Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the Proposed Development Support Document for Formaldehyde August 7, 2008

The public comment period for the proposed Development Support Document (DSD) for formaldehyde ended May 1, 2008. The Formaldehyde Council, Inc. (FCI) submitted comments on the proposed reference values (ReVs) and effects screening levels (ESLs) for formaldehyde in a May 1, 2008 letter. The Toxicology Section (TS) of the TCEQ appreciates the effort put forth by FCI to provide comments on the proposed DSD for formaldehyde. The goal of TS and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. FCI comments were divided into sections and are provided below, followed by TCEQ responses. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

Toxicology Excellence for Risk Assessment (*TERA*) conducted a review of the carcinogenic assessment (TCEQ contract 582-7-80167-02). *TERA's* comments follow the responses to FCI's comments and indicate that the carcinogenic assessment was scientifically sound and well-written, following TCEQ guidance (TCEQ 2006). The majority of *TERA*'s specific comments relate to minor presentation and clarification issues, and did not result in changes to the chronic ReV or ESL.

Although not in response to a comment, TS added Lang et al. (2008) to the acute assessment as a supporting study although the inclusion of this study did not result in a change to the acute ReV or ^{acute}ESL.

Formaldehyde Council, Inc. (FCI) Comments Regarding the TCEQ Development Support Document for Formaldehyde ReV/ESL Values

1. The Formaldehyde Council, Inc. (FCI) has been participating in the development of the Texas Commission on Environmental Quality's (TCEQ) Effects Screening Levels (ESL) for formaldehyde. In addition to our conversations, FCI previously commented on the proposed ESL and provided a review of the critical studies on chronic and acute health effects for formaldehyde.

TCEQ Response 1: Although FCI did submit important scientific information to be considered in the development of ReVs and ESLs in a February 28, 2007 letter, TS could not locate previous FCI comments on the actual proposed ESL values as derived in the DSD. TS extended the public comment period for the proposed formaldehyde DSD at the request of FCI to provide ample opportunity to FCI (and others) for preparation of technical comments on the proposed ReVs and ESLs.

2. The ESLs are intended to protect from both sensory irritation and cancer and chronic effects. "Short-term ESLs protect against short-term health effects, nuisance odor conditions, and vegetation effects." "Long-term ESLs protect against chronic health effects and vegetation effects." While the scientific literature and understanding of formaldehyde toxicology is robust, the FCI continues to invest in substantial research programs that employ the most recent advances in toxicological evaluation, methodologies, and research tools. As discussed below, on-going studies relevant to development of the formaldehyde ESL are underway and, we believe, should provide an improved scientific basis for State's decisions with regard to defensible modes of action for both cancer and noncancer effects. Because of the scope of studies currently underway and the potential significance of their results to the ESL process, we ask that TCEQ consider deferring action on the formaldehyde ESL until Spring 2009 when we expect that the studies highlighted below will be available for consideration by TCEQ.

TCEQ Response 2: FCI has been aware of both the DSD development process for formaldehyde and the referenced on-going studies for quite some time. The more appropriate time to have requested a deferral would have been near the beginning of the DSD development process, when FCI contacted TS and began submitting scientific study information for TCEQ consideration. TS appreciates FCI's substantial efforts in providing information on some of the most recent and/or significant scientific studies on formaldehyde, and providing insight on relevant on-going studies to be published in the future. However, as noted by FCI, the current scientific literature and understanding of formaldehyde toxicology is robust. Therefore, TS has decided to finalize the formaldehyde DSD at this time, after due consideration of FCI's comments.

The proposed formaldehyde ReVs and ESLs: (1) represent a significant improvement over existing ESLs as their derivation is documented and based on recent assessments of formaldehyde's acute and chronic toxicity under published guidelines (RG-442; TCEQ 2006); (2) are health-protective without being unduly restrictive; (3) incorporate an up-to-date cancer mode of action (MOA) analysis and carcinogenic assessment; and (4) represent a significant advancement over the current use of existing ESLs for both air permit application and ambient air data reviews since the more conservative formaldehyde ESL values (except for the odor-based ESL) are only needed when considering potential ambient air impacts from other sources during air permit application reviews. The formaldehyde ReVs are more relevant for health effects evaluations of ambient air data and will now be used for that purpose.

While on-going and future studies will provide additional information regarding formaldehyde's toxicity to be considered for a future formaldehyde DSD update, sufficient information exists for TCEQ (and other agencies) to derive health-protective ambient air values. TS looks forward to continuing to work with the public, the regulated community, and other interested parties (e.g., FCI) in the development of DSDs and as new data emerges in the future with implications for a subsequent formaldehyde DSD update. The DSD will be updated if TS determines

that new scientific information would significantly affect the critical acute or chronic ReVs/ESLs.

3. The January 2008 draft Development Support Document cites Moser et al. (2005) and notes that formaldehyde is produced endogenously in our bodies, with significant levels exhaled in human breath. Moser et al. (2005) involved a study of formaldehyde breath levels in 344 healthy men and women, with a median level of 4.3 ppb and levels of 6.3 ppb, 40 ppb and 73 ppb for the 75th, 97.5th and maximum, respectively. Based on these data, it seems incongruous to establish ESLs for formaldehyde in the range of human breath levels. It is suggested that some consideration be given to the utility of ESLs that would clearly be exceeded by normal human breath levels.

ESLs are used as guideline levels in health effects evaluations of off-site modeled air concentrations for facility air permit applications and for screening ambient data. The intended uses for the ESL at both the established and proposed values are seemingly undermined by the human breath levels of formaldehyde. For ambient air monitoring data evaluations, the proposed acute Reference Value (ReV) of 41 ppb and chronic non-cancer ReV of 8.9 ppb would be used as the critical values (both of which are exceeded by human breath levels), so the ambient air screening values would change by factors of 3.4 and 7.4, respectively, compared to those currently being used. As with any screening value, exceedance of a value means further evaluation is warranted, rather than implying that a toxicological threshold has been crossed. However, since normal human breath levels already exceed these levels, the ESLs as currently established do not appear to have any real health-based value. The higher values of the odor-based ESL (500 ppb) and nonlinear cancer-based ReV (15 ppb) are also applicable to ambient air data evaluations. Thus, FCI believes it is critical that state of the art science be used by TCEQ in developing the ELSs, as these values have significant impact on health effects evaluations and ambient air screening. With virtually all ESLs now falling into the range of normal human breath levels, the implication for ESLs should be re-examined.

TCEQ Response 3: TS agrees with FCI that state-of-the-art science be used by TCEQ in developing ReVs/ESLs. For that reason, TS published a process for the development of ReVs, ESLs, and unit risk factors (URFs) in November 2006 (RG-442) which had been peer reviewed by internationally-renowned scientists. The methodologies in RG-442 were designed to provide a framework for deriving scientifically-defensible, health-protective values using established and up-to-date methods. However, exactly how human breath data (of known quality) should be considered in the context of setting health-protective ambient air screening concentrations for a given chemical is unclear. Consideration of human breath data by regulatory and other agencies (e.g., ATSDR) in deriving inhalation toxicity factors for formaldehyde (and other chemicals which may be present in human breath) appears to be without precedent, and a process for doing so has not been established by regulatory agencies.

FCI relies on human breath data from Moser et al. (2005) for the comments given above. The Moser et al. (2005) study was cited to make readers (e.g., public, FCI)

aware of the potential for formaldehyde to be contained in human breath because formaldehyde is produced endogenously (i.e., within the body). However, TS has serious concerns about the data, and a statement to that effect has been added to the DSD.

First, TS has significant reservations about the use of proton-transfer-reaction mass spectrometry (PTR-MS) for the identification and quantification of formaldehyde in human breath. Moser et al. (2005) acknowledges that a limitation of PTR-MS is that substances are detected according to their molecular weight (MW; along with their proton affinity in relation to water), so interference by other substances is a potential source of error. The Lindinger et al. (1998) study cited by Moser et al. (2005) indicates that the problem of chemical identification is a crucial one as there are several compounds which can produce a response at *m/z* 31 (i.e., have the same nominal mass as formaldehyde). The study further suggests that PTR-MS is an appropriate method for on-line monitoring (of known and limited components) and not primarily for gas analysis (of complex mixtures), and thus use of gas chromatography-mass spectrometry (GC-MS) methods or other confirmatory techniques is strongly recommended for gas compound analysis. Furthermore, Moser et al. (2005) does not indicate that any of the identification methods discussed in Lindinger et al. (1998) were used in an attempt to distinguish between chemicals with a response at *m/z* 31 and identify specific chemicals, much less provide detailed information or data on the matter. Holzinger et al. (2007) indicates that there are PTR-MS issues with compounds such as formaldehyde, the proton affinity of which is just slightly above that of water. Inomata et al. (2008) indicates that other compounds (e.g., methyl hydroperoxide, methanol, ethanol) may interfere with the ion signal (*m/z* 31) used for PTR-MS analysis of formaldehyde, resulting in a positive bias (although increasing humidity decreases sensitivity). Thousands of chemicals have been reported as present in human breath (Phillips et al. 1999), and contribution from isobaric molecules of known or unknown origin (and fragmentation of larger molecules) can never be ruled out because PTR-MS is only mass sensitive, not species sensitive. Therefore, accurate chemical identification in complex mixtures is very difficult and should be verified by separatory measurement techniques such as GS-MS (i.e., a more definitive analytical method). Formaldehyde can only be tentatively identified and quantified by PTR-MS unless significant efforts are made to identify and correct for interferences and a confirmatory technique is used to verify reported concentrations. TS believes the above-referenced studies identify significant uncertainties in the identification and determination of formaldehyde levels in human breath by PTR-MS, and Moser et al. (2005) gives few details (e.g., no calibration information).

Secondly but equally important, while Moser et al. (2005) indicates that background concentrations were negligible for the volatile organic compounds (VOCs) presented, no background data are presented and indoor concentrations of formaldehyde are known to be significant compared to the reported breath levels. As indicated in the formaldehyde DSD, indoor means have been reported to be around 30 ppb (excluding mobile homes), which is significantly higher than even the

75th percentile (6.3 ppb) reported by Moser et al. (2005) for formaldehyde in breath, and approaches the reported 97.5th percentile (39.8 ppb). The formaldehyde concentration in inhaled air certainly contributes to the level in exhaled air, and should have been adjusted for empirically. Additionally, no information is given regarding precautions taken to prevent infiltration of indoor air into the samples during collection.

The PTR-MS method as employed/described in Moser et al. (2005) does not provide adequate detail to insure that the calibration was performed in a matrix similar to the samples analyzed, that interferences were properly identified and corrected for, or that adequate tests were conducted to characterize the potential for positive bias (i.e., does not appear to definitively identify and quantify formaldehyde). Air background levels should also have been taken into account. These concerns were confirmed by the TCEQ analytical laboratory. Furthermore, TS did not find additional studies corroborating the formaldehyde levels reported using a superior, chemical-specific method. For example, Phillips et al. (1999) and Phillips (1997) used GC-MS to analyze for VOCs in human breath, and formaldehyde was not among the detected chemicals reported in the study based on frequency of occurrence, abundance, positive alveolar gradient (i.e., alveolar breath minus room air concentration), etc.

Assuming formaldehyde is present in human breath at some level as a result of endogenous production, possible subsequent elimination through expiration does not mean that exogenous (i.e., external) exposure is without toxicological consequence. Formaldehyde in ambient air results in an exogenous exposure which increases the toxic burden of the respiratory system. FCI indicates that ESLs are for screening ambient data, and that normal breath levels as reported by Moser et al. (2005) exceed this value. However, the proposed formaldehyde ESLs would not be used for screening ambient air data, the formaldehyde ReVs are to be used for this purpose. Temporarily disregarding TS's serious concerns about the Moser et al. (2005) data, the acute ReV (41 ppb) is greater than the reported median (4.3 ppb), 75th percentile (6.3 ppb), and 97.5th percentile (39.8 ppb) values. Additionally, both the chronic non-carcinogenic ReV (8.9 ppb) and chronic carcinogenic ReV (15 ppb) are greater than the reported median (4.3 ppb) and 75th percentile (6.3 ppb) values. Therefore, the ReV values to be used to evaluate ambient air data are greater than the alleged formaldehyde breath levels for most individuals as reported by the Moser et al. (2005) study. However, these (and similar) comparisons are not considered particularly relevant as TS does not have confidence in the reported breath data for reasons cited in previous paragraphs.

FCI asserts that since human breath levels exceed the proposed ESLs, they do not appear to have any real health-based value. However, as indicated previously, TS does not have confidence in the reported data which form the basis of this comment (and others). The ReV and ESL values are indeed health-based as they are derived based on points of departure (PODs) from scientific studies on the health effects of formaldehyde. ReVs and ESLs are designed to be concentrations which do not

result in adverse health effects over the specified duration (as opposed to a bright-line demarcation between safe and unsafe concentrations), and TS is confident that the proposed values achieve that goal. In regard to non-carcinogenic effects, while there are uncertainties in the assessment process (e.g., assignment of sufficient uncertainty factor values), TS utilized studies previously used by other agencies for the assessment of non-carcinogenic effects and a peer-reviewed methodology (RG-442) to calculate values that are similar to those derived by other agencies. As indicated in the formaldehyde DSD, the proposed acute ReV (41 ppb) is similar to acute health-protective values used by other agencies (e.g., ATSDR's acute minimal risk level (MRL) of 40 ppb, CalEPA's 2007 draft acute REL of 44 ppb), as is the proposed chronic non-carcinogenic ReV (8.9 ppb) value (e.g., ATSDR chronic MRL of 8 ppb, CalEPA's 2007 draft chronic REL of 7 ppb). In regard to carcinogenic effects, Toxicology Excellence for Risk Assessment (*TERA*) conducted a review of the carcinogenic assessment (TCEQ contract 582-7-80167-02). *TERA's* comments follow the responses to FCI's comments. *TERA's* comments indicate that the carcinogenic assessment is generally well-written, scientifically sound, and follows ESL guidelines (TCEQ 2006). Most of *TERA's* comments relate to minor presentation and clarity issues.

Importantly, the proposed ReVs and ESLs for formaldehyde represent a significant improvement over existing ESLs as their derivation is documented and based on recent acute and chronic assessments of formaldehyde's toxicity under published guidelines (RG-442). TS strongly believes the proposed ReVs/ESLs are protective of public health. In addition, they are health-protective without being unduly restrictive. The use of formaldehyde ReVs (plus the odor-based ESL) for the evaluation of ambient air data and ESLs (health- and odor-based) for the evaluation of air permit applications (per RG-442) represents a significant advancement over the current use of ESLs for both purposes since the more conservative ESL values are only needed when considering ambient air impacts from other sources. Furthermore, the carcinogenic ReV and ESL values are based on an up-to-date cancer MOA analysis and carcinogenic assessment which *TERA* indicates was scientifically sound and well-written, following TCEQ guidance (TCEQ 2006).

4. On-Going Studies

With the discovery in 1979 that formaldehyde caused nasal cancer in rats following lifetime exposure to very high levels, an extensive effort was undertaken, and continues today, to understand better the potential for similar effects in humans. Highly regarded experts in the field of toxicology have concluded that formaldehyde is not likely to be carcinogenic to humans under low exposure conditions, specifically, at exposures that do not cause cytotoxic effects. Lacking sufficient evidence showing cancer in humans exposed to formaldehyde at environmental levels, risk assessors have historically made predictions of hypothetical cancer risk posed by low-dose formaldehyde exposure using the highly conservative linearized multistage model in conjunction with numerous default assumptions to extrapolate potential risks to humans from laboratory animal data. However, estimates of the risk of developing cancer as the result of exposure to

formaldehyde have been lowered over time as new experimental data have replaced default assumptions and mathematical models for extrapolating from animals to humans and high doses to low doses have become more sophisticated.

Risk estimates associated with exposure to formaldehyde have continually decreased as scientific knowledge has increased and newer, more complete scientific studies have become available. For example, for lifetime exposure to 0.1 ppm, the 1987 and 1991 EPA risk value declined from 1.6 in 1,000 to 3.3 in 100,000. In 1999, the CIIT biologically based risk assessment model estimated the risk from the same exposure (i.e., 0.1 ppm) to be 3.3 in 10,000,000. In other words, as the mode of action became better understood, the risk levels were adjusted to be consistent with this evolving body of knowledge.

To further increase our understanding of formaldehyde and its acute and chronic effects, FCI has sponsored several studies. The four listed below are all in various stages of completion and could have direct bearing on TCEQ's evaluation of formaldehyde:

21 Day Genomics Study at CIIT (now Hamner Institutes for Health Sciences): The validity of the CIIT model has now been further supported by the most recent genomics data involving formaldehyde-induced nasal tumors in rodents. In this recently published study by Andersen et al. (2008) rats were exposed to formaldehyde at the same doses (i.e., 0, 0.7, 2 and 6 ppm) as used in the definitive cancer study (i.e., Monticello et al. 1996) 5 days/week for three weeks. Epithelium from nasal tissues that had tumors in 2-year inhalation studies at 10 and 15 ppm was evaluated by histopathology and microarray analysis. In this study, no genes were statistically altered at 0.7 ppm at any time points indicating a clear threshold for formaldehyde-induced effects. At 2 ppm, 15 genes were significantly changed on day 5 and many more were changed at 6 ppm. Most importantly, no genes were significantly changed at 2 ppm at day 15. In other words, these data show that even at 2 ppm, nasal cells initially show some minor effects, but after a few days rapidly adapt to formaldehyde at this concentration and return to a pattern of gene expression identical to 0 and 0.7 ppm. This study provides additional empirical support at the genomic level for the approach used in a biologically based dose-response model (BBDR model) (Conolly et al. 2004) (i.e., CIIT model).

90-Day Genomic research at the Hamner Institutes for Health Sciences: Building on the 21-day genomics study, CIIT is conducting a 90-day formaldehyde inhalation study at exposure levels of 0, 0.7, 6, 10 and 15 ppm to obtain definitive data on cell proliferation, mutation, and genomic responses in regions of the upper respiratory tract from the anterior nose to the nasopharynx. Completion is expected in 2009.

Modeling of Cancer Model Genomic Data (Sensitivity Analysis): The Hamner Institutes is in the process of conducting a multi-step uncertainty and sensitivity analysis of risk estimates using the CIIT biologically based modeling approaches for formaldehyde carcinogenicity. This effort will address issues raised by the U.S. Environmental Protection Agency (EPA) and subsequently referenced by TCEQ regarding model sensitivity around certain assumptions and key input parameters. Importantly, scientists from both Hamner and EPA are working together on this project. The contract began in

2006 is expected to be completed by December 31, 2008. Together with the genomic research results, these efforts should answer questions raised by TCEQ and USEPA and collectively provide the basis for adoption of the BBDR model (Conolly et al. 2004) by TCEQ in the development of the formaldehyde cancer ESL.

Pending NCI Studies: Studies by the National Cancer Institute (NCI) published by Hauptmann et al. (2003, 2004) addressed both nasopharyngeal cancer (NPC) and lymphohematopoietic cancers. These studies have been the principal basis for cancer risk assessments (including the IARC 2006 evaluation), as well as the evaluations being undertaken by TCEQ. However, the conclusions drawn from the NCI data have been subject to considerable debate, as reflected in Marsh and Youk (2004) and Marsh (2007), which provides data indicating that NPC in the NCI cohort may not be etiologically related to formaldehyde exposure but rather to metal working and acid mist exposures in other workplaces. Prompted in part by such critiques, NCI is in the process of updating its epidemiology studies with regard to both NPC and lymphohematopoietic cancers. These updates from NCI on leukemia and nasopharyngeal cancer are critical to any comprehensive risk assessment. NCI began is update in 2007 and, based on informal comments from NCI, the authors expects that the final manuscripts should be available in late 2008.

The genomic studies, BBDR model refinements and updated NCI studies should be available for consideration in early 2009 and permit TCEQ to refine its chronic, carcinogenic ESL determination. In the interim, we ask that TCEQ reconsider whether the application of default assumptions in the derivation of both cancer and noncancer ESLs for formaldehyde is scientifically supportable if the resulting ESL is at or below the levels of formaldehyde that are naturally exhaled in human breath. Such actions would result in biologically implausible ESLs when an evidence-based approach consistent with biological plausibility is warranted. With regard to the development of a chronic ESL based on cancer effects, the results of these ongoing studies should further support the use of a widely accepted BBDR model rather then default assumptions that arrive at scientifically untenable ESLs.

TCEQ Response 4: The proposed ReVs and ESLs are scientifically tenable. As discussed in TCEQ Response 3, they are derived based on PODs from scientific studies on the health effects of formaldehyde and a peer-reviewed methodology (RG-442). The same studies have been used by other agencies to calculate health-protective values based on the non-carcinogenic effects of formaldehyde, and those calculated by TS are similar to those derived by other agencies. The carcinogenic health-protective values are based on an up-to-date cancer MOA analysis and carcinogenic assessment which were reviewed by *TERA*. The CIIT BBDR model was not selected to derive carcinogenic-based values for reasons cited in the DSD. Even if TS were to adopt the CIIT model subsequent to completion of the uncertainty and sensitivity analysis referred to by FCI, the critical ReV and ESL values would not change as they are based on non-carcinogenic effects and are not from the carcinogenic assessment. The proposed ReVs and ESLs (and the methodology and processes used to derive them) are scientifically-defensible.

As indicated in TCEQ Response 2, while on-going and future studies will provide additional information to be considered for a future formaldehyde DSD update, sufficient information currently exists for TCEQ (and other agencies) to derive health-protective ambient air values. Although the 21-day and 90-day genomics studies referred to may provide additional empirical support at the genomic level for the CIIT model approach, the proposed ReV and ESL values resulting from the carcinogenic assessment are not the critical values as the chronic non-carcinogenic ReV and ESL are lower. Additionally, while the CIIT model uncertainty and sensitivity analysis referred to by FCI may help alleviate some TCEQ/USEPA concerns regarding adoption of the CIIT model, the critical proposed ReV and ESL values are not from the carcinogenic assessment. TS is very interested in the findings of the updated NCI studies. However, as other data are available for the carcinogenic assessment, these studies are not viewed as critical (especially if the studies do not include dose-response modeling). TS does not believe the pending NCI studies justify a delay in finalizing the proposed DSD. The DSD will be updated and the cancer assessment refined if TS determines that new scientific information from the updated NCI studies would significantly affect the critical chronic ReVs/ESLs. Studies critical of the conclusions drawn from the previous NCI studies are already cited in the formaldehyde DSD.

Please see TCEQ Response 3 regarding significant TS reservations about the referenced human breath data.

5. FCI and its members continue to invest in research to support the scientific community's efforts to better understand the toxicological properties of formaldehyde and refine risk assessment methodologies to continue to protect human health and the environment with increasing levels of certainty. While FCI hopes that the data and insights produced through these studies will complement and clarify the existing data set, because this is research, there is always the possibility that the studies will raise new issues or uncertainties. Nonetheless, we strongly urge TCEQ to defer finalization of the formaldehyde ESL as ongoing research is likely to clarify some important issues fundamental to the ESL development process. The additional scientific data that will be gathered this year can only benefit TCEQ's development of the formaldehyde ESL, and we ask that you consider postponing final action until Spring 2009. Naturally, if TCEQ would like additional information on these studies or updates on their progress, we would be happy to discuss the agency's needs.

TCEQ Response 5: TS commends FCI's support of scientific research to better understand the toxicological properties of formaldehyde. Although on-going and future studies will provide additional information relevant to a future formaldehyde DSD update, the current scientific literature and understanding of formaldehyde toxicology is robust, and sufficient information exists for TCEQ (and other agencies) to derive health-protective ambient air values. Therefore, TS has decided to finalize the formaldehyde DSD at this time. TS looks forward to continuing to work with FCI, the public, the regulated community, and other interested parties in the

development of DSDs and as new data emerges with implications for subsequent DSD updates.

References :

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Formaldehyde Development Support Document
Technical Review – Lynne Haber, *TERA*

The DSD is generally well-written, scientifically sound, and follows ESL guidelines. Most of the key decision points were based on assessments developed and documented by other organizations, and so have already been vetted by other review mechanisms. These decisions and rationales provided by the TS for the key decision points are reasonable. This includes the choice of data for the quantitative analysis, presentation of multiple modeling approaches for comparative purposes, choice of model, and choice of UFs. (I did not review in detail the choice of data to model, since this has previously been vetted by numerous organizations.) Therefore, most of my comments relate to minor presentation and clarity issues.

Technical comments:

P. 25: Unlike ATSDR, Health Canada does routinely assign cancer classifications to chemicals. Therefore, the fact that Health Canada chose not to assign a classification for formaldehyde is informative. According to the ITER database, the Health Canada conclusion was: "Based primarily upon data derived from laboratory studies, therefore, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans." The formaldehyde assessment from Health Canada is available at the citation noted below. Although the DSD extensively cites what is presumably the published version of that assessment (Liteplo and Meek, 2003), government assessments have additional weight, and it would be useful to also cite the Health Canada assessment as a government assessment wherever appropriate in the document. (Page 39 does cite the Health Canada assessment, but it does not appear in the reference list.)

Section 4.2.1.2.2: This section was generally well-written, but seemed to assume more knowledge of the reader than in some of the other sections, and seemed to gloss over lines of reasoning in reaching conclusions. Although many researchers dismiss the leukemia as not biologically plausible, that conclusion is controversial, and the controversy and related issues should be noted to ensure transparency. Some specific comments;

--It can be useful to present the overall conclusions before going into details, as was done for this section. However, the introductory paragraph of this section was potentially confusing by jumping to the conclusion and discussion of biological plausibility before presenting the epidemiology data. It may be clearer to present a brief introduction, followed by the epidemiology data, and then a discussion of biological plausibility (or the lack thereof).

--Although there are many publications discussing the biological implausibility or improbability of an association between formaldehyde and leukemia, the potential for this association is controversial, and the controversy should be addressed in further detail. The current text acknowledges the IARC conclusion, but it appears that biological

implausibility is a key reason for TS dismissing the weak epidemiology evidence, without only a brief mention of the reasons for biological implausibility and associated arguments. Most specifically, USEPA has proposed a MOA for an association between formaldehyde and leukemia. Unfortunately, it appears that this proposal has not been published, but it has been presented at professional society meetings. There is also a publication that has become available since the DSD was completed (Pyatt et al., 2008), which addresses the EPA proposal, based on the presentations and discussions with the EPA author. I have not fully reviewed the EPA proposal or the recent publications to determine if they should sway any conclusions, but I think that the controversy should be addressed.

P. 31, line 5: This is the first mention I could find of saturation of glutathione-mediated metabolism of formaldehyde. It would be useful to discuss this saturation and its implications in the section on metabolism of formaldehyde. Also, for chemicals with multiple metabolic pathways, colloquial discussion often describes a "switch" from one pathway to another as dose increases. In reality, a low-affinity pathway does have some contribution at lower doses (below saturation of the high-affinity pathway), although the percentage may be small enough that the contribution of the low-affinity pathway may be considered *de minimis*. However, this determination requires at least some consideration of the relative contribution of different pathways at low doses, rather than just considering whether the chemical is above or below a threshold for saturation.

Section 4.2.2.2: This section is generally well-written and addresses the key points. However, a more rigorous consideration of the WOE for MOA, in the context of the modified Hill criteria, would be useful. (At least part of the utility may be in communicating to stakeholders the issue of how high the bar is for showing a nonmutagenic MOA. As written, some of the language, such as "this MOA satisfies several criteria for WOE," may give a misimpression regarding the data needed to show a nonmutagenic MOA.) While TS does not need to reinvent the wheel and repeat all of the supporting data, it would be useful to highlight in a few sentences for each criterion what the supporting data are, or that the nature of the data are insufficient to address the criterion (e.g., for specificity).

P. 32, lines 38-40: As you know, USEPA's methods also specify use of linear-low dose extrapolation if the MOA cannot be determined – not only if it is a purely mutagenic MOA.

P. 33, lines 10-13: Consider emphasizing MOA more and the shape of the dose-response relationships less in the choice of nonlinear extrapolation. It is possible to misinterpret the text here as supporting the decision to use nonlinear extrapolation (for other chemicals) based primarily on the shape of the dose-response curves.

Section 4.2.3.1.1: As noted, Schlosser used two different approaches to extrapolate the rat BMCL to humans, and lines 7-8 of p. 34 states that the flux-DPX approach to extrapolation was used for the TS assessment. It would be useful to add some discussion

on why that approach was chosen, and the implications of choosing it over the other extrapolation approach.

P. 34, line 10: I recognize that the first sentence is in accordance with ESL methods, but do feel obligated to note that the standard approach to BMD/BMC modeling is to define a consistent response across studies. This is a bit different for cancer modeling, for which the EPA guidelines do talk about finding the lowest POD that is consistent with the data. I also want to note that, as a general statement, the $BMCL_{01}$ is not *necessarily* more conservative than a $BMCL_{10}$, if linear extrapolation is used and if the two doses are in the linear range of the dose-response curve. However, for the current assessment, in which a nonlinear approach is being used, I agree that the $BMCL_{01}$ is more conservative.

P. 34, lines 12-18: As written, the text is a bit confusing, since it talks about the 1% tumor response being in the range of the bioassays, but the endpoint modeled is cell proliferation. On an initial read, it can look as though tumors were modeled.

Section 4.2.3.1.2: Another conservative consideration in the assessment that is worth noting is that the POD is based on a precursor to tumors, not tumors.

Section 4.2.3: I recognize the advantage for TCEQ of building off of other assessments, and avoiding re-inventing the wheel by referring to tables of other assessments, rather than presenting all of the data and analyses. However, some additional data presentation would help the reader significantly. In particular, it would be useful to present the actual concentration-response data for tumors and cell proliferation, as well as key BMC model results for the key models chosen from the Schlosser et al. analysis. It would also be useful to better define the BMR for the continuous endpoint of cytotoxicity, since an excess risk of 1% is ambiguous for a continuous endpoint. It appears that the BMR was a 1% increase in unit length labeling index (ULLI), but please confirm.

P. 36, line 36: Please clarify. I assume that the *structure* of the clonal growth model is the same as for other MVK models, but the *parameters* are specific to the tissue of interest.

P. 37, lines 30-33: Nice comment on uncertainties and nice discussion of the implication of using an additional uncertainty factor.

Section 4.2.3.2.3: It would be useful to explicitly note that under the current (2005) EPA cancer guidelines, the ADAF is applied only when a chemical is affirmatively shown to act via a mutagenic MOA. It is not applied for chemicals for which the MOA is not known, or for chemicals that clearly have multiple MOAs. (In other words, the default is *not* to apply the ADAF, while the default for extrapolation, of course, is to linear extrapolation.) Therefore, it may make sense to discuss the ADAF only in the context of the linear extrapolation shown for comparison.

P. 38, lines 17-32: The previous point may make this text unnecessary. If TS keeps this text, I would suggest reframing it in terms of the data supporting a nonmutagenic MOA.

As written, the text is addressing both human relevance (which is separate from the ADAF issue) and MOA in animals. (Recall that the first step in the human relevance framework is to establish the MOA in animals. So the order would be first supporting the nonmutagenic MOA, and then showing that this MOA is also relevant to humans.) Also, as written, the text seems to rely mostly on biological plausibility to show the nonmutagenic MOA, rather than addressing the full range of the modified Hill criteria.

P. 42, lines 18-20: It would be useful to remind the reader what the ESLs for each of the options are based on. (For example, that the CIIT model was used to calculate an air concentration at 1 in 100,000 excess risk for smokers, and that linear extrapolation corresponds to the same risk level). This helps to remind the reader that there are multiple differences among the approaches used, not just the extrapolation approach.

P. 43, lines 26-31: TS has already made the case that the nonlinear approach is more appropriate than the linear approach, and that the CIIT model is more appropriate than the linear extrapolation. The bigger question is whether to use the CIIT model or the nonlinear BMD approach, and this issue is not fully addressed. The italicized text does provide a good explanation, but the "however" statement implies that this statement relates to the previous statement about CIIT vs. linear extrapolation. The rationale presented by TS for using the nonlinear as the basis for the cancer assessment is a reasonable one. Furthermore, as noted in the DSD, the choice between these approaches is of no consequence, since the noncancer endpoint would end up determining the longer-term ESL. Therefore, I did not spend additional time investigating whether the nonlinear or CIIT approach is more appropriate, but I could consider this issue further if desired by TS.

References:

Environment Canada, Health Canada. 2001. Priority substances list assessment report: Formaldehyde. Ottawa. Ministry of Public Works and Government Services. February. Available at http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index_e.html or at the Inquiry Centre at 1-800-668-6767 (in Canada) or 819-997-2800 (outside Canada).

Pyatt D, Natelson E, Golden R. 2008. Is inhalation exposure to formaldehyde a biologically plausible cause of lymphohematopoietic malignancies? Regul Toxicol Pharmacol. 2008 Mar 18. [Epub ahead of print]

Editorial/Minor comments:

P. 28, line 35: I believe that "only" is meant to modify "rats exposed…", rather than "markedly." The sentence may be clearer as: "Nasal tumors are markedly increased only in rats exposed…"

P. 31, line 2: It may be worth reminding the reader that the increased proliferation is related to cytotoxicity.

P. 35, line 5: The full name for *TERA* is Toxicology Excellence for Risk Assessment. (The Schlosser article also got the name wrong.) Also please note that the abbreviation is italicized.

Table 6, first line: For clarity, it would help to note that the Schlosser et al. (2003) study was an analysis of the data from Kerns et al. (1983) and Monticello et al. (1996), since the study details refer to the experimental studies, not Schlosser's paper. Based on my brief read of the Schlosser paper, it also appears that 94 rats not included in the initial two papers were included in the modeling.

P. 36, line 16: Absorption is misspelled.

General comment: The writing is generally very clear and does a nice job of presenting a number of complicated concepts. However, it could be made less dense by some additional attention to sentence structure and length. The burden on the reader can be decreased by breaking some of the long complex sentences into two sentences.