organic species in the PM2.5, averaged values from the samples used here for the cell studies and those from the different samples used by CE-CERT were compared with the assumption that exhaust samples

from the same fuels would, on average contain the same components. The results from that assessment are shown in figure 8B, together with the best fit line from regression analysis. This analysis indicates that TNFa expression correlated with redox metal content and the HO-1 response correlated with water soluble organic compound content (WSOC).

Figure 8B Regression of HO-1 and TNFa responses of PM2.5 against chemical analyses (N = 4) .



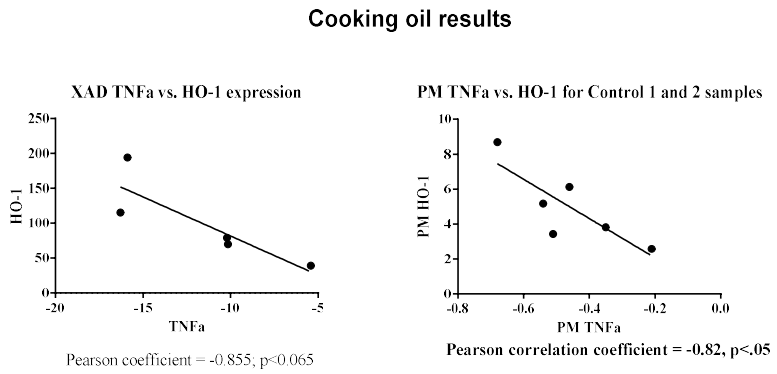
TNFα = 0.015*[Redox active metals] -0.011

HO-1 = 4.65*[WSOC] -0.41

The averaged TNFa response to the particle samples (expressed as LPS units) were compared to averaged redox active metal content for samples from the same fuels (Correlation coefficient was 0.95, with p<.05). Analogously, the HO-1 response with WSOC content of the sample with a correlation coefficient of 0.953 and p<.047)

Similar observations were made with samples from cooking oil smoke (figure 9). The chemical constituents of cooking oil smoke contain prooxidants and electrophiles but not necessarily the same compounds as those from engine exhaust. The vapor phase components induced HO-1 much more strongly than the particle phase but the relationship between the two protein markers was an inverse one with higher levels of HO-1 expression associated with greater suppression of TNFa expression.

Figure 9. Cellular responses to cooking oil particle and vapor phase samples.



Cells were exposed to the samples at fixed concentrations and the proteins measured by ELISA procedures. The negative values reflect the differences between the sample effect and that of a filter (PM) or the solvent (XAD) and are interpreted to reflect a net suppression of TNFa expression.

Chemical properties and cell responses

Using the available data, the potential for the DTT and GAPDH assays as predictors of the cellular response was assessed by determining Pearson correlation coefficients for the DTT values and the cell responses. We found positive correlations for DTT activity-based prooxidant content with particle based HO-1 (0.86; $p<.016$), TNFa (0.96; $p<.04$) for the biodiesel samples and HO-1 (0.905; $p<0.013$) for the cooking smoke samples. The vapor phase chemical reactivities did not correlate with either cell response. These results suggest that the prooxidant content of the particles could be predictors of cell responses but there is insufficient data to be conclusive.

Conclusions

The quantitative nature of the data obtained has provided the ability to compare and further characterize combustion based air pollutants from different locations, seasons and fuel sources. The results show that the analyzed samples contained common chemical reactivities and elicited similar biological activities but with quantitative differences. The major findings from the application of the assays are the following:

1. There are seasonal differences in the nature of ambient air samples which can affect the potential health effects. Specifically, the decrease in volatile organic species associated with the winter season may enhance the potential adverse effects of the particle phase.

2. The vapor phase with its semi volatile organic components has been largely ignored in studies of air pollution because of the focus on particulates. The results here show that the volatile fraction includes both prooxidants and electrophiles and reacts in the chemical and biological assays accordingly. The higher electrophile content observed may be responsible for adaptive responses associated with this fraction. It is possible however, that adaptation could result in suppression of the immune system resulting in a greater susceptibility to infections. Thus, the vapor phase of air pollution mixtures is clearly an important component of the exposome that should be monitored and studied.
3. There appears to be an inverse relationship between the inflammatory and adaptive responses by the cells upon exposure to the samples, with the vapor phase components more effective in promoting the adaptive response. One interpretation of this finding is that the vapor phase components reduce the inflammatory or potential adverse health effects of the particles. Thus, when assessing the health effects of air pollution mixtures, the combined effect of both particle and vapor phases need to be examined.
4. The relationship between the inflammatory and adaptive responses were discernable because of the quantitative nature of the assays performed and demonstrate the importance of quantitative data. However, cellular responses are variable so that values from separate experiments are often difficult to compare. To address this variability, we are now collecting data with selected agents to identify appropriate standards.

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From: Froines, John <jfroines@ucla.edu>
Sent: Thursday, August 25, 2016 12:33 PM
To: Jo Kay Ghosh
Subject: FW: relevant references
Attachments: Detailed summary for JF_NL_Asthma.docx; DEP_Ozone_Alexis N-2014.pdf; Outdoor air pollution_Balmes JR-2014_highlighted.pdf

Dear Jo. Here are more relevant referemces. I hope they are useful. The Balmes paper is particularly good.
John

The following attachment(s) were included with Comment Letter #19 submitted by Dr. John Froines. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachments, however, interested parties can obtain access at the links provided below:

Alexis, N. E. and C. Carlsten (2014). "Interplay of air pollution and asthma immunopathogenesis: a focused review of diesel exhaust and ozone." Int Immunopharmacol **23**(1): 347-355

http://www.sciencedirect.com/science/article/pii/S1567576914003233

Guarnieri, M. and J. R. Balmes (2014). "Outdoor air pollution and asthma." Lancet **383**(9928): 1581-1592.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60617-6/abstract

A hard copy of copyrighted material, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

Summary for JF

DEP, ozone, asthma

Alexis NE[1], Carlsten C[2]. *Interplay of air pollution and asthma immunopathogenesis: a focused review of diesel exhaust and ozone. Int Immunopharmacol. 2014 Nov;23(1):347-55.*

Diesel:
"In summary, research over recent decades suggests that diesel exhaust can enhance allergen-driven airway immunopathology, but the ability of diesel exhaust to do so appears highly dependent on a wide range of variables and the evidence is stronger for the exacerbation of an existing disease than for the development of a new disease. To the extent that this enhancement occurs, the augmentation of Th2-type immunity seems a common element, but a diversity of mechanisms have been implicated and our perspective regarding mechanisms is evolving rapidly in face of an explosion of basic knowledge regarding immunity and genetics."

Ozone:
"Although not all studies support the assertion that asthmatics (compared to non-asthmatics), have increased susceptibility to the deleterious effects of air pollution, several human and animal exposure studies, both past and recent, have shown that asthmatics have heightened immuno-inflammatory responses to air pollutants like PM2.5–10 [39] and ozone [40–43]. Several factors likely play a role in contributing toward the predisposition of asthmatics to the adverse health effects of ozone, but chief among them are constitutively altered innate immune function [44–46]; other factors may include depleted antioxidant defense capabilities [47]."

"In summary, there is mounting evidence that air pollutants such as diesel exhaust and ozone impact both inflammatory and immune responses in the airways of asthmatics. The interplay therefore between these air pollutants and asthma immunopathogenesis is an ongoing concern in terms of understanding how exposure to these agents can lead to worsening of disease. Key innate immune cells in the airways such as macrophages, monocytes, dendritic cells, eosinophils and neutrophils are adversely affected following exposure to diesel exhaust and ozone, and both pollutants have priming capabilities making exposure to subsequently inhaled allergens or pathogens more problematic for those with pre-existing airway disease. Adding to the issue is the fact that asthmatics may be pre-disposed to the deleterious effects of pollutants like ozone, having constitutively modified host defense functions and gene signatures. More research is needed to better understand the interplay between air pollution and asthma immunopathogenesis."

Guarnieri M[1], Balmes JR[2]. *Outdoor air pollution and asthma. Lancet. 2014 May 3;383(9928):1581-92.*

"In view of the burden of asthma attributed to outdoor air pollution, a better understanding of why asthmatic individuals are susceptible to this exposure should enable the design of effective preventive strategies. The idea that air pollution can cause exacerbations of pre-existing asthma is supported by an evidence base that has been accumulating for several decades,[7–10] but evidence has emerged that suggests air pollution might cause new onset asthma as well.[11–21]"

"Why are individuals with asthma so aff ected by exposure to air pollution? At the lower concentrations that are more typical in high-income countries, other mechanisms are probably in operation. Specific pollutants can induce airway inflammation (eg, ozone, nitrogen dioxide, and PM <2.5 μm in diameter [PM2.5])[23–28] and airway hyper-responsiveness (ozone and nitrogen dioxide),[23,29] two characteristic features of asthma. In addition, oxidative stress (a feature of severe asthma) has been associated with pollutant exposures (ozone, nitrogen dioxide, and PM2 · 5).[30–32] Therefore, exposure to these pollutants is unsurprisingly associated with exacerbations and possibly even the onset of asthma."

“A framework for how air pollution might contribute to the development and exacerbation of asthma proposed by the UK’s Committee on the Medical Effects of Air Pollutants identified four main mechanisms: oxidative stress and damage, airway remodelling, inflamatory pathways and immunological responses, and enhancement of respiratory sensitisation to aeroallergens (figure 2).[33] Variation in the genes that regulate these mechanisms could confer increased susceptibility to development of new-onset asthma or exacerbations of existing disease with exposure to air pollution.”

“Because the pollutants of interest, including TRAP, can cause oxidative stress, the ability of antioxidant defences to handle the increased load of reactive oxygen species generated in the lungs after exposure is an important determinant of risk for subsequent adverse effects. Specific polymorphisms in antioxidant enzyme genes, such as glutathione S-transferase genes, GSTM1 and GSTP1, can modify risk of asthmatic responses to pollutants[34,35] and these variants (GSTM1 null and GSTP1 Ile105Val) might also interact with a tumour necrosis factor (TNF) promoter variant (G-308A) that affects expression of TNF and hence the early infl amatory response.36 Additionally, neonatal rats are more prone to oxidative stress from PM exposure at least in part due to relative defi ciency of nuclear factor-like 2 (Nrf2).[37]”

Particulate Matter:

“The composition and size distribution of PM varies according to the source, whether it is natural or anthropogenic, and whether it is derived from combustion or not.[50] Transition metals, polycyclic aromatic hydrocarbons, and environmentally persistent free radicals are constituents of PM of special interest because of their potential to cause oxidative stress and many of the phenotypic changes associated with asthma. Additionally, PM frequently contains various immunogenic substances, such as fungal spores and pollen, which have been independently associated with exacerbation of asthma symptoms.[51,52]”

“Experimental exposure to PM results in oxidative stress, airway hyper-responsiveness, and airway remodelling, either alone or in combination with allergic sensitisation.[53] Short-term exposure to ambient PM2.5 and PM of diameter 2.5–10 μm in prospective cohorts of asthmatic children and adults has been associated with asthma symptoms, especially in children with allergic sensitisation.[54,55] Long-term exposure to PM is associated with poorly controlled asthma and decrements in lung function in children and adults.[30,56]”

Gases:

“In view of the central role of oxidative stress in asthma morbidity associated with air pollutants, oxidising gases continue to be an area of substantial research.”

“Responses to controlled exposure of short-term ozone and sulphur dioxide at relevant concentrations have been studied extensively. Ozone exposure results in airway inflammation, airway hyper-responsiveness, and decrements in lung function in healthy and asthmatic adults,[23] whereas sulphur dioxide causes more prominent bronchoconstriction, especially in asthmatic individuals (table 1).[68]”

“By contrast with the inconsistent experimental data on nitrogen dioxide, the body of observational data supporting its role in the exacerbation of asthma and asthma incidence continues to grow in breadth and consistency. Studies of asthmatic children and adults in the past 5 years have identified associations between nitrogen dioxide and symptoms of asthma,[54,72] reduced response to bronchodilators,[73] decrements in lung function,30 and exacerbation of asthma.[57,60,62] Notable, several studies have identified an increase in asthma incidence or prevalence associated with exposure to nitrogen dioxide.[11–15].”

“Although short-term exposure to ozone has been well documented as a cause of asthma exacerbation in adults and children,[58,78] whether long-term exposure can lead to new-onset asthma is somewhat less clear. Studies of adult-onset asthma have identifi ed an increased risk associated with ozone exposure, although this effect was restricted to male individuals.[79,80] In children, ozone has been associated with incident allergic sensitisation, a known risk factor for subsequent asthma, and prevalence of wheeze and

asthma as diagnosed by a doctor.[65,81] Studies of asthma incidence in children have identified an association with ozone, although the risk might be confined to heavily exposed, physically active children.[15,82] Taken together, the available evidence suggests that ozone might be a cause of new-onset asthma in some subgroups of children."

"Notably, the phase 3 ISAAC study, representing over 500,000 children and adolescents across five continents, identified a dose-response association between symptoms of asthma (ever asthma, current wheeze, and severe asthma symptoms) and self-reported exposure to truck traffic.[6] Effects of short-term ambient exposure to PM2.5, nitrogen oxides, and carbon monoxide were increased by exposure to higher than median modelled traffi c exposure, showing the strength of considering both regional air pollution and long-term TRAP exposure in studies of health effects.[95] A study[72] of two communities in Southern California estimated that reductions in traffic-related nitrogen dioxide and ozone to background levels would reduce bronchitic episodes in asthmatics by 36–70%. The London Low Emission Zone provides an opportunity to study the impact of reduced TRAP on asthma morbidity.[96] Collectively, these data suggest that TRAP exposure, especially in urban areas, has a tremendous effect on disease morbidity in individuals with asthma."

Risk modefiers:
"Young children with asthma have long been regarded as a group who are very susceptible to adverse effects from air pollution because of their developing lungs, immature metabolic pathways, high ventilation rates per bodyweight, and increased time exercising outdoors.[99,100]"

"Dietary factors can play a part in susceptibility to pollutant effects independent of socioeconomic status. The body of evidence on the protective eff ects of a diet high in fruits and vegetables and of antioxidant vitamin supplements is sufficient to support an important role for oxidative stress in the pathways by which outdoor air pollution adversely affects asthma.[109–111] Obesity might also increase susceptibility to the adverse effects of air pollution.[112–114]".

Clinical implications:
"Patients with asthma should ideally live at least 300 m from major roadways, especially those with heavy truck traffic. TRAP can exacerbate asthma,[10,120] but concentrations of motor vehicle emissions such as ultrafine PM and black carbon particles decrease substantially by 300 m.[121] In-vehicle exposure during commuting with open windows can also be very high.[122]"

From: Cho, Arthur <ACho@mednet.ucla.edu>
Sent: Thursday, August 25, 2016 4:19 PM
To: Jo Kay Ghosh
Subject: Commentary
Attachments: 160825 Commentry by AKC.docx

Hi Jo Kay
John Froines has suggested I send you my comments in a more formal commentary. Let me know if you have questions.
Best regards
Art Cho

Commentary by Arthur K. Cho

On the current status of air pollution research.

1. A recent review by Kelly and Fussell (1) summarized important issues in the status of current air pollution research. In it the authors indicated the following issues to be addressed in the future:
    a. Identify what it is in ambient PM that affects health—information that in turn will inform policy makers how best to legislate for cleaner air.
    b. A better understanding of exposure and health effects plus further progress in comparing and synthesizing data from existing studies is therefore needed before concluding that additional indicators (be they BC or UFPs) have a role in protecting public health more effectively than the targeting total PM mass
    c. To unravel the underlying biological basis of toxicity by identifying pathways that ultimately link pollution-induced pulmonary and systemic oxidative stress with an associated risk of cardiovascular and obstructive pulmonary diseases.
2. Comments:
    a. There have been many studies examining air pollution content which have demonstrated, for example, that metals and quinones are associated with the adverse effects attributed to PM. What is lacking is a methodical and quantitative assessment of the relationship between these measurements and biological effect. For example, the studies that have examined the toxicity of air samples have not "resynthesized" the toxic components, i.e., have not examined the toxicity of the proposed toxins in studies that used the concentrations of the proposed metal(s) found in PM and compared the effects with those of the actual PM sample.
    b. Perhaps a study with better coordination between experimental and epidemiological studies is needed, i.e., a study in which quantitative air pollutant data is collected in sites at which epidemiological studies were performed. The SC PM center performed such a study in collaboration with the Children's Health Study group at USC but the results were too preliminary and lacked a better evaluation of potential toxicity. This study needs to be repeated with different experimental measurements.
    c. Investigators are addressing this issue of the biological basis for the effects with in vivo and in vitro studies using experimental animals. Jesus Araujo at UCLA is one such investigator of whom I am aware, but there are many others.
3. Ovrevik et al., (2) have reviewed findings on the proinflammatory responses to PM and raise the very important point that the causal components may not be pro-oxidants but instead other chemical species that indirectly increase the oxidative state of cells.
    a. Comment: There is evidence that electrophiles can induce an oxidative stress state by depleting cellular reducing agents such as glutathione, hydrogen sulfide and other polysulfides. Electrophilic metals such as zinc as well as organics can affect cells in this way.
4. On Carbon monoxide (3)

a. Comment: Although commonly thought of as a hemoglobin binding toxin, carbon monoxide is also a so-called gasotransmitter, a term used to describe small molecules such as CO, NO and H_2S which are intracellular signaling molecules. The compound is generated by hemeoxygenase-1 in the degradation of heme to carbon monoxide, bilirubin and water. The CO generated is an effective antioxidant acting in part by binding to heme proteins such as cyclooxygenases that generate inflammatory cytokines. Thus, CO toxicity is clearly concentration dependent and at low concentrations is beneficial to the cell.

5. My thoughts on the current needs:
    a. As I stated in my report on quantitative measurements in air pollution research, a systematic collection and analysis of air samples is needed in which the results can be used to compare and assess the relationships between the chemical and biological findings. Such a study is needed in the Los Angeles Basin which has communities whose atmosphere could be distinct. For example, the importance of vanadium and nickel as components of ship engine exhaust and as exudates of oil refineries can be examined by collection of air samples near the Los Angeles Harbor, Carson and El Segundo as sources to be compared with air samples collected in San Bernardino as a photochemically generated pollutant mixture and Commerce as a vehicle exhaust source.
    b. In such a study, however, simple toxicity studies are not likely to be fruitful; a careful fractionation based study of the samples is needed to address the issue of the total particle as opposed to the individual metals. There is evidence to suggest that the metals have greater bioavailability because they are complexed with organic compounds; the resulting metal-organic complex may have greater intracellular access. Accordingly, studies examining the role of such complexes are needed.
    c. Finally, as we now understand that any concentration of air pollution has adverse health effects, we must also recognize that while controls may decrease pollutants in our atmosphere, they will be with us for the foreseeable future. Perhaps we should be thinking about ameliorating the exposure we know to exist by providing the general public with knowledge and sources of antioxidants such as flavonoids and garlic extracts, the latter being a source of the anti-inflammatory hydrogen sulfide.

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2. Ovrevik J, Refsnes M, Lag M, Holme JA, Schwarze PE. 2015. Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. *Biomolecules* 5:1399-440
3. Otterbein LE, Bach FH, Alam J, Soares M, Tao Lu H, et al. 2000. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. *Nat Med* 6:422-8

From: Bill <BillLaMarr@msn.com>
Sent: Friday, August 26, 2016 3:14 PM
To: Jo Kay Ghosh
Subject: COMMENT LETTER-2016 AQMP-APPENDIX I HEALTH EFFECTS
Attachments: comment Ltr-2016AQMP.APX-I-08262016.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dr. Ghosh –

Per your request, attached is my comment letter on Appendix I of the 2016 AQMP. If you have any questions regarding the, se comments, please do not hesitate to contact me to discuss.

I want to thank you, and the Home Rule Advisory Group, for selecting me once again to serve on this important council.

Sincerely,

Bill La Marr
Executive Director
California Small Business Alliance

CALIFORNIA Small Business Alliance

Dedicated to Environmental Progress and Economic Growth

August 26, 2016

Jo Kay Ghosh, PhD
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
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Subject: Comments on Appendix I Draft 2016 A3ir Quality Management Plan

Dear Dr. Ghosh:

I appreciate the opportunity to represent the Home Rule Advisory Group (HRAG) on the Advisory Council and submitting comments on the draft Health Effects Appendix. My comments are focused primarily on Ozone (O_3, and $PM_{2.5}$, as they are set forth in Appendix I of the 2016 Draft Air Quality Management Plan (AQMP). Speaking on behalf of the HRAG, we understand that the AQMP promises to have significant impacts on all who are participating in the process applaud the time and effort required to produce a science-based and economically feasible plan.

Following are my comments:

Notwithstanding Staff's admonition for the Council to focus our review and comments solely on health effects, as reported in Appendix I, I found it too much of a challenge to ignore such important elements as the cost and practicality of basing the likelihood of meeting the emission reduction commitments in the AQMP based solely on the findings in the draft Appendix. Recognizing that the total implementation costs of the Draft 2016 AQMP are projected to be:

SCAQMD Stationary Source	$ 8.0	(billions of 2015 dollars)
SCAQMD Mobile Sources	$ 1.5	(billions of 2015 dollars)
CARB Mobile Source	$28.7	(billions of 2015 dollars)
Total:		$38.2 (billions of 2015 dollars)

20-1

and accepting the fact that the District and the sources it regulates will be held accountable for achieving the emission reductions commitments associated with these costs, I strongly urge Staff to seriously consider these constructive remarks and recommendations:

- **HEALTH EFFECTS OF AIR POLLUTION**

  - In the recent three AQMPs (2007, 2012, 2016), as well as the 1997 AQMP, Staff has asserted that ambient air pollution is a major cause of public health concern. And most would agree. It is confusing - to me at least - that while Staff has added

Table I-1 in the current Appendix I, to support the addition of a few more recent review articles discussing the health impacts of Ozone, $PM_{2.5}$, NO_2, and SO_2, on the Southern California population, that the weight of evidence descriptors for causal determination of [adverse] health effects seems to call in to question the reliability of the findings and conclusions reported in these research papers. For example, most of the determinations made by U.S. EPA regarding the causality of air pollution health effects, is that there is "**likely** to be a causal relationship," "**suggestive** of a causal relationship," "**not likely** to be a causal relationship" or "**inadequate to infer** a causal relationship." On its face, the degree to which important uncertainties seem to permeate the research cited in Appendix I, strongly suggests that **more definitive research is urgently needed, especially in an AQMP that is projected to cost regulated sources $38.2 billion dollars, reduce health impacts, and improve air quality.**

20-1 Con't

- **OZONE**

  - In the process of updating Appendix I, I commend the Staff for including EPA's lowering the 8-hour ozone standard to 0.070 ppm.
  - In reviewing Table I-2, Summary of Causal Determinations for Short-Term Exposures to Ozone, I observed similar uncertainty in the assignment of causal determinations for the following health categories:

    - ✓ Cardiovascular Effects – **Likely** to be a causal relationship
    - ✓ Central Nervous System Effects – **Suggestive** of a causal relationship
    - ✓ Effects on Liver and Xenobiotic Metabolism – **Inadequate** to infer a causal relationship
    - ✓ Effects on Cutaneous and Ocular Tissues – **Inadequate** to infer a causal relationship, and most important……
    - ✓ Mortality – **Likely** to be a causal relationship

    20-2

    Again, it strongly suggests that **more research is urgently needed,** especially in an AQMP that is projected to cost regulated sources $38.2 billion dollars, reduce health impacts, and improve air quality.

  - In reviewing Table I-3, Summary of Causal Determinations for Long-Term Exposures to Ozone, I observed even more **uncertainty in the assignment of causal determinations** for the following health categories:

    - ✓ Respiratory Effects – **Likely** to be a causal relationship
    - ✓ Cardiovascular Effects – **Suggestive** of a causal relationship
    - ✓ Reproductive and Developmental Effects – **Suggestive** of a causal relationship
    - ✓ Central Nervous System Effects – **Suggestive** of a causal relationship

Once again, it strongly suggests that **more research is urgently needed**, especially in an AQMP that is projected to cost regulated sources $38.2 billion dollars, reduce health impacts, and improve air quality.

20-2 Con't

- Finally, among the **scientific studies** cited in the paragraph entitled: Long-Term Effects of Ozone; many of which or all were **conducted at locations other than California/Southern California**, we were glad to see an almost imperceptible reference to smoking as one of a number of behavioral and demographic factors accounting for increased risk of all-cause, cardiovascular, and respiratory mortality. Curiously, **the causal relationship between smoking and morbidity and mortality are far more conclusive than the causal relationship between ozone and the health categories mentioned previously**.

  According to the CENTER FOR DISEASE CONTROL:

  20-3

  - ✓ 16 million Americans are living with a disease caused by smoking.
  - ✓ For every person who dies because of smoking, at least 30 people live with a serious smoking-related illness.
  - ✓ Smoking causes cancer, heart disease, stroke, lung diseases, diabetes, and chronic obstructive pulmonary disease.
  - ✓ **Cigarettes are responsible for more than 480,000 deaths per year in the U.S.**
  - ✓ **42,000 people die annually from second-hand smoke.**
  - ✓ Smokers die, on average, 10 years earlier than non-smokers.

  (CDC Statistics as of 2015)

- **PARTICULATE MATTER**

  - I commend Staff for acknowledging that in spite of U.S. EPA setting standards for $PM_{2.5}$ in 1997, lowering them in 2006 to 35 ug/m3 for a 24-hour average and reaffirming 15 ug/m3 for annual average standard, and again revising the average annual standard in 2012 to 12.0 ug/m3, **there continues to be considerable controversy and debate surrounding the review of particulate matter health effects and the consideration of ambient air quality standards**. Staff also mentions that: "*numerous studies have been published and some of the key studies were closely scrutinized and the data reanalyzed by additional investigators.*" Staff goes on to write: "*The reanalyses confirmed the original findings, and there are now additional data confirming and extending the range of the adverse health effects of* $PM_{2.5}$ *exposures.*"

    20-4

- **SHORT-TERM EXPOSURE EFFECTS OF PM**

  - While we commend Staff for citing some recent epidemiological studies on morbidity and mortality, on Page I-19 of the Appendix, they appear to be on PM10, and involve populations in Europe, Asia, and South America. Apparently

there was also a study "*.... involving communities across the U.S.*," but **it isn't clear that any of these communities were located in Southern California, and that the findings are applicable to our local population**.

20-4 Con't

- On Pages I-20 – I-21 of the Appendix, Staff cites a National Morbidity, Mortality, and Air Pollution study of 20 of the largest U.S. cities. It is reported that the findings determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 ug/m3 increase in PM10 (Samet et al 2000a). A further reading of the conclusions reached by Samet reveals that there were a number of confounding findings with regard to the extent by which PM10 contributes to mortality rates. Samet attributes some of the confusion to a software package with inappropriate default settings. Curiously, in a reanalysis of the 90 city study (Dominici et al 2002L Health Effects Institute 2003), where the estimates were recalculated, **the estimate changed from 0.41% increase in mortality for a 10 ug/m3 increase in PM10 to a 0.27% increase.**

20-5

- On Page I-23 of the Appendix, Staff writes that: "*The relative importance of both $PM_{2.5}$ and PM10-2.5 may vary in different regions depending on the relative concentrations and components, which can also vary by season.*" "*A major knowledge gap is the relative paucity of direct measurements of PM2.5-10.*" To their credit, Staff goes on to write: "***More research is needed better access the relative effects of coarse (PM10-2.5) fractions of particulate matter.***" This is exactly what we are advocating throughout these comments.

20-6

- Finally, on Page I-25 of the Appendix, Staff writes: "*Some studies have examined the health effects of short-term exposures to specific PM constituents and sources (Lippman 2014; Basagana et al 2015; Atkinson et al 2016). While there is some evidence suggesting possible links with specific constituents or sources, such as diesel exhaust, sulfates (related to coal combustion), and certain metals,* ***the U.S. EPA determined there were not enough studies evaluating the short-term constituents of source-specific exposures at the time of previous Integrated Science Assessment to be able to make a causal determination*** **(U.S. EPA 2009)."**

LONG-TERM PARTICULATE MATTER EXPOSURES AND MORTALITY

- Our review of this part of Appendix I revealed more controversy and debate over the association of and exposures to $PM_{2.5}$ (Page I-26). **While a number of studies are cited, and a few claim to include some Southern California cities, most studies seem to involve cohorts in other regions of the U.S, like the Harvard Six Cities Study, and there seems to be an abundance of strong scientific opinions that contradict each other.**

20-7

SUMMARY - PARTICULATE MATTER HEALTH EFFECTS

- Our reading of this segment of Appendix I (Page I-41), suggests that **Staff may be experiencing some of the frustration that those in the business community have long felt**. While **Staff seems to favor the body of epidemiological studies that point to PM as causing thousands of deaths per year, and thousands more hospitalizations for a variety of diseases, they do concede that**

20-8

coexisting pollutants contribute to increases in cases of morbidity and mortality in the community. This should be another clarion call for more and balanced research before the business community is presented with a bill for $38.2 billion dollars.which

20-8 Con't

At the meeting of the Advisory Council, Staff presented us with some materials from **Dr. James E. Enstrom, a renowned and respected epidemiologist. We also had the opportunity to hear some of his theories and conclusions about the health effects of PM which contradict those made by Staff.** And while his remarks were made in haste, due to time constraints imposed by the Staff, it was clear to me at least that **his research has been acknowledged by scores of reputable scientists across the U.S**. In view of the controversy that exists over the health effects of PM, and the **highly suspicious methodology that Staff insists on using to factor the value of a human life and the price that society is willing to pay to avoid cancer, I strongly recommend that an opportunity be given for all stakeholders to actually hear and evaluate the scientific findings by Dr. Enstrom and some other scientists before the 2016 AQMP is adopted.**

20-9

To add emphasis to this request**, I have attached a comment letter by Jonathan M. Samet, MD, MS - Professor and Flora L. Thornton Chair, Dept. of Preventive Medicine, Keck School of Medicine of USC, and Director, USC Institute for Global Health**. The letter was written in response to a request by Dr. Jean Ospital, former AQMD Health Effects Officer, wherein Dr. Samet was invited to critique Appendix I of the 2012 AQMP. To avoid any confusion, I have attached only the letter and transmittal form. Originally, Dr. Samet attached his comments on a complete copy of the Appendix. I have assumed that Staff has a copy of the complete document on file. If not, I will be happy to transmit it to you.

20-10

You will note that while **Dr. Samet agrees that coverage of criteria pollutants, ultrafine particulates, and toxic air contaminants are appropriate to the development of the AQMP, he questions the degree to which the District is able to act impartially when presenting ALL scientific conclusions.**

In closing, I want to express my sincere appreciation for inviting me to serve once again on the AQMP Advisory Council, and comment on this important Appendix to the 2016 AQMP

Sincerely,

Bill La Marr
Executive Director
California Small Business Alliance

Keck School of Medicine of USC

Department of Preventive Medicine
Jonathan M. Samet, MD, MS
Professor and Flora L. Thornton Chair
Director, USC Institute of Global Health

September 25, 2012

Jean Ospital, MPH, PhD
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, CA 91765

Dear Jean,

As you requested, I attach comments concerning the Health Effects Appendix of the District's draft Air Quality Management Plan. Please do not hesitate to contact me if you have questions with regard to these comments.

Yours sincerely,

Jonathan M. Samet, MD, MS
Professor and Flora L. Thornton Chair
Department of Preventive Medicine
Director, USC Institute for Global Health

University of Southern California
2001 N. Soto St., SSB 330A, MC 9239, California 90089-9239 • Tel: 323 865 0803 • Fax: 323 865 0854

Review: Health Effects Appendix
South Coast Air Quality Management District
Jonathan M. Samet, MD, MS

General Comments:

This relatively brief document provides an overview of the health effects of various air pollutants, giving emphasis to pollution by airborne particulate matter. The document also covers other "criteria pollutants" as well as ultrafine particulate matter and toxic air contaminants. This range of topics is appropriate to the development of an Air Quality Management Plan.

As presented, the document represents a summary, and an apparent updating of an earlier report. It is necessarily selective in its coverage and relies to an extent on the review documents prepared by the US Environmental Protection Agency for the "criteria" pollutants. I have the following general comments:

- Preparation of reviews of the health effects of air pollution is a daunting task, given the extensive data available and its continuing and rapid accrual. The South Coast Air Quality Management District is not well positioned to prepare a comprehensive and up-to-date review. Consequently, there are deficiencies of this review related to its scope and timeliness. The basis for the document's development is provided in the last paragraph on page I-2. While the statement is clear, the methods are not fully transparent. In particular, several older reviews are mentioned, along with more recent documents from the US Environmental Protection Agency and several prepared by the California EPA. I suggest that more careful attention be given to describing the basis for this review and to consideration of its methodology. For example, given the complexity and scope of the literature, the developers of the review might rely solely on summary documents or to also summarize documents and research published based on studies in California. In the present version, I could not readily identify why particular studies were included.

- I understand that the South Coast Air Quality Management District is required to provide a review in support of its air quality management plan. As stated, the California Health and Safety Code Section 40471(b) requires the preparation of report on "the health impacts of particulate matter in the South Coast Air Basin (SCAB) in conjunction with the preparation of the Air Quality Management Plan revisions." This document does not directly address the health impacts, if some quantification of burden is implicit in the requirement. The identification of health effects and selected of examples of risks from the literature represents a starting point in estimating the health impact. As noted in my next comment, the review might have establishing the relevance of the broad body of evidence to the South Coast Air Quality Management District as one objective.

- There is an extensive literature on airborne particulate matter and health, as well as on the risks of various other air pollutants. One question that might be reasonably addressed in this report is the generalizability of findings from this broad literature to California. Here, a careful review of studies in California might be of benefit. Additionally, considerations might be given to the mixture of pollutants in the South Coast Air Basin to support conclusions about the generalizability of findings.

- The document needs further editing in part to improve clarity and in part to bring in some of the most recent and relevant references. Additionally, if the most recent US EPA documents are to be used as the basis of the report, some updating is needed.

Specific comments:

See attached.

there was also a study "*.... involving communities across the U.S.*," but **it isn't clear that any of these communities were located in Southern California, and that the findings are applicable to our local population**.

- On Pages I-20 – I-21 of the Appendix, Staff cites a National Morbidity, Mortality, and Air Pollution study of 20 of the largest U.S. cities. It is reported that the findings determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 ug/m3 increase in PM10 (Samet et al 2000a). A further reading of the conclusions reached by Samet reveals that there were a number of confounding findings with regard to the extent by which PM10 contributes to mortality rates. Samet attributes some of the confusion to a software package with inappropriate default settings. Curiously, in a reanalysis of the 90 city study (Dominici et al 2002L Health Effects Institute 2003), where the estimates were recalculated, **the estimate changed from 0.41% increase in mortality for a 10 ug/m3 increase in PM10 to a 0.27% increase.**
- On Page I-23 of the Appendix, Staff writes that: "*The relative importance of both $PM_{2.5}$ and PM10-2.5 may vary in different regions depending on the relative concentrations and components, which can also vary by season.*" "*A major knowledge gap is the relative paucity of direct measurements of PM2.5-10.*" To their credit, Staff goes on to write: "***More research is needed better access the relative effects of coarse (PM10-2.5) fractions of particulate matter.***" This is exactly what we are advocating throughout these comments.

- Finally, on Page I-25 of the Appendix, Staff writes: "*Some studies have examined the health effects of short-term exposures to specific PM constituents and sources (Lippman 2014; Basagana et al 2015; Atkinson et al 2016). While there is some evidence suggesting possible links with specific constituents or sources, such as diesel exhaust, sulfates (related to coal combustion), and certain metals,* ***the U.S. EPA determined there were not enough studies evaluating the short-term constituents of source-specific exposures at the time of previous Integrated Science Assessment to be able to make a causal determination*** **(U.S. EPA 2009)."**

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Professor and Flora L. Thornton Chair
Department of Preventive Medicine
Director, USC Institute for Global Health

University of Southern California
2001 N. Soto St., SSB 330A, MC 9239, California 90089-9239 • Tel: 323 865 0803 • Fax: 323 865 0854

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South Coast Air Quality Management District
Jonathan M. Samet, MD, MS

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Specific comments:

See attached.

Afif El-Hasan, MD
513 E. 1st St., Suite B
Tustin, CA 92780

August 26, 2016

Dear AQMP committee,

I am in full support of the data as presented in the 2016 AQMP, Appendix 1, and I agree with the conclusions reached based on the accrual of the different studies related to air pollution and its effects on human health. The data presented in this appendix confirms the need to comply with State and Federal guidelines for Air Quality.

Sincerely,

Afif El-Hasan, MD
State Board Member
American Lung Association of California

From: Froines, John <jfroines@ucla.edu>
Sent: Sunday, August 28, 2016 9:40 AM
To: Jo Kay Ghosh
Subject: FW: relevant references
Attachments: Ref summary_Lung Cancer.doc; PM_Lung Ca_Hamra GB-2014_highlighted.pdf; PM2.5 _Lung Ca_Eckel SP-2016.pdf; PM2.5_Lung Ca_Gharibvand L-2016.pdf; PM Ctr mouse asthma refs.doc; UCLA_Mobile lab_UFP_Asthma_Ning Li.pdf; UCLA_PM Ctr_UFP_adjuvant_Ning Li.pdf; UCLA_PM Ctr_UFP_adjuvant_Proteomics_Kang X.pdf

Dearr Jo: Attached are some additional references relevant to air pollution. I hope you find them useful.
John

The following attachment(s) were included with Comment Letter #23 submitted by Dr. John Froines. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachments, however, interested parties can obtain access at the links provided below:

Hamra, G. B., N. Guha, A. Cohen, F. Laden, O. Raaschou-Nielsen, J. M. Samet, P. Vineis, F. Forastiere, P. Saldiva, T. Yorifuji and D. Loomis (2014). "Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis." Environ Health Perspect **122**(9): 906-911.

http://dx.doi.org/10.1289/ehp.1408092

Eckel, S. P., M. Cockburn, Y. H. Shu, H. Deng, F. W. Lurmann, L. Liu and F. D. Gilliland (2016). "Air pollution affects lung cancer survival." Thorax **71**(10): 891-898.

http://thorax.bmj.com/cgi/pmidlookup?view=long&pmid=27491839

Gharibvand, L., D. Shavlik, M. Ghamsary, W. L. Beeson, S. Soret, R. Knutsen and S. F. Knutsen (2016). "The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study." Environ Health Perspect.

http://dx.doi.org/10.1289/EHP124

Li, N., J. R. Harkema, R. P. Lewandowski, M. Wang, L. A. Bramble, G. R. Gookin, Z. Ning, M. T. Kleinman, C. Sioutas and A. E. Nel (2010). "Ambient ultrafine particles provide a strong adjuvant effect in the secondary immune response: implication for traffic-related asthma flares." Am J Physiol Lung Cell Mol Physiol **299**(3): L374-383.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951067/

Li, N., M. Wang, L. A. Bramble, D. A. Schmitz, J. J. Schauer, C. Sioutas, J. R. Harkema and A. E. Nel (2009). "The adjuvant effect of ambient particulate matter is closely reflected by the particulate oxidant potential." Environ Health Perspect **117**(7): 1116-1123.

http://dx.doi.org/10.1289/ehp.0800319

Kang, X., N. Li, M. Wang, P. Boontheung, C. Sioutas, J. R. Harkema, L. A. Bramble, A. E. Nel and J. A. Loo (2010). "Adjuvant effects of ambient particulate matter monitored by proteomics of bronchoalveolar lavage fluid." Proteomics **10**(3): 520-531.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021977/

A hard copy of copyrighted material, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

Animal studies on the adjuvant effect of ultrafine PM on asthma (from UCLA PM Center)

Kang X[1], Li N, Wang M, Boontheung P, Sioutas C, Harkema JR, Bramble LA, Nel AE, Loo JA. Adjuvant effects of ambient particulate matter monitored by proteomics of bronchoalveolar lavage fluid. Proteomics. 2010 Feb;10(3):520-31.

Ambient particulate matter (PM) from air pollution is associated with exacerbation of asthma. The immunological basis for the adjuvant effects of PM is still not well understood. The generation of ROS and the resulting oxidative stress has been identified as one of the major mechanisms. Using a new intranasal sensitization model in which ambient PM is used as an adjuvant to enhance allergic inflammation (Li et al., Environ. Health Perspect. 2009, 117, 1116-1123), a proteomics approach was applied to study the adjuvant effects of ambient PM. The enhanced in vivo adjuvant effect of ultrafine particles correlates with a higher in vitro oxidant potential and a higher content of redox-cycling organic chemicals. Bronchoalveolar lavage fluid proteins from normal and sensitized mice were resolved by 2-DE, and identified by MS. Polymeric immunoglobulin receptor, complement C3, neutrophil gelatinase-associated lipocalin, chitinase 3-like protein 3, chitinase 3-like protein 4, and acidic mammalian chitinase demonstrated significantly enhanced up-regulation by UFP with a polycyclic aromatic hydrocarbon content and a higher oxidant potential. These proteins may be the important specific elements targeted by PM in air pollution through the ability to generate ROS in the immune system, and may be involved in allergen sensitization and asthma pathogenesis.
PMID: 20029843

Li N[1], Wang M, Bramble LA, Schmitz DA, Schauer JJ, Sioutas C, Harkema JR, Nel AE. The adjuvant effect of ambient particulate matter is closely reflected by the particulate oxidant potential. Environ Health Perspect. 2009 Jul;117(7):1116-23.

BACKGROUND:
It has been demonstrated that ambient particulate matter (PM) can act as an adjuvant for allergic sensitization. Redox-active organic chemicals on the particle surface play an important role in PM adverse health effects and may determine the adjuvant effect of different particle types according to their potential to perturb redox equilibrium in the immune system.
OBJECTIVES:
We determined whether the adjuvant effect of ambient fine particles versus ultrafine particles (UFPs) is correlated to their prooxidant potential.
METHODS:
We have established an intranasal sensitization model that uses ambient PM as a potential adjuvant for sensitization to ovalbumin (OVA), which enhances the capacity for secondary OVA challenge to induce allergic airway inflammation.
RESULTS:
UFPs with a greater polycyclic aromatic hydrocarbon (PAH) content and higher oxidant potential enhanced OVA sensitization more readily than did fine particles. This manifests as enhanced allergic inflammation upon secondary OVA challenge, leading to eosinophilic inflammation and mucoid hyperplasia starting at the nasal turbinates all the way down to the small pulmonary airways. The thiol antioxidant N-acetyl cysteine was able to suppress some of these sensitization events.
CONCLUSIONS:
The adjuvant effects of ambient UFP is determined by their oxidant potential, which likely plays a role in changing the redox equilibrium in the mucosal immune system.
PMID: 19654922

Li N[1], Harkema JR, Lewandowski RP, Wang M, Bramble LA, Gookin GR, Ning Z, Kleinman MT, Sioutas C, Nel AE. Ambient ultrafine particles provide a strong adjuvant effect in the secondary immune response: implication for traffic-related asthma flares. Am J Physiol Lung Cell Mol Physiol. 2010 Sep;299(3):L374-83.

We have previously demonstrated that intranasal administration of ambient ultrafine particles (UFP) acts as an adjuvant for primary allergic sensitization to ovalbumin (OVA) in Balb/c mice. It is important to find out whether inhaled UFP exert the same effect on the secondary immune response as a way of explaining asthma flares in already-sensitized individuals due to traffic exposure near a freeway. The objective of this study is to determine whether inhalation exposure to ambient UFP near an urban freeway could enhance the secondary immune response to OVA in already-sensitized mice. Prior OVA-sensitized animals were exposed to concentrated ambient UFP at the time of secondary OVA challenge in our mobile animal laboratory in Los Angeles. OVA-specific antibody production, airway morphometry, allergic airway inflammation, cytokine gene expression, and oxidative stress marker were assessed. As few as five ambient UFP exposures were sufficient to promote the OVA recall immune response, including generating allergic airway inflammation in smaller and more distal airways compared with the adjuvant effect of intranasally instilled UFP on the primary immune response. The secondary immune response was characterized by the T helper 2 and IL-17 cytokine gene expression in the lung. In summary, our results demonstrated that inhalation of prooxidative ambient UFP could effectively boost the secondary immune response to an experimental allergen, indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized subjects.
PMID: 20562226

Summary: Lung cancer

Ghassan B. Hamra et al, Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, Environ Health Perspect, 122:906-911, 2014

"Outdoor air pollution is a complex mixture containing a number of known carcinogens and has been associated with increased lung cancer risk in many studies over the past 50 years. Past reviews of the body of evidence regarding outdoor and household air pollution indicated that both were associated with lung cancer risk; specifically, exposures to increased levels of particles, as well as other indices of air pollution, were associated with increased lung cancer risk."

"The International Agency for Research on Cancer (IARC) recently concluded that exposure to outdoor air pollution and to particulate matter (PM) in outdoor air is carcinogenic to humans (IARC Group 1) and causes lung cancer (IARC, in press; Loomis et al. 2013)."

"We conducted meta-analyses of the relationship between exposure to ambient PM and lung cancer incidence and mortality. Meta estimates combine incidence and mortality studies due to the high fatality rate among incident lung cancers. These quantitative analyses complement the qualitative classification of the evidence by the Monograph 109 Working Group (IARC, in press). Most of the data were obtained from cohort studies, and our analytical results are similar across diverse study populations, potential confounders considered, as well as exposure assessment methods; this consistency supports the IARC Working Group's conclusion that PM from outdoor air pollution is a Group 1 carcinogen and causes lung cancer. Air pollution is ubiquitous, and all populations are exposed to it at some level, albeit with considerable variation between the most and the least polluted areas (Brauer et al. 2012). Thus, these results are important for policy makers and public health practitioners across the world."

"In this analysis, we focused attention on PM2.5 and PM10, which are prominent components of the ambient air pollution mixture. Of course, PM10 includes the PM2.5 size fraction; however, these particle size groups are believed to differ in regard to human health effects. PM2.5 includes a higher proportion of mutagenic species (Buschini et al. 2001; Valavanidis et al. 2008), many of which are products of combustion (Brauer et al. 2001). Further, smaller particles penetrate more deeply into the lung and are more likely to be retained (Stuart 1976). On the other hand, the coarse fraction of the PM10-size group consists mainly of minerals and biologic materials (Valavanidis et al. 2008). Thus, PM2.5 is generally believed to be most relevant to health effects, including cancer."

"**Conclusion: "**The results of these analyses, and the decision of the IARC Working Group to classify outdoor air pollution as a Group 1 carcinogen, further justify efforts to reduce exposures to air pollutants, which can arise from many sources. The Global Burden of Disease collaboration estimated that approximately 3.22 million deaths were caused by exposure to air pollution in 2010, an increase from 2.91 million deaths attributed to air pollution in 1990 (Lim et al. 2012). Cancers of the trachea, bronchus, or lung represent approximately 7% of total mortality attributable to PM2.5 in 2010. The results of the meta analysis provided here could be useful for better quantifying the burden of lung cancer associated with air pollution. The Group I classification raises questions regarding individual components in the air pollution mixture regarding, for example, the carcinogenic potential of each component as well as through what pathways they may contribute to cancer risk."

Gharibvand L*[1], *Shavlik D*[2], *Ghamsary M*[3], *Beeson WL*[1,2], *Soret S*[3], *Knutsen R*[1,2], *Knutsen SF*[1,2]. ***The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study. Environ Health Perspect. 2016 Aug 12. [Epub ahead of print]

"**BACKGROUND:**
There is a positive association between ambient fine particulate matter ($PM_{2.5}$) and incidence and mortality of *lung cancer* (LC), but few studies have assessed the relationship between ambient $PM_{2.5}$ and LC among never smokers."

"**OBJECTIVES:**
To assess the association between $PM_{2.5}$ and risk of LC using the Adventist Health and Smog Study-2 (AHSMOG-2), a cohort of health conscious non-smokers where 81% have never smoked. **METHODS:** A total of ***80,285*** AHSMOG-2 subjects were followed for ***an average of 7.5 years*** with respect to incident LC identified through linkage with U.S. state cancer registries. Estimates of ambient air pollution levels at subjects' residences were obtained for 2000 and 2001, the years immediately prior to study start."

"**RESULTS:**
A total of 250 incident LC cases occurred during 598,927 person-years of follow-up. For each 10-$\mu g/m^3$ increment in $PM_{2.5}$, adjusted hazard ratio (HR) with 95% confidence interval (CI) for LC incidence was 1.43 (95% CI: 1.11, 1.84) in the two-pollutant multivariable model with O_3. Among those who spent more than 1 hr/day outdoors or who had lived 5 or more years at their enrollment address, the HR was 1.68 (95% CI: 1.28, 2.22) and 1.54 (95% CI: 1.17, 2.04), respectively."

"**CONCLUSION:**
Increased risk estimates of LC were observed for each 10-$\mu g/m^3$ increment in ambient $PM_{2.5}$ concentration. The estimate was higher among those with longer residence at enrollment address and those who spent more than 1 hr/day outdoors."
PMID: 27519054

Eckel SP*[1], *Cockburn M*[1], *Shu YH*[2], *Deng H*[1], *Lurmann FW*[3], *Liu L*[1], *Gilliland FD*[1]. ***Air pollution affects lung cancer survival. Thorax. 2016 Aug 4. pii: thoraxjnl-2015-207927.

"**RATIONALE**
Exposure to ambient air pollutants has been associated with increased lung cancer incidence and mortality, but due to the high case fatality rate, little is known about the impacts of air pollution exposures on survival after diagnosis. This study aimed to determine whether ambient air pollutant exposures are associated with the survival of patients with lung cancer."

"**METHODS**
Participants were 352,053 patients with newly diagnosed lung cancer during 1988-2009 in California, ascertained by the California Cancer Registry. Average residential ambient air pollutant concentrations were estimated for each participant's follow-up period. Cox proportional hazards models were used to estimate HRs relating air pollutant exposures to all-cause mortality overall and stratified by stage (localised only, regional and distant site) and histology (squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma and others) at diagnosis, adjusting for potential individual and area-level confounders."

"**RESULTS**
Adjusting for histology and other potential confounders, the HRs associated with 1 SD increases in NO_2, O_3, PM_{10}, $PM_{2.5}$ for patients with localised stage at diagnosis were 1.30 (95% CI 1.28 to 1.32), 1.04 (95%

CI 1.02 to 1.05), 1.26 (95% CI 1.25 to 1.28) and 1.38 (95% CI 1.35 to 1.41), respectively. Adjusted HRs were smaller in later stages and varied by histological type within stage ($p<0.01$, except O_3). The largest associations were for patients with early-stage non-small cell cancers, particularly adenocarcinomas."

"**CONCLUSIONS**
These epidemiological findings support the hypothesis that air pollution exposures after lung cancer diagnosis shorten survival. Future studies should evaluate the impacts of exposure reduction."
PMID: 27491839

From: StanYoung <genetree@bellsouth.net>
Sent: Tuesday, September 6, 2016 5:44 AM
To: avol@usc.edu; Rob Scot McConnell; Jo Kay Ghosh; alovera@aqmd.gov
Cc: Ben Benoit (GBM); Judith Mitchell (GBM); Duncan Campbell Thomas; Juliet Shaffer; heejung bang; Jessica Utts; dmrocke@ucdavis.edu; ywu@stat.ucla.edu; Robert Obenchain; Wyzga, Ron; Carlos Dobkin; Paddock, Susan
Subject: Air quality and mortality in South Coast Air Basin
Attachments: Young 2016 NAS Presentation Slides with Notes c.pdf; Young Short Bio 2016.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

All:

I find no association of acute mortality with either PM2.5 or ozone in the South Coast Air Basin. Literature supports no chronic association in all of California.

I am willing to work with others on analysis of the data set that I have. The mortality data is from a public source.

It seems premature to increase regulations in the air basin until the mortality question is resolved/agreed upon.

Stan

Short Bio 2016

Dr. S. Stanley Young worked at Eli Lilly, GlaxoSmithKline and the National Institute of Statistical Sciences on questions of applied statistics. His current mission is the evaluation of statistical claims particularly from observational studies. His research indicates that well over 50% of claims made fail to replicate when tested rigorously. His current interest is air pollution environmental epidemiology.

Dr. Young graduated from North Carolina State University, BS, MES and a PhD in Statistics and Genetics. He worked in the pharmaceutical industry on all phases of pre-clinical research. He has authored or co-authored over 60 papers including six “best paper” awards, and a highly cited book, Resampling-Based Multiple Testing. He has three issued patents. He is interested in all aspects of applied statistics, with special interest in chemical and biological informatics. He conducts research in the area of data mining.

Dr. Young is a Fellow of the American Statistical Association and the American Association for the Advancement of Science. He is an adjunct professor of statistics at North Carolina State University, the University of Waterloo, and the University of British Columbia where he has co-directed thesis work. He is also an adjunct professor of biostatistics at Georgia Southern University.

From: StanYoung [mailto:genetree@bellsouth.net]
Sent: Tuesday, September 20, 2016 12:55 PM
To: Jo Kay Ghosh <jghosh@aqmd.gov>
Cc: James E. Enstrom <jenstrom@ucla.edu>; kzu@gradientcorp.com; Anthony Oliver <aoliver@aqmd.gov>; Margarita Felix (Ben) <mafelix@rcbos.org>; Marie Patrick (Bur) <mwpatrick@aqmd.gov>; JudyM@ci.Rolling-Hills-Estates.ca.us
Subject: Zu Wildfires Mortality.docx

Dear Jo Kay Ghosh:

This paper, open access, is of interest. It is a so called Natural Experiment. Forest fires increase the levels of PM2.5 in NYC and Boston, yet deaths did not go up. They say, "We examined temporal patterns of natural-cause deaths and 24-h ambient $PM_{2.5}$ concentrations in July 2002 and did not observe any discernible increase in daily mortality subsequent to the dramatic elevation in ambient $PM_{2.5}$ levels."

I've seen the same no effect in LA multiple times during the years 2000-2012. Using satellite images and also ground based monitors, smoke is seen, PM2.5 increases, yet deaths do not.

Stan Young

The following attachments were also included with Comment Letter #24 submitted by Dr. Stan Young. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachment, however, interested parties can obtain access at the link provided below:

- Long-range fine particulate matter from the 2002 Quebec forest fires and daily mortality in Greater Boston and New York City
  http://link.springer.com/article/10.1007/s11869-015-0332-9

A hard copy of all materials included in the comment letters, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

From: StanYoung [mailto:genetree@bellsouth.net]
Sent: Thursday, October 20, 2016 10:53 AM
To: Jo Kay Ghosh <jghosh@aqmd.gov>
Cc: Anthony Oliver <aoliver@aqmd.gov>; har@indecon.com; Margarita Felix (Ben) <mafelix@rcbos.org>; Marie Patrick (Bur) <mwpatrick@aqmd.gov>
Subject: Another paper to enter into you deliberations on air quality and health effects

Dear Dr. Ghosh:

Here is a pdf showing no effect if air quality on mortality. The data is from Pope et al. NEJM 2009.

I'm happy to send you a copy of the data.

Sincerely,

S. Stanley Young, PhD, FASA, FAAS
genetree@bellsouth.net
919 782 2759

CC: Anthony Oliver aoliver@aqmd.gov
Henry A. Roman har@indecon.com
John Benoit mafelix@rcbos.org
William A. Burke mwpatrick@aqmd.gov

The following attachments were also included with Comment Letter #25 submitted by Dr. Stan Young. Due to copyrights held by publishing entities, SCAQMD cannot reproduce the following attachment, however, interested parties can obtain access at the link provided below:

- A publication of the American Council on Science and Health. Standing with Giants, A Collection of Public Health Essays in Memoriam to Dr. Elizabeth M. Whelan http://acsh.org/news/2016/08/23/standing-with-giants-a-collection-of-public-health-essays-in-memoriam-to-dr-elizabeth-m-whelan

A hard copy of all materials included in the comment letter, as provided by the submitter, is available for viewing by request and in person by contacting:

Jo Kay Ghosh
SCAQMD Headquarters
21865 Copley Drive
Diamond Bar, CA 91765
(909) 396-2582

RESPONSES TO COMMENT LETTERS RECEIVED ON APPENDIX I

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #1)

Response to Comment 1:

The roles for U.S. EPA, CARB, and SCAQMD in air pollution health effects science and air quality regulation have been clarified in the Health Effects of Air Pollution section. In summary, the U.S. EPA is tasked with assessing new and emerging air quality science, including health studies, as part of the process of setting the federal air quality standards. In other words, the U.S. EPA's role is to assess the causal relationships between the pollutants and the different types of health endpoints. It is then SCAQMD's role is to describe the public health impacts of poor air quality in our region, as well as to develop and implement an emission reduction strategy to attain the federal and state ambient air quality standards. Therefore, it is not the intention of this Appendix to assess whether there is or is not an effect of a specific air pollutant on any particular health endpoint, but rather to summarize the health effects and causal determinations as assessed by U.S. EPA and other scientific agencies, to discuss some recent studies published since the latest U.S. EPA reviews, to give some quantitative estimates of the health impacts of particulate matter air pollution in the South Coast Air Basin, and to present a "local perspective" by highlighting studies conducted in the South Coast Air Basin, Southern California, or California.

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #2)

The Wang 2015 and Milojevic 2014 articles have been added as citations in the PM short-term effects section.

Responses to Comment Letter from Dr. John Froines (Comment Letter #3)

Text has been added to Appendix I to describe that ozone creates secondary oxidation products that are electrophilic, and certain genetic factors influence a person's ability to metabolize these electrophiles, which can affect respiratory function. Because cancer effects for ozone are lower on the causal determination scale, these were not discussed in Appendix I.

Responses to Comment Letter from Dr. Ed Avol (Comment Letter #4)

This comment letter has been superseded by the revised comment letter from the same Advisory Council member (see Comment Letter #13).

Responses to Comment Letter from Dr. John Dunn (Comment Letter #5)

See response to Comment Letter #1.

Responses to Comment Letter from Dr. Gordon Fulks (Comment Letter #6)

See response to Comment Letter #1.

With regard to the Linear No Threshold assumption used in the analyses presented in the Socioeconomic Report, this practice was recommended by Industrial Economics, Inc. and is based on the latest scientific evidence, including the evidence summarized in the U.S. EPA Integrated Science Assessments. It is also consistent with the current analytical approach adopted by the U.S. EPA in its regulatory impact analyses. Citations for these reports are provided in the Socioeconomic Report.

Responses to Comment Letter from Dr. James Enstrom (Comment Letter #7)

Response to Comment 7-1:

The Socioeconomic Report provides an analysis of the socioeconomic impacts of the AQMP in order to further inform public discussions and the decision-making process associated with the adoption of the Plan. However, to clarify, the analysis of public health benefits associated with the AQMP is not intended as a justification for the need for or cost of the Plan. The legal requirements for the AQMP are described in Chapter 1.

Response to Comment 7-2:

See response to Comment Letter #1.

Response to Comment 7-3:

Appendix I already describes the legal requirement for SCAQMD to provide this summary document. To clarify, the SCAQMD staff are not conducting scientific reviews to ascertain whether a pollutant causes or does not cause any health effects. Instead, Appendix I is a summary of the U.S. EPA's causal determinations, and presents a summary of some of the studies reviewed by U.S. EPA in their assessments, as well as some more recent literature.

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #8)

See response to Comment Letter #1.

Responses to Comment Letter from Dr. Michael Kleinman (Comment Letter #9)

The staff acknowledge that Appendix I summarizes the U.S. EPA's assessments of causality, and additionally summarizes some more recent literature published since the most recent Integrated Science Assessment for PM2.5, which was last published in 2009.

Responses to Comment Letter from Dr. John Froines (Comment Letter #10)

Text has been added to the PM section to note the cellular responses associated with the particle phase and vapor phase pollutants. The Cho final report to SCAQMD has been cited in Appendix I.

Responses to Comment Letter from Dr. John Froines (Comment Letter #11)

Text has been added to the PM section to note the cellular responses associated with the particle phase and vapor phase pollutants. The Eiguren-Fernandez 2015 paper has been cited in Appendix I.

Responses to Comment Letter from Dr. Emily Nelson (Comment Letter #12)

Response to Comment 12-1:

The purpose of Appendix I has been clarified in the introduction, including a statement clarifying important issues raised in the Advisory Council meeting that were addressed in other AQMP chapters and appendices or in the Socioeconomic Report, rather than in this Appendix.

Response to Comment 12-2:

A statement has been added to clarify that the causality conclusions are the result of U.S. EPA scientific evaluations of the research studies they have reviewed. A definition of FEV1 has been added.

Response to Comment 12-3:

The roles for U.S. EPA, CARB, and SCAQMD in air pollution health effects science and air quality regulation have been clarified in the Health Effects of Air Pollution section. Statements have also been added to distinguish the federal and California standards.

Responses to Comment Letter from Dr. Ed Avol (Comment Letter #13)

Response to Comment 13-1:

The purpose of Appendix I has been clarified in the introduction, and the categories of health effects which are discussed in more detail are defined in the Health Effects of Air Pollution section. The focus is on those health effects categorized as having a causal or likely causal relationship with the pollutant, while the other categories of health effects may be mentioned briefly. The sections describing the specific pollutant effects have also been modified to be consistent with this approach, acknowledging that greater detail is presented for ozone and PM, because of the non-attainment status in the SCAB.

Response to Comment 13-2:

The Ultrafine Particles section has been moved so that it is a sub-section within the PM section. However, PM2.5 and PM10 are still discussed together in the Short-Term and Long-Term effects sections, with the focus on PM2.5, since that is the the particle fraction with the most evidence linking it to health endpoints. Notably, the health impacts are estimated for PM2.5, since a large body of scientific evidence supports its link to premature deaths from cardiopulmonary causes.

Response to Comment 13-3:

The heading has been changed.

Response to Comment 13-4:

A description of the purpose of the Attachment has been added to the Introduction, and to the beginning of the Attachment.

Response to Comment 13-5:

Text has been added to the Toxics section of Appendix I to provide a high level description of some of the health effects of VOCs, particularly as assessed by the latest MATES study.

Response to Comment 13-6:

This list has been removed, and a more general sentence has been added to introduce the reader to the breadth of health effects that have been linked to air pollution.

Response to Comment 13-7:

The text has been modified so that toxicology studies are also included in this description.

Response to Comment 13-8:

The text has been modified accordingly.

Response to Comment 13-9:

The text has been modified to clarify that while multi-pollutant effects may be important, the air quality standards address each criteria pollutant separately, and this is reflected in the way Appendix I is organized.

Response to Comment 13-10:

The text has been added to the Health Effects of Air Pollution section.

Response to Comment 13-11:

The text has been modified accordingly.

Response to Comment 13-12:

The text has been modified to clarify that the depth of the breaths also increases, and that the ozone can reach deeper into the lungs.

Response to Comment 13-13:

This paragraph has been modified to clarify the focus on the health outcomes that have a causal or likely causal relationship with short-term ozone exposures, which are the respiratory effects, cardiovascular effects, and mortality.

Response to Comment 13-14:

The text has been modified accordingly.

Response to Comment 13-15:

The text has been modified accordingly.

Response to Comment 13-16:

The paragraph has been modified to clarify the attenuated response in some individuals.

Response to Comment 13-7:

The text has been modified accordingly.

Response to Comment 13-18:

The text has been modified accordingly.

Response to Comment 13-19:

The text has been modified accordingly.

Response to Comment 13-20:

The text has been modified accordingly.

Response to Comment 13-21:

Text has been added to quantify the ozone concentrations in the "high" versus "low" ozone communities studied.

Response to Comment 13-22:

This paragraph has been removed from the document.

Response to Comment 13-23:

This sentence has been removed from the document.

Response to Comment 13-24:

The paragraph has been condensed, and this sentence has been removed from the document.

Response to Comment 13-25:

The paragraph has been condensed, and this sentence has been removed from the document.

Response to Comment 13-26:

The section has been edited to reflect the evidence as presented in the 2013 ISA for Ozone, and a table was added to further detail the factors and the evidence classifications in the ISA document.

Response to Comment 13-27:

The summary section has been modified to strengthen the summary and clarify the health endpoints that were high on the causal determination scale.

Response to Comment 13-28:

More specific references and discussion of individual studies were added to the Ozone section, to make it more consistent with the PM section. The staff believe the discussion of the key studies in the PM section is quite relevant, since these studies are frequently referenced, and provide important evidence in the causal determination for PM health effects.

Response to Comment 13-29:

The sentence has been modified to provide further clarity on the wide range of particles and their properties.

Response to Comment 13-30:

This sentence has been modified accordingly.

Response to Comment 13-31:

This sentence has been modified accordingly.

Response to Comment 13-32:

This sentence has been modified accordingly.

Response to Comment 13-33:

This sentence has been modified accordingly.

Response to Comment 13-34:

This sentence has been modified accordingly.

Response to Comment 13-35:

The sentence has been modified to clarify that a PM10 standard remains in effect.

Response to Comment 13-36:

This sentence has been modified accordingly.

Response to Comment 13-37:

This sentence has been modified accordingly.

Response to Comment 13-38:

This sentence has been modified to say "these results suggest that the effects reported in the study are likely due to …"

Response to Comment 13-39:

This paragraph has been modified accordingly.

Response to Comment 13-40:

These sentences have been modified for clarity.

Response to Comment 13-41:

The notation has been standardized to "PM10-2.5".

Response to Comment 13-42:

This sentence has been modified accordingly.

Response to Comment 13-43:

This sentence has been modified accordingly.

Response to Comment 13-44:

This sentence has been modified accordingly.

Response to Comment 13-45:

These changes have been made to the paragraph.

Response to Comment 13-46:

The text has been standardized to use "new-onset asthma" and "term low birth weight" where appropriate, and the text on page I-40 has been corrected. The staff believe that "term low birth weight" is the correct term that is used to describe babies born at full term who weigh less than 2,500 grams at birth.

Response to Comment 13-47:

Sub-headings were added to this section, which has been reorganized and grouped with some other health endpoints in a section titled "Long-Term Particulate Matter Exposures and Emerging Areas of Interest". A definition of metabolic syndrome has been added to the text, and a clarification that these health endpoints are markers of metabolic syndrome rather than the syndrome itself.

Text has been added to this paragraph to discuss briefly the results of some of these recent human and animal studies that focused on PM and metabolic syndrome, including some studies evaluating PM and the development of metabolic syndrome, and other studies evaluating whether individuals with pre-existing metabolic syndrome may be more sensitive to the effects of PM. This section is intentionally brief, however, since it is describing health endpoints that are relatively newly studied. Since many of these studies were published after the 2009 ISA, they were not included in that review, and this health endpoint was not assessed to be high on the causal determination scale at the time of the 2009 ISA. However, we are including a brief mention of these studies because this is an area of emerging interest in the study of the health effects of PM.

Response to Comment 13-48:

References to several of these studies have been added to the section discussing PM and neurological outcomes.

Response to Comment 13-49:

A table has been added to summarize the U.S. EPA's summary of susceptibility factors for PM health effects.

Response to Comment 13-50:

This section has been divided into a brief summary of the PM health effects, and a separate section where the estimates of the health burdens of PM are described.

Response to Comment 13-51:

The Ultrafine Particles section has been moved so that it is a sub-section within the PM section. However, PM2.5 and PM10 are still discussed together in the Short-Term and Long-Term effects sections, with the focus on PM2.5, since that is the particle fraction with the most evidence linking it to health endpoints. Notably, the health impacts are estimated for PM2.5, since a large body of scientific evidence supports its link to premature deaths from cardiopulmonary causes.

Response to Comment 13-52:

These lines were part of the figure caption, and staff have reformatted it so that the caption appears on the same page as the figure to minimize potential confusion.

Response to Comment 13-53:

The intent of this paragraph is to describe the effect of the change in the risk assessment methodology on the estimate of air toxic cancer risk, and also to put these estimates in the context of long-term trends in air toxics cancer risk. However, we agree this sentence may be confusing, and have deleted this sentence to avoid potential confusion.

Response to Comment 13-54:

Text has been added to expand this section. This section now touches on the types of effects most strongly associated with ozone and PM air pollution, the carcinogenic effects of some air pollutants, and the factors that may increase a population's susceptibility to the negative effects of air pollution. The conclusion also ties in how such research on the health effects of air pollution is informative in the development of air quality standards, such as the NAAQS, and in evaluating air toxics risk.

Response to Comment 13-55:

A description of the purpose of the Attachment has been added to the Introduction, and to the beginning of the Attachment.

Responses to Comment Letter from Dr. John Husing (Comment Letter #14)

The staff is well aware of the ACES study and its findings, but did not include it in the initial draft of Appendix I since the study relates to the carcinogenicity of a specific toxic air contaminant (diesel PM), and the primary focus of Appendix I is the health impacts of criteria pollutants (i.e., ozone and PM2.5). While there is obviously some overlap, the detailed discussion below explains the initial staff thinking regarding this study and its relevance, and common misinterpretations of its findings. Nevertheless, based on the comment received, the staff have added a brief discussion of this study to Appendix I, similar to what is provided below.

The study showed that the amount of diesel PM emissions from the newer engines were lower than the older engines, as required by recent regulations. Because of this, the rats breathing the lower emissions did not develop cancer, while the rats breathing the higher emissions (from previous studies) did develop cancer. However, the study did not evaluate whether the PM from the newer engines was any more or less toxic compared to the older engines on a gram per gram basis; the study was not designed to determine such differences. Therefore, without any additional data on the toxicity of PM from the newer diesel engines, the analysis done in the MATES-IV study used the same risk factor for both, applied to the mass of PM. For example, whether you are exposed to 10 micrograms per cubic meter (ug/m3) of particulate matter from a single old diesel engine or several new diesel engines, the cancer risk would be the same because it is calculated based on 10 µg/m3 of exposure.

Appendix I presents a summary of the health effects of key air pollutants, including particulate matter. The studies described in Appendix I evaluate the health effects of total PM2.5 exposures by mass, regardless of whether they were from newer diesel engines, older diesel engines, or other sources. While this new diesel technology is very effective in terms of reducing the amount of emissions from diesel trucks, what people are being exposed to is the total concentration of PM from many sources. It is that

concentration that is then used in these health studies to analyze whether or not there is an effect on the specific health outcomes evaluated.

Additionally, it is important to distinguish the health effects associated with PM2.5 exposure in general (cardiovascular, respiratory, premature death, etc.) from the specific cancer risk associated with direct PM2.5 emissions from diesel engines. Direct PM2.5 emissions from diesel engines represent a small portion of overall PM2.5 exposure. NOx emissions from diesel engines that eventually lead to PM2.5 formation in the atmosphere, however, represent a larger component of PM2.5 exposure.

Responses to Comment Letter from Dr. John Froines (Comment Letter #15)

The staff agree that the Li 2016 article provides a discussion of some of the more recent studies on UFPs that have been conducted. The Li 2016 article, along with some studies that were discussed within this review article, has been added to Appendix I section on ultrafine particles.

Responses to Comment Letter from Dr. John Froines (Comment Letter #16)

Text has been added to the PM section to note the cellular responses associated with the particle phase and vapor phase pollutants. The Cho final report to SCAQMD has been cited.

Responses to Comment Letter from Dr. John Froines (Comment Letter #17)

The year when ARB listed diesel exhaust as a TAC has been corrected from 1989 to 1998, and the text has been clarified to note that this decision was based on the human carcinogenic properties. Additional text has been added to Appendix to describe how lead is stored in the bone and released into the blood, and that there is no established threshold for the health effects of lead.

Responses to Comment Letter from Dr. John Froines (Comment Letter #17)

The Alexis 2014 and Guarnieri 2014 references and some key findings from these studies have been added to Appendix I to clarify the effects of ozone and PM on asthma.

Responses to Comment Letter from Dr. Arthur Cho (Comment Letter #19)

Response to Comment 19-1:

The staff agree these are important issues that would increase the knowledge of the mechanisms of action for air pollution's health effects.

Response to Comment 19-2:

The report notes the potential action of electrophilic components of air pollution, including their ability to suppress inflammatory responses.

Response to Comment 19-3:

The report notes the endogenous COHb levels as summarized in the most recent ISA for CO. In other words, this is a naturally occurring level of CO (in the form of COHb) in healthy individuals. The focus of

air pollution controls on CO is on ambient exposure, which is the focus of the discussion of CO health effects in this section.

Response to Comment 19-4:

The staff agree these are important issues that would increase the knowledge of the mechanisms of action for air pollution's health effects, and potential interventions that could be effective in preventing some adverse health effects.

Responses to Comment Letter from Bill La Marr (Comment Letter #20)

Response to Comment 20-1:

Appendix I is a summary of causal determinations as assessed by U.S. EPA and other scientific agencies tasked with assessing causality. The document acknowledges uncertainty where appropriate, while also describing the strength and consistency of the associations where appropriate. Appendix I has been edited to focus on discussing health endpoints that are high on the causal determination scale, as assessed in by U.S. EPA in their most recent Integrated Science Assessments.

Since uncertainties are inherent in all scientific research and studies, the U.S. EPA framework for assessing causality includes an assessment of the uncertainties. Details regarding the framework for the U.S. EPA assessments are provided in the Integrated Science Assessments. The weight of evidence scale for causal determinations used by EPA defines 5 categories of causal relationships, and the category highest on the scale is called a "Causal Relationship". Within the definition of the weight of evidence required to determine that a pollutant has a "Causal Relationship" with a health outcome, the definition states that "the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence". Examples of relationships determined by U.S. EPA to be "Causal Relationships" include long-term exposures to PM2.5 and mortality, long-term exposures to PM2.5 and cardiovascular health outcomes, and short-term exposures to ozone and respiratory health effects.

Response to Comment 20-2:

The ozone section has been reorganized to focus on health endpoints that are high on the causal determination scale.

Response to Comment 20-3:

The staff agree that smoking is an important potential confounder in the studies of PM and mortality. In fact, the majority of these studies discussed in Appendix I adjusted for the potential confounding effect of smoking. Staff has added text to Appendix I to clarify when studies adjusted for smoking, particularly the studies of PM and mortality.

Response to Comment 20-4:

Some of the studies that are referred to in this paragraph were conducted in California, but it is critical to note the importance of assessing results from studies from many different locations. The

repeatability and consistency of results across many locations strengthens the determination of causality. Text has been added to this paragraph to clarify this point.

Response to Comment 20-5:

The text in Appendix I describes the study results as reported.

Response to Comment 20-6:

Appendix I already describes the assessments of the evidence for coarse PM and constituent- or source-specific PM in the U.S. EPA's 2009 Integrated Science Assessment, noting that there were few studies available at the time to assess causality in these specific cases.

Response to Comment 20-7:

See response to Comment #20-4.

Response to Comment 20-8:

While copollutant exposures may contribute to increases in morbidity and mortality, such co-occurring exposures are often assessed and accounted for in epidemiologic studies. The possibility of co-occurring exposures contributing to the effects observed is assessed as a part of the U.S. EPA's Integrated Science Assessments.

Response to Comment 20-9:

See response to Comment Letter #1. Regarding the methodology used in estimating the VSL, the VSL range used in the socioeconomic analysis is based on recommendations by expert consultants at Industrial Economics, Inc., as described in their memo titled, “Review of Mortality Risk Reduction Valuation Estimates for use in 2016 Socioeconomic Assessment”. This memo is available on the www.aqmd.gov website.

Response to Comment 20-10:

The staff acknowledges Dr. Samet's comments from the 2012 AQMP Appendix I, and note that, in fact, the draft 2016 AQMP Appendix I document includes a more detailed description of the methodology employed in drafting this summary, and the basis and rationale behind what is included in this document. Additional information has been added to the Health Effects of Air Pollution section to clarify the focus of this document, and the main review articles or literature searches from which the studies were drawn. Furthermore, Dr. Samet's statement that a quantification of burden should be included in the document has already been addressed with the inclusion of the estimates of the mortality and morbidity associated with PM2.5 exposure in the SCAB. These numbers are presented in the section now titled "Estimates of the Health Burden of Particulate Matter in the South Coast Air Basin".

Responses to Comment Letter from Dr. Afif El-Hasan (Comment Letter #21)

The staff thank Dr. El-Hasan for his comments and his participation on the Advisory Council.

Responses to Comment Letter from Dr. John Froines (Comment Letter #22)

The Hamra 2014 EHP article is already discussed in Appendix I, in the section describing long-term PM exposures and cancer. Descriptions of the Gharibvand 2016 EHP and Eckel 2016 Thorax studies have been added to Appendix I, in the discussion of PM and cancer.

The Li 2010 Am J Phyiol Lung Cell Mol Physiol article is already discussed in Appendix I, in the ultrafine particles section, which is now part of the Particulate Matter section. Brief descriptions of the Li 2009 EHP and Kang 2010 Proteomics studies have been added to Appendix I, in the discussion of UFP health effects.

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #23)

See response to Comment Letter #1.

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #24)

The Zu 2016 article has been added as a citation in the PM short-term effects section.

Responses to Comment Letter from Dr. Stanley Young (Comment Letter #25)

See response to Comment Letter #1.