

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF RESEARCH AND DEVELOPMENT

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MEMORANDUM

- Subject: Provisional Evaluation of Newly Identified Controlled Human Exposure Studies in the context of the 2020 Integrated Science Assessment for Ozone and Related Photochemical Oxidants
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To: The Review of the Ozone National Ambient Air Quality Standards (NAAQS) Docket, EPA-HQ-OAR-2018-0279

On October 29, 2021, the U.S. Environmental Protection Agency (U.S. EPA) announced that it is reconsidering the 2020 decision to retain the 2015 National Ambient Air Quality Standards (NAAQS) for Ozone and Related Photochemical Oxidants. In support of this reconsideration, the U.S. EPA has performed a provisional evaluation of recent controlled human exposure studies of respiratory or cardiovascular effects that have been published since the literature cutoff date for the 2020 Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (U.S. EPA, 2020). Controlled human exposure studies of respiratory effects were the primary focus of this evaluation given the importance of these studies in informing 2008, 2015, and 2020 decisions on the primary standard (73 FR 16436, March 27, 2008; 80 FR 65292, October 26, 2015; 85 FR, 87256, December 31, 2020). A secondary focus of this evaluation was controlled human exposure studies of cardiovascular effects in light of the 2020 ISA causality determination for short-term ozone exposure on cardiovascular effects, which was changed from "likely to be a causal relationship" in the 2013 ISA (U.S. EPA, 2013) to "suggestive of, but not sufficient to infer, a causal relationship" in the 2020 ISA (U.S. EPA, 2020). This memo describes the process for conducting the literature search and provisional evaluation of studies identified in this search. The provisional evaluation of respiratory and cardiovascular controlled human

exposure studies described in this memorandum is in addition to a provisional consideration submitted to the docket (EPA-HQ-OAR-2018-0279) in December 2020 for studies that were cited in public comments on the July 2020 proposed rule (85 FR 49830, August 14, 2020) for the primary and secondary NAAQS (Luben et al., 2020)¹.

Newly published literature in the targeted fields was identified using the citations from the respiratory and cardiovascular controlled human exposure sections from both the 2013 and 2020 ISAs as "seed" references. References listed in PubMed from January 2018 (providing some overlap with the 2020 ISA, which covered literature up to March 2018) to January 2022 were searched for studies that cited one or more of these "seed" references. The resulting 1,756 references were screened at the title and abstract level to identify relevant controlled human exposure studies using a predefined Population, Exposure, Comparator, Outcome, Study Design (PECOS) statement that was developed for this purpose (Appendix 1). Given the limited information contained in the title and abstracts, a broad PECOS statement was used to identify studies with the potential to be relevant. Nineteen studies were identified from the title and abstract screen and were subjected to full text review by three independent subject matter experts. A more focused PECOS statement was used to select relevant studies from the initially identified subset (Appendix 1). The final result of the search, after filtering out studies that were not responsive to the PECOS (e.g., were not controlled human exposure studies, had been included in the 2020 ISA, and/or did not include exposure to ozone alone), was 8 new controlled human exposure studies of which 4 reported respiratory outcomes, 3 reported cardiovascular outcomes, and 1 reported both respiratory and cardiovascular outcomes (Figure 1 and Table 1).

The U.S. EPA provisionally evaluated these eight studies in the context of the findings of the 2020 ISA. Based on its provisional evaluation the U.S. EPA has concluded that none of these studies materially change any of the broad conclusions of the ISA regarding the respiratory or cardiovascular effects of ozone in ambient air or warrant reopening the air quality criteria for this review. A description of the results of this evaluation is reported below.

Respiratory Effects

Among the five studies reporting respiratory outcomes, one study (Hernandez et al., 2021) reported statistically significant decrements in forced expiratory volume in one second (FEV₁) following prolonged (6.6 hr) exposures of 14 healthy adults primarily at rest to a continuously varying ozone concentration ranging from 60 to 80 ppb that averaged 70 ppb. Figure 2 illustrates the FEV₁ results of Hernandez et al. (2021) in comparison to all prolonged (6.6 hr) exposure studies at 80 ppb and below reported in the 2013 and 2020 ISAs. It is important to note that all studies in Figure 2 exposed subjects to ozone during quasi-continuous exercise except for Hernandez et al. (2021), who exposed subjects primarily at rest. One of the most salient observations from controlled human exposure studies is that "young healthy adults exposed to \geq 80 ppb ozone develop significant reversible, transient decrements in pulmonary function and symptoms of breathing discomfort if minute ventilation (Ve) or duration of exposure is increased sufficiently."² The prolonged (6.6 hr) controlled human exposure study of 31 healthy adults by Schelegle et al. (2009) showed that the combination of statistically significant

¹ None of the studies that were considered for this provisional assessment were identified in the public comments addressed in the Luben 2020 memo.

² See pages 6-2 and 3-11 of the 2013 and 2020 ISAs (U.S. EPA, 2013, 2020), respectively.

decrements in pulmonary function and respiratory symptoms occur at time-weighted average exposure concentration of 73 ppb across the full 6.6 hour exposure period, when subjects were engaged in moderate quasi-continuous exercise³. At a constant exposure concentration of 60 ppb, Kim et al. (2011) found statistically significant decrements in FEV_1 in a group of 59 healthy adults with exercise. This was consistent with the Brown et al. (2008) reanalysis of data for 30 subjects exposed to 60 ppb with exercise. No other controlled human exposure study other than Hernandez et al. (2021) has investigated prolonged (6.6 hr) exposure to 70 ppb ozone in subjects predominantly at rest. The model from McDonnell et al.⁴ (2013) predicts an average FEV_1 decrement of 0.5% (using Model 3 coefficients for 32-year-old with a body mass index [BMI] of 25 kg/m² at rest with a Ve of 6.5 L/min per m²). The predicted 0.5% FEV₁ decrement (estimated from the McDonnell model) falls within the 95% confidence interval of the Hernandez study (mean 2.5% decrement, 95% CI 0.3 to 4.7%). While the magnitude of the FEV₁ decrement in primarily resting subjects exposed to a mean concentration of 70 ppb ozone in Hernandez et al. (2021) was greater than predicted, the FEV_1 decrement is within the range of variability observed in controlled human exposure studies of subjects of varying age and BMI (Figure 2).

Of the other four studies reporting respiratory outcomes provisionally evaluated here, Rich et al. (2020) reexamined respiratory effects at 70 ppb following 3 hr exposures of older adults in the context of ambient pollutant levels preceding the in-chamber controlled exposure to ozone but did not report new respiratory effects of ozone.⁵ Other new respiratory studies (Ørby et al., 2019; Niu et al., 2020; Muttray et al., 2018) used considerably higher (100-200 ppb ozone) concentrations, with the results reinforcing existing evidence.

Cardiovascular Effects

The four new studies investigating cardiovascular endpoints showed mostly null effects of ozone. Subtle effects were reported for some endpoints but taken together the data were largely inconsistent (Rich et al., 2020⁵; Jantzen et al., 2018; Wang et al., 2022; Balmes et al., 2019⁶).

³ Moderate quasi-continuous exercise consists of 50 minutes periods of exercise (20 L/min per m² body surface area) followed by 10 minutes of rest each hour. Following the 3rd hour of exposure, subjects had an additional 35-minute rest period for lunch. ⁴ For more information about the model see section 4.1.3.1.1 of the 2020 ISA

⁵ The Rich et al. 2020 paper is a continuation of Multicenter Ozone Study in Older Subjects (MOSES) study that was presented in the 2020 ISA that appears as part of a new Health Effects Institute publication: Rich, DO; Frampton, MW; Balmes, JR; Bromberg, PA; Arjomandi, M; Hazucha, MJ; Thurston, SW; Alexis, NE; Ganz, P; Zareba, W; Koutrakis, P; Thevenet-Morrison, K. Multicenter Ozone Study in oldEr Subjects (MOSES): Part 2. Effects of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiovascular and Pulmonary Function. Research Report 192, Part 2. Boston, MA:Health Effects Institute. ⁶ The Balmes et al. 2019 paper is a reanalysis of Multicenter Ozone Study in Older Subjects (MOSES) study that was presented in the 2020 ISA that appears as part of the 2017 Health Effects Institute publication: Frampton, MW; Balmes, JR; Bromberg, PA; Stark, P; Arjomandi, M; Hazucha, MJ; Rich, DQ; Hollenbeck-Pringle, D; Dagincourt, N; Alexis, N; Ganz, P; Zareba, W; Costantini, MG. (2017). Multicenter Ozone Study in oldEr Subjects (MOSES: Part 1. Effects of exposure to low concentrations of ozone on respiratory and cardiovascular outcomes) [HEI]. (Research Report 192, Pt 1). Boston, MA: Health Effects Institute.



Figure 1: PRISMA Diagram for the provisional literature assessment. References that were excluded for "other" in the title and abstract screening include review articles or systematic reviews with no original data/analysis, foreign language studies, journal commentaries, or conference abstracts. The authors would like to acknowledge the assistance of Jean-Jacques Dubois and Byron Rice of the United States Environmental Protection Agency (Center for Public Health and Environmental Assessment) for their help in performing the literature search.

Study	n	Exposure	Activity Level	Endpoints
Balmes et al. 2019	87	0, 70, or 100 ppb O ₃ for 3 hours	Alternating 15- minute periods of exercise and rest	Cardiovascular Systemic inflammation Oxidative stress Endothelial function Prothrombotic state
Hernandez et al. 2021	14	0 or 70 ppb O ₃ time weighted average for 6.6 hours	Rest (allowed for light exercise when requested)	Respiratory • FEV ₁ • FVC • Sputum neutrophilia
Jantzen et al. 2018	23	Filtered air or 100 ppb O ₃ for 5.5 hours	Rest	 Cardiovascular Endothelial progenitor cell count Blood Cell Reactive Oxygen Species Production Blood Cell Genotoxicity Blood Cell Gene Expression
Muttray et al. 2018	Air 13 O ₃ 15	Filtered air or 100 ppb O ₃ for 2 hours	Two 15-minute exercise periods (15 and 70 minutes into the exposure)	Respiratory Respiratory Symptom Scoring
Niu et al. 2020	30	Filtered air or 200 ppb O ₃ for 2 hours	Alternating 20 minutes rest and 10 minutes exercise	Respiratory Nasal microbiome FEV1 FVC Lung cell injury
Ørby et al. 2019	36	Approximately 1 hour of no O ₃ or 120 ppb O ₃ prior to specific inhalation challenge with Birch or Grass allergen	Not Reported	Respiratory Allergen-specific Airway Reactivity
Rich et al. 2020	87	0, 70, or 100 ppb O ₃ for 3 hours	Alternating 15 minutes of exercise and rest	Respiratory FEV ₁ FVC Lung injury Airway inflammation Cardiovascular Heart rate variability ST segment change Vascular function Systemic inflammation Systemic oxidative stress Prothrombotic state
Wang et al. 2022	22	Clean air or 200 ppb O ₃ exposure for 2 hours	Alternating 20 minutes rest and 10 minutes exercise	Cardiovascular • Heart Rate Variability • Serum Hormone levels • Serum Metabolome

Table 1: Controlled Human Exposure Studies Provisionally Evaluated by the U.S. EPA



Note: All responses at and above 70 ppb (targeted concentration) were statistically significant. For all studies other than Hernandez et al. (2021), during each hour of the exposures, subjects were engaged in moderate quasi-continuous exercise (20 L/min per m^2 body surface area) for 50 minutes and rest for 10 minutes. Following the 3rd hour, subjects had an additional 35-minute rest period for lunch. The data at 60 and 80 ppb have been offset along the *x*-axis for illustrative purposes. The curved solid lines for McDonnell et al. (2013) illustrates the predicted FEV₁ decrements using Model 3 coefficients at 6.6 hours as a function of ozone concentration for a 23.8-year-old with a BMI of 23.1 kg/m² during quasi-continuous exercise and continuous rest.

¹Statistically significant FEV₁ responses to square-wave chamber exposures at 60 ppb based on the analysis of Brown et al. (2008).

² Kim et al. (2011) reported statistically significant FEV₁ responses at 60 ppb.

³ Of the 14 subjects in the Hernandez et al. (2021) study, 12 were exposed at rest and 2 exercised no more than 10 minutes of each hour on a treadmill at a speed of no more than 3 miles per hour. The average ozone-induced FEV₁ decrement of 2.5% (95% confidence interval: 0.3, 4.7) was statistically significant. McDonnell et al. (2013) predicts an average FEV₁ decrement of 0.5% (Model 3 coefficients at 6.6 hours for a 32-year-old with a BMI of 25 kg/m²), which is within the 95% confidence interval of the Hernandez et al. (2021) study.

 4 80 ppb data for 30 healthy subjects were collected as part of the Kim et al. (2011) study, but only published in Figure 5 of McDonnell et al. (2012). The statistical significance of these FEV₁ responses was not assessed.

Source: Adapted from Figure IS-2 of 2020 Ozone ISA (U.S. EPA, 2020).

Figure 2: Cross-study comparisons of mean ozone-induced forced expiratory volume in 1 second (FEV1) decrements in young healthy adults following 6.6 hours of exposure to ozone.

Provisionally Evaluated Studies

- Balmes, JR; Arjomandi, M; Bromberg, PA; Costantini, MG; Dagincourt, N; Hazucha, MJ; Hollenbeck-Pringle, D; Rich, DQ; Stark, P; Frampton, MW (2019) Ozone effects on blood biomarkers of systemic inflammation, oxidative stress, endothelial function, and thrombosis: The Multicenter Ozone Study in oldEr Subjects (MOSES). <u>http://dx.doi.org/10.1371/journal.pone.0222601</u> HERO ID: 6387460
- 2) Hernandez, ML; Ivins, S; Chason, K; Burbank, AJ; Rebuli, ME; Kobernick, A; Schworer, SA; Zhou, H; Alexis, NE; Peden, DB (2021) Respiratory Effects of Sedentary Ozone Exposure at the 70-ppb National Ambient Air Quality Standard: A Randomized Clinical Trial. <u>http://dx.doi.org/10.1164/rccm.202006-2597LE</u> HERO ID: 10172667
- 3) Jantzen, K; Jensen, A; Kermanizadeh, A; Elholm, G; Sigsgaard, T; Møller, P; Roursgaard, M; Loft, S (2018) Inhalation of House Dust and Ozone Alters Systemic Levels of Endothelial Progenitor Cells, Oxidative Stress, and Inflammation in Elderly Subjects. <u>http://dx.doi.org/10.1093/toxsci/kfy027</u> HERO ID: 10172665
- 4) Muttray, A; Gosepath, J; Schmall, F; Brieger, J; Mayer-Popken, O; Melia, M; Letzel, S (2018) An acute exposure to ozone impairs human olfactory functioning. <u>http://dx.doi.org/10.1016/j.envres.2018.07.006</u> HERO ID: 7497312
- 5) Niu, Y; Chen, R; Wang, C; Wang, W; Jiang, J; Wu, W; Cai, J; Zhao, Z; Xu, X; Kan, H (2020) Ozone exposure leads to changes in airway permeability, microbiota and metabolome: a randomised, double-blind, crossover trial. <u>http://dx.doi.org/10.1183/13993003.00165-2020</u> HERO ID: 10172670
- 6) Ørby, PV; Bønløkke, JH; Bibby, BM; Ravn, P; Hertel, O; Sigsgaard, T; Schlünssen, V (2019) Dose-response curves for co-exposure inhalation challenges with ozone and pollen allergen. <u>http://dx.doi.org/10.1183/13993003.01208-2018</u> HERO ID: 10173885
- 7) Rich, DQ; Thurston, SW; Balmes, JR; Bromberg, PA; Arjomandi, M; Hazucha, MJ; Alexis, NE; Ganz, P; Zareba, W; Thevenet-Morrison, K; Koutrakis, P; Frampton, MW (2020) Does Ambient Ozone or Other Pollutants Modify Effects of Controlled Ozone Exposure on Pulmonary Function? <u>http://dx.doi.org/10.1513/AnnalsATS.201908-597OC</u> HERO ID: 6387486
- 8) Wang, C; Lin, J; Niu, Y; Wang, W; Wen, J; Lv, L; Liu, C; Du, X; Zhang, Q; Chen, B; Cai, J; Zhao, Z; Liang, D; Ji, JS; Chen, H; Chen, R; Kan, H (2022) Impact of ozone exposure on heart rate variability and stress hormones: A randomized-crossover study. <u>http://dx.doi.org/10.1016/j.jhazmat.2021.126750</u> HERO ID: 10172662

References

- 1) Adams, WC. (2000) Ozone dose-response effects of varied equivalent minute ventilation rates. J Exposure Anal Environ Epidemiol. 10: 217-226.
- 2) Adams, WC. (2002). Comparison of chamber and face-mask 6.6-hour exposures to ozone on pulmonary function and symptoms responses. Inhal Toxicol 14: 745-764.

http://dx.doi.org/10.1080/08958370290084610

- Adams, WC. (2003). Comparison of chamber and face mask 6.6-hour exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal Toxicol 15: 265-281. http://dx.doi.org/10.1080/08958370390168283
- Adams, WC. (2006). Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal Toxicol 18: 127-136. <u>http://dx.doi.org/10.1080/08958370500306107</u>
- 5) Adams, WC; Ollison, WM. (1997) Effects of prolonged simulated ambient ozone dosing patterns on human pulmonary function and symptomatology. Presented at: 90th annual meeting of the Air & Waste Management Association; June; Toronto, Ontario, Canada. Pittsburgh, PA: Air & Waste Management Association; paper no. 97-MP9.02.
- 6) Brown, JS; Bateson, TF; Mcdonnell, WF. (2008). Effects of exposure to 0.06 ppm ozone on FEV₁ in humans: A secondary analysis of existing data. Environ Health Perspect 116: 1023-1026. http://dx.doi.org/10.1289/ehp.11396
- 7) Folinsbee, LJ; McDonnell, WF; Horstman, DH. (1988) Pulmonary function and symptom responses after 6.6-hour exposure to 0.12 ppm ozone with moderate exercise. JAPCA 38: 28-35.
- Folinsbee, LJ; Horstman, DH; Kehrl, HR; Harder, S; Abdul-Salaam, S; Ives, PJ. (1994) Respiratory responses to repeated prolonged exposure to 0.12 ppm ozone. Am J Respir Crit Care Med. 149: 98-105.
- 9) Horstman, DH; Folinsbee, LJ; Ives, PJ; Abdul-Salaam, S; Mcdonnell, WF. (1990). Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. Am J Respir Crit Care Med 142: 1158-1163. http://dx.doi.org/10.1164/ajrccm/142.5.1158
- 10) Kim, CS; Alexis, NE; Rappold, AG; Kehrl, H; Hazucha, MJ; Lay, JC; Schmitt, MT; Case, M; Devlin, RB; Peden, DB; Diaz-Sanchez, D. (2011). Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. Am J Respir Crit Care Med 183: 1215-1221. http://dx.doi.org/10.1164/rccm.201011-1813OC
- 11) Luben, T; Lassister, M; Herrick, J. (2020). List of Studies Identified by Public Commenters That Have Been Provisionally Considered in the Context of the Conclusions of the 2020 Integrated Science Assessment for Ozone and Related Photochemical Oxidants. Memorandum to the Integrated Science Assessment (ISA) for Ozone Docket, (EPA–HQ–ORD–2018–0274). December 17, 2020. Docket Document ID: EPA-HQ-OAR-2018-0279-0560. https://www.regulations.gov/document/EPA-HQ-OAR-2018-0279-0560
- 12) McDonnell, WF; Kehrl, HR; Abdul-Salaam, S; Ives, PJ; Folinsbee, LJ; Devlin, RB; O'Neil, JJ; Horstman, DH. (1991). Respiratory response of humans exposed to low levels of ozone for 6.6 hours. Arch Environ Occup Health 46: 145-150. http://dx.doi.org/10.1080/00039896.1991.9937441
- 13) McDonnell, WF; Stewart, PW; Smith, MV. (2013). Ozone exposure-response model for lung function changes: An alternate variability structure. Inhal Toxicol 25: 348-353.

http://dx.doi.org/10.3109/08958378.2013.790523

- 14) McDonnell, WF; Stewart, PW; Smith, MV; Kim, CS; Schelegle, ES. (2012). Prediction of lung function response for populations exposed to a wide range of ozone conditions. Inhal Toxicol 24: 619-633. http://dx.doi.org/10.3109/08958378.2012.705919
- 15) Schelegle, ES; Morales, CA; Walby, WF; Marion, S; Allen, RP. (2009). 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. Am J Respir Crit Care Med 180: 265-272. http://dx.doi.org/10.1164/rccm.200809-1484OC
- 16) U.S. EPA (U.S. Environmental Protection Agency). (2019). Integrated Review Plan for the Ozone National Ambient Air Quality Standards. Office of Air Quality Planning and Standards. Research Triangle Park, NC. U.S. EPA. EPA-452/R-19-002. https://www.epa.gov/sites/production/files/2019-08/documents/o3-irp-aug27-2019_final.pdf.
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Appendix 1

Population, Exposure, Comparison, Outcome, and Study Design (PECOS) Tool Used for Provisional Evaluation of New Controlled Human Exposure (CHE) Studies for Ozone

Purpose: The purpose of this appendix is to outline the criteria used for screening references from the provisional literature search. References that were identified from the literature search were screened in a multilevel process to identify studies relevant to the scope of the provisional review. References were first screened at the title and abstract level to remove studies that were not CHE studies or were clearly unrelated to ozone exposure. The full text of studies that were considered relevant at the title and abstract level were further reviewed to ensure relevancy to the reconsideration. PECOS statements were used to predefine the study elements meeting the objectives of the reconsideration. Given the limited information presented in the title and abstract of a paper, a broader PECOS statement was used in the title and abstract screening compared to the full text review.

Population, Exposure, Comparison, Outcome, and Study Design (PECOS) Tool for Title and Abstract Screening

The studies screened at the title and abstract level should be included if they satisfied all the components of the following PECOS tool. Furthermore, a study should be included if access to the full text is required to determine if all aspects of the following PECOS were met:

Experimental Studies for Title and Abstract Screening⁷:

- Population: Include any studies that perform or analyze data from controlled human exposure
 - Studies of cells/tissues isolated from controlled ozone-exposure in humans is acceptable
 - Studies that reanalyze or are a meta-analysis of CHE study data are acceptable
- Exposure: Controlled inhalation exposure to ozone
 - For title and abstract screening, the exposure concentration of ozone is not used as an inclusion/exclusion criterion
- Comparator: Appropriate comparison group exposed to filtered air or room air
- **Outcome:** Outcomes of interest are those that relate to the respiratory system or cardiovascular system. This includes measures of lung/heart health, structure, and function as well as endpoints that relate to allergy or host defense with the lung/heart as the site of action.
 - For the title and abstract screen, papers with other endpoints can be included if there is reason to believe that heart/lung outcomes may be present in the full text but not mentioned explicitly in the abstract.
- Study Design: Studies meeting the above criteria.

⁷ Review papers, foreign language references, and abstract only citations should be excluded. For papers that only have a title and no abstract, the reviewer should try to obtain the abstract online and if not available, should use their best judgement on whether the paper will likely contain relevant information for the include/exclude decision.

Appendix 1

Population, Exposure, Comparison, Outcome, and Study Design (PECOS) Tool for Full Text Screening

The studies evaluated and subsequently discussed within this section should be included if they satisfied all of the components of the following PECOS tool:

Experimental Studies for Full Text Screening⁸:

• Population: Include any studies that perform or analyze data from <u>controlled human exposure</u>

- Studies of cells/tissues isolated from controlled ozone-exposure in humans is acceptable
- Studies that reanalyze or are a meta-analysis of existing CHE study data are acceptable

• **Exposure:** Controlled inhalation exposure to ozone (i.e., ozone only without simultaneous co-pollutant exposure)

- Controlled in this context means that the concentration and duration of ozone exposure was controlled by the investigators
- For the purposes of this reconsideration, only studies that include at least one exposure group with a mean ozone concentration of 0.4 ppm or lower will be considered relevant
- Comparator: Appropriate comparison group exposed to filtered air or room air

• **Outcome:** Outcomes of interest are those that relate to the respiratory system or cardiovascular system. This includes measures of lung/heart health, structure, and function as well as endpoints that relate to allergy or host defense with the lung/heart as the site of action.

• For the purposes of this reconsideration, only respiratory or cardiovascular related endpoints are considered relevant.

• Study Design: Studies meeting the above criteria.

⁸ Review papers, foreign language references, and abstract only citations should be excluded.