Questions for Non-Member Consultants on the Ozone ISA from Dr. Tony Cox

Background: *The Ozone ISA states (p. E1) that "Key scientific conclusions (i.e., causality determinations; Section ES.4) are presented and explained. They provide the scientific basis for developing risk and exposure analyses, policy evaluations, and policy decisions for the review. …The ISA thus provides the policy-relevant scientific information that supports the review of the NAAQS."*

Overarching Questions: I have the following overarching methodological questions about the ISA. (I do *not* request direct responses to these overarching questions, although I welcome answers from experts who care to provide them. I do seek answers to the more specific questions that follow these overarching ones.)

1. Is the scientific information provided by the ISA *clear*?
    a. Is it clear how the ISA's causal determination conclusions can be tested, and either verified or refuted (or left undecided), by observations?
    b. Do the concepts and terms used to express key scientific conclusions in the ISA, especially the causal determination categories, have clear scientific meanings (e.g., unambiguous operational definitions)?
    c. Is it clear and generally understood and agreed what the key conclusions mean? Specifically, are the causal determination categories used to communicate key conclusions unambiguous and well defined?
    d. Do those who read the ISA have a shared, unambiguous understanding of what its key scientific conclusions (i.e., causality determinations) imply about how or whether changes in ozone air pollution would change public health outcomes?
2. Is the scientific information provided by the ISA *sound*?
    a. Are its conclusions logically implied by the data and analyses on which they are based?
    b. Are its conclusions correctly stated and caveated?
    c. Is it clear than conclusions do not reflect selection bias in the choice of studies relied on? Are its conclusions consistent with other relevant data and studies not included in the ISA?
    d. Is it clear how studies were selected for inclusion in the ISA, and why individual studies were included or excluded?
    e. Are there other studies that are omitted from the Draft ISA that should be included?
    f. Are the studies relied on to draw conclusions themselves sound (i.e., do their conclusion follow from the data and analyses presented, are potential confounders and modeling biases correctly accounted for, and have other criteria for study quality been systematically and correctly applied?)
    g. Is the implementation of the PECOS approach (p. IS-4 and Appendix 10) and the use of quality assurance and peer review (p. IS-5) adequate to assure that relevant studies were selected and that unsound conclusions were detected and avoided?
3. Are the key scientific conclusions provided by the ISA *scientific*?
    a. Do they deal with testable (and potentially falsifiable) facts about the observable world?

b. Can the information provided be independently verified? If so, how?

4. Is the scientific information provided by the ISA *policy-relevant*?
    a. Does the information presented address how changing ozone NAAQS would change (probable) public health outcomes?
    b. Is uncertainty about the changes in risks caused by changes in exposure appropriately characterized for use in policy making?
    c. Are effects of other factors that modify the health effects of ozone (e.g., co-exposures, co-morbidities, poverty, lagged daily high and low temperatures, etc.) and of confounders characterized, so that the effects on health from changing ozone alone, without changing other factors, are made clear?

These overarching questions motivate the following more specific questions, on which I seek your advice.

1. **Background:** *The ISA states (p. I-6) that "This ISA draws conclusions about the causal nature of relationships between exposure to ozone and health and welfare effects for categories of related effects (e.g., respiratory effects) by integrating recent evidence across scientific disciplines and building on the evidence from previous assessments. Determinations are made about causation, not just association, and are based on judgments of consistency, coherence, and biological plausibility of observed effects, as well as related uncertainties."* I think "observed effects" here probably means "observed associations," since associations can be calculated from data, but causal effects of exposures (e.g., the difference between the outcome that occurred and the outcome that would have occurred had exposures been different) are inherently unobservable. (Also, consistency, coherence, biological plausibility, and other Bradford Hill considerations apply specifically to associations.) However, associations are not effects (Petitti DB. Associations are not effects. Am J Epidemiol. 1991 Jan 15; 133(2):101-2.) As noted in a recent review, "The field of environmental health has been dominated by modeling associations, especially by regressing an observed outcome on a linear or nonlinear function of observed covariates. Readers interested in advances in policies for improving environmental health are, however, expecting to be informed about health effects resulting from, or more explicitly caused by, environmental exposures. The quantification of health impacts resulting from the removal of environmental exposures involves causal statements. Therefore, when possible, causal inference frameworks should be considered for analyzing the effects of environmental exposures on health outcomes." (Bind MA. Causal Modeling in Environmental Health. Annu Rev Public Health. 2019 Apr 1;40:23-43. doi: 10.1146/annurev-publhealth-040218-044048.)
    Question: My question is: *Can valid determinations of manipulative or interventional causation – that is, how and whether changing exposure would change health risks – be made based on observed associations of the types analyzed in the ISA?* I emphasize manipulative and interventional causation (rather than predictive (Granger) causation, but-for causation, epidemiological (attributive) causation, mechanistic causation, etc.) because it is most relevant for policy makers. (Further background for this question and references to relevant technical literature are in Cox LA

Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. 2018 Nov 15:1-31. doi: 10.1080/10408444.2018.1518404.)

2. **Background:** *The ISA states that "The ISA uses a formal causal framework to classify the weight of evidence using a five-level hierarchy [i.e., 'causal relationship'; 'likely to be a causal relationship'; 'suggestive of, but not sufficient to infer, a causal relationship'; 'inadequate to infer a causal relationship'; 'not likely to be a causal relationship' as described in Table II of the Preamble (U.S. EPA, 2015)] that is based largely on the aspects for causality proposed by Sir Austin Bradford Hill, as well as other frameworks to assess causality developed by other organizations."* I worry that the causal determination categories, and conclusions expressed using them, lack clear scientific meanings. (I understand that they may have clear implications for action, e.g., that effects labeled "causal" or "likely to be causal" may be considered further as grounds for possible revision of NAAQS regulations.) I would like to learn whether expert readers of the ISA have a common, unambiguous understanding of what these categories mean. Since the causal determination framework is used to communicate the key findings of the ISA, I believe it is important to obtain a thorough understanding of what its terms mean.
Questions: The following questions are intended to help assess the conceptual clarity and meaning of the causal determination categories, and of key conclusions expressed using them, such as those in Table ES-1 (p. E-5) of the Draft ISA. Some of the questions are quite specific (of the form "Does this category mean or imply this condition?"). For clarity, *please provide, if possible, an explicit "yes" or "no" answer to each question*, in addition to any further answer you may choose to give. If neither response is appropriate, please provide, if possible, an explicit "unsure of the answer/answer is not clear to me/ unknown" or "answer depends on conditions" in addition to any further answer you may give. Where your answers are "yes" or "no," please provide specific supporting references. Where they are "answer depends on conditions", please specify the conditions on which the answer depends.
    a. A preliminary question: *Is this actually a "formal causal framework*"? (It seems to me to be excessively informal, akin to a Rorschach test, insofar as I have been unable to obtain any formal, unambiguous or operational definitions of the quoted terms 'causal relationship', 'likely to be a causal relationship', 'suggestive of, but not sufficient to infer, a causal relationship', 'inadequate to infer a causal relationship', and 'not likely to be a causal relationship' described in Table II of the Preamble. This seems to me to leave users to make up their own (possibly different) implicit definitions, or to avoid specifying definitions at all. I would greatly appreciate references to any formal, unambiguous operational definitions of these terms. The descriptions in Table II of the Preamble seem to me to be logically incoherent and ambiguous, as discussed further in Cox LA (2019), Improving causal determination. www.sciencedirect.com/science/article/pii/S2590113319300045.)
    b. *Does the ISA's causal determination framework clearly distinguish between necessary and sufficient causation?* Does a causal determination of "causal relationship" between ozone exposure and a health response imply that exposure is *sufficient* to cause (or increase the risk of) the response? Does it imply that absence of exposure is sufficient to prevent (or reduce the risk of) the response? If exposure is sufficient to cause a response, but absence of

exposure does not reduce the risk of response (because other factors that are always present are also sufficient to cause it), then is the exposure-response relationship still considered "causal" in the ISA framework? (For background, see Gleiss A, Schemper M. Quantifying degrees of necessity and of sufficiency in cause-effect relationships with dichotomous and survival outcomes. Stat Med. 2019 Oct 15;38(23):4733-4748. doi: 10.1002/sim.8331.)

c. Does a determination that exposure has a "causal relationship" with a health effect in a population imply that reducing exposure would reduce risk of the health effect in the population, other factors being held fixed? In other words, *does a "causal relationship" determination imply a manipulative causal relationship?*
d. *Can causal determinations be incorrect*? (Or, to the contrary, are they performative utterances?)
e. If causal determinations can be mistaken, then *is it clear how uncertainty about which category is correct should be (or has been) resolved* in assigning a final causal determination category, as in Table ES-1 p. ES-5) of the ISA?
f. If causal determinations can be incorrect, then *is it clear how observations could be used to test and falsify a given causal determination if it is not correct?* For example, is it completely clear how someone can use relevant data to show that a determination of "causal relationship" or "likely to be causal" in the ISA is incorrect, if indeed that is the case?
g. If causal determinations can be incorrect, then *is the correctness of each causal determination in table ES-1 formally and transparently evaluated in the ISA?* In other words, have formal rules for determining the correctness of the causal determinations in Table ES-1 (p. ES-5) from the data and evidence presented been explicitly stated, applied systematically, and the results documented? (If so, where?)
h. *Does a determination that an exposure-response (or concentration-response (C-R)) relationship is a "causal relationship" imply that it is entirely causal*, with no contribution from incompletely controlled confounding, modeling errors and biases, or other non-causal sources? If not, is there a clearly defined lower bound on how much of the relationship (e.g., how much of the slope of a C-R regression line) must be causal in order for the whole relationship to be classified as causal? (If so, what is it?)
i. *Does a determination that a C-R relationship is a "causal relationship" imply 100% certainty that it is causal?* If not, is there a clearly specified lower bound on how probable it must be that the relationship is causal in order for it to be classified as causal? (If so, what is it?)
j. *Does a determination that a C-R relationship is a "causal relationship" imply that it is causal for every member of a population,* or might it be deemed "causal" if it is causal for a sensitive subpopulation only? In the latter case, is there a clearly specified lower bound on the fraction of the exposed population for which the relationship must be causal, in order for the whole relationship to be classified as causal? (If so, what is it?)
k. *Are the five categories mutually exclusive?* (Again, please answer yes, no, or unclear, in addition to any other answer you may give. If the answer is yes or no, please cite supporting references.) Might a body of mixed evidence satisfy the definitions for more than one of these categories? (Background for this question is in Cox LA, Improving causal

determination. www.sciencedirect.com/science/article/pii/S2590113319300045.) For example, does evidence justifying a causal determination of "causal relationship" preclude (or, conversely, does it imply) a causal determination of "likely to be a causal relationship"? Is evidence categorized as "inadequate to infer a causal relationship" a superset of, a subset of, a disjoint set from, or an overlapping set with, evidence categorized as "suggestive of, but not sufficient to infer, a causal relationship"? Is it possible for a body of evidence to be both "suggestive of, but not sufficient to infer, a causal relationship" and also "inadequate to infer a causal relationship"?

l. *Are the five categories collectively exhaustive?* For example, is evidence satisfying "not a causal relationship" included in any of the five categories? (If so, in which one(s)?) Similarly, is each of the following possible characterizations of evidence compatible with exactly one of the five causal determination categories? (If so, which one? If it is compatible with none, or more than one, then is it clear how one of the five categories should be selected to describe such evidence?)
    i. "likely not to be a causal relationship"
    ii. "likely to be a non-causal relationship" (e.g., a relationship due to confounding or modeling biases)
    iii. "likely to be a predominantly non-causal relationship (e.g., due to residual confounding or to coincident historical trends), but some causal component cannot be ruled out"
    iv. "likely to be a predominantly causal relationship, but some non-causal component cannot be ruled out"
    v. "equally likely to be a causal relationship or a non-causal relationship"
    vi. "more likely than not to be a causal relationship, but evidence is inadequate to infer a causal relationship"
    vii. "likely to have been a causal relationship in the past, when conditions were different, but unlikely to be a causal relationship in the future"
    viii. "likely to be a causal relationship for a few individuals in the population, but not likely to be a causal relationship for the rest of them"
    ix. "causal relationship in the sense of Bradford Hill, but not a causal relationship in the sense of Granger" (more succinctly, "attributive cause but not predictive cause")
    x. "predictive cause but not a mechanistic cause and not a manipulative cause"

m. Can a body of evidence be categorized as "likely to be causal" if the probability of causality based on the evidence is less than 50%?

3. **Background:** The preceding questions essentially ask about whether the scientific information provided by the ISA is *meaningful,* and what the terms used in the ISA to communicate it mean. The following questions (a through g) ask whether the scientific information provided by the ISA is *sound,* i.e., are its conclusions derived by valid inference from true premises? Are the stated conclusions implied by the data and analyses used to support them? Are they consistent with other data and analyses that are at least as good as those selected? Are they appropriately caveated?

a. *Study selection and interpretation.* **Background:** Appendix 10 of the ISA describes the study selection process for the ISA. To quickly spot check the results, I searched PUBMED for "ozone respiratory effects causal." Three of the top seven articles returned are as follow, shown here with selected conclusions (emphases added):

- Qian Z, He Q, Lin HM, Kong L, Zhou D, Liang S, Zhu Z, Liao D, Liu W, Bentley CM, Dan J, Wang B, Yang N, Xu S, Gong J, Wei H, Sun H, Qin Z; HEI Health Review Committee. Part 2. Association of daily mortality with ambient air pollution, and effect modification by extremely high temperature in Wuhan, China. Res Rep Health Eff Inst. 2010 Nov;(154):91-217. "Among the gaseous pollutants, we also observed statistically significant associations of mortality with NO, and SO2, and that the estimated effects of these two pollutants were stronger than the PM10 effects. The patterns of NO2 and SO2 associations were similar to those of PM10 in terms of sex, age, and linearity. ***O3 was not associated with mortality***."
- Cox LA Jr, Popken DA. Has reducing fine particulate matter and ozone caused reduced mortality rates in the United States? Ann Epidemiol. 2015 Mar;25(3):162-73. doi: 10.1016/j.annepidem.2014.11.006. "***There were no significant positive associations between changes in PM2.5 or O3 levels and corresponding changes in disease mortality rates*** between 2000 and 2010, nor for shorter time intervals of 1 to 3 years."
- Goodman JE, Prueitt RL, Chandalia J, Sax SN. Evaluation of adverse human lung function effects in controlled ozone exposure studies. J Appl Toxicol. 2014 May;34(5):516-24. doi: 10.1002/jat.2905. "Overall, ***these studies do not demonstrate a causal association between ozone concentrations in the range of the current National Ambient Air Quality Standard and adverse effects on lung function***."

None of these negative results is mentioned in the ISA.

For studies that that *are* cited in the ISA, I performed the following spot checks and found the following results.

- Page 3-91 of the ISA states that "A limited number of recent studies provide evidence of an association between long-term exposure to ozone and asthma development in children. … An overview of the evidence is provided below. A recent CHS analysis examined asthma incidence in relation to improved air quality in nine southern California communities (Garcia et al., 2019). ***Decreases in baseline ozone concentrations in three CHS cohorts, enrolled in 1993, 1996, and 2006, were associated with decreased asthma incidence.***" However, Garcia et al. (2019) actually state that "Among children in Southern California, decreases in ambient nitrogen dioxide and PM2.5 between 1993 and 2014 were significantly associated with lower asthma incidence. ***There were no statistically significant associations for ozone*** or PM10." (Garcia E, Berhane KT, Islam T, McConnell R, Urman R, Chen Z, Gilliland FD. Association of Changes in Air Quality With Incident Asthma in Children in California, 1993-2014. JAMA. 2019 May 21;321(19):1906-1915. doi: 10.1001/jama.2019.5357. Emphasis added.)
- Table 3-3 on "Summary of evidence for a likely to be causal relationship between long-term ozone exposure and respiratory effects" cites the study of Moore et al. (2008)

("Ambient ozone concentrations cause increased hospitalizations for asthma in children: An 18-year study in Southern California") as providing "key evidence" for the ISA's causal determination that there is "a likely to be causal relationship between long-term ozone exposure and respiratory effects." Specifically, Moore et al. is cited as providing "***Consistent evidence of an association between long-term ozone concentrations and hospital admissions*** and ED visits for asthma." Yet, follow-up work by Moore et al. (2013) noted methodological limitations of the 2008 paper (especially, that its results may have resulted from incorrect untested modeling assumptions, rather than from information in the data) and provided and applied an improved methodology ("CMRIER" or "causal models for realistic individualized exposure rules"). A key result was that the previous significant effect of ozone was no longer found. (Moore et al. (2013) state that "The results from the original HRMSM analysis based on the continuous ozone variable estimated with the G-computation method resulted in an estimate of an increase of 1.44e-06 in the proportion of asthma-related hospital discharges for a one-unit increase in ozone. [This is the 2008 study cited in Table 3-3 of the ISA.] ***Unlike results from the HRMSM analysis with the continuous ozone variable, the CMRIER results are not significant.*** Note that the HRMSM analysis was based on G-computation estimation which ***artificially relies on untestable parametric modeling assumptions*** to estimate HRMSM parameters when the ETA assumption is violated. Thus, in this ozone study [the 2008 study cited by the ISA], ***significant results from the G-computation analysis may be a consequence of the approach taken and not solely based on the information in the data***." (Moore KL, Neugebauer R, van der Laan MJ, Tager IB. Causal inference in epidemiological studies with strong confounding. Stat Med. 2012 Jun 15;31(13):1380-404. doi: 10.1002/sim.4469.) This more recent paper is not mentioned in the ISA. The ISA cites the 2008 results as "key evidence" without noting that the authors subsequently revised them in the 2013 paper.

Questions: Based on these spot checks, I have the following questions:

i. *Is it clear that the ISA's study selection process has successfully provided a comprehensive, trustworthy, and unbiased selection of the best available science on ozone and health effects?*

ii. Is it clear why results from Moore (2008) are included and cited as "key evidence" but contrary results from Moore (2013) are excluded? More generally, *is it clear that study inclusion and exclusion criteria were applied systematically and neutrally to identify and select the best and most up-to-date studies to inform the ISA's conclusions?*

iii. *Are there other studies that are omitted from the ISA that should be included?*

iv. *Are there studies included in the ISA that should be omitted* (e.g., because of uncontrolled confounding, obsolete or incorrect modeling assumptions, conclusions dependent on unverified assumptions, ecological fallacy, lack of causally relevant information, lack of design that can support valid causal inferences, or other methodological problems?)

v. *Is it clear that the process followed in selecting and summarizing scientific studies in the ISA was sufficient to assure accurate, unbiased, up-to-date, and trustworthy summaries of the relevant scientific literature to inform causal determination judgments?*

vi. *Do you find in the Executive Summary a clear explanation of the extent to which the key evidence supporting the ISA's causal determinations consists of, is sensitive to, or is derived from unverified modeling assumptions, or from modeling assumptions that more recent literature has found to be incorrect or inadequate? Have you found information in the ISA on sensitivity of causal determination conclusions to untested, uncertain, or incorrect assumptions? (If so, where? See Table Annex 6-1, cf p. 6-67 for a discussion of what should be done. Has it be done, and is it clear what the results were?)*

b. *Were the epidemiological studies used to support the causal determinations summarized in Table ES-1 (p. ES-5) and Figure ES-2 (p. ES-6) appropriately designed and analyzed to provide valid scientific information and valid causal conclusions about effects of possible future interventions (rather than just conclusions about historical statistical associations)?* More specifically, were studies relied on for the "causal" (for short-term respiratory effects) and "likely to be causal" (for short-term and long-term metabolic effects) determinations appropriately designed and analyzed to support valid inferences about manipulative/interventional causality? (See Appendix 3, for a discussion of epidemiological studies. See Table 3-3, p. 3-112, for a "Summary of evidence for a likely to be causal relationship between long-term ozone exposure and respiratory effects.") For these observational studies, *were criteria for valid study design and analysis for causal inference (specifically for interventional causation) explicitly stated, systematically applied, and the results transparently presented?* (If so, where?) For background on such criteria, see Campbell DT, Stanley JC (1963), Experimental and Quasi-Experimental Designs for Research, www.sfu.ca/~palys/Campbell&Stanley-1959-Exptl&QuasiExptlDesignsForResearch.pdf. (My concern here is about whether Table 3-3 and other parts of the ISA seek to draw causal conclusions from non-causal premises and from studies that were neither designed nor analyzed to produce valid causal conclusions or information about effects of future interventions. My key question here is: Is this concern justified?)

c. *Is it clear that the individual studies cited in support of the ISA's causal determinations of "causal" or "likely to be causal" adequately controlled for potential confounding and residual confounding by variables such as income and weather variables?* **Background:** (For background on the importance of confounding by temperature, see e.g., Kai et al. (2018), "Does temperature-confounding control influence the modifying effect of air temperature in ozone-mortality associations?" This article concludes that using a categorical variable (e.g., a season indicator) to control for temperature yields highly significant ozone effects at high temperatures, but also significant residual confounding; and that adjusting for (nonlinear) effects of temperatures "substantially reduced ozone effects at high temperatures and residual confounding.") For example, Table 3-3 cites a study by Tétreault et al. as providing "Key Evidence" of "Cohort studies demonstrating an *association* with asthma

development in children," which the ISA then interprets as "Evidence for a *likely to be causal* relationship between long-term ozone exposure and respiratory effects."(Emphases added.) In discussing potential confounding, Tétreault et al. state that "We present two confounder models in the results. The first was adjusted for sex and deprivation, whereas the second was adjusted for the same variables as well as the year of birth*."* The article does not mention temperature or weather variables. Tétreault et al. also note their "lack of information on risk factors at the individual level (e.g. socioeconomic status and smoking). We attempted to control for these factors with adjustments of our models using ecological deprivation variables, which are imperfect and ***may result in residual confounding***." (Emphasis added.) **Questions:** *Is the ISA well justified in interpreting the statistical association found by Tétreault et al. as key evidence for a "likely to be a causal relationship"*, given its design and limitations? Is it possible (or plausible) that the association instead reflects uncontrolled or incompletely controlled confounding?

d. *Is it clear that the individual studies cited in support of the ISA's causal determinations of "causal" or "likely to be causal" have adequately controlled for biases due to exposure estimation errors or exposure misclassification errors?* For example, Tétreault et al. caution that "First, individual exposure was modeled and not measured through the follow-up, so the quality of the associations depends on the quality of the exposure models. All associations reported in this study were estimated according to the exposure at the centroid of the residential postal code. This assumes that children would stay at home all day. Because a large proportion of a child's day can be spent outside the home (e.g., at school), where exposure to air pollutants might differ, ***misclassification bias may have been introduced in our study***. Additionally, summer average O3 levels were used to estimate annual averages. Because summer O3 levels are higher than winter levels (Environment Canada 1999) in Canada, we may have overestimated annual average levels. Furthermore, although postal codes circumscribe a relatively small area in urban regions, postal codes may include much larger areas in rural regions. This difference in postal code size could lead to a degree of higher imprecision in exposure estimation in regions of the province that are less densely populated." (Emphasis added.) Does the ISA make adequately clear that the exposure concentrations that it reports (e.g., "32.1 ppb mean summer ozone concentration, based on 8-h midday avg" in Table 3-3) are in fact "modeled and not measured" values? Does it adjust correctly (e.g., using appropriate errors-in-variables methods) for potential biases due to such errors before interpreting the results as key evidence of a likely causal relationship? (If so, where?)

e. *Do you find in the Executive Summary, or elsewhere in the ISA, a clear explanation of the extent to which the key evidence supporting the ISA's causal determinations is sensitive to uncontrolled or incompletely controlled confounding and/or ecological associations?* Page 3-193 of the ISA states that "Sensitivity analyses with alternate specifications for potential confounding inform the stability of findings and aid in judgments of the strength of inference from results." Is it clear how such sensitivity analyses were applied to individual studies (e.g., in interpreting the Tétreault et al. study as adequate to supply "Key Evidence" of a "likely to be causal" relationship)? Is it clear what the results of these sensitivity analyses

were? Does the ISA make clear how such sensitivity analyses were used in informing specific causal determinations, and how sensitive the resulting causal determinations are to incompletely controlled confounding? (If so, where?)

f. *More generally, is it clear how criteria for individual study quality were applied to each study used in making causal determinations, and what the results were?* (See Table Annex 6-1, cf p. 6-67.) *Is it clear how the limitations of each individual study were taken into account in causally interpreting their reported associations and in making causal determinations?*

g. *Does the ISA make clear how its causal determinations would change if evidence from associations caused by confounding, residual confounding, measurement error, or unverified modeling assumptions were excluded?*

4. *Is the biological evidence presented in the ISA to support causal determinations correctly stated, correctly interpreted, relevant for predicting effects of changes in the ozone NAAQS, and up-to-date?* For example, should the role of the NLRP3 inflammasome in ozone-induced lung injury be discussed? (See e.g., Michaudel C, Couturier-Maillard A, Chenuet P, Maillet I, Mura C, Couillin I, Gombault A, Quesniaux VF, Huaux F, Ryffel B. Inflammasome, IL-1 and inflammation in ozone-induced lung injury. J Clin Exp Immunol. 2016 Mar 23;5(1):33-40; Xu M, Wang L, Wang M, Wang H, Zhang H, Chen Y, Wang X, Gong J, Zhang JJ, Adcock IM, Chung KF, Li F. Mitochondrial ROS and NLRP3 inflammasome in acute ozone-induced murine model of airway inflammation and bronchial hyperresponsiveness. Free Radic Res. 2019 Jul;53(7):780-790. doi: 10.1080/10715762.2019.1630735.) Is NLRP3 inflammasome activation relevant for ozone risk assessment and for determining whether changes in currently allowed ambient concentrations of ozone would affect public health?
5. *Does the biological evidence presented in the ISA provide well-validated scientific information suitable for predicting the effects on public health of changing NAAQS standard for ozone?*
6. *Is each of the causal determinations summarized in Table ES-1 (especially those labeled "causal relationship" or "likely to be causal relationship") the only possible causal determination conclusion that is justified by, or consistent, with current scientific evidence? Could different causal determinations be equally well justified (or better justified) by the information presented, or by the totality of current scientific evidence?*
7. *Are there changes in the design, analysis, selection, or interpretation of individual studies or in the ISA's processes for interpreting and summarizing them that would improve the validity, credibility, and transparency of the ISA's scientific reasoning and conclusions?*