Texas Commission on Environmental Quality
Responses to Comments Received on the

Nickel Development Support Document
Preliminary Draft Dated May 2009

January 25, 2011

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INTRODUCTION

Toxicology Excellence for Risk Assessment (TERA) supported the Texas Commission on Environmental Quality (TCEQ) by conducting an expert external peer review as a letter peer review of the *Development Support Document for Nickel, Preliminary Draft May 2009*. The review materials, including draft document, charge to reviewers, and key references (available at http://www.tera.org/Peer/nickel/nickel.html) were distributed to the panel in July 2009. Panel members reviewed the nickel DSD and submitted written comments that addressed the charge questions in August 2009. These written comments represent the panel's review of the preliminary draft Nickel Development Support Document (DSD) and are available in the final peer review report. On October 1, 2009, TERA facilitated a follow-up conference call between the panel and TCEQ. Conference call materials (available at the above website) were distributed prior to the call; members of the public were allowed to listen to the call. The purpose of this call was to allow TCEQ to ask the panel questions regarding their written comments and to allow the panel members to discuss issues on which there were divergent opinions expressed in the written comments. A TERA staff member took notes during the call to create a record of the panel's discussion and recommendations. This report of the conference call (December 2, 2009, *Expert External Peer Review of the Development Support Document for Nickel Report of Conference Call*) is available at the above-referenced website. Therefore, the written comments submitted by the panel and the report of the follow-up conference call comprise the complete peer review on the nickel DSD.

The Toxicology Division (TD) of the TCEQ appreciates the significant effort put forth by the panel members to provide technical comments on the preliminary draft DSD for nickel. The TD

made appropriate revisions to the May 2009 preliminary draft DSD based on panel member comments consistent with the goal of the TCEQ to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD) given the studies available and use of the derived values (i.e., evaluation of ambient air data and air permit applications). The TD's careful consideration and evaluation of panel member comments furthered that goal. The comments within each section below (e.g., 1-4) begin with issue #1 for that subject (e.g., cancer weight of evidence and URF). The comments are followed by TCEQ responses which include what changes, if any, were deemed appropriate and made to the DSD in response to the comment. Similarly, public comments made by the Nickel Producers Environmental Research Association and reported in Appendix C of the December 2, 2009, *Expert External Peer Review of the Development Support Document for Nickel Report of Conference Call* report are addressed in Section 4.

Panel Conference Call Comments

There were various opinions expressed by the reviewers during the conference call. For some issues, a consensus statement from a majority of the reviewers was provided in the report, but for other issues there were differing opinions and only a concluding statement was provided. After due consideration, the TD has attempted to address the issues where consensus was reached, or if a consensus was not reached, has attempted to address issues in the concluding statement. Summary reviewer consensus or concluding statements are presented in the sections below and are followed by the TD responses. Refer to the December 2, 2009, *Expert External Peer Review of the Development Support Document for Nickel Report of Conference Call* for complete comments.

Panel Written Comments

For the most part, the TD did not prepare responses to issues in the written comments that were previously addressed in the conference call comments. Rather, only comments or significant issues that were not discussed or resolved in the conference call are summarized and addressed in these sections. For example, if a consensus was reached on the conference call that the most appropriate critical study or dose metric (e.g., total nickel) was used in the DSD, then that matter is resolved and duplication of written comments concerning that matter was not considered necessary for the purpose of this document, which is to provide responses to potentially significant issues identified by the panel. Additionally, written comments on the same issue which appear in more than one section of the written comments (i.e., reiterated written comments) are only stated and addressed once below to avoid redundancy. Extraneous text contained in written comments is also not provided below, such as text extraneous to the charge question posed (e.g., summaries of studies referred to), text unnecessary for an understanding of the potential issue identified, and comments concurring with the approach in the DSD (i.e., not identifying potential issues).

1. Cancer Weight of Evidence and URF

1.1 Panel Conference Call Comments

Issue #1: Given the wide spectrum of toxicity of the different nickel species, the needs that the TCEQ faces in dealing with mixtures, and the fact that the TCEQ only receives total nickel data, is using a mixtures approach appropriate for a nickel cancer assessment?

> **Comment:** The panel unanimously agreed to the following conclusions and recommendations:

Because of TCEQ's regulatory process and the fact that only data on total nickel are available from air monitoring, the panel agreed that the derived ESL should be based on total nickel.

a. The panel agreed that there are insufficient data to accurately describe the actual nickel speciation in Texas air. However, available data on air composition of nickel species in other states as well as any data and assumptions that TCEQ used in making conclusions about relative prevalence of nickel species in Texas air should be added to the DSD document to enhance the discussion.
b. TCEQ should also add a discussion in the document of its purpose for describing the data regarding the air composition of nickel species and how such data would be used for the ESL program.
c. If the ESL is based on data sets with significant exposures to sulfidic nickel, then the risk characterization should note the resulting ESL value as likely to be conservative. This is because, overall, the data appear to support the conclusion that in ambient air sulfidic forms are minimally present as compared to the occupational epidemiology studies.
d. The document should more fully separate the concepts of how the range of data was used to support the hazard characterization versus the dose-response assessment. A brief discussion could be presented of the range of suggestions from panel members, including using all the human data, using a subset of most representative epidemiology studies, and using animal bioassays to help characterize the uncertainty in the epidemiology approach.

> **Response:** No response was required to address comment "a" as ESLs were already based on total nickel in the preliminary draft DSD. Additional information regarding likely nickel species in Texas air based on available data (e.g., Galbreath et al. 2003, TRI data) was added to Section 4.2.4 of the DSD in response to comment "b" to provide an enhanced discussion. In regard to "c," the topic sentence of the first paragraph of Section 4.2.4 adequately conveys the importance and purpose of discussing and describing the likely forms of nickel in Texas air in the context of the carcinogenic assessment, and indicates that the URF (and consequently the ESL) will be developed based on studies with exposure profiles most similar to nickel in Texas air. The TD has also made the relevance of discussing nickel species in Texas air clear in Section 4.2.5, which identifies similarity in study exposure profile to that expected in Texas air as a criterion for study selection. Additionally, text was added at the end of Section 4.2.5 which puts into context the importance of having discussed likely forms of nickel in Texas air for the carcinogenic risk assessment, and also addresses comment "d" by noting conservatism in

having used studies where workers were still likely exposed to significantly more nickel subsulfide than that expected for Texans. In regard to "e," the TD believes the expert external peer review documents provided on the TERA website are the most appropriate documents to provide a discussion of panel member suggestions, and the range of data used to support the hazard identification and dose-response assessment is sufficiently apparent upon reading the discussions provided in the DSD.

Issue #2: If a mixtures approach to nickel assessment is appropriate, would a WOE for mixtures of nickel be defensible? If so, how should data for the different nickel species be taken into account and how should the WOE narrative address the different forms of nickel likely to be present in the mixture?

Comment: The panel agreed to the following conclusions and recommendations regarding the weight of evidence statement for nickel:

a. The panel recommended that TCEQ incorporate more of the available data on the carcinogenicity and mode of action for each nickel species into the weight of evidence discussion. It is important to better integrate the epidemiology, animal data, and mode of action studies in developing a weight of evidence statement. In addition, the document should discuss the weight of evidence of each nickel species and how each species contributes to the overall weight of evidence for nickel compounds as a group.
b. The panel recommended that TCEQ estimate the composition of nickel species in Texas air and use this to weight the overall weight of evidence and clearly describe the assumptions and conditions under which the descriptor applies, including key uncertainties and their impacts on the interpretation of the weight of evidence descriptor.

Response: In response to comment "a," various information was added to the DSD. For example, more information was added to Section 4.2.3 regarding mode of action related to the carcinogenicity/WOE for various forms of nickel (e.g., soluble, nickel sulfate, insoluble, nickel subsulfide, nickel oxide), and information on nickel form-specific animal carcinogenicity data relevant to the WOE was added to Section 4.2.1. Also, a discussion of the WOE for metallic nickel which considers animal carcinogenicity data, human epidemiology data, and mode of action information was added to Section 4.2.2. As DSDs are meant to primarily document the derivation of values, they often rely on and reference more extensive summary or review documents on a chemical for more detailed discussions. While an exhaustive discussion of WOE information is outside the scope of the DSD, the DSD does discuss and provide references to various agency documents and WOE designations for various forms of nickel, and now provides a WOE discussion for metallic nickel in light of more recent research. As Texas-specific data are not available to estimate the composition of nickel in Texas air (and that composition could certainly vary with location anyway depending on point and area sources), comment "b" essentially cannot be adequately addressed with an acceptable degree of certainty.

Issue #3: Given the issues discussed above for hazard characterization, and the preference

of TCEQ for human data, which studies are considered superior by the reviewers for deriving a somewhat conservative generalization of risk to the population of Texas and why? What specific URF analyses do the reviewers suggest as more applicable for the evaluation of total nickel in ambient air data? What epidemiology studies would be appropriate for TCEQ to use to develop a URF? If nickel compound-specific URFs were derived based on animal data, how should they be applied to a nickel mixture so as to not grossly over- or underestimate risk? Given the cohort in Enterline and Marsh 1982 appears to have been exposed to a nickel mixture appropriate for Texas air, is it reasonable to exclude this study from use in URF derivation because it does not have statistical significance? Could the Enterline and Marsh study be used as a supporting study and how? What is the panel's opinion of the Grimsrud study given that is appears to contradict findings in animals regarding carcinogenicity of soluble nickel compounds?

Comment: The panel provided the following summary feedback on the above questions:

a. Overall, the panel reached consensus that the animal studies should not be the primary approach for quantifying risks from nickel. However, two panel members concluded that deriving quantitative estimates from animals would be useful as a test for reasonableness of the proposed URF in light of the uncertainties in the epidemiology. In contrast, three panel members concluded that the challenges to deriving a quantitative estimate from the animal studies limit the usefulness of using the animal data directly to inform the dose-response assessment. The panel agreed that an approach based on the epidemiology studies would be appropriate.
b. Individual panel members provided their own preferences for refinements to the degree to which various studies should be used and the relative weight each study should be given in the ultimate dose-response used by TCEQ. However, the panel members all agreed that TCEQ should improve the description of the selection criteria for choice of studies in the document.
c. Also, the panel suggested that TCEQ conduct a sensitivity analysis to evaluate the impact of adding epidemiology studies to the URF estimate. In addition, the panel recommended that TCEQ expand the qualitative characterization of uncertainties, including the concept that risk to the nickel mixture in Texas air may be as low as 0.

Response: No response to comment "a" is necessary since an approach based on the epidemiology studies had already been used by the TD and the panel ultimately agreed that such an approach would be appropriate. Additionally, human data are preferable and there would be significant uncertainty (e.g., accounting for nickel form interactions and potential species differences in sensitivity) in comparing nickel form-specific risk estimates based on data from the most sensitive animal species to nickel mixture-based estimates in humans. In regard to "b," the topic sentence of the first paragraph of Section 4.2.4 adequately conveys the importance of selection of studies with nickel species exposure profiles most similar to nickel emissions from Texas facilities and sources for development of the URF (i.e., indicates that the URF (and consequently the ESL) will be developed based on studies with exposure profiles most similar to nickel in Texas air). The TD has ensured that factors used for selection of studies and URF development (e.g., preference for human data, availability of adequate data for dose-response assessment,

generalizability to the public based on the most similarity in exposure profile) are apparent to readers of the DSD in Section 4.2.5. In regard to "c," the TD used the most appropriate epidemiological studies available for dose-response modeling for the most reasonable yet conservative evaluation of Texas ambient air data based on the most similarity (although certainly still different) between worker exposure and that expected for Texas. To add other epidemiological studies, those higher in absolute and relative sulfidic nickel exposure for example, would only likely compound the already likely conservative carcinogenic risk assessment. However, in response to "c," the TD has added an uncertainty section, which includes a statement to the effects that risk to the nickel mixture in Texas air may be as low as 0.

Issue #4: Is the central estimate or the 95% UCL estimate the best estimate and why? Is the URF weighting procedure used to calculate the final URF reasonable and justified?

Comment: In summary:

a. Two panel members suggested use of an upper bound estimate, two members agreed with use of the central estimate, and one had no opinion. However, all reviewers agreed that TCEQ should better describe the uncertainties in the URF, including the possible direction and magnitude of the different factors contributing to uncertainties.
b. Two reviewers thought the weighting approach used by TCEQ was reasonable but two reviewers suggested that TCEQ should consider the two data sets separately, and choose the one that gives the highest URF. However, the panel agreed that the document needs to expand the discussion of the uncertainties in the approach. In addition, the weighting techniques are overly precise given the overall uncertainties.

Response: In response to comments in both "a" and "b," an uncertainty section was added to the DSD. After careful consideration of reviewer comments in "a," the TD decided to continue to use the central estimate for the reasons cited in the DSD. Two reviewers had agreed, and two disagreed. Under the TCEQ guidelines (2006), an important consideration in determining the need to use upper bounds is, "when estimates of mortality are available rather than incidence because survival rates for different cancers vary." Lung cancer incidence and mortality rates are sufficiently similar to the respiratory cancer mortality rates as to be comparable for purposes of the TD's assessment (see revised Figure 3 of the DSD). The guidelines also add support to using central estimates, "when well-conducted meta-analysis based on several epidemiologic studies are performed, the risk calculation can be done with greater precision thus decreasing uncertainty." The final URF is derived using a meta-analysis approach that combines URFs based on the preferred individual epidemiological studies. Though meta-analyses usually combine results of primary research, herein the meta-analysis combines URFs estimated from published data of primary epidemiological research studies. After careful consideration of reviewer comments in "b," the TD decided to continue to use the weighting approach in the draft DSD. Two reviewers had agreed, and two disagreed. The TD is committed to using the best methodology available to combine URFs (none of the reviewers indicated that there was a better method of combining the URFs) to insure that

the method used to estimate a final URF does not add to the uncertainty and variability of the epidemiological data. The weighting procedure used in deriving the final URF uses only objective measures of the quality of the data (number of person years in the study) and the model fit to the data (variance of the estimated slope). To simply use the highest URF, as suggested by two reviewers, would disregard these objectively quantified measures of quality of data and model fit.

Issue #5: General Recommendations for the Cancer Assessment

Comment: In summary:

a. The panel recommended that the document should also characterize uncertainties associated with exposure.
b. In addition, the panel suggested that TCEQ should expand the discussion of the epidemiology studies and animal studies so that the document gives a fuller picture of the available data.
c. Finally, the inclusion criteria for studies used for calculation of the URF should be better discussed.

Response: In regard to comment "a," there are many uncertainties associated with exposure assessments for epidemiological studies in general, as well as study-specific exposure assessment uncertainties. A discussion of these numerous uncertainties is simply outside the scope of DSDs and should be left to the scientific literature, especially for those uncertainties not shown to be significant and clearly applicable to a specific study with an acceptable degree of certainty. In regard to "b," epidemiological data are discussed in Section 4.2.1 and a discussion of animal nickel form-specific carcinogenicity data has been added to that section as well. In response to "c," the TD has made sure that the important factors used for study selection and URF development (e.g., preference for human data, availability of adequate data for dose-response assessment, generalizability to the public based on the most similarity in exposure profile) are apparent to readers of the DSD in Section 4.2.5.

1.2 Panel Written Comments

Issue #6: Please identify any relevant studies or data that have not been cited. Explain how they may impact the assessment.

Comment: R1: While the NTP (1996a,b,c) toxicity studies are all cited in the DSD, the data in these studies were not adequately reviewed. These studies provide data on the threshold for toxicity of the sulfidic, oxidic, and soluble nickel and can be used to calculate chronic ReV, URF, and ESL values. The DSD did not cite a recent study by Oller et al. (2008)…This robust study in rats did not show evidence of carcinogenicity for metallic nickel. While the DSD does describe the toxicity of nickel, it does not fully explore the findings from the NTP and Oller et al. (2008) studies that soluble and metallic nickel were not carcinogenic in animals via inhalation, whereas insoluble forms were. Several studies (e.g., Benson et al., 1995a,b; Dunnick et al., 1995; Yu et al., 2001) describe differences between the forms of nickel in accumulation in and clearance from

the lung, factors which help explain the carcinogenicity findings in these carcinogenicity studies…These studies are…reviewed by Goodman et al. (2009).

Response: Text has been added to Section 4.2.1 which discusses the findings of the NTP studies. Oller et al. (2008) is also discussed, particularly in a new WOE discussion for metallic nickel in Section 4.2.2. The Goodman et al. study is discussed, for example, in regard to the carcinogenic MOA in Section 4.2.3 as it provides information relevant to potential differences in carcinogenic potential. In summary, the implications of these various studies for the carcinogenicity of nickel species are discussed in the DSD.

Comment: R2: A recent study of the inhalation carcinogenicity of nickel metal powder was not cited (Oller et al. 2008). As described in the context of the cancer weight of evidence, this animal study provides important information on sorting out the contribution of individual nickel species, in light of the coexposures seen with most of the epidemiology studies...The lack of respiratory tumors in the present animal study is consistent with the findings of the epidemiological studies.

Response: As indicated above, the implications of this study for the carcinogenicity of metallic nickel is discussed in the DSD, particularly in a new WOE discussion for metallic nickel in Section 4.2.2.

Comment: R3: The TCEQ has not performed a thorough hazard assessment and has instead focused primarily on key studies. This detracts from transparency and obscures the process by which the key studies were chosen. The TCEQ has relied heavily on material from secondary sources, especially the ATSDR and ICNCM documents. This reliance on authoritative secondary sources is understandable, in that it provides a cost-effective evaluation of the literature. However, this approach detracts from reader confidence in TCEQ expertise and is especially a problem when the TCEQ departs from the conclusions and recommendations of these secondary sources that are otherwise heavily relied upon…The authors of the TD need to make it clear that they are departing from federal precedent, and provide a rationale for this departure. An almost universal aspect of the TD is that reference values developed by TCEQ are more conservative than those of otherwise conservative agencies, such as ATSDR, USEPA, and CalEPA. The authors of the TD need to justify this extreme conservatism, especially given the fact that (as already stated) the TCEQ apparently places great confidence on secondary sources from these agencies. The TCEQ has not attempted critical review of the epidemiologic literature, which suggests a lack of familiarity with the limitations of this discipline…Lack of critical review is especially of concern for the cancer epidemiology, which consists of a large number of occupational studies with varying levels of quality and widely varying results. Misuse of epidemiologic jargon also suggests lack of familiarity with epidemiologic methods. For example, page 26 of the TD document concludes that data are "confounded by poor Ni exposure," when this is actually a case of exposure misclassification rather than confounding. Similarly, page 37 of the TD indicates that use of Ni equivalents alleviates misclassification. However, combining all Ni exposure into one, without knowing the important species, does not remove misclassification, and actually enhances it to some degree. The authors of the TD also suggest that the "Grimsrud et al. (2003) cohort is more reliable because it includes greater

than seven times more workers than the…case-control study" (p 33)…The Grimsrud et al. (2002) study is a case-control approach nested within the larger cohort, and therefore has comparable numbers of cases and comparable power. The TCEQ has relied upon 'Ni equivalents' in all their assessments. However, I was somewhat confused about how these values were derived and whether or not they make the assumption that all nickel species as equivalent based on nickel content (even though soluble nickel is most toxic). The method and assumptions underlying Ni equivalents should be discussed, either within the body of the text or as an appendix.

Response: As the primary purpose of a DSD is to document the derivation of values, DSDs do rely heavily on existing hazard assessments in review documents (ATSDR). Frequently, there is scientific consensus that such documents have identified the key effects and studies, although the TD does perform a thorough literature search to identify studies not reviewed in those review documents. Scientifically-defensible rationales are provided in the DSD (and ESL guidelines) for the methodologies used, which may differ somewhat from other agencies depending upon scientific judgment (e.g., UFs). The DSD provides justifications at each step, which to the TD's judgment and the extent practicable, leads to reasonable conservatism given TCEQ's role in protecting public health (and considering the alternatives) but not "extreme conservatism" as indicated by R3. A detailed critical review of the epidemiologic literature is simply beyond the scope of the DSD, and the TD defers to the scientific literature for a detailed discussion of known limitations. The quote referred to by R3 on page 26 of the draft DSD was taken directly from ATSDR (2005), and therefore is not the TD's misuse of epidemiologic jargon. Revised text has been added to the DSD regarding the TD's views on use of nickel equivalents and reasons for use of the Grimsrud et al. (2003) cohort. The TD's use of DSD values for evaluation of ambient air data and permit applications does in effect inherently treat all nickel species as equivalent based on nickel content. The DSD does now acknowledge that use of total nickel as the dose metric inherently treats all nickel species as equivalent based on nickel content, and also contains an example nickel equivalent calculation.

Issue #7: Other General Issues

Comment: R2: As note by the assessment authors, total nickel can be used as the dose measure if the study population in the epidemiology study(s) used for the quantitative assessment was exposed to a mixture of nickel compounds similar to the mixture in Texas air. However, information presented in the DSD about the Enterline and Marsh (1982) study, and issues raised by Goodman et al. (2009) about methods for speciation of nickel (and implications of that analysis for understanding of the Grimsrud et al. (2003) study and other studies of the Kristiansand cohort) suggest that neither of the cohorts used for the quantitative assessment were exposed to mixtures comparable to that in Texan air. Instead, it is likely that both were exposed to substantially more nickel subsulfide than in Texas air, which would result in an over- estimation of cancer risk for the Texas population.

Response: There simply is not a worker cohort study with a nickel species exposure profile similar to what might be expected in Texas air. Epidemiology studies were

selected by the TD which had nickel species exposure profiles believed to be *most similar* to that expected in Texas air, although important differences are still certainly expected. Use of worker studies with exposure profiles most relevant to that in Texas air increases confidence in the URF estimates. Text was added at the end of Section 4.2.5 which notes the significant difference in nickel subsulfide exposure between cohort workers and that expected for the Texas general population may drive URF estimates towards conservatism (i.e., the overestimate risk to an unknown extent).

Issue #8: Please discuss other issues specific to developing URFs for carcinogenic effects that have not been adequately addressed in the document.

Comment: R2: Section 4.2.4 does a nice job of presenting information relevant to this consideration and comparing emissions in Texas with the nature of exposure in the epidemiology data. This is a very important comparison, but some additional information is needed…There may be little or no information on actual exposures, but this should be addressed explicitly…Recognizing that some data may not be available, it is very important that TCEQ provide what is known and what is not known with regard to nickel speciation in ambient air…As noted by the authors, a critical issue in determining whether there are appropriate epidemiology data to use to estimate the risk of exposure to nickel in Texas air is the relative proportion (not absolute amount) of nickel subsulfide in the Texas air and under the worker exposure conditions in the epidemiology studies. This helps in the determination of whether the two mixtures are sufficiently similar that the epidemiology data can be used to estimate the risk from exposure to total nickel in the ambient air. (The proportion is the key metric, rather than absolute amount, because risk is expressed per amount of total nickel, and the proportion is assumed constant as total dose decreases.)…Chapter 2 mentions metallic nickel, nickel sulfate, and nickel oxide in Texas air, with no indication of anything above *de minimis* nickel subsulfide levels. Together, these characterizations of Texas air would suggest that the appropriate mixture for worker exposures in the epidemiology studies used for risk calculation would also include only *de minimis* levels of nickel subsulfide…This has significant implications with regard to the appropriateness of using total nickel as the exposure measure from the epidemiology studies…If nickel subsulfide constitutes a substantially higher percentage of the total nickel in the epidemiology studies than in Texas air, this would result in a substantial over-estimate of cancer risk to the population of Texas…Conversely, if the risk estimate is based on total nickel in an epidemiology study, the closer the composition of the nickel species in the Texas air and the worker exposure in the epidemiology studies, the greater the confidence in using the risk estimates (because the mixtures are more similar).

Response: In response to this comment, additional information regarding likely nickel species in Texas air based on available data was added to Section 4.2.4 of the DSD to provide an enhanced discussion. Consistent with these comments, the topic sentence of the first paragraph of Section 4.2.4 adequately conveys the importance of selection of studies with nickel species exposure profiles most similar to nickel emissions from Texas facilities and sources for development of the URF. The TD agrees that use of worker studies with exposure profiles most relevant to that in Texas air increases confidence in the URF estimates. The TD used the most appropriate epidemiological studies available

for dose-response modeling for the most reasonable yet conservative evaluation of Texas ambient air data based on the most similarity (although certainly still different) between worker exposure and that expected for Texas. The TD has also made the relevance of discussing nickel species in Texas air clear in Section 4.2.5, which identifies similarity in study exposure profile to that expected in Texas air as a criterion for study selection. Additionally, text was added at the end of Section 4.2.5 which notes conservatism in having used studies where workers were still likely exposed to significantly more nickel subsulfide than that expected for Texans. In regard to the importance of relative proportions of nickel subsulfide, information has been added to the text of Section 4.2.5 and Table 7 of the DSD.

Issue #9: Was the proper weight of evidence (WOE) classification using the new USEPA carcinogenic guidelines given to nickel compounds? If not, what WOE classification should be given to nickel compounds, specifically metallic nickel?

Regarding issues not already addressed above for Issue #2 or #6…

Comment: R2: Based on the animal data alone, this study would suggest that metallic nickel is not likely to be carcinogenic to humans…I would lean towards "likely to be carcinogenic to humans" for Texas air, based on the animal data for oxidic nickel and the potential for soluble nickel to enhance the carcinogenicity of other forms of nickel, although a biphasic approach ("suggestive evidence of carcinogenicity" under certain conditions and "likely evidence under others").

Response: The DSD does not attempt to classify metallic nickel into a single definitive WOE classification. Rather, after a new WOE discussion, the DSD indicates the TD interprets the overall WOE, including the latest scientific studies (e.g., Oller et al. 2008, Goodman et al. 2009, Grimsrud et al. 2002), as *at most* adequately supporting that there is "Suggestive Evidence of Carcinogenic Potential" for metallic nickel via inhalation. As a result, as indicated in the DSD, the TD will consider the potential conservativeness of applying URFs in evaluations when it is known that exposure will be to metallic nickel alone, given the negative results from the inhalation rat study (Oller et al. 2008) and the lack of evidence for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers (ATSDR 2005). Additionally, the TD did not feel the need to attempt to specifically provide a WOE classification for nickel in Texas air given the lack of state-specific data and other uncertainties (e.g., likely form changes with location due to point/area sources), although R2 indicates a preference for "likely to be carcinogenic to humans" for Texas air. In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to the cancer-based value, the TD will take form-specific carcinogenicity information (e.g., metallic nickel) into account to properly put health risk into context as part of the further evaluation conducted in such cases. Consistent with R1 comments, the TD considers nickel compounds as a group to be "Carcinogenic to Humans" via inhalation.

Comment: R3: A classification for metallic nickel based on the weight of evidence should more reasonably be 'suspect' or 'unlikely' human carcinogen.

Response: As indicated above, the DSD does not put metallic nickel into a definitive single WOE classification. Rather, after a new WOE discussion, the DSD indicates the TD interprets the overall WOE as *at most* adequately supporting that there is "Suggestive Evidence of Carcinogenic Potential" for metallic nickel via inhalation. As a result, as indicated in the DSD, the TD will consider the potential conservativeness of applying URFs in evaluations when it is known that exposure will be to metallic nickel alone, given the negative results from the inhalation rat study (Oller et al. 2008) and the lack of evidence for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers (ATSDR 2005).

Issue #10: The cancer assessment relied upon human epidemiological studies. There are also animal studies; were the animal data used appropriately to support the weight of evidence conclusions?

Comment: R1: The animal data were not given enough weight in the analysis. Although the epidemiology studies were reviewed at great length, there was very little information provided on the animal data…The animal studies provide clear information on which forms are carcinogenic (and this is supported by MOA studies and studies of lung accumulation and clearance)…These models are more appropriate than the human data for calculating cancer risks, and risks should be calculated separately for sulfidic, oxidic, soluble, and metallic nickel. R2: I would recommend that additional weight be given to the animal studies, particularly the impact of the negative metallic nickel study. R3: Results from animal studies are only mentioned in passing within a paragraph that refers to the ATSDR and ICNCM documents (p29). R4: As stated at the end of the previous comment, I believe the animal data could be used to support a conclusion about weight of evidence. R5: I saw only one reference to an animal carcinogenesis study…

Response: In response, additional information was added to the DSD. For example, information on nickel form-specific animal carcinogenicity data relevant to the WOE was added to Section 4.2.1, more information was added to Section 4.2.3 regarding mode of action related to the carcinogenicity/WOE for various forms of nickel (e.g., soluble, nickel sulfate, insoluble, nickel subsulfide, nickel oxide), and a discussion of the WOE for metallic nickel which considers animal carcinogenicity data, human epidemiology data, and mode of action information was added to Section 4.2.2. As the TD will most frequently not know what form of nickel is present in ambient air, for example, the utility of form-specific URFs is questionable. The TD used the most appropriate epidemiological studies available for dose-response modeling for the most reasonable yet conservative evaluation of Texas ambient air data, which is in the interest of public health, based on the most similarity (although certainly still different) between worker exposure and that expected for Texas. In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to the cancer-based value, the TD will take form-specific carcinogenicity information into account to properly put health risk into context as part of the further evaluation conducted in such cases.

Issue #11: Is the epidemiological evidence in Grimsrud et al. (2003) and Enterline and Marsh (1982) properly used in the characterization of chronic cancer risks? Is use of these

two studies for calculating URFs justified?

Regarding issues not already addressed above for Issue #7 or #10…

Comment: R1: In addition, while the DSD acknowledges the overall lack of statistical significance in the Enterline and Marsh (1982) study, this does not seem to play a role in the derivation of the URF. The DSD should not calculate a risk value based on a study for which there were very few statistically significant risks.

Response: While there is a general lack of statistical significance for the SMRs in Enterline and Marsh (1982), lack of statistical significance is not proof of lack of effect in carcinogenicity risk assessments. Also, there is a need for TCEQ to characterize cancer risk due to nickel exposure in the interest of public health, and there is regulatory agency precedent for use of such studies for risk characterization (e.g., USEPA 1986).

Comment: R2: Based on these considerations, I conclude that there are too many uncertainties regarding the actual nature of the exposure at Kristiansand to use that study as a basis for the quantitative assessment. Using total nickel exposure (instead of speciated nickel) does not resolve the issue, in light of the animal data showing high potency for nickel subsulfide, and the likely/potential differences in the proportion of nickel subsulfide at Kristiansand and in Texas…If a policy decision is made to use the "all worker" data as a health-protective approach due to inadequate speciation data for Texas air, this needs to be clearly stated, along with a characterization of the uncertainties and likely over-protectiveness of this approach.

Response: There are many uncertainties associated with exposure assessments for epidemiological studies in general, as well as study-specific exposure assessment uncertainties. The TD views the nickel form concerns expressed about the Kristiansand study to be generally speculative in nature, meaning these concerns have not been established to be clearly applicable to this study with an acceptable degree of certainty (i.e., analytical problems have not been shown to have in fact occurred for the Kristiansand study). For example, there are no analyses of historical samples which indicate that sulfidic nickel was appreciably underestimated using the previous analytical method. Thus, the TD does not know that there is in fact an issue with this study that needs to be resolved. There simply is not a worker cohort study with a nickel species exposure profile similar to what might be expected in Texas air. Epidemiology studies were selected by the TD which had nickel species exposure profiles believed to be *most similar* to that expected in Texas air, although important differences are still certainly expected. Use of worker studies with exposure profiles most relevant to that in Texas air increases confidence in the URF estimates. In regard to the use of "all worker" data, Section 4.2.6.2.4 of the DSD indicates that: 1) a health-protective science policy-decision was made to select the β value based on the dataset for all workers combined as the preferred β considering TCEQ's important role in the protection of public health, the possibility of some nickel subsulfide exposure due to emissions from Texas facilities cannot be entirely excluded, and the dataset for all workers is the most robust for development of the β; and 2) while a conservative decision in the face of uncertainty, the preferred β (all workers) may tend to overestimate risk for the Texas population (e.g., the

β for workers hired after 1946 + non-refinery workers is about an order of magnitude lower). Additionally, an uncertainty section has been added to the DSD.

Comment: R3: The TCEQ provide no substantive or critical review of the epidemiologic literature, as was done in the ICNCM document…Most importantly, the rationale for selection of the Grimsrud et al. (2003) and Enterline and Marsh (1982) studies is deeply flawed…This rationale is flawed on several levels: 1) It sounds like circular reasoning that uses loosely related arguments to reach a predetermined goal, 2) It runs directly contrary to their previous assertion that all species of Ni are potentially carcinogenic, so that the species of nickel is unimportant, and 3) It ignores issues of data quality, such as sample size and lack of bias, and selects studies based solely on generalizability of exposure…The best approach to study selection would have probably been to include all studies with suitable exposure estimates (based on objective criteria), summarize the strengths and limitations of each study, and calculate a meta-summary or meta-regression using appropriate weighting factors (e.g., sample size and study quality).

Response: As indicated previously, a detailed critical review of the epidemiologic literature is simply beyond the scope of the DSD, and the TD defers to the scientific literature for a detailed discussion of known limitations. The primary purpose of a DSD is to document derivation of the values, which the nickel DSD accomplishes. The DSD is not meant to be a comprehensive review document such as an ATSDR Toxicological Profile or a critical review document published in the peer-reviewed literature. After carful consideration, the TD disagrees that the rationale for selecting the Grimsrud et al. (2003) and Enterline and Marsh (1982) studies is flawed. The only predetermined goal for study selection was, to the extent possible based on available studies, to estimate nickel risk using studies which would not result in a gross overestimation of risk based on the ambient air data and expected forms of nickel in Texas air. This is an entirely legitimate and desirable goal which is consistent with the proper identification of potential environmental issues and the appropriate focusing of agency and other resources. For this reason, epidemiology studies were selected by the TD which had nickel species exposure profiles believed to be *most similar* to that expected in Texas air, although important differences are still certainly expected. Using all worker studies of acceptable quality would likely result in better estimates of risk for nickel refinery workers than the general public due to even more significant differences in nickel exposure profiles overall (e.g., even higher overall worker sulfidic nickel exposure). Although the TD is treating nickel compounds as a group as carcinogenic (with special consideration if the form is known to be metallic), the TD recognizes that the carcinogenic evidence is strongest for the sulfidic form and that Texas air is expected to have unappreciable levels of this form (if any). The TD's selection of studies with lower (both relative and absolute) levels of sulfidic nickel is in recognition of these facts and consistent with the goal of, to the extent possible, not grossly overestimating risk based on the ambient air data and expected forms of nickel in Texas air. This is an objective criterion relevant to generalizability to the public, which is important for helping put risk into the proper perspective and appropriately focusing resources for the protection of public health. Following study selection, the weighting procedure used in deriving the final URF uses objective measures of the quality of the data (number of person years in the study) and the model fit to the data (variance of the estimated slope) for the studies

selected. The final URF is derived using a meta-analysis approach that combines URFs based on the preferred individual epidemiological studies. Though meta-analyses usually combine results of primary research, herein the meta-analysis combines URFs estimated from published data of primary epidemiological research studies. The purpose of this meta-analysis is to integrate the findings based on the preferred individual studies into a final URF that objectively incorporates the value of the data (measured by the size of the study) and the significance of the results (measured by the precision or variance of the model fit to the data).

Comment: R4: Therefore, I would conclude that while the use of the data from Enterline and March and Grimsrud has been appropriate, and that they can be used to derive URFs, there may be one additional cohort (or subcohort of those employed at Clydach after 1930) that could also have been used.

Response: Epidemiology studies were selected by the TD which had nickel species exposure profiles believed to be *most similar* overall to that expected in Texas air, although important differences are still certainly expected. Relative percent sulfidic nickel data have been added to Table 7 of the DSD for the various studies. Workers in the Clydach study were exposed to relatively high levels of sulfidic nickel, generally both in terms of absolute and relative concentrations (Seilkop and Oller 2003). Although there is uncertainty in the calculations, the Clydach study had an estimated overall relative percent for sulfidic nickel of 39%, while the Huntington and Kristiansand studies have lower relative percents (generally less than 15%) (see Table 7 of the DSD). For this reason, the DSD continues to utilize the Huntington and Kristiansand studies.

Issue #12: Were the statistical and modeling approaches used for calculating URFs appropriate?

Comment: R3: In my opinion, the modeling approaches used by the TCEQ were too complicated given the uncertainty and variability inherent in the underlying data…The sophisticated modeling adds an illusion of certainty, precision, and objectivity, but this is not borne out by the underlying data…As mentioned previously, either the simple approach used by EPA or a meta-summary would probably have been preferable …Furthermore, the authors of the TD provide no details on how the various modeling exercises were performed. Appendix B provides general guidance on how the linear multiplicative risk model should be performed, but does not appear to describe the actual process and specific calculations performed by the TCEQ. Descriptions or summaries of the actual modeling exercises should be included either in the text or with an appendix. Perhaps most importantly, the TCEQ provides no information regarding whether regression diagnostics were performed, or the results of those diagnostics. Regression diagnostics provide important information on model fit, the integrity of modeling assumptions, collinearity of variables, and the influence of outlying observations.

Response: TCEQ is committed to make the best use of the most accurate exposure data, use the most applicable background cancer rates, include the impact of competing causes of death and use the best methodology for analyzing the available epidemiological data.

These are provided by the methods in the DSD, not the simplistic average risk model used by USEPA. As clearly indicated in the nickel DSD…

> The average relative risk model used by USEPA for Magnus et al. (1982) and Enterline and Marsh (1982) is a simplistic approach which provides only a rough estimate of incremental risk per unit dose and should only be used when more detailed information is lacking and better methods cannot be used (e.g., only one dose-response data point). The simplicity of the USEPA average relative risk model may produce biased estimates of the URF for at least three reasons. First, it does not reflect time-dependent exposure and dose-response information. Second, it ignores age-dependent competing causes of death when calculating the URF. Lastly, it does not allow for an estimate of the confidence limits on the URF.
>
> The TD did not use the average relative risk model for the Grimsrud et al. (2003) update of Magnus et al. (1982), or for Enterline and Marsh (1982), because the multiplicative relative risk model with Poisson regression modeling or least squares linear regression to approximate the relative risk model along with the BEIR IV methodology can be used and provides a better analysis for estimating lifetime excess risk. For example, the BEIR IV methodology accounts for competing causes of death and age-specific background population risks, and may also be used to incorporate other potentially important factors (e.g., exposure lag, windows of exposure). It is not justifiable or desirable to use the average relative risk model when there are sufficient data for the TD to use the multiplicative relative risk model.

The TD believes the fact that epidemiological data includes variability and uncertainty should not be used as an argument to discard models that are more appropriate and that do not introduce more variability and uncertainty in favor of simpler, less appropriate models that can only add other layers of variability and uncertainty to the estimation of URFs. In regard to the meta-analysis comment, a meta-regression combines all the data into a single data set and assumes some homogeneity among the different data sets. A meta-regression analysis in the case of nickel is complicated because: 1) the data cannot be combined due to lack of consistency in the published presentation of summary statistics, 2) the individual epidemiological data are not available, and 3) the nickel species are different in the different epidemiological studies. Furthermore, the TD's estimation of a URF is analogous to a meta-analysis in that the final nickel URF, based on total nickel exposures, combines the results of the individual epidemiological analyses to estimate a single URF. Detailing every aspect of fitting the well-known Poisson regression models commonly used in epidemiological research is beyond the scope of the DSD. However, Appendix B gives more detail, some addition information was added to Section B.1 of Appendix B, and additional information (if needed) is included in the references: Crump, K.S., and B.C. Allen. 1985. Methods for quantitative risk assessment using occupational studies. Journal of the American Statistical Association 39 (4):442-450, or Feldman, R. M and C. Valdez-Flores, Applied Probability and Stochastic Processes, Second Edition, Springer-Verlag Berlin Heidelberg, 2010.

In regard to diagnostics, there is only one predictive variable (exposure to nickel). Multi-collinearity effects can only occur when there are more than one predictive variable in the models. The effects of multi-collinearity of predictive variables were not explored in the models fit in the nickel DSD because there is only one predictive variable (exposure to nickel). Therefore, assessing multi-collinearity of predictive variables is meaningless in this case. Regarding the influence of outlying observations, the impact of "outlying" observations was not explored in the nickel DSD because only summary data were available for model fitting. The impact of specific individuals on the overall risk estimates could not be assessed with the available summary data. The impact of each of the summary SMRs, SIRs and RRs was not assessed either because these summary statistics contain partial information of the history of all the individuals in the cohort and it is inappropriate to exclude SMRs, SIRs or RRs from model fitting for sensitivity analyses purposes. Information on model fit diagnostics has been added as Appendix H to the DSD.

Comment: R4: I have one specific comment about portions of the analysis. When using the maximum likelihood approach for estimation of parameters, I think it would be much better to derive bounds on those parameters (in particular on β which is used as the basis for URF determination) through the use of the profile likelihood method. Bounds that are based on asymptotic approximations to the variance, i.e., the ones reported in the nickel DSD, are known to be problematic in certain cases. The profile likelihood method is one that avoids the asymptotic approximation of the variance and which finds bounds while simultaneously considering the variability of the other parameters.

Response: In response, the TD has derived the profile likelihood upper and lower confidence limits on the estimates of the slopes for those data fit using maximum likelihood estimation and presents them in the DSD (see Tables 10 and 13 of the DSD).

Comment: R5: Although detailed information on the BEIR IV approach to calculating URFs is given in Appendix E, the DSD needs to spell out in greater detail in the body of the document (e.g., page 42, lines 19-27) exactly how air concentrations were calculated using the BEIR methodology.

Response: In response, explicative text has been added to Appendix E of the DSD.

Issue #13: Is use of total nickel for both studies, and all workers for Enterline and Marsh (1982), justified given the purpose of the URF and carcinogenic ESL and in light of the recent work by Goodman et al. (2009)?

As there was consensus on the conference call for use of total nickel as indicated in Issue #1 above:

Comment: R2: Similarly, as noted above, inclusion of the refinery workers in the Enterline and Marsh (1992) study means that a group with relatively high subsulfide exposure is included. Use of total nickel may be appropriate for the non-refinery workers and/or the workers hired after 1946, because they had low subsulfide exposures – a key criterion in the choice of cohort to use for the analysis.

Response: This comment may be suggesting use of non-refinery worker and/or worker hired after 1946 data (low subsulfide exposures) as opposed to using "all worker" data, which includes refinery workers (relatively high subsulfide exposure). The TD recognizes the use of "all worker" data as conservative. In regard to the use of "all worker" data, Section 4.2.6.2.4 of the DSD indicates that: 1) a health-protective science policy-decision was made to select the β value based on the dataset for all workers combined as the preferred β considering TCEQ's important role in the protection of public health, the possibility of some nickel subsulfide exposure due to emissions from Texas facilities cannot be entirely excluded, and the dataset for all workers is the most robust for development of the β; and 2) while a conservative decision in the face of uncertainty, the preferred β (all workers) may tend to overestimate risk for the Texas population (e.g., the β for workers hired after 1946 + non-refinery workers is about an order of magnitude lower).

Comment: R3: However, there appears to be little compelling evidence of a substantive carcinogenic hazard from metallic nickel, so it is not appropriate to apply the derived potency to metallic exposure, which is the predominant exposure in TX.

Response: The DSD does not put metallic nickel into a definitive single WOE classification. Rather, after a new WOE discussion, the DSD indicates the TD interprets the overall WOE as *at most* adequately supporting that there is "Suggestive Evidence of Carcinogenic Potential" for metallic nickel via inhalation. As a result, as indicated in the DSD, the TD will consider the potential conservativeness of applying URFs in evaluations when it is known that exposure will be to metallic nickel alone, given the negative results from the inhalation rat study (Oller et al. 2008) and the lack of evidence for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers (ATSDR 2005). In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to the cancer-based value, the TD will take form-specific carcinogenicity information (e.g., metallic nickel) into account to properly put health risk into context as part of the further evaluation conducted in such cases.

Issue #14: Are the most appropriate URFs from each study used to calculate the final URF?

Comment: R1: The smoking-unadjusted URF in the Grimsrud et al. (2003) study should not be included in the calculation of the final URF. R5: However, I do not follow the logic of the statement in lines 8-10, page 44, which seems to justify choosing the smoking-unadjusted SIR…

Response: Smoking-adjusted analysis on epidemiological studies and lung cancer should be favored over non-adjusted analyses *of the same data*. However, in the Grimsrud et al. (2003) study, the quality of the data for dose-response modeling of the smoking-unadjusted lung cancer incidence rates given in their Table 7 is much better than the quality of the data for dose-response modeling of the smoking-adjusted lung cancer incidence rate ratios given in their Table 8. As indicated in Section 4.2.6.1.4 of the DSD, although not adjusted for smoking, the TD utilizes the URF based on available SIRs as

the variability of the estimated parameter based on the SIRs is smaller (e.g., there is only about a 1.5 fold difference between the URFs calculated using the SIR-based β and β (95%UCL) and the β (95%LCL) is still positive, while there is a 3.2 fold difference between the URFs calculated using the RR-based β and β (95%UCL) and the β (95%LCL) is actually negative). Additionally, the URF based on SIR data may be somewhat more robust because it was calculated using a β obtained from the multiplicative relative risk model and Poisson regression instead of a least squares linear regression which approximates the relative risk model. Had the data been of the same or better quality for dose-response modeling, the URF based on the smoking-adjusted RRs would have been assigned all the weight. No changes were made to the DSD.

Issue #15: Is use of the central estimate URFs justified for reasons discussed in the DSD?

Comment: R4: The use of the central estimate was justified in part because incidence data were available (as opposed to mortality data) in the analysis of the Grimsrud data. But that is not the case for the Enterline and Marsh data analysis, which used mortality for all respiratory cancers…For one thing, how do the age-related rates compare to one another? At the very least, the document should show some additional supporting evidence (like Figure 3, but plotting respiratory cancer mortality and lung cancer incidence)…The truly health protective choice would be to use the upper bound β estimates to derive the URFs. This is even more the case because many significant uncertainties not associated merely with model fit and uncertainty about model parameter values have not been considered in this document at all. Uncertainties about exposure reconstruction, misclassification (even for total nickel exposure), choice of reference rates, use of summary data, selection of study cohorts, and many others are likely to contribute much more uncertainty than that associated with the estimation of β in the dose-response models. Until and unless those potentially substantial uncertainties are shown to be not important (or to be such that risk would only, or predominantly, be overestimated by the choices made in the current analysis), I would recommend the use of the upper bound β estimates (improved, where possible, by using the profile likelihood approach to deriving those bounds as mentioned in a response to an earlier question). R5: The use of the central estimate URFs might be justified, but additional clarification and justification are needed…Thus, the justification in the DSD is not clear, and the guidance itself is not clear. The rationale for using a central estimate needs to be clarified in the DSD.

Response: In response, Figure 3 of the DSD was revised per the comment. Under the TCEQ guidelines (2006), an important consideration in determining the need to use upper bounds is, "when estimates of mortality are available rather than incidence because survival rates for different cancers vary." Revised Figure 3 shows that respiratory cancer mortality is not appreciably less than the lung cancer incidence. Lung cancer incidence and mortality rates are sufficiently similar to the respiratory cancer mortality rates as to be comparable for purposes of the TD's assessment. The guidelines also add support to using central estimates, "when well-conducted meta-analysis based on several epidemiologic studies are performed, the risk calculation can be done with greater precision thus decreasing uncertainty." The final URF is derived using a meta-analysis approach that combines URFs based on the preferred individual epidemiological studies.

Though meta-analyses usually combine results of primary research, herein the meta-analysis combines URFs estimated from published data of primary epidemiological research studies. Based on all R4 comments on the matter in the report, it seems R4 would have preferred the DSD to indicate that the reason lung cancer incidence was used is because Grimsrud et al. only presented incidence summary results. Therefore, the sections of the DSD which discuss the combination of lung cancer incidence and respiratory cancer mortality have been revised (Sections 4.2.6, 4.2.6.2.4, and 4.2.6.2.5). In regard to the recommendation of using the 95% upper confidence limit on the slope to account for the uncertainties in the studies, although there is no way to eliminate uncertainty and variability in epidemiological studies, the uncertainty and variability can be discussed and presented. Thus, an uncertainty section has been added to the DSD.

Issue #16: Other comments on the assessment.

Comment: R5: I recommend that all the statements in the DSD regarding the carcinogenicity of soluble nickel be reviewed for consistency…I believe that it needs to be clarified whether the unadjusted or adjusted BEIR methodology was use for Enterline and Marsh…

Response: In response, appropriate revisions were made to the DSD.

2. Health-Based Acute ReV and ^{acute}ESL

2.1 Panel Conference Call Comments

Issue #1: Should the Graham mouse study be designated a "co-principle" study since data needed for the MPPD model were not available? How would it made a difference in the final ReV value that was chosen?

Comment: Overall the panel agreed with the use of the Cirla study as the critical study. The panel also concluded that adding the Graham study as a co-critical study would not provide significant additional relevant information.

Response: No response by the TD was necessary. The Graham mouse study will continue to be a supporting study in the DSD.

Issue #2: Upon review of all opinions and rationales, what is the reviewers' consensus on the most appropriate value for the LOAEL-to-NOAEL UF and the database UF?

Comment: Although individual panel members made recommendations to increase or decrease individual factors based on various arguments, the panel reached consensus that the composite uncertainty factor of 30 is adequate. The panel suggested that TCEQ add more discussion about the contributions of the available animal data to the limited database and add more description of considerations that might increase or decrease the selected values.

Response: The draft DSD already used a composite uncertainty factor of 30, which was considered adequate by the panel. In response to this comment, the TD added significant additional information to the discussion and justification of uncertainty factors in Section 3.1.5.1.1.

2.2 Panel Written Comments

Issue #3: For the supporting animal study (Graham et al. 1978), were the appropriate default dosimetry adjustments from animal-to-human exposure conducted? Specifically, were appropriate estimates (i.e. mass median aerodynamic diameter (MMAD) and geometric particle size distribution (σg)) for conducting the regional deposition dose ratio (RDDR) chosen when the supporting study did not report the required parameters?

Comment: R1: TCEQ used an equation from USEPA (1994) to convert the adjusted POD to a human equivalent POD. This involves multiplying the adjusted POD by a dosimetric adjustment factor for the respiratory tract region, which is the regional deposited dose ratio (RDDRr) for particles. TCEQ used a model to estimate RDDRr that used species-specific parameters (e.g., surface area, body weight, and ventilation rate) and particle parameters as inputs. TCEQ presents the model output, which includes all input values. It is not clear whether TCEQ chose the species-specific parameter inputs or whether they were built into the model. If the former, TCEQ should provide sources for transparency. Particle parameter values (MMAD and σ_g) were not provided in the key animal study, so TCEQ used input terms from other studies as surrogates. The values used (MMAD = 1.80 and σ_g = 1.60 µm) are on the lower side of the ranges provided in NTP (1996a,b,c) and Oller et al. (2008). It is not clear how changes in particle input parameters affect the magnitude and direction of the model output. Model sensitivity to these parameters should be described for a greater understanding of their influence on the output.

Response: Section 3.1.4.2 has been revised to identify the various sources of model input parameters. In regard to the MMAD and σ_g used in the preliminary draft DSD, additional surrogate values were identified by the TD which represented the high-end of the ranges available and yielded the smallest (i.e., most conservative) RDDR values for the respiratory tract region of interest. This is consistent with the recommended default approach in USEPA (1994). This is explained and these more conservative values are used in the final DSD.

Comment: R2: The approach used for estimating the MMAD and GSD appear reasonable. However, the authors state that the RDDR for the total respiratory tract was used because the critical effect is a systemic effect. If the effect is truly a systemic effect, with the appropriate internal dose measure being the amount of nickel that is absorbed from the respiratory tract and systemically available, then the RDDR should be calculated for the extrarespiratory region.

Response: The TD appreciates this comment and the DSD was revised accordingly.

Comment: R4: Although the standard exposure duration adjustment is to assume n=1 when no additional information is available, I question the statement (p. 13, line 12) that it is conservative to adjust from 30 minutes to 60 minutes by a simple ratio of 30/60. In fact, if n < 1, then that adjustment would not be conservative. I am not arguing that TCEQ adjust for duration in another way, I just think that (unless it can be strongly argued that n would not be less than 1) the document should just say that the policy decision is that the assumption of n=1 is the basis for the adjustment in the absence of additional information. With respect to the animal dosimetric adjustment, the use of the RDDR methodology is a good choice. However, because of a lack of MMAD and σ_g data for the study in question (Graham et al., 1978), the document under-represents the uncertainties in the animal-based estimates…It might suffice to give a little bit more information about the other studies cited (from which MMAD and σ_g were obtained) with respect to how they compare to the Graham et al. study (similarity of exposure conditions, of the method of generating the test exposures, of the nickel compounds being tested). Moreover, a quick-and-dirty assessment of the impact of some other reasonable choices for MMAD and σ_g could show how much impact there was on the final adjusted animal POD estimate. The fuller elaboration of the uncertainty associated with the animal-based POD is important because the POD derived from the primary, human study is supported by the claim that the latter is lower than the former (p. 16, line 4).

Response: Text in Section 3.1.4.1 was revised regarding use of n=1 for the exposure duration adjustment. In regard to the MMAD and σ_g used in the preliminary draft DSD, additional surrogate values were identified by the TD which represented the high-end of the ranges available and yielded the smallest (i.e., most conservative) RDDR values for the respiratory tract region of interest. This is consistent with the recommended default approach in USEPA (1994). This is explained and these more conservative values are used in the final DSD. As they represent the high and conservative end of the range, they viewed to adequately support the assertion that the human-based POD is lower (more conservative) than the animal-based POD.

3. Health-Based Chronic ReV and $^{chronic}ESL_{noncancer}$

3.1 Panel Conference Call Comments

Issue #1: Which form of nickel should be selected for deriving the ReV/ESL appropriate given the purpose of these values? If nickel species-specific ESLs were derived from the NTP study, how should they be applied to a nickel mixture?

Comment: In summary:

a. Overall, the reviewers agreed with TCEQ's approach, and agreed with the choices of critical study, critical effect, dosimetry, and uncertainty factors.
b. One reviewer noted that the same issues discussed for the cancer assessment with regard to discussion of the animal data also apply to the noncancer assessment. This reviewer stated that if TCEQ has decided to choose a single representative nickel species, then nickel sulfate is the most appropriate surrogate for noncancer effects. The panel agreed with this conclusion.

c. Overall, the panel members agreed with the UF choices presented in the document based on the information cited. However, regarding the choice of uncertainty factors for animal to human differences, one reviewer agreed with the submitted public comment that human data (Berge and Skyberg 2003) support the conclusion that humans are less sensitive than animals. Therefore, this reviewer concluded that it would be reasonable to decrease the uncertainty factor to account for extrapolating from an animal study. Other panel members agreed that TCEQ should reevaluate the factor on animal to human differences in toxicodynamics in light of these data.

Response: No response to "a" is necessary. As the panel ultimately agreed that nickel sulfate is the most appropriate surrogate for noncancer effects considering TCEQ's decision to choose a single representative nickel species, no response to "b" is necessary. After consideration of "c," the TD conservatively retained the standard animal-to-human toxicodynamic uncertainty factor of 3.

3.2 Panel Written Comments

Issue #2: Was the animal study selected for the non-cancer estimates the most appropriate study? Was the form of nickel selected (nickel sulfate) for deriving the ReV/ESL appropriate given the purpose of these values?

Comment: R1: The most appropriate animal study was selected regarding soluble nickel. Although soluble, oxidic, sulfidic, and metallic nickel have all been associated with pulmonary fibrosis and chronic inflammation in the lung (NTP 1996a,b,c; Oller et al., 2008), the toxicity of each varies, with nickel sulfate being the most toxic. Each of these studies can and should be used to calculate a separate ReV/ESL for each form of nickel.

Response: As indicated in section 3.1 above, the panel agreed that if TCEQ has decided to choose a single representative nickel species, then nickel sulfate is the most appropriate surrogate for noncancer effects. However, further discussion is provided here. As the TD will most frequently not know what form of nickel is present in ambient air, for example, the utility of form-specific ReV and ESL values is questionable. TD conservatively selected the most toxic form to develop the Rev/ESL to evaluate whatever form(s) may be present, which is in the interest of public health. In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to appropriate comparison values, the TD will take form-specific toxicity information into account to properly assess health risk/hazard as part of the further evaluation conducted in such cases. No changes were made to the DSD.

Comment: R3: The choice of NTP (1996) appears reasonable…The choice of nickel sulfate also seems reasonable, given that this is among the most toxic forms. However, one needs to know how the reference values derived using the most toxic form will be applied to less toxic forms, such as metallic or insoluble nickel.

Response: As indicated in Section 3.1 above, overall the reviewers agreed with the choice of critical study, so there is no need to discuss that choice here. In regard to how the reference values derived using the most toxic form will be applied to less toxic forms, as indicated above, the values will be used o evaluate whatever form(s) may be present (e.g., ambient air samples). In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to appropriate comparison values, the TD will take form-specific toxicity information into account to properly assess health risk/hazard as part of the further evaluation conducted in such cases. This specific issue is more pertinent to the ambient air data review process than an issue to be discussed in the DSD.

Issue #3: Were the appropriate default dosimetry adjustments from animal-to-human exposure conducted? Specifically, was the Multiple Pass Particle Dosimetry (MPPD) Model used appropriately and is the (RDDR) appropriate? Were the parameters used scientifically defensible?

Comment: R2: Mostly correct adjustments were made. The one caveat is that there was an inconsistency in the calculation of the RDDR from the deposition fraction. For the human breathing rate, the DSD used the EPA default of 13,800 mL/min. However, the deposition fraction was calculated with MPPD using the default scenario of light activity, which results in a different minute volume. The minute volume used by MPPD can be calculated as follows: 1) the output provides human tidal volume (volume/breath) of 625 mL and a breathing frequency of 12/min., and 2) the product of tidal volume and breathing frequency is the volume/minute = 7500 mL/min. This human minute volume would then be used to calculate the RDDR based on the MPPD default values. Similarly, the rat minute volume used in the deposition calculation is the product of 2.1 mL x 102/min = 214.2 mL/min. Alternatively, the authors could calculate the deposition with MPPD using the human tidal volume and breathing frequency corresponding to the default EPA parameters. The choice of which human minute volume to use is a science policy decision, but internal consistency in the calculation is needed.

Response: The TD appreciates this comment and the DSD was revised to address this issue. More specifically, the default minute ventilation (V_E) used by MPPD for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TD used human tidal volume and breathing frequency values from deWinter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model (see Appendix F of the DSD). For the rat, the V_E corresponding to that in the MPPD model was used in the RDDR calculation. Thus, the final DSD uses V_E values for the human and rat that are consistent between the MPPD model and the RDDR calculation.

Issue #4: The choice of point of departure.

Comment: R1-2, R4-5: In summary, these four reviewers indicated that the authors should explain further why the data were considered not amenable to standard BMC modeling.

Response: The DSD was revised to include additionally information. More specifically, a NOAEL of 0.03 mg Ni/m^3 from the NTP (1996c) study for chronic active lung inflammation in rats was selected by the TD for use as the POD as the data for chronic inflammation were not amenable to standard BMC modeling (i.e., adequate model fits could not be obtained based on goodness-of-fit p-values, scaled residuals, and visual inspection). However, some adequate model fits were obtained by BMC modeling for two lesions considered components of chronic inflammation by NTP (1996c) (i.e., alveolar proteinosis and macrophage hyperplasia), and the significant similarity of these BMCs to the NOAEL support use of the NOAEL for chronic active lung inflammation as the POD (see Appendix G of the DSD).

4. Public Comments by the Nickel Producers Environmental Research Association

The following addresses public written comments submitted by the Nickel Producers Environmental Research Association and reported in Appendix C of the December 2, 2009, *Expert External Peer Review of the Development Support Document for Nickel Report of Conference Call* report.

Issue #1: Speciation of air nickel exposures

Comment: The TCQS nickel Development Support Document (DSD) does not provide any measured data on the speciation of nickel in ambient air in Texas. Rather, it relies on personal communications regarding the kind of processes that are present in Texas and the expected emissions to ambient air based on the nature of those processes. Although this approach can be acceptable as a first approximation, it is only a first approximation. For example, some activities like grinding nickel metal or alloys in massive forms can produce very large particles (visible dusts). These particles (containing metallic nickel) will be fairly course for the most part and not contribute to PM_{10} or $PM_{2.5}$. The small particles that contribute to Texas ambient air could have a completely different composition. The enclosed papers by Galbreath et al. report on nickel in ambient air measurements in Florida and provide concrete speciation data on these exposures. Galbreath et al. report that complex nickel oxides and nickel sulfate are the predominant forms of nickel in ambient air, with very small amounts of nickel sulfide (not nickel subsulfide) present and no metallic nickel. It may be prudent to take these published data into consideration in the DSD report.

Response: Relevant information from the Galbreath et al. (2003) report was considered and added to the DSD.

Issue #2: Mode of action and carcinogenicity tumor sites

Comment: The DSD does not cite the Heim et al. (2007) study (listed as Reference not cited). Yet, this study is important for two reasons: 1) it confirms that nickel cannot cause tumors at sites other than the respiratory tract, and 2) it adds to the WOE evaluation of the carcinogenicity of soluble nickel compounds. In the Heim et al. study, rats exposed by gavage to nickel sulfate hexahydrate did not demonstrate increased incidence of tumors even though blood nickel levels were several hundred-fold higher than in control rats. This also indicates that it is unlikely that cell membrane-mediated effects of nickel ions (e.g., HIF-mediated effects) can result in tumor induction or promotion of naturally occurring tumors. Rather, this supports the premise that Ni ions have to be present in the nucleus of target respiratory cells to see any tumors and that Ni ions (from water soluble nickel compounds) do not have an efficient way to get to the nucleus of the cells.

Response: In response to other comments, additional information (relevant to the carcinogenic MOA) on nickel form differences (soluble versus insoluble forms) in nickel ion availability to the nucleus and additional information on animal data relevant to the WOE for particular forms has already been added to the DSD. Although Goodman et al. (2009) is the citation, the TD views this as adequately addressing the main points of this comment.

Issue #3: Health Based Chronic ReV

Comment: The use of an uncertainty factor of 3 to account for toxicodynamic differences in response between rats (assumed to be less sensitive) and humans (assumed to be more sensitive) for respiratory toxicity/inflammation effects is likely to be overly conservative. Rats are known to be more (not less) sensitive to the toxicity effects of particulates than mice and primates…

Response: As indicated in response to a similar comment in Section 3.1, the TD conservatively retained the standard animal-to-human toxicodynamic uncertainty factor of 3.

Issue #4: Selection of Studies Used in Determination of URF

Comment: As mentioned by some reviewers, the most thorough approach to URF determination would be to use a combination of derivations based on animal studies with single pure exposures to various nickel compounds expected to be present in Texas air and key epidemiological studies of cohorts with exposures that closely match the composition of Texas air. Since increased cancer risks have not been observed outside workers refining sulfidic nickel mattes (who had mixed and complex exposures), the use of any of these cohorts to represent ambient air composition will overestimate risks. We concur that it is appropriate to also include non refinery cohorts. In this regards, the Arena et al. (1998) study together with the recent Sivulka and Seilkop (2009) study should be considered for incorporation into the derivation of an URF for the following reasons: 1) the Enterline and Marsh cohort (West Virginia) is just one of the 13 cohorts included in the Redmond et al. (1983; 1996) and Arena et al. (1998) studies, 2) improved information on exposures for these cohorts is now available through the work of Sivulka and Seilkop (2009), indicating that exposures are mostly to oxidic nickel with some

metallic nickel exposures, and 3) the cohort is very large (31,000 workers). The Arena study and the earlier Redmond study are cited in the text but are not included in the Reference list. The references cited here are provided below.

Response: As the TD will most frequently not know what form of nickel is present in ambient air, for example, the utility of form-specific URFs is questionable. The TD's selection of studies with lower (both relative and absolute) levels of sulfidic nickel is consistent with the goal of, to the extent possible, not grossly overestimating risk based on the ambient air data and the expected forms of nickel in Texas air. The TD used the most appropriate epidemiological studies available for dose-response modeling for the most reasonable yet conservative evaluation of Texas ambient air data, which is in the interest of public health, based on the most similarity (although certainly still different) between worker exposure and that expected for Texas. In the unlikely case in which the form of nickel in ambient air is known with some degree of certainty and ambient air data suggest a potential concern as compared to the cancer-based value, the TD will take form-specific carcinogenicity information into account to properly put health risk into context as part of the further evaluation conducted in such cases. As noted during the conference call, neither the Arena study nor the Sivulka study relate SMRs to measures of exposure. Therefore, these studies were not added to the DSD derivation of URFs.

Several studies, including Arena et al. (1998) and Sivulka and Seilkop (2009), have absent or insufficient dose-response data for dose-response modeling. A minimum amount of quantitative epidemiological data is necessary for a scientifically-defensible, quantitative dose-response model of how the probability of a specified response (cancer) changes with exposure. Certainly, the better the quality of the data and the greater the amount of epidemiological data (e.g., individual jobs histories, individual time-dependent exposure estimates, information on confounding factors, etc.), the better it is for quantitative dose-response modeling. At the opposite extreme from quality data is one response frequency and some composite measure of exposure (e.g., a rough average exposure among exposed individuals). This minimal information is insufficient to scientifically defensibly model how the response changes with the exposure. Multiple data points are needed. For nickel, the Enterline and Marsh and Grimsrud et al. studies provide far better data for dose-response modeling than the rest of the studies where only one value for the overall SMR was given. The dose-response models fit to the Enterline and Marsh and the Grimsrud et al. studies are much more reliable because they are based on several exposure levels and based on fewer assumptions than the one-point studies published by other authors. Lastly, as the Redmond and Arena studies are cited in a quote from ATSDR (2005), the reader of the DSD is referred to that document for citations.

5. References

Arena, V.C., Sussman, N.B., Redmond, C.K., Costantino, J.P., Trauth, J.M. 1998. Using alternative comparison populations to assess occupation-related mortality risk. J Occup Environ Med 40: 907-916.

ATSDR. 2005. Toxicological profile for nickel. Place Published: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp15.html (accessed May 2009).

Benson, J.M., Chang, I.-Y., Cheng, Y.S., Hahn, F.F., Kennedy, C.H., Barr, E.B., Maples, K.R., Snipes, M.B. 1995a. Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. Fundam Appl Toxicol 28:232–244.

Benson, J.M., Cheng, Y.S., Eidson, A.F., Hahn, F.F,, Henderson, R.F., Pickrell, J. A. 1995b. Pulmonary toxicity of nickel subsulfide in F344/N rats exposed for 1–22 days. Toxicology 103(1):9–22.

Berge, S. R., and K. Skyberg. 2003. Radiographic evidence of pulmonary fibrosis and possible etiologic factors at a nickel refinery in Norway. *J Environ Monit* 5 (4):681-8.

de Winter-Sorkina, R., and F.R. Cassee. 2002. From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. *RIVM report 650010031/2002*:1 - 36.

Dunnick, J.K., Elwell, M.R., Radovsky, A.E., Benson, J.M., Hahn, F.F., Nikula, K.J., Barr, E.B., Hobbs, C.H. 1995. "Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung." Cancer Res 55:5251-5256.

Enterline, P. E., and G. M. Marsh. 1982. Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. *J Natl Cancer Inst* 68 (6):925-33.

Galbreath, K.C., Crocker, C.R., Nyberg, C.M., Huggins, F.E., Huffman, G.P., Larson, K.P. 2003. Nickel speciation measurements of urban particulate matter: method evaluation and relevance to risk assessment. J Environ Monit 5: 56N-61N.

Goodman, J. E., R. L. Prueitt, D. G. Dodge, and S. Thakali. 2009. Carcinogenicity assessment of water-soluble nickel compounds. Crit Rev Toxicol 39 (5):365-417.

Graham, J. A., F. J. Miller, M. J. Daniels, E. A. Payne, and D. E. Gardner. 1978. Influence of cadmium, nickel, and chromium on primary immunity in mice. *Environ Res* 16 (1-3):77-87.

Grimsrud, T. K., S. R. Berge, T. Haldorsen, and A. Andersen. 2002. Exposure to different forms of nickel and risk of lung cancer. *Am J Epidemiol* 156 (12):1123-32.

Grimsrud, T. K., S. R. Berge, J. I. Martinsen, and A. Andersen. 2003. Lung cancer incidence among Norwegian nickel-refinery workers 1953-2000. *J Environ Monit* 5 (2):190-7.

Heim, K. E., H. K. Bates, R. E. Rush, and A. R. Oller. 2007. Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. *Toxicol Appl Pharmacol* 224 (2):126-37.

Magnus, K., A. Andersen, and A. C. Hogetveit. 1982. Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer* 30 (6):681-5.

NTP. 1996a. NTP technical report on the toxicology and carcinogenesis studies of nickel oxide (CAS no. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). In *NIH publication ;; no. 96-3367.; National Toxicology Program technical report series ;; no. 451.* Place Published: [Research Triangle Park, N.C.] : U.S. Dept of Health and Human Services, Public Health Service, National Institutes of Health ; [Springfield, Va. : Available from the National Technical Information Service. http://purl.access.gpo.gov/GPO/LPS77424 (accessed May 2009).

NTP. 1996b. NTP technical report on the toxicology and carcinogenesis studies of nickel subsulfide (CAS no. 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). In *NIH publication ;; no. 96-3369.; National Toxicology Program technical report series ;; no. 453.* Place Published: [Research Triangle Park, N.C.] : U.S. Dept of Health and Human Services, Public Health Service, National Institutes of Health ; Springfield, Va. : Available from the National Technical Information Service. http://purl.access.gpo.gov/GPO/LPS77231 (accessed May 2009).

NTP. 1996c. NTP technical report on the toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS no. 10101-97-0) in F344/N rats and B6C3F1s mice (inhalation studies). In *NIH publication, National Toxicology Program technical report series ;; no. 454*. Place Published: [Springfield, Va. http://purl.access.gpo.gov/GPO/LPS77230 (accessed May 2009).

Oller, A. R., D. T. Kirkpatrick, A. Radovsky, and H. K. Bates. 2008. Inhalation carcinogenicity study with nickel metal powder in Wistar rats. *Toxicol Appl Pharmacol* 233 (2):262-75.

Redmond, C.K., LaGasse, A.A., Bass, G. 1983. Cancer mortality in workers in the high nickel alloys industry. Unpublished Report. University of Pittsburgh. Submitted to the U.S. Environmental Protection Agency, Central Docket Section, Washington, DC, Docket No. ECAO-HA-81-1 IIA.E.4.

Redmond, C.K., Sussman, N.B., Arena, V.C., Constantino, J.P. 1996. Supplemental Analysis of High Nickel Alloy Workers. Final Report to NiPERA. July 26, 1996. Available upon request.

Sivulka, D. J., and S. K. Seilkop. 2009. Reconstruction of Historical Exposures in the U.S. Nickel Alloy Industry and the Implications for Carcinogenic Hazard and Risk Assessments. *Regul Toxicol Pharmacol*.

USEPA. 1986. *Health assessment document for nickel and nickel compounds : final report*. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

USEPA. 1994. *Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry*. Research Triangle Park, NC: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency.

Yu, C.P., Hsieh, T.H., Oller, A.R., Oberdorster, G. 2001. Evaluation of the human nickel retention model with workplace data. Regul Toxicol Pharmacol 33:165–172.