Questions for Non-Member Consultants on the Ozone ISA from Dr. Steven Packham

Question 1 Background Statement of Fact:

Evidence from controlled human exposures is sufficient to conclude with certainty that a causal relationship exists between measurable decrements in FEV1 and subjective symptoms in healthy human adults.

Question 1: *When a causal relationship is conclusive to a high degree of scientific certainty as it is in this case, should this take precedence over causal inference when drafting a NAAQS ISA?*

Question 2 Background Statements of Fact:

1. The shape of the ozone induced FEV1 and subjective symptoms dose-response curve is a function of the inhaled hourly dosage rate and the cumulative dose inhaled over several hours immediately prior to the onset of the effect.
2. The mean cumulative dose threshold for ozone induced FEV1 and symptom effects in healthy adult humans exposed 6.6 hours to ozone concentrations from 60 to 87 ppb is estimated to be 1,362 mg. (Schelegle et al. 2009)
3. This is equivalent to inhaling a dose of 2,439 trillion highly reactive oxidizing molecular moieties.
4. Whatever the oxidative challenge of PM air pollution is to the human lung, it pales in significance to that of ozone.
5. The inhaled hourly dosage rate and cumulative dose thresholds appear to be lower for ozone induced FEV1 and symptom responses than those necessary for inducing clinical signs of injurious pulmonary inflammation.
6. Ozone induced FEV1 decrement and subjective symptoms may be species-specific protective and defensive responses and warning signs for human organisms.
7. Ozone exposures have been shown to stimulate peripheral mucus flow into central bronchi thereby enhancing particle transport from peripheral to central airways and mucociliary clearance of inhaled particulate matter. This beneficial dose dependent response to ozone "…is of interest since it characterizes the reaction of a primary defense mechanism essential to the protection of mucosal surfaces of the tracheobronchial tree." (Forster et al. 1987)

Question 2: *Given evidence available from controlled human exposures substantiating causal relationships with a number of physiological responses, including beneficially confounding interactions of ozone on PM clearance, should Sub-section ES4.1 Health Effects in the Draft's Executive Summary, and the entire Integrated Synthesis section of the Draft be rewritten?*

Question 3 Background Information: Figure ES-3 in the Ozone ISA External Review Draft (shown below) is adapted from the 2013 Ozone ISA which was based on eight human studies published between 1988 and 2013. The 2009 study by Schelegle et al. played a decisive role in the 2015 revision of the O3 NAAQS from 75 to 70 ppb (80 FR 65292 Oct 26, 2015).

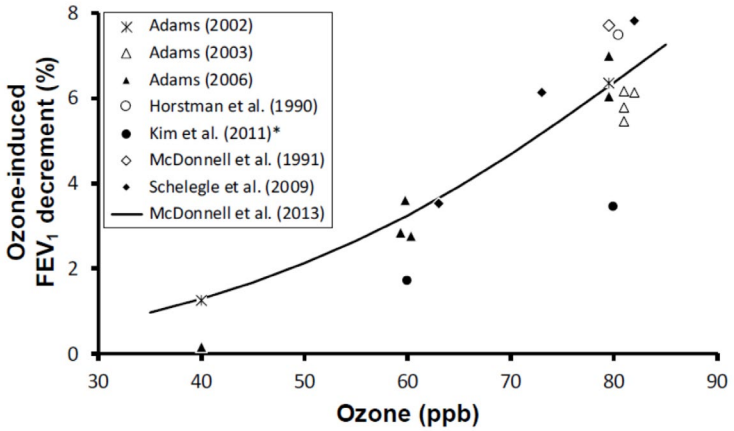


Figure ES-3 was adapted from Figure 6-1 of 2013 Ozone ISA (U.S. EPA, 2013) which was based on studies by Adams (2006), Adams (2003), Adams (2002), Folinsbee et al. (1988), Horstman et al. (1990), Kim et al. (2011), McDonnell et al. (2013), McDonnell et al. (1991), and Schelegle et al. (2009).

Figure 1 below (from Schelegle et al. 2009), on the other hand, depicts the actual mean accumulative doses of 31 healthy adult human subjects who completed four 6.6-hour chamber exposures to target mean O_3 concentrations of 60,70, 80, and 87 ppb. The original data presented *in this way* conveys critical information to toxicologists and biomedical researchers that is "lost in translation" in the concentration/risk-effect picture presented in Figure ES-3.

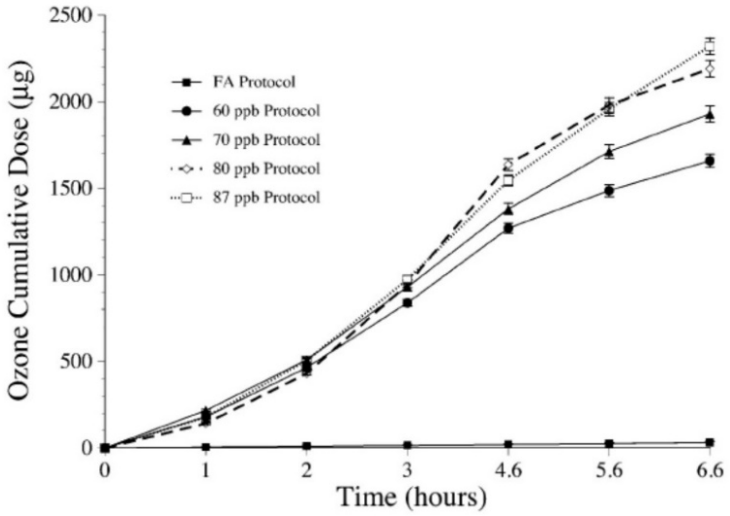
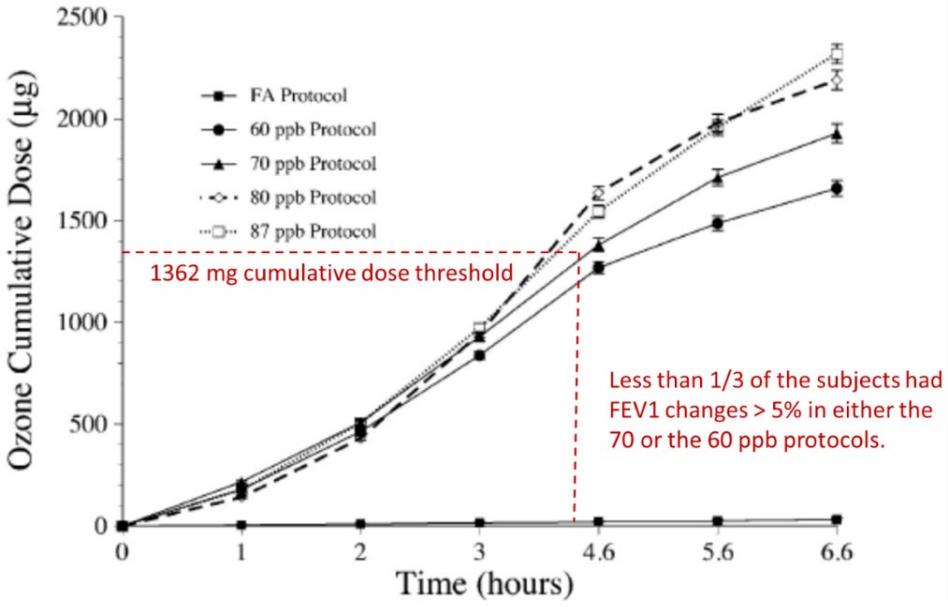


Figure 1. Diagram of mean group values for cumulative dose of ozone (micrograms) against time of exposure for each of the five protocols. Values represent means ± SEM.

To quote Schelegle et al. (2009),

> "We were able to obtain reliable estimates of a Dose of Onset [i.e., a threshold for the FEV1 effect], using the pooled FEV1from the 80 and 87 ppb ozone exposure protocols, …but not from the pooled FEV1 data from the 60 and 70 ppb ozone exposure protocols. The inability to estimate [a threshold] using the FEV1 data from the 60 and 70 ppb ozone exposure protocols is most likely because *less than one third* of the subjects had changes in FEV1 *greater than 5%* in either of these protocols. (Emphasis added)



Packham Figure 1. Adapted from Schelegle et al. (2009) with toxicological annotations by author, 2019.

The notable differences between Figure ES-3 compared with Packham Figure 1 are driven by how data are interpreted by different scientific disciplines. By superimposing Schelegle's descriptive conclusion-narrative onto the Sigmoid shaped dose-response curves, one sees the beginning of an increased trend of dose-response curve separation between hour 3 and hour 4: Indicative of the cumulative Dose of Onset threshold between the respective exposure protocols.

Figure ES-3 is the product of adapting (i.e., *imposing*) an ISA Preamble quantal risk-assessment mindset upon graded data collected from continuous response gradients characteristic of living biological organisms. The narrative associated with Figure ES-3 (found on page ES-7) is grossly misleading with respect to the epidemiologically "associated" adverse health effects and completely overlooks the confounding health benefit of enhanced PM clearance stimulated by 200 ppb ozone exposures mentioned above under Question 2 Background Statements of Fact.

The controlled human studies by Folinsbee, Adams, Horstman, Kim, McDonnell and Schelegle, and others cited below in the References and reading list, prove with absolute certainty that exposures to elevated ambient levels of O3 can cause measurable decrements in FEV1 pulmonary test results in healthy adults. These studies document that the effect of O3 on reduced FEV1 volumes is temporary, and suggest that hourly mean ambient O3 concentrations below 70 ppb are not likely to cause FEV1 effects in most healthy adults.

Question 3 Background Statement of Facts:

Several nonmember consultants have expressed reluctance to comment on certain questions because of limited familiarity with pulmonary physiology and inhalation toxicology. Here are few facts to keep in mind.

1. Lungs have an evolutionary history in which surfactant was key to the evolution of all air breathing species on the surface of the planet, (Daniels and Orgeig (2003.)
2. Antioxidant secretions from epithelial Type II cells into the liquid lining of the lungs is one of most important natural defenses the human organism has against naturally occurring ozone levels in the atmosphere near the earth's surface.
3. All known effects of ozone on the human respiratory system are dose dependent.
4. Ozone stimulation of the respiratory airways evokes a number of organism defensive and adaptive responses in humans.
5. Ozone alters tracheobronchial mucociliary function in humans resulting in enhanced transport and clearance of particles deposited in the peripheral air ways, (Foster, et al (1987).
6. Ozone is a potent oxidizing agent, (Pryor et al. (1991).

Question 3 Overarching Conceptual Contexts: An accurate understanding of the causal dose-response relationship between ambient ozone exposure and responses elicited in the human organism opens up a number of important options that could be considered in reviewing and setting NAAQS standards and in how those standards might be used to protect, and even promote, public health. For instance, the realization that the ozone-induced FEV1 effects are temporary, reversible, and occur at a lower inhaled dose than a truly adverse health effect (such as a nonhealing, injurious inflammatory response) could be considered a tenable rationale for classifying them as natural, organism-specific margin-of-safety benchmark indicators.

Another application of hourly MSS inhalation dosage models and thresholds would be to imbed them into web and mobile platform applications for public education and development of user-friendly air quality risk management tools by the EPA. As proof of this concept's possibility, there are two air pollution exposure apps presently in the public domain: A web app http://webapp0.myairhealth.com/# and a free downloadable smartphone app https://apps.apple.com/us/app/myair-health/id790049340.

Question 3: *Looking ahead, do you think toxicology, clinical human studies, and biomedical research disciplines should be given more explicit and balanced consideration in the development of the present, and future, O3 ISAs with the objective to validate causal relationships and determine hourly inhalation dosage rates for adverse inflammatory responses in pulmonary tissues?*

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