11-15-22 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC) Ozone Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Preliminary Comments from Mr. Ed Avol on the 10-25-22 Draft CASAC Review of the EPA's Integrated Science Assessment (ISA) for **Ozone and Related Photochemical Oxidants (Final Report - April 2020)** 11-15-22

6 Health Effects – Overarching Comments

8 The CASAC suggests that for future ISAs the EPA considers revising its approach in interpreting 9 data from CHE and epidemiologic studies. Relative weightings of study findings are

10 scientifically more robust when based on individual study details, strengths, design, and

11 infrastructural study planning and execution rather than a more generic up-scaling or weighting

- 12 of one approach over another.
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14 In the case of CHE and epi studies, both study paradigms (in addition to toxicological

15 investigations involving animals, benchtop cellular testing or even *in silico* modeling using

computer technologies) have relative strengths and weakness. Multiple study designs have and 16

17 will be developed within each paradigm. CHE studies can provide unique insights regarding

18 mechanisms of effect and concentration-response data that can lead to causal implication

19 determinations. However, CHE studies are routinely performed on a limited number of generally

20 healthy volunteers, for a limited time duration, with few opportunities for delayed-effects follow-

21 up. CHE study volunteers are most usually young, healthy, and fit adults. Clinically important 22

and significant segments of the general population (such as children, pregnant mothers, senior 23 adults, or those with pre-existing severe or unstable respiratory or cardiovascular diseases) are

24 excluded from study participation for ethical or safety reasons, but this limits the potential

25 relevance of any findings to the general population.

26

27 Epidemiologic studies allow for a wider range of study participants over a longer timeframe under a range of "real-life" activities. However, they often do not or cannot address (or even 28 29 identify) many of the confounding variables that may be of importance (such as co-pollutant

30 exposures, sociodemographic differences, or possible exposure misclassification), leading to

31 possible determinations of association rather than causality.

32

33 CASAC suggests consideration of the various study paradigms on their own merit, to combine

the relative strengths of the various design approaches to arrive at the most informed 34

35 interpretation given study uncertainties. This could be especially relevant when interpreting the

36 various data streams to help identify and establish exposure levels associated with adverse health effects.

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39 A second consideration, one particularly relevant for the PA, is how to use CHE studies to

40 characterize health effects at low concentrations. The following summarizes the primary reasons

41 why ozone CHE studies may underestimate or miss ozone effects at low concentrations: 11-15-22 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC) Ozone Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

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2	1.	Participants are not representative of the general population. They are most usually
3		young, healthy, and fit. Individuals with severe or unstable respiratory or cardiovascular
4		disease are not studied, for appropriate ethical reasons.
5	2.	Exposures are usually single and of relatively short duration. Few studies include
6		outcome measurements beyond 24 hours after exposure, so delayed effects are missed.
7	3.	Exposures are to "pure" laboratory-generated ozone: intake air is usually filtered through
8		HEPA and charcoal to virtually eliminate concomitant exposure to particles or ozone
9		reaction products. Ambient exposures may include other oxidants that not only track with
10		ambient ozone concentrations but are also explicitly included as part of this criteria air
11		pollutant.
12	4.	Prior ambient pollutant exposures may affect the CHE ozone responses but are not
13		typically characterized in CHE studies

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