TCEQ Comments on
EPA First External Review Draft Document:
Integrated Science Assessment for Oxides of Nitrogen-Health Criteria
EPA Docket ID No. EPA-HQ-ORD-2013-0232

General Comments

It is not clear how the draft ISA evaluates the aspects listed in the Preamble (consistency, coherence, biological plausibility, exposure-response, strength of association, experimental evidence, temporal relationship, specificity of the observed association, and analogy) or how they were integrated into causal determinations. The tables at the end of the various chapters are a positive development, but the narratives in the summary sections do not indicate how each aspect was evaluated and evidence was integrated across realms. In particular, there is a notable lack of mechanistic data, and that introduces significant uncertainty in the interpretation of certain realms of evidence, especially epidemiologic studies. Throughout the document, the evidence for specific endpoints is often inconsistent or weak and effects estimates small and/or not statistically significant. Nevertheless, the document then proceeds to combine these and draw causal determinations for the overall endpoint. Please include a discussion addressing the rationale for this practice.

It is not clear how studies were selected for inclusion in the draft ISA, how those studies were organized in tables and graphs, or why some of the available studies were omitted. In particular, when multiple effect estimates are available for a given study, it is unclear how a single estimate was selected.

It is not clear how the risk estimates were standardized in figures throughout the document. For example, in the mortality section, various concentration increments were selected, ranging from 20-60 ppb with no rationale or method presented. In addition, there is no consistency across figures with regard to presentation of risk estimates. In some places, Relative Risk is used, and in others percent increase or Hazard Ratios are employed. There should be as much consistency as possible across the figures in the draft ISA.

Use of Ecological Epidemiology Studies

1. Ecological epidemiology studies are not designed to determine if oxides of nitrogen caused the health effects observed. Instead, these studies simply report statistical associations.

For example, epidemiology studies evaluating cardiovascular diseases very often include diseases of the circulatory system such as heart disease and cerebrovascular disease. The assumption that oxides of nitrogen caused all evaluated cardiovascular health effects (i.e., cardiac causes such as MI and heart failure, heart rate and heart rate variability, cerebrovascular diseases and stroke, and other cardiovascular causes of hospital admission or ED visit) is not supported by the ecological epidemiology studies.

Ecological epidemiology studies do not collect data on when, how long, and how much exposure occurred; if exposure occurred before the health effects; or if it makes biological sense that the chemical could cause the effect. In other words, the study designs are limited. There is general agreement, that this study design does not provide enough information to determine the actual cause of studied effects.[1] Ecological epidemiology studies are not supposed to be used quantitatively and they certainly are not rigorous enough to set environmental policy.

2. Lack of personal exposure data severely limits the utility of ecological epidemiology studies.

The issue of limited or entirely absent personal exposure data is significant. Personal exposure is a measurement of the amount of an air pollutant that a person actually breathes. Ecological epidemiology studies generally rely on ambient air monitoring data as a surrogate for personal exposure. However, it is very unlikely that people would ever be exposed to those pollutants at concentrations measured at outdoor monitors for very long. This is partly because the average American spends of the majority of their time indoors (Koutrakis et al. 2005).

4. Ecological epidemiology studies have considerable uncertainty in their identification of health effects.

To determine prevalence of a health issue, epidemiologists frequently use readily-available information, including hospital admissions records and death certificates or participant surveys. This problem is compounded when paired with the lack of personal exposure data, making it impossible to know if decedents were actually well enough to be outdoors in the days preceding their deaths. The data is further confounded by the frequent use of a single monitor to represent exposures throughout the city – as if a single monitor can accurately reflect personal exposure with measurements sometimes miles away.

Health Effect Category

ISA Section 4.2 Respiratory Effects (Short-term Exposure)

In the 2008 ISA for Oxides of Nitrogen, USEPA determined that the evidence was "sufficient to infer a likely causal relationship" between short-term NO_2 exposure and respiratory effects. Similarly, in the draft ISA, USEPA determined that recent evidence gave additional support to the association between short-term NO_2 exposure and respiratory effects and concluded there was a "causal relationship." TCEQ agrees with the causal determination between short-term NO_2 exposure and respiratory effects for concentrations at or above the current 1-hour NAAQs of 100 ppb, based on evidence from controlled human and animal studies and to a limited extent, epidemiological studies.

TCEQ does not agree that USEPA presented enough evidence to determine a causal link between NO_2 exposure and increases in respiratory hospital admissions and ED visits. Major uncertainties remained regarding the causal factor(s) of respiratory effects associated with short-term ambient NO_2 exposure because of the high correlation of NO_2 with other traffic-related pollutants (i.e., ozone, carbon monoxide, PM_{10}, $PM_{2.5}$) and

[1] EPA has recently stated: "[E]pidemiological studies do not generally provide direct evidence of causation; instead they indicate the existence or absence of a statistical relationship." ATIELC v. USEPA case 1:12-cv-01066-ATJ-TCB. October 4, 2012.

the potential for NO_2 to serve primarily as an indicator for another pollutant or mixture of combustion-related pollutants.

ISA Section *4.2.2 Airway Hyperresponsiveness (AHR)*

In the 2008 ISA for Oxides of Nitrogen, the EPA stated: "Biological plausibility was provided [in support of epidemiology studies] in particular, by observations of NO_2-induced airway hyperresponsiveness (AHR) in adults with asthma following <1 to 6-hour exposures to NO_2 at concentrations in the range of 100 to 300 ppb, on the order of peak 1-h maximum ambient concentrations examined in epidemiologic studies. The 2008 ISA for Oxides of Nitrogen also noted some support for pulmonary inflammation and impaired host defenses in controlled human exposure and animal toxicological studies, albeit at higher concentrations of 1,500 to 5,000 ppb NO_2."

Increases in AHR occur after exposure to lower NO_2 concentrations than other respiratory system effects observed in controlled human exposure and animal toxicological studies (including pulmonary inflammation and impaired host defenses). In the 2008 ISA, USEPA conducted a meta-analysis of controlled human studies evaluating the effects of short-term NO_2 exposure on AHR. The USEPA meta-analysis was based on a meta-analysis conducted by Follinsbee 1992. USEPA concluded that a 1-hour exposure to 100 ppb NO_2 caused increased airway responsiveness in 66% of mild asthmatics. In addition, 67% of asthmatics experienced an increase in airway responsiveness following exposure to NO_2 concentrations from 100 to 150 ppb, 75% of asthmatics experienced an increase in airway responsiveness following exposure to NO_2 concentrations from 200 to 300 ppb, and 73% of asthmatics experienced an increase in airway responsiveness following exposure to NO_2 concentrations above 300 ppb. The fraction of resting asthmatics experiencing an increase in airway responsiveness was statistically significant at all of these NO_2 concentrations. The magnitude of response could not be determined from the meta-analysis conducted by USEPA (2008), and it was not clear if the observed effects were clinically significant. The primary short-term NAAQs of 100 ppb was based, in part, on studies showing an increase in AHR in asthmatics after a 1-hour exposure to NO_2; therefore, the results and interpretation of this meta-analysis are of particular importance.

In an attempt to address some of the limitations of the USEPA (2008) meta-analysis and one of the few recent studies on AHR in the draft ISA, Goodman et al. (2009) conducted meta-regression and meta-analyses studies evaluating the effects of NO_2 exposure (100 to 600 ppb) on AHR in asthmatics. Several effect estimates from the meta-analysis were statistically significant; however, they were so small that the clinical relevance of these effect estimates was questionable. They found no clear exposure-response associations for any effect estimates based on linear meta-regressions or analyses of effect estimates for exposure groups, and in general for analyses stratified by airway challenge, exposure method, and activity during exposure. Goodman et al. (2009) concluded that "to the extent that the effects observed are associated with NO_2 exposure, they are sufficiently small such that they do not provide evidence that NO_2 has a significant adverse effect on AHR at concentrations up to 600 ppb." Another conclusion was that exposure duration was not significantly associated with AHR for any of the effect metrics.

In the draft ISA, USEPA discussed the results of the Goodman et al. (2009) study but supported their decision to use 100 ppb as a concentration at which adverse effects on AHR have been observed in asthmatics after a 1 hour exposure. USEPA also pointed out differences in methodology used by Goodman et al. (2009) which may give rise to different conclusions. *The TCEQ believes the results and conclusions of the Goodman et al. (2009) study are of particular importance, given the way USEPA used the results of their meta-analysis of AHR studies to support the development of the current 1-hour NO_2 NAAQS of 100 ppb, and should be used to inform to weight-of-evidence (WOE) accordingly.*

ISA Section 5.2 Respiratory Effects (Long-term Exposure)

In the 2008 ISA for Oxides of Nitrogen, USEPA determined that the evidence was "suggestive but not sufficient to infer a causal relationship" between long-term NO_2 exposure and respiratory effects. In the draft ISA, USEPA strengthened the causal determination to be "likely to be a causal relationship" based on new evidence from epidemiological studies for asthma incidence and respiratory symptoms in children, and respiratory effects in adults. Epidemiological studies are designed to evaluate possible associations, not determine causation, as discussed in TCEQ general comments above. In the absence of more conclusive evidence from controlled exposure studies in humans or animals, TCEQ does not agree with strengthening the causal determination based on the information presented in the draft ISA.

ISA Section 4.3 Cardiovascular Effects (Short-term Exposure)

In the 2008 ISA for Oxides of Nitrogen, USEPA determined that the evidence was "inadequate to infer the presence or absence of a causal relationship for oxides of nitrogen to contribute to cardiovascular-related morbidity and associated mortality" However, in the draft ISA, the USEPA strengthened the causal determination to "likely to be a causal relationship" even though the WOE integrated across epidemiological, controlled human exposure, and animal toxicological studies indicate lack of consistency, coherence, and biological plausibility to fully substantiate the association that short-term exposures to environmentally relevant concentrations of oxides of nitrogen cause adverse cardiovascular effects in humans.

Considering the limited evidence between short-term exposure to oxides of nitrogen and adverse cardiovascular effects demonstrated in epidemiology studies and human controlled exposure and the uncertainties regarding the relevance of findings in animal studies, the TCEQ believes there is inadequate evidence to support the causal determination of "likely to be a causal relationship" of short-term exposure to oxides of nitrogen and adverse cardiovascular effects.

Hospital admissions

According to the draft ISA, USEPA is of the opinion that the epidemiology studies consistently demonstrate NO_2 associated hospitalizations and ED visits for cardiovascular effects and mortality from cardiovascular disease. However, the evidence from the ecological epidemiological studies does not consistently indicate positive associations. Null and/or negative associations have been reported for many cardiovascular end points. It is not clear which studies USEPA considered as key studies and how the null and/or negative associations were evaluated.

For example, the ISA indicates that the Ito et al. (2011) study reported a positive association with NO_2 and CVD hospitalization at lag 0 and that the study did not include results from copollutant models. Other epidemiology studies reported associations to be less precise when adjustments were made for copollutants such as sulfur dioxide (Guo et al.(2009); Chen et al.(2010b). Additionally, several other studies from Denmark, Spain, and Taiwan reported null or negative associations between NO_2 concentrations and risk of hospital admissions for CVD (Andersen et al., 2008b, Linares and Diaz, 2010; Chen et al., 2008).

USEPA says that administrative data are less reliable when compared to data obtained from clinical registry. However, the draft ISA included only one the study based on the clinical registry (Bhaskaran et al. 2010). The other studies were reported to be based on administrative data.

Despite the limited WOE, USEPA continues to conclude that there is consistent evidence to support the association between ambient NO_2 levels and risk of hospital admissions. USEPA further concludes that the associations observed in these studies are robust after making adjustments to the copollutants.

The TCEQ therefore disagrees with USEPA's conclusion that there is consistent evidence from epidemiological studies to support the association of Cardiovascular Diseases (CVD) and hospital admissions due to CVD with ambient NO_2 levels.

Other End Points

The results from the controlled human exposure studies also do not support the likely association. Many of the controlled human exposure studies included much higher concentrations (400 ppb - 4000 ppb), that are more than an order of magnitude higher when compared to the average ambient concentrations reported in the epidemiology studies. In comparison to the exposure concentrations used in the controlled exposure studies, the reported ambient concentrations of oxides of nitrogen in the ecological epidemiological studies are very small, and were within the range of 20-60 ppb. Many controlled exposure studies reported no changes in in heart rate (HR), cardiac output, and/or blood pressure (BP) even on high exposure concentrations of NO_2 (i.e., 400 ppb – 4000 ppb) in healthy and/or asthmatic volunteers. For example Linn et al. (1985) reported no change in BP, either in healthy or asthmatic volunteers after exposure to 4000 ppb of NO_2. Likewise, Langrish et al. (2010) did not report any effects of NO_2 on vascular endothelial tone or fibrinolytic function after exposure to 4000 ppb NO_2 for 1-h with intermittent exercise in healthy adults.

Clinical studies of both healthy (Huang et al. 2012) volunteers or individuals with coronary heart disease (Scaife et al. 2012) exposed to high concentrations of NO_2 (i.e., 400 ppb) reported no statistically significant changes in HRV or HR. Results from controlled exposures in healthy older adults to 600 ppb NO_2 (Folinsbee et al. 1978 and Drechsler-Parks 1995) or asthmatics (Gong et al.2005) also reported no changes in HR.

The main limitation in using inflammatory biomarkers such as C-Reactive Protein (CRP) to predict outcome after cardiac arrest is their poor specificity for the anoxic insult, as all inflammatory conditions can increase the circulating levels of such molecules. Many of the biomarkers that are used as predictors of outcome after cardiac arrest are also elevated in many conditions including central nervous system disorders, autoimmunity, fibromyalgia, bacterial infections, tumors, cardiac diseases, viral infections, allergies, asthma, and diabetes, among others.

ISA Section 5.3 Cardiovascular Effects (Long-term Exposure)

USEPA strengthened the causal determination for long-term NO2 exposure and cardiovascular effects to "suggestive of a causal relationship." The TCEQ disagrees with the draft ISA's conclusion because there is very limited evidence from epidemiological and animal studies to support strengthening the association. The limited evidence also does not demonstrate biological plausibility.

The evidence for CVDs was not consistent across the different disease categories and in many cases the associations seem to weaken when adjustments to other confounders were included. The draft ISA includes studies that reported both positive associations and/or null or negative associations. However, it appears that results from the studies that reported negative or null associations were not included and/or given the appropriate WOE while the studies that reported positive associations seem to have been given a greater WOE.

The long-term exposure to NO_2 and cardiac heart disease (CHD) admission was not supported by the Gan et al. (2011). Miller et al. (2007) also reported a null association between NO_2 and cardiovascular events (MI, revascularization, angina, CHF, CHD death). Despite the weak WOE for cardiovascular morbidity there seems to be a suggestion of positive correlation of long-term association of NO_2 exposure and CHD mortality.

Mortality - Overarching comments

Many of the studies presented in sections of the draft ISA dealing with mortality endpoints are for non-U.S. populations. The draft ISA should evaluate how this impacts interpretation of these results and use of these studies for subsequent steps in the NAAQS process. For example, will non-U.S. studies be utilized in the Risk and Exposure Assessment and/or serve as the basis of a NAAQS for the United States?

It is not clear how studies were selected for inclusion in the draft ISA, how those studies were organized in tables and graphs, or why some of the available studies were omitted. In particular, when multiple effect estimates are available for a given study, it is unclear how a single estimate was selected. For example, in Table 4-38, it appears that the only statistically significant estimate was selected for Dominici et al. (2003) study.

Cause Specific Mortality

ISA Section 4.2.8 Respiratory Mortality

On page 4-182, please define AHR the first time it is used in this section.

The draft ISA describes results for alterations in AHR, but then goes on to say that exposures that elicited these changes had no direct effect on changes in lung function in controlled human exposure. It is not clear, therefore, that AHR results do support biological plausibility for NO_2-induced effects.

On page 4-184, the draft ISA states that most studies found NO_2 associations that persisted after adjustment for copollutants. However, in many cases, the effect sizes were decreased with inclusion of copollutants, the 95% C.I.s were increased, or both. The draft ISA should comment on the importance of this observation.

On page 4-185 the draft ISA describes positive associations for respiratory effects found for lags ranging from 0-5 days. The plausibility of this finding should be assessed in the next draft ISA in light of the previous determination that lag times of 0-2 days are likely the most biologically plausible.[2]

On Page 4-185 the draft ISA states "Findings also point to NO_2-related effects on…respiratory mortality, but there is limited coherence among various lines of evidence." However, this directly contradicts the statement on page 4-186 "The consistency and coherence of evidence for increases in asthma morbidity, including biological plausibility and copollutant-adjusted associations found for NO_2 …is sufficient to conclude that a causal relationship exists between short-term NO_2 exposure and respiratory effects."

In Table 4-23 the key evidence is described. While this table is a good addition and an improvement over past ISAs, it is not clear how the evidence was evaluated across the various realms or whether this step was conducted at all. For instance, in Table 4-23 the draft ISA lists limited evidence for biological effects and uncertainty in effects that could lead to respiratory mortality. It is not clear how this evidence was used to inform the interpretation of the epidemiologic studies for respiratory mortality or how this evidence was integrated across realms to inform the causal determination. It appears that the causal determination was made solely on epidemiologic studies *despite* the limitations in the dataset that were also detailed in Table 4-23.

ISA Section 4.3.8 Cardiovascular Mortality

The draft ISA states on page 4-248 "An uncertainty that remains from the 2008 ISA for oxides of nitrogen is the lack of mechanistic evidence to describe a role for NO_2 in the development of cardiovascular diseases, including key events that inform the mode of action." It is not clear how the epidemiology results reported in this section should be interpreted in light of this gap in knowledge.

It is not clear how the draft ISA evaluates "positive" associations reported in epidemiologic studies with regard to strength, consistency, specificity, plausibility, etc. in accordance with the framework detailed in the Preamble.

It is not clear how the draft ISA can state "[i]nconsistencies across studies and the limited evidence available to suggest NO_2-related subclinical and clinical cardiovascular effects represent a lack of coherence across all lines of evidence to support the effects observed in hospital admission and ED visits, and cardiovascular mortality (p4-249)" and then conclude "[t]hus, the combined evidence from epidemiologic and experimental studies is sufficient to conclude that there is likely to be a causal relationship between short-term NO_2 exposure and cardiovascular effects (p4-256)." This logical inconsistency should be resolved.

On page 4.255 the draft ISA states that because epidemiologic studies have been replicated by different researchers and have adjusted for potential confounding, the level of uncertainty for bias from confounding is limited. However, in most instances,

[2] USPEA 2013 USEPA/600/R-10/076F. 1251p.

inclusion of copollutants either lowers the risk estimate, increases the 95% C.I. or both. How does this observation impact the above conclusion?

In Table 4-36 the key evidence is described. While this table is a good addition and an improvement over past ISAs, it is not clear how the evidence was evaluated across the various realms or whether this step was conducted at all. For instance, the table details uncertainty due to limited coherence with other lines of evidence, limited evidence from toxicological and controlled human exposure studies, and weak evidence for mode of action. However, it is not clear how this information informed the causal determination. It appears that the causal determination was made solely on epidemiologic studies *despite* the limitations in the dataset that were also detailed in Table 4-36.

Total Mortality

ISA Section 4.4 Total Mortality and short-term exposure to NO_2

On pg 4-258 PM is described as an effect modifier, but on page 4-266 copollutants are included in the description of potential confounding of the NOx-mortality relationship. The draft ISA should include additional discussion on this point and maintain consistency regarding effect modifiers and confounders throughout the document.

Page 4-259 outlines the uncertainties and data gaps that lead to the conclusion that there is suggestive but not sufficient evidence to infer a causal relationship with mortality. However, the same uncertainties and data gaps appear to still exist, based on the summary in section 4.4.8. Therefore, it is unclear how it was determined that there is likely to be a causal relationship between short-term NO_2 exposure and total mortality.

In the description of epidemiologic studies, please include a discussion of how *each* of the aspects described in Table 1 in the Preamble were addressed. In particular, it is unclear how "positive" associations are evaluated within this framework.

Table 4-38 seems to indicate significant heterogeneity across locations. How does this impact evaluation of these results and their use in subsequent steps of the NAAQS process?

Table 4-39 indicates that the size of the estimated effect of short-term exposure to NO_2 is very small (far less than RR 2.0 or even 1.1 in most cases). Please explain how effect size was evaluated in the draft ISA.

Regarding the shape of the concentration-response relationship between short-term NO_2 exposure and mortality, it is not clear that there is adequate evidence for a linear relationship. If one examines Figure 4-21, it appears there is no increased risk above ~25 ppb NO_2 at lag day 1. Figure 4-22 indicates no increased risk above ~70 ppb for two-day average NO_2 concentrations. These results are also consistent with the apparent lack of increased risk among Chinese cities presented in Figure 4-23 for concentrations ~60-70 ppb for 24-hour average NO_2 concentrations. These results should be considered when evaluating mortality endpoints.

ISA Section 5.5 Total Mortality and long-term exposure to NO_2

It is significant that analyses of the largest cohort study to date, the American Cancer Society study, have repeatedly (Krewski et al., 2000, Pope et al., 2002, Krewski et al.,

2009) found that NO_2 was not associated with mortality. The discussion of this study and the impact of this finding should be discussed in greater detail.

The reanalysis of the ACS cohort should be added to Figure 5-9. This is consistent with including both Krewski et al. 2000 and Pope et al. 2002 in this figure.

A number of additional studies appear to be missing from this section of the draft ISA. These include, but are not necessarily limited to:

Gan et al. 2011. Long term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environmental Health Perspectives. 119:501-507.

Raaschou-Nielsen et al. 2012. Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. Environmental Health. 11:60.

Beelen et al. 2008. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environmental Health Perspectives. 116:196-202.

Zhang et al. 2011. Long-term exposure to ambient air pollution and mortality due to cardiovascular disease and cerebrovascular disease in Shenyang, China. PLoS One. 6:e20827.

Chen et al. 2013. Long-term exposure to traffic-related air pollution and cardiovascular mortality. Epidemiology. 24:35-43.

Cesaroni et al. 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environmental Health. 11:48.

Cao et al. 2011. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. Journal of Hazardous Materials. 186:1594-1600.

Table 5-16 indicates that approximately half of the included studies report statically significant risk estimates for long-term exposure to NO_2 while half do not. In addition, some estimates are positive and some are negative. Similar observations can be made for cause-specific mortality in Tables 5-17 and 5-18. The draft ISA should include an extended discussion on the interpretation of such a dataset. Does the USEPA believe small, inconsistent risk estimates indicate true increased risk due to long-term exposure to NO_2?

In the summary for this section the draft ISA states that "…there were several well-designed, well conducted studies that did not observe and association between long-term exposure to NO_2 and mortality…" However it is not clear how this information was integrated into the causal determination nor is it clear how the framework described in the Preamble was applied to the determination for long-term NO_2 exposure as it relates to mortality. Similarly, the draft ISA indicates limited coherence with morbidity endpoints and no information on potential mode of action for this section. Therefore, it is unclear that it is appropriate to conclude the overall evidence is suggestive of a causal relationship between long-term exposure to NO_2 and mortality among adults.