Preliminary Comments on the PA from Dr. H. Christopher Frey

Generally, the policy assessment is well-written, logical, clear, and scientifically-based. This is one of the better first draft PA's that I have ever reviewed. Well done.

Answers to Charge Questions

5. The discussion of the quantitative analysis of exposure and risk (section 3.2.2) draws from the analyses described in the draft Risk and Exposure Assessment (REA).
a. Does this discussion accurately reflect the analyses contained in the draft REA, as well as associated key uncertainties and public health implications?

Yes. In fact, in some ways, the PA does a better job of explaining the exposure assessment than does the REA (see detailed comments on both the REA given separately and the PA given below).

b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

Yes. Very nice job.

7. What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current standard? Does the discussion provide an appropriate and sufficient rationale to support preliminary staff conclusions?

Very well done. Details are below.

Detailed Comments

General note on these detailed comments: Many of these include points that should be touched upon in the CASAC letter to the Administrator regarding the CASAC's scientific advice regarding the indicator, averaging time, level, form of the standard and the adequacy of the current standard.

- P. 2-2/line 11: why "likely"? delete
- 2-2/13: change "energy" to "electricity"
- Page 3-7: Concur that:
    - Protection against 5- to 10-minute exposure events can be achieved with a one-hour standard. Comparative analysis of the highest 5 minute average in an hour with the hourly concentration illustrates that these two concentrations are dependent on each other, and that one can serve as a surrogate for the other.

    - A one hour averaging time is effective at limiting 5-minute peak exposures to SO_2.
    - A one hour standard can reduce the upper end of the distribution of SO_2 concentration that are associated with more severe adverse respiratory outcomes.
    - The strongest evidence of causality for adverse effects from exposure to SO2 is for respiratory effects from short-term exposures as short as 5-minutes.
    - A one hour standard is appropriate
- Page 3-8: concur that:
    - A concentration-based form averaged over three years is more stable than a non-exceedance form.
    - A 99th percentile form is effective at limiting 5-minute exposures of concern.
    - A lower percentile would lead to a larger number of 5-minute exposures of concern
    - The 99th percentile form averaged over three years is an appropriate form
- Page 3-8 to 3-11: Concur that:
    - Controlled human exposure studies are the most direct and relevant evidence for respiratory effects from short-term exposure to SO2
    - Effect in exercising people with asthma were adverse for 5-minute exposures as low as 200 ppb. The frequency and severity of effects increases at higher doses, which indicates that there is a monotonic dose-response relationship within the range of observed data.
- Page 3-14: choice of indicator. Concur that:
    - SO2 is the most abundant sulfur oxide in the atmosphere and is most closely linked with adverse health effects. Therefore, SO2 is the appropriate choice of indicator for oxides of sulfur.
- Page 3-15: hazard identification. Concur that:
    - SO2 exposures as short as 5-minutes are causally related to respiratory effects in at-risk individuals. The key respiratory effect is asthma exacerbation. At-risk individuals include asthmatics.
    - The clearest evidence supporting causality is from controlled human studies.
    - These studies demonstrated lung function decrements, and respiratory symptoms, in people with asthma who are exposed to SO2 while at elevated breathing rates.
    - Bronchoconstriction is the most sensitive indicator of SO2-induced lung function effects.
    - Bronchoconstriction is associated with increase in airway resistance.
    - Bronchoconstriction is observed in controlled human exposure studies after exposure averaging times as short as 5-minutes at concentrations as low as 200 ppb, among people with asthma while breathing at elevated ventilation.
    - The evidence from controlled human studies is the same as from the last review.

- Epidemiologic studies provide additional support for association between SO2 exposure and asthma exacerbation. Expidemiologic studies are subject to uncertainty because they are based on using fixed site monitoring concentration as a surrogate for actual exposure concentration, and they may be confounded by co-pollutants such as particulate matter or others. However, from the available epidemiologic studies, there is consistency in a finding of association between short-term SO2 exposure and asthma exacerbation.
- The weight of evidence for a causal relationship between SO2 exposure and other short-term end points ,and regarding end-points for long-term exposure, are much weaker than for respiratory effects from short-term exposure.
- There is some emerging evidence of the potential for long-term exposure to SO2 to lead to development of new onset asthma, based on toxicological studies.

- With regard to at-risk populations (p 3-19 to 3-21), concur that:
  - People with asthma are at increased risk for SO2 related respiratory effects, particularly asthma exacerbation, from short-term exposure.
  - Children with asthma may be particularly at risk compared to adults with asthma
  - Oral breathing and increased ventilation leads to more SO2 penetration into the lower airways.
  - Children spend more time outdoors and have a higher proportion of oral breathing at high ventilation than do adults
- With regard to exposure concentrations associated with health effects (p.3-21 to 3-27), concur that:
  - SO2-induced respiratory symptoms from short-term exposures increase with increasing concentration, demonstrating a monotonic relationship between response and exposure.
  - SO2-induced bronchoconstriction occurs rapidly. Responses after 5-minutes of exposure are similar to those from somewhat longer exposures. Thus, a 5-minute basis for the exposure-response relationship is appropriate.
  - Exposures of human subjects with moderate asthma to 5- to 10- minute exposures of SO2 at concentrations as low as 200 ppb elicited moderate or greater bronchoconstriction for a portion of the exercising subjects.
  - Evidence is limited for exposure concentrations below 200 ppb down to 100 ppb, and are based on mouth breathing rather than free-breathing, and suffers from other limitations.
  - Epidemiologic evidence is generally coherent with controlled human study results, but is subject to uncertainties regarding exposure error and confounding.
  - Key uncertainties in the controlled human study data include:
    - The severity and prevalence of adverse responses to short term exposures less than 200 ppb

        - Lack of data for adults with more severe asthma and for children with asthma
        - The use of allometric principles to estimate the frequency of exceeding benchmark dose metrics for children with asthma
        - The potential synergistic effects of co-exposures to other pollutants that might amplify the response from SO2 exposure
    - There is also uncertainty regarding the potential role of long-term exposure to SO2 with respect to adverse effects, with limited evidence suggesting that long-term exposure can lead to development of asthma.
- In terms of public health implications (page 3-32):
    - People with asthma are a key population at risk from short-term exposure to SO2
    - Available evidence indicates that absolute changes in lung function are greater for individuals with more severe asthma
    - However, since controlled human studies cannot include subjects with severe asthma, there is lack of data regarding the response of people with severe asthma to short-term SO2 exposure.
    - Approximately 8% of the U.S. population has asthma
    - 10.2% of children aged 15 to 19 years old have asthma
    - Asthma is more prevalent for boys than girls, for black non-Hispanic children than children of other races or ethnicities, and for children and adults in poverty.
- Exposure/risk analysis (starting on page 3-35).
    - The three study areas were appropriately selected and analyzed.
    - The results of the exposure and dose assessments are relevant to assessment of the adequacy of the current standard
    - Since the last review, the exposure assessment has been updated in the following important ways:
        - Expanded CHAD
        - Updated NHANES data
        - Updates to the algorithms used to estimate resting metabolic rate
        - Updates to the ventilation rate algorithm
        - Updated population demographic data
        - Analysis for a three year simulation period consistent with the form of the current standard
        - Air quality data based on more recent emissions and circumstances since the 2010 revision of the standard.
    - With regard to the 300 ppb and 400 ppb benchmarks:
        - No children or adults were estimated to experience a single day or more than a single day with 5-minute exposures at these benchmarks.
    - With regard to the 200 ppb benchmark:

        - Over a three year period, less than 1 percent of children with asthma were estimated to experience exposures at or above the benchmark for a single day, while being at elevated ventilation rates.
    - With regard to the 100 ppb benchmark:
        - 20% to 25% of children with asthma are estimated to experience at least one day above this benchmark over a three year period, while being at elevated ventilation rates.
    - The estimates for adults are generally lower.
    - Based on air quality just meeting the current standard, 1.1% of children with asthma are estimated to experience at least one day in three years with lung function decrement based on a doubling or more of sRaw, with 0.2% experiencing a tripling or more of sRaw.
    - The results are not highly sensitive to the choice of air quality adjustment method.
    - In the single year with the highest concentrations, nearly 98% of the population of children with asthma in the Fall River study area would not be expected to experience a day with 5-minute exposures greater than 200 ppb and would not experience as much as a doubling of sRaw.
    - Uncertainties in the exposure and risk assessment include:
        - Estimation of the fine scale temproral pattern in 5-minute exposure concentrations
        - Lack of exposure estimation for population groups that may be more sensitive, such as adults and children with severe asthma
        - Other combinations of geographic proximity of SO2 emission sources and populations
        - Uncertainties in exposure-dose response at low dose
        - Lack of data regarding the effect of repeated or cumulative short-term exposures
        - Of these, the most significant is the lack of data for persons with more severe asthma.
    - With regard to public health, effects associated with exposures as low as 200 ppb are adverse.
- Adequacy of the current standard:
    - Controlled human studies provide conclusive scientific evidence that short term exposures to concentrations at or above 200 ppb poses adverse effects among adults with moderate asthma. Based on scientifically established and reasonable allometric extrapolation methods, such exposures are also deemed to be adverse for children with asthma.
    - Although there are improved data sets and algoritms for use in exposure assessment, and support from additional epidemiologic studies, the strongest

scientific evidence is from the same set of controlled human experiments that were available in the last review.

- The current review of the previously available controlled human studies, coupled with newer epidiemiologic studies and an updated exposure and risk assessment, does not lead to different conclusions than those reached in the last review regarding the choices of indicator, averaging time, level, and form, and provides support that the current standard is adequate.
- Although there is some controlled human study evidence of effect at 5-minute concentrations lower than 200 ppb, which is the basis for the current standard, inconsistency in study design and lack of data lead to uncertainty in estimating the exposure-response relationship at such exposures. The available controlled human study evidence does not include adult subjects with severe asthma nor children.
- It is recognized that children spend more time outdoors in terms of frequency and duration, and that when they experience high ventilation rates there is a greater proportion of oral breathing. These two factors can lead to high exposures and doses.
- There are more than 24 million people with asthma in the U.S., including more than 6 million children.
- The findings from the REA do not call into question the adequacy of the current standard with regard to the sensitive subpopulation of children and short-term exposures leading to asthma exacerbation.
- Thus, concur with the recommendation to retain the current standard without revision.
- With regard to key uncertainties, which are appropriately identified but perhaps incomplete, should also include the following:
    - Uncertainties related to causal relationships between short-term exposure to SO2 and endpoints other than asthma exacerbation, and between long-term exposure to SO2 and various endpoints, such as development of asthma.
    - The use of allometric methods in risk assessment for children versus adults