

**For discussion on the March 23, 2011 teleconference of the Ozone Review Panel for the  
Reconsideration of the 2008 National Ambient Air Quality Standard (NAAQS).  
This is a deliberative draft letter. It does not represent consensus CASAC advice or EPA policy.  
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1  
2 Dear Administrator Jackson:  
3

4 This letter provides comments of the Clean Air Scientific Advisory Committee (CASAC) in  
5 response to the charge questions submitted in the January 26, 2011 memorandum from the  
6 Office of Air Quality Planning and Standards (OAQPS). The questions are related to the current  
7 reconsideration of the 2008 proposed National Ambient Air Quality Standard (NAAQS) for  
8 Ozone.  
9

10 Previous Comments by CASAC  
11

12 As you know, CASAC has an extensive, recent record of providing independent peer review on  
13 the Agency's technical documents related to the Ozone NAAQS. From 2005 to 2008, CASAC  
14 reviewed two drafts of the Staff Paper (now called the Policy Assessment), two drafts of the  
15 Criteria Document (now called the Integrated Science Assessment), two drafts of the risk  
16 assessment and two drafts of the exposure assessment. As stated in our letters of October 24,  
17 2006, March 26, 2007 and April 7, 2008 to former Administrator Stephen L. Johnson, CASAC  
18 unanimously recommended selection of an 8-hour average ozone NAAQS within the range  
19 proposed by EPA (60 to 70 ppb). On March 12, 2008, EPA published its decision to revise the  
20 National Ambient Air Quality Standards (NAAQS) for Ozone, revising the 8-hour "primary"  
21 ozone standard<sup>1</sup>, designed to protect public health, to a level of 75 ppb. In response, CASAC  
22 offered comments in a letter to former Administrator Johnson on April 7, 2008 to the effect that  
23 CASAC did not endorse the new primary ozone standard (75 ppb) as being sufficiently  
24 protective of public health.  
25

26 In response to EPA's reconsideration of the 2008 Ozone NAAQS and the proposal published on  
27 January 19, 2010, CASAC reaffirmed its support for the selection of an 8-hour average ozone  
28 NAAQS within the 60 – 70 ppb range. In our letter of February 19, 2010, we reiterated support  
29 for this range and referred to the supporting evidence as presented in *Air Quality Criteria for*  
30 *Ozone and Related Photochemical Oxidants* (March 2006) and *Review of the National Ambient*  
31 *Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information*  
32 (OAQPS Staff Paper, July 2007).  
33

34 While we are concerned that EPA's most recent request for additional CASAC advice is  
35 redundant with our past reviews, we nonetheless are pleased for the opportunity to reaffirm our  
36 previous advice and we are submitting this letter and the attached consensus advice to further  
37 assist EPA as it takes action following this additional scientific input from CASAC.  
38

39 Here we reaffirm that the evidence from controlled human and epidemiological studies strongly  
40 supports the selection of a new primary ozone standard within the 60 – 70 ppb range for an 8-  
41 hour averaging time. As enumerated in the 2006 Criteria Document and other companion

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<sup>1</sup> An 8-hour averaging time and a form based on the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years, were adopted in 1997 and retained in the 2008 rulemaking.

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1 assessments, the evidence provides firm and sufficiently certain support for this recommended  
2 range for the standard.

3  
4 Key Findings

5  
6 Although the Clean Air Act mandates the selection of a standard that has an adequate “margin of  
7 safety,” the practical application of this term requires a policy judgment. The scientific evidence  
8 that was assembled by EPA and reviewed by CASAC shows no “threshold” or level below  
9 which there is no risk of decrement in lung function following short-term exposure to ozone.

10  
11 As you give consideration to the revision of the NAAQS, we offer the following summary of  
12 findings in the evidence available through 2006:

- 13  
14 • The evidence available on dose-response for effects of ozone shows associations  
15 extending to levels within the range of exposures currently experienced in the United  
16 States.
- 17  
18 • There is scientific certainty that 6.6-hour exposures with exercise of young, healthy, non-  
19 smoking adult volunteers to concentrations  $\geq 80$  ppb cause clinically relevant decrements  
20 of lung function.
- 21  
22 • Some healthy individuals have been shown to have clinically relevant responses, even at  
23 60 ppb.
- 24  
25 • Since the majority of clinical studies involve young, healthy adult populations, less is  
26 known about health effects in such potentially ozone sensitive populations as the elderly,  
27 children and those with cardiopulmonary disease. For these susceptible groups,  
28 decrements in lung function may be greater than in the healthy volunteers and are likely  
29 to have a greater clinical significance.
- 30  
31 • Children and adults with asthma are at increased risk of acute exacerbations on or shortly  
32 after days when elevated ozone concentrations occur even when exposures don't exceed  
33 the NAAQS concentration of 75 ppb.
- 34  
35 • Large segments of the population falls into what EPA terms a “sensitive population  
36 group,” i.e., those at increased risk because they are more intrinsically susceptible  
37 (children, the elderly, and individuals with chronic lung disease) and those who are more  
38 vulnerable due to increased exposure because they work outside or live in areas that are  
39 more polluted than the mean levels in their communities.
- 40  
41 • CASAC unanimously reaffirms its support for the previously recommended selection of  
42 an 8-hour average ozone NAAQS within the range proposed by EPA (60 to 70 ppb).
- 43

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1 Public Comments  
2

3 There were over 55 public comments presented during the teleconferences in February and  
4 March of 2011. As always, we welcome public input into our deliberations. Some  
5 commentators pointed out that even in the range of 60 – 70 ppb, there would be selected  
6 members of the population who would continue to be at risk, and thus a standard set in this range  
7 would contain a reduced margin of safety for these vulnerable populations. Other public  
8 comments touched upon topics outside the scope of our specific deliberations around the charge  
9 questions. For your information, concerns were expressed about potential deleterious economic  
10 consequences of a more stringent NAAQS, including adverse impacts on jobs and commerce,  
11 and the practical issues of implementation. Other comments touched on the possibility of  
12 deferring any change in the 2008 standard until the newer evidence has been considered. The  
13 difficulty of establishing "policy relevant background" for this naturally occurring  
14 internationally-transported pollutant also received comment.  
15

16 Evidence Considered by CASAC  
17

18 At EPA's request, our deliberations were constrained to the evidence assembled in the prior  
19 review that ended in 2008, i.e. a science record that closed in 2006. This constraint imposed an  
20 artificial boundary on our discussions. The public comments, however, were not so limited.  
21 While we appreciate the depth and scope of the public's interest in ozone regulation, we  
22 recognize that the topics raised and newer information could not be incorporated into our  
23 deliberations given our instructions from EPA and the process that has been used for assembling  
24 and reviewing evidence in considering a NAAQS revision. Although some written comments  
25 from individual panelists include more recent studies, our consensus responses to the charge  
26 questions and this letter are based on the literature considered in the last ozone NAAQS review  
27 that ended in 2008.  
28

29 Conclusion  
30

31 Again, we reaffirm our unanimous recommendation, given in Chairperson Henderson's 2008  
32 letter to the Administrator, to set the ozone NAAQS within the range of 60 to 70 ppb for an 8-  
33 hour averaging time. In that range, CASAC finds that the evidence is sufficiently certain to be  
34 confident of public health benefits and additional protection for susceptible groups.  
35

1 **Draft Responses to Charge Questions**  
2

- 3 **1. What is your advice on the overall strengths and limitations of the evidence from**  
4 **controlled human exposure and epidemiological studies and the results of the**  
5 **exposure and risk assessments, in the context of EPA's selection of a standard level**  
6 **within the proposed range that would be requisite to protect public health with an**  
7 **adequate margin of safety, including the need to protect susceptible populations,**  
8 **such as children and people with asthma?**  
9

10 The controlled human exposures to ozone were carried out in rigorous fashion by  
11 established investigators at distinguished institutions. They used state-of-the-art  
12 techniques to measure pulmonary function changes and changes in lung inflammation  
13 based on biomarkers in bronchoalveolar-lavage fluids. These studies have produced  
14 substantial data on the acute effects of short-term exposures to this respiratory irritant and  
15 the results were quite consistent over a wide range of ozone concentrations and exposure  
16 durations. While CASAC did not consider the findings of recent publications (post-2006)  
17 in reaching this judgment, it was aware that the results of these more recent studies were  
18 consistent with those of the earlier studies that formed the basis for our judgments on the  
19 effects produced by controlled human exposures.  
20

21 In interpreting these findings, we note that most of the studies that influenced our  
22 judgments on the proposed range involved healthy adult subjects and required exercise as  
23 a necessary factor for revealing adverse responses to ozone. Exercise promotes higher  
24 levels of ventilation as well as switching from predominantly nasal to oral breathing.  
25 These factors increase the penetration of ozone into the lungs, thereby increasing  
26 respiratory responses relative to quiet breathing. Since many Americans have occupations  
27 that require them to work outdoors while others exercise outdoors for recreation, these  
28 studies reflect the exposure circumstances of many people in the United States. This is an  
29 important consideration in establishing the primary NAAQS. There is also a substantial  
30 literature demonstrating that children with asthma participate in team sports and other  
31 forms of strenuous exercise as a regular part of their school and after-school activities.  
32 For such children, who represent a sensitive population, the pulmonary function  
33 decrements and inflammation observed in exercising healthy adults most likely  
34 underestimate the effects of a given ozone exposure.  
35

36 There are substantial complementary epidemiological data that have the strength,  
37 compared with clinical studies, of being based on responses in generally much larger  
38 numbers and more diverse subjects. In chamber studies, exposures are limited to ozone  
39 alone. While ambient ozone measurements used in epidemiological studies are  
40 reasonably specific to ozone, there are other strong photochemical oxidants in the  
41 ambient air as well. This is considered a strength of the epidemiological data since ozone  
42 is not, *per se*, a criteria pollutant. Rather it was selected to serve as an indicator for the  
43 Photochemical Oxidant NAAQS, and the health effects of the mixture in natural settings

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1 may be larger than if the exposure were only to ozone. The health-related functional and  
2 inflammatory changes measured in panel studies of people exposed to ozone outdoors are  
3 also seen in the controlled chamber exposure studies with ozone alone. Since these  
4 effects are not known to occur with ambient air exposures to realistic concentrations of  
5 these other photochemical co-pollutants, their presence may serve to exacerbate rather  
6 than simply add to the effects of the ozone in the ambient mixture. Thus, within the range  
7 of ozone concentrations under consideration (60 to 70 ppb), where the ratio of ozone to  
8 other photochemical oxidants is unlikely to change, reducing ozone concentrations is  
9 likely to reduce the effects of the photochemical oxidant mixture as a whole.

10  
11 The effects observed in epidemiological studies are reasonably specific to ozone.  
12 However, as discussed above, they can also be influenced by the presence of other strong  
13 photochemical oxidants in the ambient air, and thus the health effects in natural settings  
14 may be larger than expected from clinical experiments with exposure only to ozone.  
15 Another potential difference between controlled exposure and epidemiological studies is  
16 the reaction products from ozone once it enters indoor environments. These reaction  
17 products include a wide range of gas-phase respiratory irritants and ultra-fine particles.  
18 Epidemiological studies take these other oxidants into account to some greater or lesser  
19 extent with respect to the covariance of the other ambient oxidants with ozone. It should  
20 also be noted that central monitors, particularly those placed in urban areas, have ozone  
21 concentrations that are lower than those further from the urban core because nitric oxide  
22 in motor vehicle emissions scavenges ozone, thereby lowering ozone concentrations  
23 within traffic corridors. Thus, ozone levels recorded by central site monitors may not  
24 accurately portray the near-ground exposure of most individuals in the population.

25  
26 Taken together, controlled human studies and the epidemiological studies strongly  
27 support the selection of a new primary ozone 8-hour concentration limit that is well  
28 below the 1997 limit of 80 ppb over an 8-hour averaging time. There is scientific  
29 certainty that 6.6-hour exposures to ozone at concentrations  $\geq 80$  ppb with intermittent  
30 exercise, cause clinically relevant decrements of lung function in groups of young,  
31 healthy volunteers, and in one controlled human exposure study there were clinically  
32 relevant effects in some individuals at 60 ppb. The results of multiple epidemiological  
33 studies also show that children and adults with asthma are at increased risk of acute  
34 exacerbations of asthma on or shortly after days when ozone concentrations are elevated  
35 above background but less than 80 ppb, and there is no evidence of a threshold  
36 concentration limit below which there are no adverse effects in sensitive subpopulations.  
37 Given the results of EPA's exposure and risk assessments, setting a new NAAQS in the  
38 range of 60 to 70 ppb is appropriate, but would provide little margin of safety at its upper  
39 end.

40  
41 In summary, the strengths of the evidence from controlled human exposure and  
42 epidemiological studies enumerated in the Criteria Document and its update were  
43 substantial, and more than adequate to support the recommended range for the NAAQS

1 of 60 to 70 ppb. The limitations of the evidence from controlled human exposure and  
2 epidemiological studies were well and appropriately stated in the Staff Paper.  
3

4 **2. Recognizing that controlled human exposure studies at 80 ppb O<sub>3</sub> and above have**  
5 **provided evidence of other health effects, including inflammation and increased**  
6 **airway responsiveness which may occur through different physiological mechanisms**  
7 **than the reduction in FEV<sub>1</sub>, how should the results of these studies inform our**  
8 **understanding the health effects to healthy adults at exposures levels from 60 to 70**  
9 **ppb?**

10  
11 Results from earlier studies at 80 ppb ozone and above were reviewed in earlier Criteria  
12 Documents and were primarily summarized in less detail in the current Criteria  
13 Document. Dosimetry of ozone is relevant to extrapolations from higher to lower  
14 concentrations. Several articles have pointed out that pulmonary function [1] and other  
15 response indicators [2] are related to exposure concentration, ventilation rate and  
16 exposure duration, among other variables. The responses at levels below 80 ppb in the  
17 Adams and other studies are consistent with predictions using dosimetric and effective  
18 dose calculations that were influenced by results obtained at 80 ppb and higher  
19 concentrations.  
20

21 In considering the public health implications of the controlled studies relevant to ozone  
22 health effects, CASAC notes that the participants were healthy, non-smoking young  
23 adults. Chamber studies of asthmatic and non-asthmatic subjects exposed to ozone at  
24 relatively high concentrations showed that the changes in forced expiratory volume in 1  
25 second (FEV<sub>1</sub>) and mid-maximal expiratory flow (MMEF) were significantly greater in  
26 the subjects with asthma than in those without asthma [3]. For ethical reasons, controlled  
27 exposure studies are designed to limit effects to only those that are relatively mild and  
28 reversible, including decrements in pulmonary function and evidence of inflammatory  
29 changes. One characteristic response to low ozone exposure levels is mucosal  
30 neutrophilic cell inflammation probably mediated by phospholipid-derived products and  
31 by epithelial cell-derived chemokines and cytokines [4]. This response may be poorly  
32 correlated with lung function changes, perhaps because the time course of development  
33 for these responses is different from that for changes in FEV<sub>1</sub> or because the mechanism  
34 of ozone-induced reduction in lung function may not be related to airway inflammation.  
35 In fact, some individuals may exhibit inflammation without significant changes in  
36 pulmonary function. However, the data showing elevated levels of inflammatory  
37 cytokines, infiltration of inflammatory cells (macrophages and neutrophils) and evidence  
38 of oxidative changes provide important components of biological plausibility and  
39 advance our understanding of the mechanisms by which ozone affects health. The data  
40 also provide mechanistic support for the observed epidemiological associations with  
41 regard to exacerbations of asthma at concentrations below 80 ppb. The inflammatory  
42 effects are likely to be more serious for individuals with chronic lung diseases. The  
43 exposure chamber studies showed that individuals with chronic obstructive pulmonary

1 disease had significantly greater losses of pulmonary function (19% from their baseline)  
2 than did healthy controls when exposed to ozone during light exercise [5]. While these  
3 studies are often performed at exposure concentrations higher than typical ambient  
4 conditions, they serve to identify disease-relevant mechanisms and underscore the  
5 inherent variability of even healthy adult populations with respect to their responses to  
6 ozone. It is important that we consider this person-to-person variability in sensitivity to  
7 ozone as we examine whether the current or proposed ambient concentration ranges  
8 provide an adequate margin of safety for sensitive subpopulations.  
9

10 McDonnell, W.F., et al. 1997. Prediction of ozone-induced FEV<sub>1</sub> changes. Effects of  
11 concentration, duration, and ventilation. *Am J Respir Crit Care Med.* 156(3 Pt 1):715-22.  
12

13 Mudway, I.S. and F.J. Kelly. 2004. An investigation of inhaled ozone dose and the  
14 magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med.*  
15 169(10):1089-95.  
16

17 Kreit, J.W., et al. 1989. Ozone-induced changes in pulmonary function and bronchial  
18 responsiveness in asthmatics. *J Appl Physiol.* 66(1):217-22.  
19

20 Bromberg, P.A. and H.S. Koren, 1995. Ozone-induced human respiratory dysfunction  
21 and disease. *Toxicol Lett,* 82-83:307-16.  
22

23 Gong, H., Jr., et al. 1997. Responses of older men with and without chronic obstructive  
24 pulmonary disease to prolonged ozone exposure. *Arch Environ Health.* 52(1):18-25.  
25

26  
27 **3. How should the results of the controlled human exposure studies at 60 ppb O<sub>3</sub>,  
28 showing effects on FEV<sub>1</sub> and respiratory symptoms, in the context of the larger  
29 body of evidence from controlled human exposure studies, mentioned above, inform  
30 our understanding of the health effects to healthy adults at exposure levels from 60  
31 to 70 ppb?**  
32

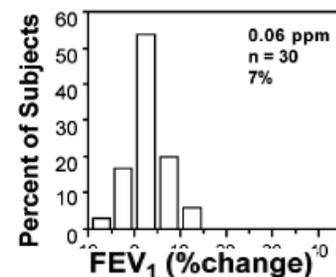
33 The results of only one controlled human exposure study of the effect of ozone at  
34 concentrations <80 ppb were available for the committee to consider (Adams, 2006).  
35 This study was well-designed and conducted with appropriate methods. The authors  
36 reported a statistically significant group mean decrement in FEV<sub>1</sub> of 4.7% after 6.6-hour  
37 exposure to 80 ppb as compared to the response to filtered air (a 1.35% increase in  
38 FEV<sub>1</sub>). They also reported group mean decrement in FEV<sub>1</sub> of 1.5% after 6.6-hour  
39 exposure to 60 ppb ozone that was not significantly different from the response to filtered  
40 air. However, eight of the 30 subjects in the Adams et al. study experienced decrements  
41 in FEV<sub>1</sub> >5% and two had decrements >10%, a decrease in lung function considered  
42 clinically relevant by the American Thoracic Society. The results of the Adams et al.  
43 study fit well with those from multiple other studies of the effect of ozone on lung

1 function at concentrations  $\geq 80$  ppb, which have consistently shown that some individuals  
2 are more sensitive to this effect of ozone than others.

3  
4 As discussed at length in the Criteria Document and Staff Paper, there is no evidence for  
5 a threshold below which ozone does not affect lung function. The magnitude of the effect  
6 of ozone diminishes with decreasing concentration, but does not reach the comparison  
7 level associated with exposure to ozone-free filtered air. Furthermore, there is a great  
8 degree of variability of response magnitude among the healthy individuals studied, with  
9 some having clinically relevant responses, even at 60 ppb.

- 10  
11 **4. With respect to the information from controlled human exposure studies at 60 ppb**  
12 **O<sub>3</sub>, what is the scientific importance of the small, group mean FEV<sub>1</sub> decrements**  
13 **relative to the findings that 7 to 20% of the subjects experienced FEV<sub>1</sub> decrements  $\geq$**   
14 **10%? Please consider this question from both a public health and a clinical**  
15 **perspective.**

16  
17 The inset plot of the Adams data (Adams 2006),  
18 derived from Figure 8-2 of Volume I of “Air Quality  
19 Criteria for Ozone and Related Photochemical  
20 Oxidants, 2006”, shows an approximately normal  
21 distribution in the ozone-induced decrements in FEV<sub>1</sub>  
22 with exposure to 0.060 ppm (60 ppb). Although the



23 mean decrement is less than 3% and would not be  
24 considered clinically important, the shift to the right in this distribution pushes a fraction  
25 of subjects (7%) into the region of clinical importance ( $>10\%$  decrement). The  
26 consistency of effects across ozone exposure levels within the Adams study, as well as  
27 the consistency with effects observed in an earlier independent study (McDonnell et al.  
28 1991) indicates that the observed deficits in FEV<sub>1</sub> at 60 ppb from the Adams study are  
29 not likely to be spurious. In other words, prolonged exposure to 60 ppb ozone probably  
30 causes a general shift in the distribution of FEV<sub>1</sub> towards lower values.

31  
32 All of the Adams study subjects were healthy adult volunteers. From a public health  
33 standpoint, these results suggest that a large number of individuals in the general  
34 population (that are otherwise healthy) are likely to experience FEV<sub>1</sub> deficits greater than  
35 10% with prolonged exposure to 60 ppb ozone.

36  
37 A 10% decrement in FEV<sub>1</sub> is often associated with respiratory symptoms, especially in  
38 individuals with pre-existing pulmonary or cardiac disease. For example, people with  
39 chronic obstructive pulmonary disease have decreased ventilatory reserve (i.e., decreased  
40 baseline FEV<sub>1</sub>) such that a  $\geq 10\%$  decrement could be associated with moderate to severe  
41 respiratory symptoms. The exposure and risk assessment conducted for the last review of  
42 the ozone NAAQS clearly document that a substantial proportion of the U.S. population  
43 is exposed to levels of ozone at the various alternative standards considered. This means

1 that even if a NAAQS of 60 ppb were to be adopted, some sensitive individuals could  
2 still be exposed to concentrations that could cause them to have a clinically relevant  
3 decrement in lung function.

4  
5 The experimental study results in healthy subjects essentially preclude extension of these  
6 studies to groups that may be more sensitive because of the ethics of carrying out clinical  
7 studies in diseased individuals. Thus, without having specific studies among asthmatics  
8 and children at these levels of exposure, it is prudent, in spite of the uncertainty, that EPA  
9 select an exposure level below the current standard (closer to the 60 ppb level) to “protect  
10 public health with an adequate margin of safety, including the need to protect susceptible  
11 populations.”

12  
13 Adams, W.C. 2006. Comparison of chamber 6.6-h exposures to 0.04-0.08 PPM ozone via  
14 square-wave and triangular profiles on pulmonary responses. *Inhal Toxicol* 18(2):127-  
15 136.

16  
17 McDonnell, W.F., H.R. Kehrl, S. Abdul-Salaam, P.J. Ives, L.J. L.J. Folinsbee, R.B.  
18 Devlin, et al. 1991. Respiratory response of humans exposed to low levels of ozone for  
19 6.6 hours. *Arch Environ Health* 46(3):145-150.

20  
21 **5. The evidence, including that summarized above, indicates that susceptible**  
22 **populations may have greater responses than healthy people. In light of this**  
23 **evidence, how can we appropriately use the results of controlled human exposure**  
24 **studies conducted on healthy adults, as well as the epidemiological studies of**  
25 **susceptible groups, to inform a judgment on the effects of ozone exposure on**  
26 **susceptible populations?**

27  
28 As discussed above, the findings from clinical studies of healthy volunteers may  
29 underestimate the risks in groups considered potentially susceptible. In the controlled  
30 human exposure studies carried out at concentrations of 80-ppb ozone and below, a  
31 percentage of healthy subjects have lung function changes much higher than the average  
32 response (e.g., FEV<sub>1</sub> changes > 10 %). While FEV<sub>1</sub> changes > 10% may not prevent  
33 healthy individuals from pursuing their normal daily activities, individuals with  
34 compromised lungs, such as persons with asthma, may incur significant health impacts  
35 with reductions of this magnitude. As CASAC has commented in the past to EPA,  
36 evidence is accumulating that persons with asthma, the elderly, and particularly children,  
37 are more sensitive and experience larger decrements in lung function due to ozone  
38 exposure than do healthy adult volunteers.

39  
40 In addition, epidemiological studies considered in the last review showed adverse effects  
41 of ozone on various health endpoints (e.g., emergency department visits and increased  
42 hospital admissions for respiratory illness) at relatively low exposure levels. These  
43 findings and the results of the clinical studies suggest the possibility of ozone effects

1 down to the lower end of the 60-70 ppb range. CASAC concluded at the last review that  
2 the lower range of consideration for revision of the NAAQS should be 60 ppb ozone,  
3 acknowledging inherently that margin of safety considerations would be better met at 60  
4 ppb than at 70 ppb ozone. Moreover, since the relative strength of the evidence is weaker  
5 at lower ozone concentrations (see # 6 below for comments on the epidemiological  
6 evidence), a range of 60 to 70 ppb ozone allows the Administrator to place her judgment  
7 on the weight that any uncertainties and limitations in the science play in selecting an  
8 exposure level protective of public health with some margin of safety.  
9

10 **6. To what extent does your confidence that the effects observed in epidemiological**  
11 **studies are attributable specifically to O<sub>3</sub> lessen or otherwise change, if at all, at the**  
12 **lower levels in the proposed range as compared to the higher levels?**  
13

14 While epidemiological studies are inherently more uncertain as exposures and risk  
15 estimates decrease (due to the greater potential for biases to dominate small effect  
16 estimates), specific evidence in the literature does not suggest that our confidence on the  
17 specific attribution of the estimated effects of ozone on health outcomes differs over the  
18 proposed range of 60-70 ppb. In framing our answer to this question, we note that the  
19 range covered is quite narrow and we would not anticipate major differences in the  
20 characteristics of the pollution mixture across this range.  
21

22 Several distinct classes of epidemiological studies are relevant in this range. For instance,  
23 mortality effects for ozone have been found in time-series studies in communities where  
24 mean ambient concentrations are well below the proposed range (e.g., Vedal et al 2003).  
25 Exercise-induced decrements in lung function, known to be causally related to ozone in  
26 controlled exposure studies, have been observed in field studies of healthy volunteers.  
27 For instance, in a cross-sectional study, Korrick et al. (1998) found hikers on Mount  
28 Washington experienced significant decreases in FEV<sub>1</sub> after prolonged exercise on days  
29 when ozone averaged 40 ppb (range 21 to 74 ppb). The magnitude of these decrements  
30 increased as mean ozone levels increased and it was nearly fourfold higher for persons  
31 with asthma than for persons without asthma. Panel studies of campers are yet another  
32 class of field studies that have shown effects on children's lung function are associated  
33 with ambient ozone. For example, in a panel of healthy children, Spektor et al. (1988)  
34 showed significant reductions in FEV<sub>1</sub> associated with one-hour average ambient ozone,  
35 even when restricted to days with ozone below 60 ppb. Similarly, in panels of children  
36 with moderate to severe asthma attending summer camp, Thurston et al. (1997) reported  
37 not only respiratory function changes, but also more clinically significant responses,  
38 including increases in physician prescribed rescue medication and respiratory symptoms.  
39 In yet another class of epidemiological studies, health care utilization for asthma has been  
40 shown to decrease when ozone concentrations decreased. For example, Friedman et al  
41 (2001) found that during the Summer Olympic Games in Atlanta in 1996 there was  
42 significantly decreased use of pediatric care for asthma that correlated best with a  
43 reduction in peak ozone concentrations. In this study, the relative risk of asthma events

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1 increased stepwise at cumulative ozone concentrations 60 to 89 ppb and 90 ppb or more  
2 compared with ozone concentrations of less than 60 ppb. The reduction of the adverse  
3 effects on asthma in this study was dependent on reduction of ozone exposures to levels  
4 below 60 ppb.

5  
6 Our confidence that the effects from epidemiological studies are attributable to ozone is  
7 also bolstered by the recognition that the endpoints of concern do not change at the lower  
8 levels of the proposed range. While it may be difficult to disentangle the effect of a  
9 single pollutant in epidemiological studies, the evidence regarding ozone-related health  
10 effects from epidemiological studies is consistent with the evidence from controlled  
11 exposure studies that involve ozone alone. Indeed, evidence from observational studies  
12 of individuals exercising outdoors indicates ozone may have even stronger lung function  
13 effects than those estimated in controlled exposure studies, suggesting the possibility that  
14 a mixture of photochemical oxidants may be more toxic than ozone alone. Finally,  
15 whether or not the effects attributed to ozone in epidemiological studies are specific to  
16 ozone vs. the entire photochemical oxidant pollutant mixture, it is likely that reductions  
17 in population exposures to ozone will result in fewer adverse health effects. Our  
18 confidence in this statement does not change at the lower levels of the proposed range.

19  
20 References Cited:

21  
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- 41  
42 **7. EPA's exposure assessment quantified the number of all children and asthmatic**  
43 **children likely to be exposed to specific benchmark levels of ozone, including in**

1 particular 60 and 70 ppb. Considering the patterns of change in the estimates of  
2 exposures of concern at and above the 60 and 70 ppb benchmark levels, and the  
3 uncertainties and limitations in the estimates, what is the relative importance from a  
4 public health perspective of the estimated reductions in exposures of concern, as  
5 well as the exposures remaining, for alternative standards across the proposed  
6 range?  
7

8 The first issue is the estimated change in exposures for alternative standards across the  
9 proposed range of 60 to 70 ppb. Table 1 in the Proposed Rules (p. 2978 in the *Federal*  
10 *Register*, January 19, 2010; included here) presents the modeled number and percentage  
11 of children with exposure (defined as at least one 8-hr average exposure per year with  
12 moderate or greater level of exercise) at each of three ozone benchmark levels of concern  
13 (80, 70 and 60 ppb) for ozone standards ranging from the old standard of 84 ppb to a  
14 lowest standard of 64 ppb, for the 12 urban areas in aggregate. Since no estimates are  
15 presented down to the lower end of the proposed range, i.e., 60 ppb, we cannot directly  
16 answer the question for the entire proposed range of the standard, based on these model  
17 estimates. However, at least for levels of concern of 70 ppb or greater, because the  
18 number and percent exposed is either zero or exceedingly small when meeting a standard  
19 of 64 ppb, depending on the year, it can be inferred that even fewer would be exposed if a  
20 standard of 60 ppb was met. For a level of concern of 60 ppb, for the year with the  
21 lowest concentrations that were considered (2004), essentially no exposures were  
22 estimated to occur when meeting the standard of 64 ppb, whereas for the year with the  
23 higher concentrations that were considered (2002), it was estimated that around 5% of  
24 children would be exposed, implying that even fewer would be exposed if a standard of  
25 60 ppb was met. Some individual city estimates of exposure were lower while others  
26 were higher than these aggregate estimates. Based on earlier uncertainty and sensitivity  
27 analyses carried out by EPA, and relative to uncertainty in health effect estimates, the  
28 extent of uncertainty in these exposure estimates is acceptable.  
29

30 The second issue relates to the public health significance of reductions in exposure for the  
31 range of standards from 70 to 60 ppb. Some of the public health significance is  
32 addressed by the risk assessment for selected endpoints (see responses to charge question  
33 #8). For endpoints for which it was not possible to carry out a quantitative risk  
34 assessment (e.g., pulmonary inflammation and bronchial hyper-responsiveness), public  
35 health significance is gauged in light of the toxicologic, human clinical and  
36 epidemiological findings. Toxicologic data (i.e., animal experimental data) are largely  
37 not helpful in this regard. In the absence of demonstrable effects in human clinical  
38 studies (in normal individuals or those with mild disease) on other than lung function  
39 decrements for exposure concentrations less than 80 ppb, we can only infer effects at  
40 lower concentrations and in the more severely diseased. Findings from epidemiological  
41 studies are less causally conclusive, but indicate effects at substantially lower  
42 concentrations than were used in the experimental studies. The benchmark levels in  
43 Table 1 correspond to greater degrees of uncertainty going from 80 down to 60 ppb. Part

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1 of this uncertainty relates to the precious little human clinical data that were available for  
2 consideration at exposure concentrations below 80 ppb, and what exists is essentially  
3 limited to effects on lung function. Uncertainty also comes from the reliance on  
4 epidemiological (non-experimental) findings at the lower concentrations. Therefore,  
5 while (in Table 1) the predicted number exposed increases for every level of the standard  
6 as the benchmark level of concern is reduced, the public health impact of this increase in  
7 number exposed becomes less certain. One could argue that since there is no clear  
8 threshold for ozone effects, increases in the number exposed translates directly into  
9 increases in health effects. This ignores not just increasing uncertainty, but also the fact  
10 that “exposure” at the decreasing benchmark levels results in an increasingly smaller  
11 percentage of people affected at the decreasing levels of exposure. These latter  
12 percentages are difficult to estimate for endpoints other than, perhaps, acute lung function  
13 changes. Consequently, the public health significance is difficult to gauge for these other  
14 endpoints.

15  
16 What then can be said about the public health significance of exposures at the different  
17 levels of concern across the different standards being considered? It is prudent to assume  
18 that for at least some segments of the population, adverse effects (in addition to acute  
19 lung function effects) occur at levels below 80 ppb and, making use of epidemiologic  
20 observations, that there is no obvious threshold ,with effects occurring even at the  
21 benchmark level of concern of 60 ppb. At some concentration the number of individuals  
22 affected must be exceedingly small, even though the number of days with these lower  
23 ozone concentrations is relatively large. From Table 1, in the year with the higher ozone  
24 concentrations (2002), less than 20% of children will experience at least one day at an  
25 exposure of concern of 60 ppb at a standard of 70 ppb, and only a small fraction of these  
26 children will be expected to experience an effect on these other health endpoints (e.g.,  
27 pulmonary inflammation and bronchial hyperresponsiveness). At a standard of 64 ppb,  
28 approximately 5% of children will be exposed, of whom only a small fraction will be  
29 sensitive. Therefore, at the lowest concentration of concern (60 ppb), a further reduction  
30 in the standard from 70 ppb would be expected to reduce an already relatively small  
31 public health impact to an even smaller impact.

32  
33

**Table 1. Number and Percent of All and Asthmatic School Age Children in 12 Urban Areas Estimated to Experience 8-Hour Ozone Exposures Above 0.080, 0.070, and 0.060 ppm While at Moderate or Greater Exertion, One or More Times Per Season, and the Number of Occurrences Associated with Just Meeting Alternative 8-Hour Standards Based on Adjusting 2002 and 2004 Air Quality Data<sup>1,2</sup>**

Benchmark Levels of Exposures of Concern (ppm)	8-Hour Air Quality Standards <sup>3</sup> (ppm)	All Children, ages 5-18 Aggregate for 12 urban areas Number of Children Exposed (% of all) [% reduction from 0.084 ppm standard]		Asthmatic Children, ages 5-18 Aggregate for 12 urban areas Number of Children Exposed (% of group) [% reduction from 0.084 ppm standard]	
		2002	2004	2002	2004
		0.080	0.084	700,000 (4%)	30,000 (0%)
	0.080	290,000 (2%) [70%]	10,000 (0%) [67%]	50,000 (2%) [54%]	0 (0%)
	0.074	60,000 (0%) [91%]	0 (0%) [100%]	10,000 (0%) [91%]	0 (0%)
	0.070	10,000 (0%) [98%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
	0.064	0 (0%) [100%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
0.070	0.084	3,340,000 (18%)	260,000 (1%)	520,000 (20%)	40,000 (1%)
	0.080	2,160,000 (12%) [35%]	100,000 (1%) [62%]	330,000 (13%) [36%]	10,000 (0%) [75%]
	0.074	770,000 (4%) [77%]	20,000 (0%) [92%]	120,000 (5%) [77%]	0 (0%) [100%]
	0.070	270,000 (1%) [92%]	0 (0%) [100%]	50,000 (2%) [90%]	0 (0%) [100%]
	0.064	30,000 (0.2%) [99%]	0 (0%) [100%]	10,000 (0.2%) [98%]	0 (0%) [100%]
0.060	0.084	7,970,000 (44%)	1,800,000 (10%)	1,210,000 (47%)	270,000 (11%)
	0.080	6,730,000 (37%) [16%]	1,050,000 (6%) [42%]	1,020,000 (40%) [16%]	150,000 (6%) [44%]
	0.074	4,550,000 (25%) [43%]	350,000 (2%) [80%]	700,000 (27%) [42%]	50,000 (2%) [81%]
	0.070	3,000,000 (16%) [62%]	110,000 (1%) [94%]	460,000 (18%) [62%]	10,000 (1%) [96%]
	0.064	950,000 (5%) [88%]	10,000 (0%) [99%]	150,000 (6%) [88%]	0 (0%) [100%]

<sup>1</sup> Moderate or greater exertion is defined as having an 8-hour average equivalent ventilation rate  $\geq 13$  l-min/m<sup>2</sup>.

<sup>2</sup> Estimates are the aggregate results based on 12 combined statistical areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, D.C.). Estimates are for the ozone season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas.

<sup>3</sup> All standards summarized here have the same form as the 8-hour standard established in 1997 which is specified as the 3-year average of the annual 4<sup>th</sup> highest daily maximum 8-hour average concentrations must be at or below the concentration level specified. As described in the 2007 Staff Paper (EPA, 2007b, section 4.5.8), recent O<sub>3</sub> air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet

□ □ the specified standards.

1       **8. EPA’s quantitative risk assessment estimated the numbers of occurrences of various**  
2       **ozone-related health effects associated with just meeting alternative standard levels**  
3       **down to a standard level of 64 ppb. Considering the patterns of change in the**  
4       **estimates of health effects in the risk assessment at the alternative standard levels,**  
5       **and the uncertainties and limitations in the estimates, what is the relative**  
6       **importance from a public health perspective of the estimated reductions in risk, as**  
7       **well as the risk remaining, for alternative standards across the proposed range?**  
8       **Please consider this question in light of the scientific evidence as a whole.**  
9

10       The evidence from epidemiological studies of ozone-related mortality published prior to  
11       2006 was not considered sufficiently robust by CASAC to serve as the sole basis for  
12       establishing a new NAAQS. However, based upon EPA estimates of effects on morbidity  
13       and mortality in the risk assessment components of the 2007 Staff Paper, CASAC previously  
14       and unanimously concluded, based primarily on the effects on morbidity, that “Beneficial  
15       effects in terms of reduction of adverse health effects were calculated to occur at the lowest  
16       concentration considered (i.e., 0.064 ppm).” (Henderson, 10/24/06, p.4).

17  
18       Table 2 in the 2007 Staff Paper and reproduced in the Federal Register as part of this  
19       Proposed Rules material (Vol. 75, No. 11/Tuesday, January 19, 2010) is provided below, as  
20       background for addressing this charge question. With regard to protecting the public health,  
21       the numbers of children aged 5-18 who would suffer at least a once per year drop in their  
22       pulmonary function of a potentially clinically relevant amount with 6-hour ambient air ozone  
23       concentrations at 74 - 64 ppb is estimated to be between 340,000 and 180,000 in the worse  
24       case vs 130,000 and 70,000 in the best case scenarios (as estimated from 15 urban sites).  
25       Among children with asthma over this same exposure range, potentially important decreases  
26       in pulmonary function would occur in 5% to 1.5% of all children with asthma (estimated  
27       from 5 urban sites). It is not clear that 2002 is the “worse case” or that 2004 is the “best  
28       case,” but these two scenarios provide bounds. Since estimates were not presented down to  
29       the lower end of the proposed range, i.e., 60 ppb, we cannot, based on the model results  
30       available, answer the charge question for the entire proposed range of the standard.  
31       However, the available estimates, which represent a substantial fraction of at-risk children,  
32       would represent a significant public health impact. Reduction of the NAAQS to 60 ppb  
33       would further reduce the number of people affected.

34  
35       As discussed at length in the Criteria Document and Staff Paper, there is no evidence of a  
36       threshold, i.e., the magnitude of the effects measured in clinical studies diminishes with  
37       decreasing ozone concentration, but does not reach the functional level associated with  
38       exposure to ozone-free clean air. Furthermore, there is a great degree of variability of  
39       response magnitude among the individuals studied, with some having clinically-relevant  
40       responses, even at 60 ppb, and more of them with such responses at higher concentrations.  
41       Importantly, these clinical studies were carried out in normal healthy adults, and even in  
42       these volunteers from 7-20% had clinically relevant changes in pulmonary function or  
43       symptoms. These findings suggest that comparable ozone exposures to more sensitive

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1 people could lead to more adverse health effects in the substantial proportion of the  
2 population with lung disease. .

3  
4 Thus, considering the available evidence and the findings of the exposure and risk  
5 assessment, a substantial number of susceptible individuals are at risk and the degree of  
6 protection afforded to them would increase as the NAAQS is lowered. The evidence  
7 available suggests that an adequate margin of safety cannot be achieved for all and that a  
8 level should be set that reduces the at-risk population to a minimally acceptable number, with  
9 a reasonable degree of certainty. The unanimous recommendation of CASAC, given in  
10 Chairperson Henderson's 2008 letter to the Administrator was to set the NAAQS within the  
11 range of 60 to 70 ppb. In that range, CASAC found that the evidence was sufficiently certain  
12 to be confident of public health benefits and additional protection for susceptible groups. We  
13 are still in agreement with that conclusion.

14

**Table 2. Number and Percent of All and Asthmatic School Age Children in Several Urban Areas Estimated to Experience Moderate or Greater Lung Function Responses One or More Times Per Season Associated with 8-Hour Ozone Exposures Associated with Just Meeting Alternative 8-Hour Standards Based on Adjusting 2002 and 2004 Air Quality Data<sup>1,2</sup>**

8-Hour Air Quality Standards <sup>3</sup>	All Children, ages 5-18 FEV <sub>1</sub> ≥ 15 percent Aggregate for 12 urban areas Number of Children Affected (% of all) [% reduction from 0.084 ppm standard]		Asthmatic Children, ages 5-18 FEV <sub>1</sub> ≥ 10 percent Aggregate for 5 urban areas Number of Children Affected (% of group) [% reduction from 0.084 ppm standard]	
	2002	2004	2002	2004]
0.084 ppm (Standard set in 1997)	610,000 (3.3%)	230,000 (1.2%)	130,000 (7.8%)	70,000 (4.2%)
0.080 ppm	490,000 (2.7%) [20% reduction]	180,000 (1.0%) [22% reduction]	NA <sup>4</sup>	NA
0.074 ppm	340,000 (1.9%) [44% reduction]	130,000 (0.7%) [43% reduction]	90,000 (5.0%) [31 % reduction]	40,000 (2.7%) [43% reduction]
0.070 ppm	260,000 (1.5%) [57% reduction]	100,000 (0.5%) [57% reduction]	NA	NA
0.064 ppm	180,000 (1.0%) [70% reduction]	70,000 (0.4%) [70% reduction]	50,000 (3.0%) [62% reduction]	20,000 (1.5%) [71% reduction]

<sup>1</sup>Associated with exposures while engaged in moderate or greater exertion, which is defined as having an 8-hour average equivalent ventilation rate ≥ 13 l-min/m<sup>2</sup>.

<sup>2</sup>Estimates are the aggregate central tendency results based on either 12 urban areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, D.C.) or 5 urban areas (Atlanta, Chicago, Houston, Los Angeles, New York). Estimates are for the O<sub>3</sub> season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas.

<sup>3</sup>All standards summarized here have the same form as the 8-hour standard set in 1997, which is specified as the 3-year average of the annual 4<sup>th</sup> highest daily maximum 8-hour average concentrations. As described in the 2007 Staff Paper (section 4.5.8), recent O<sub>3</sub> air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard set in 1997 and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet the specified standards

<sup>4</sup>NA (not available) indicates that EPA did not develop risk estimates for these scenarios for the asthmatic school age children population.